

Immune responses during spontaneous control of HIV and AIDS: what is the hope for a cure?

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4 **AIDS: what is the hope for a cure?**
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Abstract

HIV research has made rapid progress and led to remarkable achievements in recent decades, the most important of which are combination antiretroviral therapies (cART). However, in the absence of a vaccine, the pandemic continues, and additional strategies are needed. The “towards an HIV cure” initiative aims to eradicate HIV or at least bring about a lasting remission of infection during which the host can control viral replication in the absence of cART. Cases of spontaneous and treatment-induced control of infection offer substantial hope. Here, we describe the scientific knowledge that is lacking and the priorities that have been established for research into a cure. We discuss in detail the immunological lessons that can be learned by studying natural human and animal models of protection and spontaneous control of viremia or of disease progression. In particular, we describe the insight we have gained into the immune mechanisms of virus control, the impact of early virus-host interactions and why chronic inflammation, a hallmark of HIV infection, is an obstacle to a cure. Finally, we enumerate current interventions aimed towards improving the host immune response.

Key index words or phrases:

HIV controllers, post-treatment controllers, Natural hosts of SIV, eradication, inflammation

1. Introduction

Since the first human immunodeficiency virus (HIV) was isolated 30 years ago [1], remarkable progress has been made in research and drug development, but an efficient vaccine against HIV/AIDS is still not available. Multiple obstacles must be overcome, including the fact that HIV has a remarkable capacity to accumulate mutations and escape adaptive immune responses. During the viral life cycle, the genetic material of the virus is integrated into the cellular genome, which is believed to allow the virus to evade the host's immune responses. In this way, HIV can persist for months and years. Furthermore, HIV infection is characterised by the induction of immunological dysfunction and consequently, the host fails to control viral replication. Moreover, the preferential target cells of HIV are activated CD4+ T cells. Indeed, large quantities of virus particles are produced in activated CD4+ T cells, whereas resting CD4+ T cells are weakly or not permissive for HIV, and other CD4+ cells, such as macrophages, only produce small numbers of virions. HIV infection is characterised by a significant and persistent increase in activated CD4+ T cells. In other words, HIV creates and multiplies in its own target cells. Many open questions remain. For example, it remains a matter of debate whether a vaccine against AIDS should induce anti-HIV T cells or anti-HIV antibodies or both, which qualities anti-HIV T cells should possess to be efficient and how and where antibodies must be produced. In the absence of a vaccine, alternative strategies have become more important. Recent progress in HIV research has raised hopes for a cure for HIV. The "towards an HIV cure" initiative launched by the International AIDS Society has established a number of priorities with the aim of HIV eradication or at least lasting remission of infection during which the host can control viral replication in the absence of antiretroviral drugs (Figure 1) [2]. Timothy Brown, an HIV-infected patient who received a double stem cell transplant from CCR5 32 donors [3], has lived for more than 6 years without signs of the virus and represents the closest example to an HIV cure to date [4, 5]. However, achieving HIV eradication in a large population of patients seems farfetched at present. The natural models of AIDS control and the cases of patients able to control replication after treatment interruption encourage us to believe that HIV remission may be an achievable goal.

2. Spontaneous protection against HIV/AIDS

The capacity to control HIV replication and the speed of progression towards AIDS vary among patients. Approximately 10% of individuals infected with HIV-1 maintain their CD4+ T cell counts at near-normal levels for more than 7 years in the absence of anti-retroviral treatment. These individuals are called long-term non-progressors (LTNP). Although LTNPs are a heterogeneous population, most LTNPs exhibit low levels of viremia. Two extreme

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3 profiles within the LTNP population have been reported (Table I). On the one hand, very few
4 LTNPs maintain their CD4+ T cells despite high levels of viremia (at least 10.000 copies of viral
5 RNA/ml of plasma). These individuals are called viremic non-progressors (VNP). Because viral
6 replication is not controlled in VNPs, these individuals must possess a mechanism that protects
7 them against CD4+ T cell loss and HIV-induced immunodeficiency. On the other hand, less than
8 0.5% of individuals infected with HIV-1 exhibit a spontaneous, highly efficient control of viral
9 replication. This control is so effective that the viral load is often undetectable in the blood by
10 routine clinical assays. Patients exhibiting such control for long periods are termed “elite
11 controllers” or “HIV controllers (HIC)” [6]. The HLA alleles B27 and B57 are highly enriched in
12 this population. However, the presence of these protective HLA alleles is neither sufficient nor
13 always necessary to achieve control of infection.
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21 3. Early virus-host interactions and their impact on disease progression

