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HIV controllers: a multifactorial phenotype of spontaneous viral suppression

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Abstract

A small minority of HIV-infected individuals, known as HIV controllers, is able to exert long-term control over HIV replication in the absence of treatment. Increasing evidence suggests that the adaptive immune system plays a critical role in this control but also that a combination of several host and/or viral factors, rather than a single cause, leads to this rare phenotype. Here, we review recent advances in the study of these remarkable individuals. We summarize the epidemiology and clinical characteristics of HIV controllers, and subsequently describe contributing roles of host genetic factors, innate and adaptive immune responses, and viral factors to this phenotype. We emphasize distinctive characteristics of HIV-specific CD4 T cell responses and of CD4 T cell subpopulations that are frequently found in HIV controllers. We discuss major controversies in the field and the relevance of the study of HIV controllers for the development of novel therapeutic strategies and vaccines.

Keywords

HIV; CD4 T cell; Pathogenesis; controllers; long-term non progressors; Protective Immunity

INTRODUCTION: CLINICAL DESCRIPTION OF “HIV CONTROLLERS”

In the absence of antiviral therapy, the large majority of HIV-infected individuals have uncontrolled viremia and undergo progressive immune impairment that ultimately leads to AIDS. However, a very small percentage ($\leq 1\%$) of HIV-infected persons spontaneously control viral replication in the absence of therapy. There is no universally accepted

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definition for this rare group of HIV-infected subjects. In the USA these patients are called “elite controllers”, “elite suppressors” or “elite non progressors”, terms that cover individuals with viremia below the limit of detection of standard viral load assays (50 or 75 copies/mL) for at least one year [1]. In France, these patients are more readily referred to as “HIV controllers” when they are able to maintain viremia at ≤ 400 copies/ml for five years or more after infection [2].

These individuals should not be confused with another group of patients whose condition progresses very slowly to AIDS, e.g. long-term survivors (LTS), long-term asymptomatics (LTA) and long-term non-progressors (LTNP). The definition of “HIV controllers” is virological whereas that of long-term survivors is immunological, based on a maintained CD4 lymphocyte count $> 500/\text{mm}^3$ for several years without therapy. These patients were first described in the 1990s but over time the majority experienced a decrease in CD4 counts and a significant fraction progress to AIDS [3]. In contrast, HIV Controllers appear to have a very low risk of progressing to AIDS [3].

“HIV controllers” are seropositive, as determined by Elisa and Western blot analyses conventionally used to diagnose HIV infection. Although, by definition, their plasma contains very low quantities of viral RNA in the absence of ART under steady-state conditions, punctual viral rebounds, called viral replication blips, may be observed. HIV cellular DNA can be detected in the white blood cells of these subjects but at far lower levels than in viremic patients [2]. The vast majority of HIV controllers do not progress to AIDS and maintain high CD4 lymphocyte levels, although a few experience significant CD4 loss and even AIDS-defining events [3]. Recent detailed studies of HIV “elite” controllers, however, show that a very low-level viremia can be detected by ultrasensitive viral load assays in a majority of the subjects examined [4, 5]. This low level of residual viremia was associated with a slow loss of CD4 cells over time compared to individuals in whom no residual viral replication was detected by this assay [4] and with the expression of inhibitory molecules that affect CD4 T cell function [6].

HIV controllers cannot be distinguished from other HIV-infected patients based on gender or mode of contamination, which include homosexual and heterosexual transmission, intravenous drug use, and blood transfusion [3, 4]. Currently, epidemiological studies are too few to determine whether HIV controllers are also “resistant” to other viral or bacterial infections. HIV control does not appear to lower the incidence of hepatitis B or hepatitis C infection in the ANRS CO18 HIV Controller cohort (Olivier Lambotte, personal communication). The HIV controller status appears to occur sporadically and its frequency is not greater in any particular ethnic group, region or profession. Various studies have shown specific genetic associations in HIV controllers [7, 8]. In particular, some alleles of the Major Histocompatibility Complex (MHC) class I (or Human [9]) that can be presented to CD8 T cells (as HLA–epitope complexes recognized by TCRs) these results can be considered as the strongest evidence supporting the role of adaptive immunity and HIV-specific CD8 T cells in spontaneous control of viral replication. The most extensive data for association with controller status has been established for HLA B*5701, B5703 and HLA B*2705 [7, 10]. Interestingly, HLA*B57 has also been associated with control of HCV infection [9] and HLA*B27 is associated with various autoimmune diseases, suggesting unique properties of these HLA alleles beyond their role in HIV infection. HLA B*5801 (but not HLA B*5802) has been associated with lower viral loads in African ethnicities [11]. Further studies support a beneficial impact of B14, B52 and likely Cw1402 ([7] and Mary Carrington, personal communication). Whereas additional HLA molecules have also been associated viral loads, the real significance of those not confirmed in independent cohorts and/or by genome-wide association studies (GWAS) remains uncertain. The hypothesis that levels of HIV epitope expression on infected cells affect the efficacy of CTL responses *in*

vivo was strongly supported by a recent study showing that differential microRNA regulation associated with higher HLA-C expression was associated with viral control [12]. It is important to note that most subjects carrying so-called “protective” alleles still progress to AIDS in the absence of therapy, indicating that several factors are likely necessary to achieve spontaneous HIV control.

From a clinical point of view, it may be concluded that the precise mechanisms underlying HIV suppression in these rare patients are still largely unknown, but that their clinical situation is extremely interesting given that it provides the opportunity to study a human immune system capable of controlling HIV. Here, we review known and putative factors contributing to this remarkable clinical phenotype, and discuss the relevance of the study of HIV controllers for the development of novel therapeutic strategies and vaccines against HIV. Tables 1 and 2 summarize the potential mechanisms discussed in this review.

THE ROLE OF HIV REPLICATIVE CAPACITY IN HIV CONTROLLERS

It is generally agreed that a severe primary HIV infection (severe symptoms or opportunistic infections at time of presentation, profound CD4 depletion) is associated with faster subsequent disease progression. Conversely, a primary infection of moderate intensity may contribute to subsequent HIV controller status, as suggested by a few reported cases [13, 14]. Factors that may reduce the severity of the primary infection stage in HIV controllers include host factors (innate and adaptive immunity) and potentially, viral factors (infecting strains of reduced virulence).

Although multiple studies have investigated the role played by the characteristics of the autologous virus in the HIV controller phenotype, there is currently few data unambiguously demonstrating infection with attenuated HIV strains in individuals who subsequently become HIV controllers. These limitations are due to the challenges in getting viral samples from the sources and clinical samples at time of acute infection in those individuals. Multiple factors influence the overall capacity of HIV to replicate. This capacity, also known as “viral fitness” can impact viral load *in vivo*. It is well established, for example, that the drug mutation M184V in reverse transcriptase is associated with a loss of viral fitness, and that infection of antiretroviral-naïve patients with M184V-harboring HIV strains leads to significantly lower viral loads relative to patients without this mutation [15]. Similarly, mutations caused by pressure from the immune responses can impair viral replicative capacity, in particular when they involve functionally or structurally important parts of HIV proteins [16]. It has been shown that transmission of viral variants with a greater number of escape mutations to HIV-specific CD8 T cell responses correlated with lower viral loads in the newly infected partners [17]. Can therefore HIV controller status be established following infection with an attenuated viral strain? This important question is experimentally difficult to address because of the challenge of isolating replication competent viruses from HIV controllers. The Sydney Blood Bank Cohort Study was the first to demonstrate that infection with a defective HIV strain lacking *nef* and a portion of the LTR could lead to a more benign clinical course [18]. However, such viruses harboring gross deletions and/or absent gene products seem to be very rare in HIV controllers. In contrast, a moderate decrease in viral fitness appears to be a frequent characteristic of HIV controller viruses. Recent progress in experimental approaches allowed demonstration that the Gag and protease coding regions [19] and Env region [20] from “elite” controllers (i.e., HIV controllers with a viral load < 50 copies/mL) are associated with a reduction in replicative capacity as compared to sequences from typical HIV progressors. A longitudinal study of individuals enrolled at the time of acute infection [14] showed a lower peak viral load and reduced viral fitness in patients who went on to become HIV controllers. Taken together, these data suggest that reduced replicative capacity may contribute to viral

suppression in a fraction of HIV controllers. However, these results do not prove that these subjects were infected with defective viruses as the decreased viral fitness could be explained by effective immune responses in the host. Indeed, other studies have shown that control of fully pathogenic viral strains is possible [21]. Furthermore, sampling could be an issue: in the presence of very low copy number, a higher proportion of viral sequences retrieved might come from replication incompetent virus. Further studies are thus needed to determine the respective contributions of transmission of attenuated strains versus novel mutations subsequent to immune pressure early after infection in the new host who ends up becoming an HIV controller. Additionally, sequencing of the viral genome demonstrated viral evolution and thus an ongoing slow viral replication in HIV controllers – therefore demonstrating that the genes regulating HIV replication were functional [22].

UNWILLING TARGETS? THE ROLE OF SUSCEPTIBILITY OF CD4 T CELLS TO HIV INFECTION AND CELL DEATH IN HIV CONTROLLERS

Besides attenuated infecting viral strains, data suggest that reduced susceptibility of CD4 T cells and other targets to HIV entry as well as intracellular host restriction factors could contribute to decrease viral replication in HIV controllers. Such mechanisms could also decrease the intensity of primary HIV infection, and subsequently facilitate sustained viral control. For example, homozygosity for a 32 base pair deletion within the gene encoding CCR5, a coreceptor for HIV entry into CD4-bearing cells, strongly protects against acquisition of HIV, whereas heterozygosity for the CCR5 $\Delta 32$ allele is associated with delayed disease progression [23]. The prevalence of CCR5 $\Delta 32$ heterozygosity is about 10% in Caucasians, but reached 17.5% in a cohort of 126 controllers [24]. This difference reached statistical significance in a large genetic study of HIV controllers and progressors [7].

A number of intrinsic intracellular host factors that limit HIV replication have been recently described. These restriction factors include the cytidine deaminase APOBEC3G, which introduces mutation in recently reverse-transcribed HIV DNA, the protein Trim5 α , which interferes with HIV decapsidation, the protein tetherin, which impairs the release of HIV particles, and the recently identified protein SAM-HD1, which limits HIV-1 replication in macrophages [25]. Although their roles have been demonstrated *in vitro* and in animal models, the extent to which HIV restriction factors play a role in limiting viral replication in HIV controllers remains to be clarified. The contribution of an intrinsic resistance of CD4 T cell to HIV controller status remains a somewhat controversial issue in the field, as the use of different *in vitro* systems have yielded discrepant results. Some studies showed no clear intrinsic resistance of CD4 T cells from controllers to infection with exogenous HIV strains [26, 27], whereas two groups recently reported a reduced susceptibility of CD4 T cells to HIV infection in controllers compared to HIV progressors and HIV negative persons [28, 29]. The different experimental strategies used, in particular the procedures used to stimulate and infect CD4 T cells, likely play an important role in these apparent contradictory findings and the approaches is most relevant to HIV infection dynamics *in vivo* remain to be defined. Furthermore, the mechanism leading to the identified resistance to infection in these two reports is currently uncertain: whereas both studies found that the resistance can be overcome by high viral inoculum and documented an upregulation of a known tumor suppressor gene called p21 in HIV controller CD4 T cells, one study suggested a causal role of p21 in the resistant phenotype [28], whereas the other paper found no impact of p21 knockdown on susceptibility of CD4 T cell to infection [29]. Further studies are thus necessary to investigate this important issue, as identifying factors associated with partial resistance to infection may have therapeutic potential.

The persistence of central memory CD4 T cells (T_{CM} cells) is an important correlate of immunological protection in HIV and SIV infections, as the rate of T_{CM} decline predicts disease progression [30]. Multiple mechanisms contribute to CD4 T cell depletion in HIV infection (reviewed in [31]), including increased programmed cell death (apoptosis) of CD4 T cell subsets that is enhanced by chronic immune activation. This raises the question as to whether CD4 T cells in HIV controllers have enhanced survival compared to subjects with progressive disease. A recent study [32] demonstrated that T_{CM} and effector memory CD4 T cells (T_{EM} cells) from elite controllers are less susceptible to Fas-mediated apoptosis and persist longer after multiple rounds of T cell receptor triggering when compared to CD4 T cells from patients successfully treated with ART and, notably, from HIV negative donors. The authors demonstrated that this relative resistance to cell death was related to inactivation of the FOXO3a pathway, an important transcription factor modulating T cell function. As above discussed for the role of p21, these findings may lead to new targets for therapeutic interventions.

INNATE IMMUNITY AND SPONTANEOUS HIV CONTROL

Innate immunity is naturally present prior to the sensitization to an antigen and thus kicks in before adaptive T and B cell responses are generated. As very early events after HIV transmission are thought to be critical for the clinical course of infection, there has been over the past few years a renewed interest for the roles played by innate immune responses in HIV controllers. In particular, natural killer (NK) cells can have multiple antiviral functions, and also act as immunoregulators (reviewed in [33, 34]). Recent studies suggest that having protective HLA class I alleles in conjunction with specific NK cell receptors increases the likelihood of achieving HIV controller status [35, 36]. It is therefore possible that an early antiviral effect of NK cells in primary HIV infection may “blunt” peak viral replication, thus reducing the widespread damage typically occurring to the lymphoid compartment, and allowing for subsequent development of effective adaptive immune responses. NK cells in HIV controllers show better functionality than in subjects with progressive disease [37]. Like for many other observations in HIV controllers, it is difficult to determine whether this phenotype is the cause or the consequence of a preserved immune system. In addition to their direct antiviral role, NK cells can also mediate Antibody-Dependent Cellular Cytotoxicity (ADCC) that eliminates material opsonized by antigen-specific antibodies, thus linking innate and adaptive immunity. A recent study identified stronger ADCC-inducing antibody responses in controllers compared to other HIV-infected patients [38]. This observation is promising, as it suggests that there may be a potential for harnessing innate responses by vaccines to improve viral control.

Could preservation of specific dendritic cells subsets, which are the most powerful antigen-presenting cells in the body, contribute to the HIV controller phenotype? Plasmacytoid dendritic cells (PDCs), which are important for responses against viral infections, are decreased in the blood of patients with progressive HIV disease [39]. However, whether this corresponds to a true depletion or to changes in homing and/or function remains to be defined, as one study found in chronically HIV-infected individuals an accumulation of PDCs in the spleen that fail to produce type I interferons [40]. PDCs frequencies are higher in HIV non-progressors than in progressors, but whether this difference contributes to the different disease course or merely reflects a better integrity of the immune system is currently unclear. More recently, it has been shown that myeloid dendritic cells (mDC) in elite controllers have enhanced antigen-presenting properties compared to those of subjects with progressive HIV infection, and interestingly, also compared to those of healthy HIV negative controls [41].

CD4 T CELLS: KEY PLAYERS IN SPONTANEOUS CONTROL OF HIV REPLICATION?

Studies in animal models and data in humans show that CD4 help *in vivo* is critical for the persistence of effective, long lasting CTL and B cell responses [42] and for mobilizing CTLs to infected mucosa [43]. Through secretion of multiple cytokines, CD4 T cells also modulate functions of APCs and of cells that contribute to innate immunity, including monocytes/macrophages and NK cells. Whereas CD8 T cells recognize epitopes associated with MHC Class I, the TCR of CD4 T cells recognize epitopes associated with MHC Class II. Depending on the context of T cell activation, undifferentiated interleukin-2 (IL-2)-secreting CD4 T cells can differentiate into several subsets of CD4 T cells, which secrete different cytokines and mediate different functions. Th1 lymphocytes predominantly produce interferon- γ (IFN- γ) and tumor necrosis factor α (TNF- α) and preferentially activate cell-mediated responses; Th2 lymphocytes, which predominantly secrete interleukin-4 (IL-4), IL-5, and IL-13, induce humoral responses whereas Th17 lymphocytes, which secrete IL-17, stimulate inflammatory responses with antibacterial and antifungal functions in many organs and tissues [44]. More recently, another subset, called T follicular helper cells, which produce IL-21, has been identified. It is thought to play an important role for help to maturing B cells and CD8 T cells [45]. CD4 T cells are the primary targets of HIV infection, and the dysfunction of this compartment is critical for HIV pathogenesis. Studies suggest that both the CD4 T cell subset as a whole and the HIV-specific CD4 T cell subset can present distinctive features in HIV controllers that play a causal role in their phenotype.

CD4 T cell lymphopenia, a hallmark of HIV infection, is due to combined effects of destruction of HIV-infected cells, increased cell death of uninfected CD4 T cells, and impaired renewal [46]. The persistence of functional memory T cells represents the basis for a long-lasting protection after exposure to pathogens [11–13]. A better preservation of the central memory (T_{CM}) CD4 T cell compartment was observed in HIV controllers than in individuals with untreated progressive HIV disease and subjects with controller viral load on therapy [47] [48, 49]. T_{CM} of HIV controllers also showed a higher expression of the IL-7 receptor and of CCR7, which suggests differences in T_{CM} homing patterns [47].

Reduced IL-2 production and a lack of response to this cytokine critically contribute to the anergy that is one of the first signs of the immune deficiency that precedes CD4 lymphopenia in HIV-infected patients [50–52]. Furthermore, progressive HIV infection is associated with a decrease in responsiveness to IL-7 [53–56], a cytokine that is crucial to the central production of CD4 lymphocytes and to their peripheral homeostasis (reviewed in [57]). Interestingly, it has recently been shown that collagen deposition in lymphoid tissue restricted T cell access to IL-7 on the fibroblastic reticular cell network, resulting in apoptosis and depletion of T cells [58]. Results from two clinical trials of IL-7 administration in ART-treated subjects gave promising results in terms of reconstitution of CD4 T cell subsets [59, 60]. Whether adjuvant therapy with cytokines like IL-7 could further functionally restore the immune system of HIV-infected subjects with progressive infection, in particular in individuals with persistently low CD4 T cell count in spite of viral control on therapy, and lead to an “HIV controller-like” status, remains to be tested. Furthermore, although IL-7 has been recently shown to play an important role in viral control in the murine LCMV model of viral infection [61], the direct role of IL-7 in viral suppression in HIV controllers remains to be determined.

Although the preferential infection of HIV-specific CD4 T cells raised the concern that this subset might fuel viral replication rather than contribute to its control [62], this relative increase is small and the large majority of HIV-specific CD4 T cells are not infected *in vivo*, even in the presence of high viral loads [62]. It is thus likely that vaccine-induced HIV-

specific CD4 T cells would significantly contribute to effective immune responses against HIV (reviewed in [63]). As a cohort, HIV-specific CD4 T cells controllers have significantly more robust, polyfunctional HIV-specific CD4 T cells capable of secreting multiple cytokines (e.g, IFN- γ and IL-2) than subjects with progressive infection [24, 47, 48, 64, 65]. The magnitude of HIV-specific CD4 T cell responses in controllers is stronger than in people with controlled viral load on ART [47]. The maintenance of virus-specific CD4 T cell responses in HIV controllers suggests a more functional, long-lived memory T cell population and/or a better capacity to respond to limited antigen amounts. The importance of the cytokine IL-21 in mediating CD4 help to both CD8 T cells and B cells has been highlighted by a number of recent studies in both murine models and humans (reviewed in [66]). IL-21 is primarily produced by subsets of activated CD4 T cells, including T follicular helper cells (TFH). Studies in the murine LCMV model demonstrated that IL-21 produced by virus-specific CD4 T cells was critical in controlling chronic infection and in preventing exhaustion of CD8 T cells. In HIV infection, decreased levels of plasma IL-21 have been observed in chronic progressors, with a positive correlation of plasma IL-21 levels with CD4 counts[67]. Only controllers maintained normal plasma levels of IL-21 compared with HIV negative subjects and ART only partially restored production of this cytokine[68]. Other studies have found somewhat contradictory results. Yue *et al* [69] showed that in progressors, higher frequencies of IL-21 producing CD4 T cells correlated with lower viral load but that control of viremia in controllers and ART-treated subjects was associated with low frequency of IL-21-secreting HIV-specific CD4 T cells. In contrast, Chevalier *et al*[70], using a different technical approach, found higher levels of IL-21 secretion by HIV-specific CD4 T cells in controllers than individuals on ART, with the lowest levels detected in chronic progressors. Examining mechanisms of T cell help, the authors found that IL-21 increased perforin, granzyme A and B, and the degranulation marker CD107 in HIV-specific CTL and that addition of IL-21 increased the capacity of CTLs to inhibit viral replication *in vitro*. Another report compared IL-21 production by HIV-specific CD4 and CD8 T cells[71]. Both subsets were able to produce IL-21 in response to HIV-1 infection, with IL21+ CD8 T cells more closely associated with viral control. Furthermore, IL-21-producing HIV-1-specific CD4 T cells (compared to those producing other cytokines) were the best indicator of functional CD8 T cells. These data suggest that HIV-specific IL-21+ T cells contribute to the control of viral replication in controllers and may be important for an effective vaccine.

Focusing on immunodominant HIV CD4 epitopes, growth kinetics and avidity for antigen of HIV-specific CD4 T cell lines derived from PBMC of HIV controllers and progressors was examined [72]. HIV-specific CD4 T cells from HIV controllers divided more rapidly than comparable lines from viremic patients or patients receiving effective antiviral treatment. This study also identified a subpopulation of HIV-specific CD4 T cells in HIV Controllers endowed with a higher functional avidity compared to non-controllers. Assessing differences for a Gag epitope previously shown to be immunodominant for HIV-specific CD4 T cell responses [73], a higher TCR binding avidity to the HLA class II-peptide complex was also demonstrated in controllers. This capacity to respond to minimal amounts of HIV antigen may contribute to the higher magnitudes of HIV-specific CD4 T cell responses in controllers compared to ART-treated subjects. The high TCR avidity may also facilitate the rapid induction of recall responses upon transient increases in HIV replication (“viral blips”), and may thus limit the cumulative damage inflicted by HIV on the immune system. Whether HIV-specific CD4 T cells can also have significant antiviral effects *in vivo* remain to be determined.

In the setting of HIV infection and other chronic infections, T cell exhaustion, defined as the progressive loss of functions in antigen-specific T cells leading to ineffective T-cell responses, is thought to play an important role in the lack of pathogen clearance. Various inhibitory molecules have been shown to contribute to this exhaustion and to mediate an

active suppression of HIV-specific CD4 T cell responses. Identified molecules include PD-1 [74–76], CTLA-4 [6] and IL-10 [77] (reviewed in [78, 79]). These pathways have been shown to be less active in HIV controllers than in progressors, suggesting that these cells are not exhausted. One of these molecules, CTLA-4, has been shown to be significantly less expressed by HIV-specific CD4 T cells of elite controllers compared to those of subjects with treated or untreated progressive disease [6]. Clinical trials to assess the impact of blockade of the PD-1 pathway with a blocking antibody in ART-treated patients are currently under consideration.

In contrast to the robust HLA Class I data, the association between specific HLA Class II alleles and HIV controller status has been less clearly demonstrated. Higher prevalences of HLA-DRB*13 [80–82], have been reported in some cohorts, though such associations remain to be confirmed in larger studies. A recent investigation of individuals chronically infected by HIV-1 Clade B and C strains showed an association of DRB1*1303 with lower viral loads [82], but a recent large GWAS study did not find class II association reaching genome-wide significance [7]. However, as the same epitopes can frequently be presented by multiple HLA alleles (so-called “promiscuous” epitopes), such a lack of genetic association should not be retained as an argument against the importance of virus-specific CD4 T cell responses in HIV control.

ROLE OF REGULATORY T CELLS AND TH17 CELLS IN VIRAL CONTROL

Two specific subsets of CD4 T cells, Th17 cells and FoxP3+ CD25+ Tregs, may play a particular role in HIV pathogenesis and therefore impact HIV controller status. There is increasing evidence that these two cell types play an important immunomodulatory role in chronic infections. Th17 usually induce inflammation and are an important line of defense against infection, in particular at mucosal surfaces, whereas regulatory T cells are critical for maintenance of tolerance to self-antigens. Treg and Th17 cells often function in opposite ways and share developmental links (reviewed in [83]). In the setting of HIV infection, Treg could potentially have both harmful effects (e.g. by inhibiting HIV-specific immune responses) and a beneficial impact (by inhibiting chronic immune activation) (reviewed in [84]). Published studies on Treg frequency and activity in HIV infection have been somewhat contradictory, although recent studies tend to suggest a slight increase in peripheral Treg populations [85], and data in HIV controllers are currently limited. Whereas one study found similar frequencies of Tregs in elite controllers, HIV negative individuals and progressors [86], other results suggest that Treg are lower in lymphoid tissue in HIV controllers [87], which might contribute to more effective immune responses but also, importantly, to less fibrosis, given the recently demonstrated role of profibrotic factors secreted by Treg in the disruption of lymphoid tissue architecture caused by HIV infection [58]. Of note, qualitative differences in the Treg subset may contribute to some apparent contradictory findings: low levels of the immunoregulatory molecule CD39 were demonstrated on Treg of HIV controllers compared to those of subjects with progressive infection [85]. Rapid Th17 cell depletion during acute SIV infection is predictive of subsequent chronic immune activation [88] and the Th17/Treg ratio in both peripheral blood and gut associated lymphoid tissue (GALT) decreases with HIV disease progression [89]. A recent study showed that elite controllers maintained a balance between Treg and Th17 cells compared to viremic patients and ART treated subjects [90]. Additional studies are needed to determine whether there is a preferential preservation of the Th17 subset in HIV controllers, in particular in GALT, which could contribute to a better maintenance of epithelial barrier integrity and may thus limit chronic immune activation.

THE ROLE OF HIV-SPECIFIC CD8 T CELL IMMUNITY

The clear association between certain HLA Class I alleles and spontaneous viral control, the documentation of viral escape mutations to HIV-specific CD8 T cell (CTL) responses, and CD8 depletion experiments in non-human primates suggest that effective CD8 T cell immunity plays an important role in HIV controllers. The association of specific HLA Class I alleles with HIV controller status (including, but not limited, to B57 and B27) is discussed in the section on the clinical and epidemiological characteristics of this population. [10] [7, 8]. Why these specific alleles would confer protection is still incompletely understood, and it is important to note that although overrepresented in HIV controllers, most HLA-B*57+ or HLA-B27+ HIV-infected individuals have progressive infection in the absence of therapy. Possible contributory factors include: i) unique properties of the HLA-B57 peptide binding groove and the nature of the MHC-peptide interaction, with specific amino acids in the Class I sequence being associated with HIV control [7]; ii) differential thymic selection leading to a more cross-reactive T-cell repertoire for B57-restricted clones [91]; iii) localization of immunodominant B57/B27-restricted epitopes in highly constrained regions that extract a high fitness cost when mutated [92]; and iv) specific interactions with other molecules of the immune system, for example specific Killer-cell immunoglobulin-like receptors (KIR) [93].

The functionality of HIV-specific CTL is clearly higher in many HIV controllers compared to noncontrollers. This includes superior proliferative capacity [94], the ability to produce cytotoxic proteins like perforin [94–96], a higher expression of T-bet expression [95] and the capacity to produce multiple cytokines simultaneously [97] (so-called “polyfunctional” T cells). Interestingly, as reported for HIV-specific CD4 T cells responses, HIV-specific CD8 T cells from elite controllers produce more IL-21 than those of individuals with progressive infection [71]. CTL responses of HIV controllers are also generally more effective at controlling HIV replication *in vitro* in autologous CD4 T cells [94, 98, 99]. To which extent this effect, frequently reported as “viral suppressive capacity”, is due to direct killing of infected cells or to production of antiviral chemokines/cytokines is unclear at the present time. Furthermore, a significant fraction of elite controllers do not present such antiviral activity *in vitro* [99], thus suggesting that other mechanisms for controlling viral replication are also being used. Although the question of cause versus effect is always an issue in these studies, the fact that neither the proliferative capacity of HIV-specific CD8 T cells nor their ability to suppress viral replication are restored by ART [100] suggests that these specificities are not a mere consequence of low viral load and could therefore explain how at least some of these patients control viremia. Furthermore, whole genome transcriptional analysis of HIV-specific CTL has shown significant differences in gene expression between controllers and progressors [101].

Several studies have shown that antigen specificity and TCR avidity are important determinants of the qualitative characteristics of HIV-specific CTL responses, including immunodominance, polyfunctionality and capacity to suppress viral replication *in vitro*. Preferential targeting of Gag as opposed to Env proteins has been associated with better control of HIV replication [102] and preferential targeting of Gag has also been reported in HIV controllers [24]. It has been proposed that a better efficacy of Gag-specific CTL responses may be linked to an early expression (4h) of Gag epitopes on the surface of infected cells, whereas epitopes from Env are not presented until 24h after infection, thus delaying the cytotoxic response [103]. It has been shown that HIV-specific CTL of high affinity, which will rapidly react to small amounts of antigen, show superior effectiveness at suppressing viral replication *in vitro* [104]. Recruitment of high-affinity TCRs has been documented during acute HIV infection, when CTL responses are associated with viral load decline [105]. The majority of these cells disappears during subsequent disease course, but

their maintenance seems to be associated with lower viral setpoint. Another study showed that immunodominant responses of high affinity were associated with lower cell-associated viral load in HLA-B27+ individuals [106]. New data [107] suggest that HIV Gag-specific CTL responses in controllers are of higher affinity than in non-controllers. These data suggest that elicitation of responses with high affinity by preventive or therapeutic interventions will be desirable for immune control.

HUMORAL IMMUNITY

A major goal of HIV vaccine development is to elicit neutralizing antibodies, which are thought to be a critical component of any strategy to prevent HIV infection. However, it is unclear whether they play any role in HIV controller status. High-titer neutralizing antibodies are actually rare in these patients [108, 109]. However, non-neutralizing antibodies may have a role through enhanced ADCC in HIV controllers [38], as discussed above.

A recent study showed that broad neutralizing activity correlated with viral load and indicated that at low viral antigenemia, like the one found in elite controllers, there is insufficient antigen stimulation to maintain high neutralization levels [110]. In accordance with these observations, another study showed that neutralizing antibodies were detected only in a small number of elite controllers and that the median neutralizing activity was similar to the lowest end of the values for the chronic viremic individuals [111]. Interestingly, elite controllers were found to have higher anti-p24 IgG titers compared to progressors [112], and a higher fraction of HIV-specific antibodies of the IgG1 subclass, which may suggest different rates of class switching due to better preserved T helper responses. Another study also found that neutralizing antibodies titers were similar or lower in HIV controllers than in viremic individuals, but that ADCC was more effective in controllers, as discussed above [38]. Overall, the understanding of the potential role of humoral responses in HIV controller status is currently limited, and further studies necessary, in particular to clarify the potential role of ADCC antibody responses.

THE IMPORTANCE OF THE INTEGRITY OF LYMPHOID TISSUE AT MUCOSAL SURFACES

Studies in SIV-infected macaques, [113, 114] (and HIV-infected humans have demonstrated that an early and massive destruction of the memory CD4 T cell compartment occurs in lymphoid tissues at the time of acute HIV infection, in particular in the gut-associated lymphoid tissue (GALT). This early insult to the immune system is thought to play a key role in HIV pathogenesis. As discussed above, the GALT CD4 compartment recovers less on ART than peripheral blood CD4 T cell counts may suggest [115]. Ongoing microbial translocation caused by alterations in the intestinal mucosa is thought to be a driving factor in HIV-associated chronic immune activation [116], which is a key mechanism leading to accelerated turnover and death of CD4 T cells [46]. Published data on mucosal immunity in elite controllers are currently limited. Higher GALT T cell responses and particular gene expression profiles correlated with the HIV nonprogressor status [117]. Studies of CD8 and CD4 responses in biopsies of the intestinal tract (obtained by endoscopy) showed differences between HIV controllers and progressors, but as in studies of peripheral blood, there was a significant overlap amongst cohorts for each of the parameters investigated. Importantly, HIV Gag-specific CD8 T cell responses dominated in mucosal tissues of HIV controllers [118], and mucosal HIV-specific CD8 and CD4 T cell responses in controllers were more polyfunctional than in untreated and treated progressor patients [81, 119]. Interestingly, the degree of T cell activation is lower in HIV controllers than in untreated viremic subjects, but higher than in HIV negative persons and individuals on successful

ART [47, 120]. Consistent with these findings, the presence of bacterial translocation measured by LPS levels in plasma can be detected in HIV controllers [120], while this is not the case in HIV negative controls. This suggests that HIV controllers, in spite of successful viral control, present signs of chronic immune activation that may have detrimental consequences in the long term, including CD4 T cell loss [120] and accelerated atherosclerosis [121]. Thus, studies of mucosal immunity in controllers have yielded important information [81, 119] but additional efforts are necessary, in particular to better understand the link between mucosal responses and immune activation.

CHRONIC IMMUNE ACTIVATION IN HIV CONTROLLERS: TO TREAT OR NOT TO TREAT?

Chronic immune activation associated with HIV infection is thought to play a critical role in HIV disease progression. The disruption of the gastrointestinal mucosal barrier with ongoing translocation of microbial products is thought to be a major contributor to this ongoing immune activation of HIV pathogenesis [116]. Of note, studies have shown that in spite of their capacity to contain viral replication, a large fraction of HIV controllers present signs of chronic immune activation when compared to healthy HIV negative subjects [120]. Furthermore, higher CD4 and CD8 T cell activation was associated with lower CD4 T cell counts in HIV controllers [122] [120]. Is there a sufficient rationale to treat HIV controllers? This is to date an unresolved issue. Current drug regimens have improved tolerance and toxicity profiles and there is increasing evidence that initiation of therapy early in the course of HIV infection can be beneficial. Thus, the current International AIDS Society–USA guidelines [123] recommend ART for all subjects with a CD4 count < 500 cell/uL and state that ART should also be considered in asymptomatic patients with CD4 counts ≥ 500 cell/uL and detectable viral load (> 50 copies/mL). ART may also be beneficial for the few HIV controllers experiencing a significant CD4 loss, possibly due to a decrease in chronic immune activation: a study in a small group of elite controllers showed a CD4 gain on ART, although the average CD4 gain was smaller than what is observed in non-controllers [124]. Controlled studies directly addressing this issue are currently lacking and the impact of ART in HIV controllers will soon be tested in an AIDS Clinical Trials Group (ACTG) study.

WHAT CAN ONE LEARN FROM ANIMAL MODELS?

Experimental models of lentiviral infection in non-human primates may also contribute to our understanding of HIV control. Simian Immunodeficiency Virus (SIV) leads induces either pathogenic or non-pathogenic infections depending on both the viral strain and the species of the infected monkeys. Whereas rhesus macaques, usually present with rapid progression to AIDS, other species that are naturally infected by SIV, such as African green monkeys and sooty mangabeys, do not usually suffer from immunosuppression. However, these models of non-progressive infection differ from the situation in HIV controllers for several reasons. In particular, these monkeys present sustained high viremia without becoming ill: they are healthy carriers, rather than “controllers”. These species are thought to have been infected by SIV for thousands of years, resulting in mutual adaptation of the host and the viral strains, and leading to an attenuated course of infection. In contrast, SIV strains are at the source of the HIV epidemic, with good evidence that SIV from chimpanzee and other apes are the ancestors of HIV-1, whereas SIVs that infect sooty mangabeys are very similar to HIV-2. In spite of these differences, comparisons of pathogenic and non-pathogenic models of SIV infection have been extremely valuable to understand HIV pathogenesis (reviewed in [125]). A model that may be more relevant for understanding spontaneous HIV control is the study of SIV infection in Indian rhesus macaques. Whereas most of these animals experience progressive infection, those carrying the MHC Mamu-B*08 and to a lesser extent the Mamu-B*17 alleles are enriched in “SIV controllers”

macaques, with a profile similar to HIV controllers, with a very low viral load and potent T cell responses (reviewed in [126]). Association with specific HLA Class II alleles has also been described for SIV control [127]. Studies in non-human primates have shown that HIV-specific CD4 T clones can suppress viral replication in macrophages and suggest that virus-specific cytotoxic CD4 T cells can contribute to viral suppression [128]. The unique advantages of the non-human primate models, including the ability to control the sequence of the infecting virus and the timing of infection, and the possibility to frequently sample various body compartments, should make them valuable in future “controller” studies.

SEARCHING FOR THE GENETIC BASIS OF VIRAL CONTROL

As known viral and host factors are not sufficient to entirely explain the HIV controller phenotype, large-scale human genome analyses have been performed in an attempt to identify novel gene variants associated with spontaneous viral control. Genome-Wide Association Studies (GWAS) aim at correlating gene polymorphisms with a clinical phenotype. They are designed to reduce biases and false-positive results, but are not powerful to identify uncommon variants. The large-scale studies performed so far have confirmed the importance of the MHC class I locus in spontaneous HIV control [7, 8, 129] and gave a weaker but significant signal for the CCR5- region, but failed to consistently identify novel genes reaching “genome-wide significance”. A recent report investigating viremic individuals maintaining high CD4 counts compared to subjects with rapid disease progression (thus focusing on “long term non progressors” and not HIV controllers) found that the stability of CD4 counts was associated with a lower expression of interferon-stimulated genes and shared a common gene regulation profile with nonpathogenic SIV-infected sooty mangabeys [130]. A set of genes (CASP1, CD38, LAG3, TNFSF13B, SOCS1, and EEF1D) showed significant correlation with time to disease progression. As the power of these studies depends on the number of subjects enrolled, meta-analyses of different GWAS studies are being performed to identify additional genes. Other experimental designs and technologies are currently being applied in an attempt to identify either punctual mutations in the genome (e.g. full genome or exome sequencing), or differences in gene regulation (mRNA and microRNA expression, epigenetic mechanisms including DNA methylation, etc). These converging approaches may yield new insights into mechanisms leading to the HIV controller status.

CONCLUSION: RELEVANCE OF STUDIES ON HIV CONTROLLERS

In this review, we have tried to show that studies in HIV controllers have fostered significant advances in our understanding of HIV immunopathogenesis and may have therapeutic implications.

First, work on HIV controllers has shown that the human immune system is capable of controlling HIV replication and progression to AIDS. The infection in “HIV Controllers” is reminiscent of other chronic viral infections, such as with herpes viruses, where the immune system controls the pathogen in the long term, even though the virus may occasionally escape this regulation. In the case of HIV infection, we know that even extended treatment with antiretroviral drugs fails to eradicate the virus, which persists in drug-unreachable reservoirs. The existence of HIV controllers gives hope that adequate stimulation of the immune system could result in the establishment of a similar equilibrium in subjects with progressive infection.

Second, HIV Controllers may provide us with useful correlates of protection against HIV, which should help in the design of new vaccinal strategies. For instance, if development of a vaccine that provides full protection against viral contamination does not appear to be an

achievable goal in the foreseeable future, it will be imperative to seek a vaccine that prevents the massive disorganization of the immune system that occurs during primary infection and thus allows the appearance of effective immune responses such as those possessed by HIV Controllers. This is a debated topic in the HIV field, and some experts strike a cautious note on the applicability of findings in controllers to HIV vaccine development (see [131]). As controllers do experience a systemic viral infection, the understanding of protective mechanisms in exposed uninfected individuals would, at least in theory, be more in line with the development of protective vaccine. This is however a research area that presents major challenges in study design (reviewed in [132, 133]).

Third, by identifying molecular pathways that are differentially expressed in HIV controllers and in subjects with progressive infection, such studies may provide promising targets for novel therapies to complement existing antiretroviral therapies. On the other hand, whether it is possible to use the knowledge gathered on some critical, non-modifiable genetic factors contributing to spontaneous HIV control (e.g. HLA molecules) to develop practical therapeutic approaches is currently unclear.

We believe that research to understand spontaneous viral control remains highly relevant in the fight against HIV. Currently, general limitations in the field include in particular i) the insufficient number of mechanistic studies that aim at determining the cause-effect relationships (is the observation a contributing factor of HIV control or a mere consequence of a preserved immune system?); ii) the multiplication of association studies that are not validated in separate cohorts, thus increasing the risk of spurious findings; and iii) the lack of “integrative models” combining different types of data in order to try to predict HIV controller status, given that no single parameter delineate HIV controllers from progressors. Thus, additional efforts are needed and will continue to yield important knowledge on one of the most important infectious diseases of our time.

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Highlights

- HIV controllers: rare HIV-infected patients able to control the virus without therapy
- To date, the critical mechanism(s) determining controller status remain to be defined
- In most subjects, multiple factors likely contribute to this remarkable phenotype
- They include viral factors, genetic factors, and innate and adaptive immune responses
- Studies of HIV controllers may help design effective HIV vaccines and novel therapies

TABLE 1

POTENTIAL MECHANISMS OF VIRAL SUPPRESSION IN HIV CONTROLLERS

Mechanism	Results of studies in HIV controllers	References
Viral factors (attenuated virus)		
Gene deletion	Deletion of a key regulatory gene, e.g. Nef (Sidney cohort).	[18]
Mutations	Viral strains with mutations decreasing viral replicative capacity, located in particular in conserved regions of Gag.	[14, 17–20]
Decreased susceptibility of target cells to HIV		
Reduced viral entry	Genetic polymorphisms in the CCR5 co-receptor are enriched in HIV controllers.	[7, 23, 24]
Intracellular factors inhibiting viral replication	Decreased susceptibility of CD4 T cells to HIV infection	[28, 29]
	Upregulation of the tumor suppressor gene p21 may inhibit viral replication in CD4 T cells	[28]
Decreased cell death	Inactivation of the FOXO3a pathway renders memory CD4 T cells less susceptible to programmed cell death (apoptosis).	[32]
Innate immunity		
NK cell function	Specific NK receptors in conjunction with protective HLA	[35, 36]
	Class I alleles increase the likelihood to achieve controller status.	[37]
	Better NK functionality in HIV controllers.	[38]
	Stronger Antibody-dependent Cellular Cytotoxicity (ADCC).	
Dendritic cell function	Higher frequencies of plasmacytoid dendritic cells (pDCs).	[39]
	Better antigen-presenting properties of myeloid dendritic cells (mDCs).	[41]
CD4 T cell subpopulations		
Memory CD4 T cell compartment	Better preservation of the central memory CD4 T cell compartment in HIV controllers	[47–49].
	Maintained capacity to produce IL-2	[41; 42; 43]
	Maintained capacity to respond to IL-7	[53, 54]
	Maintained capacity to produce IL-21	[68–70]
Regulatory T cells	Lower Treg frequencies in lymphoid tissue of controllers.	[87]
	Contradictory data on Treg frequency in the blood.	[85]
	Lower expression of the immunoregulatory molecule CD39 on Treg in controllers.	
Th17 CD4 T cells	Maintained balance between Th17 and Treg in controllers, whereas the Th17/Treg ratio decreases with HIV disease progression	[89, 90]

TABLE 2

POTENTIAL MECHANISMS IN HIV CONTROLLERS -ADAPTIVE IMMUNITY

Mechanism	Results of studies in HIV controllers	References
Adaptive immunity		
HIV-specific CD4 T cells	Association of some HLA Class II alleles with lower viral loads reported in some reports. So far not confirmed in GWAS studies of HIV controllers.	[80, 82]
	Polyfunctional HIV-specific CD4 T cells, with secretion of multiple cytokines. Maintained magnitude of these responses in spite of low antigen load, in contrast to ART-treated subjects in whom HIV-specific CD4 T cell responses decrease on therapy. This has also been shown in mucosal tissue.	[24, 47, 48, 64, 65] [81]
	Greater production of IL-21 by HIV-specific CD4 T cells in HIV controllers	[69, 70, 134]
	Higher functional avidity and TCR binding affinity of HIV-specific CD4 T cells in HIV controllers	[72]
	Lower expression of CTLA-4, an important inhibitory molecule, on HIV-specific CD4 T cells of elite controllers	[6]
HIV-specific CD8 T cells	Strong genetic association of HIV controller status with specific HLA Class I alleles. Confirmed in multiple cohorts and by Genome-Wide Association (GWAS) studies.	[7, 8, 10]
	Difference in thymic selection of the TCR repertoire for protective alleles	[91]
	Unique properties of the epitope binding groove of protective HLA Class I alleles	[7]
	Escape mutations in CD8 T cell epitopes leading to reduced viral fitness	[92]
	Superior proliferative capacity	[94]
	Higher frequency of “polyfunctional” CTL producing multiple cytokines in both peripheral blood and tissues	[97] [119]
	Greater ability to produce cytotoxic proteins (e.g., perforin)	[94–96]
	Greater production of IL-21	[71]
	Superior capacity to suppress viral replication in vitro	[94, 98, 99]
	Preferential targeting of some viral proteins (e.g. Gag)	[24]
Humoral responses	Dominance of Gag-specific CTL responses in Gut-Associated Lymphoid Tissue (GALT)	[118]
	Higher functional avidity of HIV-specific CTL	[106, 107]
Humoral responses	Role currently unclear. Overall, HIV controllers have low titers of neutralizing antibodies. However, Antibody-dependent Cellular Cytotoxicity (ADCC), which can also be mediated by non-neutralizing antibodies, has been shown to be higher in HIV controllers in one study.	[38]