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23 The risk of progressing rapidly or slowly towards AIDS can be somewhat predicted shortly
24 after infection. Viremia levels at 6 months post-infection predict the rate of disease
25 progression [7]. The levels of T cell activation as measured by the frequency of CD8+ T
26 cells expressing HLA-DR and CD38 also predict the disease progression profile [8].
27 Notably, T cell activation is a stronger predictor than is viremia [8, 9] and is predictive even
28 before seroconversion [10]. Recent studies demonstrate that inflammatory and coagulation
29 biomarkers, such as IL-6, sCD14 and D-dimer, are better correlated with mortality than is T
30 cell activation [11, 12]. Moreover, the levels of certain inflammatory molecules during acute
31 infection, such as IP-10, are better predictors of rapid disease progression than viremia or
32 CD4+ T cell counts [13].
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38 Early virological and immunological features may be strongly prognostic because they reflect
39 the presence of protective host factors (such as HLA-B27) and/or because the balance that is
40 established between the virus and the host during the early phase of infection impacts the
41 subsequent evolution of the infection [14, 15] (Figure 2). Therefore, beginning antiretroviral
42 therapy during primary infection may provide significant benefits to HIV-infected patients. It has
43 been suggested that early treatment could have a favourable impact on the reduction of viral
44 reservoirs, the preservation of immune responses and protection from chronic immune
45 activation [16]. It was recently reported that some HIV-infected patients who interrupted
46 prolonged antiretroviral therapy that was initiated shortly after primary infection can control
47 viremia [17]. Such post-treatment controllers (PTCs) have achieved control of infection through
48 mechanisms that are, at least in part, different from those commonly observed in HICs. Indeed,
49 PTCs had more severe primary infections than did HICs (Figure 2). Importantly, most PTCs
50 lacked the protective HLA B alleles and instead carried risk-
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3 associated HLA alleles (i.e., HLA*B35) that were largely absent among the HICs.
4 Accordingly, PTCs had poorer CD8+ T cell responses than did HICs. PTCs also had lower
5 levels of T cell activation than HICs. Therefore, the mechanism of virus control seems
6 different between PTCs and HICs.
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9 It is likely that infection control in PTCs was not achieved spontaneously but was favoured
10 by the early initiation of therapy. The frequency of PTCs is estimated between 5% and 15%
11 of patients beginning combination antiretroviral therapy (cART) shortly after primary HIV
12 infection (PHI) [17-20], which is significantly higher than the proportion of HICs [21, 22].
13 Such a significant proportion of PTCs has only been observed after early initiation of
14 treatment and not when therapies were begun during the chronic phase, where reported
15 cases are even scarcer [23]. The rarity of PTCs worldwide may be explained by the fact
16 that only a very small proportion (approximately 2%) of patients in the French Hospital
17 Database on HIV who initiated cART early during PHI experienced a treatment interruption
18 [17]. Indeed, in the absence of a reliable marker to predict the outcome after therapy
19 discontinuation, even if started early, is not recommended outside clinical structured
20 protocols. Non-controlled infection after treatment interruption increases risks of morbidity
21 and mortality [24] and also of infection transmission.
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25 PTCs were able to control viral replication on the long term and in some cases, even
26 exhibited a progressive decrease in viral reservoir [17]. This may be at least partially related
27 to the weak contribution of long-lived cells, such as central memory CD4+ T cells (T_{CM}), to
28 the total circulating reservoir in these individuals. It will be of interest to understand why
29 PTCs can control viral replication. The fact that it may be feasible to help the host develop
30 protective responses gives substantial hope for the development of a cure. However, most
31 patients are diagnosed with HIV only after several years of infection and in addition the
32 ability to translate the PTC's mechanisms of control to other patients is as yet uncertain.
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42 43 4. Animal models of spontaneous protection

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45 Animal models allow a deeper understanding of early virus-host interactions, particularly with
46 respect to the compartments that are crucial for the education of adaptive immune responses or
47 that represent the major sites of viral replication (lymph nodes and mucosa). The only animal
48 model that fully reproduces the physiopathology of AIDS consists of Asian monkeys (macaques)
49 infected with SIVmac. In recent years, the macaque/SIVmac model has revealed key
50 characteristics of HIV-1 pathogenesis. For example, this model has demonstrated the impact of
51 the viral protein Nef in maintaining a high viral load *in vivo* and for disease progression [25, 26].
52 This model has also highlighted the role of CD4+ T_{CM} as main targets of the virus *in vivo* [27-
53 29], as well as the dramatic and rapid depletion of CD4+ T cells in the
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3 gut [30] and contributed to demonstrate that microbial translocation is associated with
4 disease progression [31]. Finally, the macaque/SIVmac model has revealed the significant
5 trafficking of immune cells, such as of natural killer (NK) cells and plasmacytoid dendritic
6 cells (pDCs), from the periphery to the gut mucosa during infection [32, 33]. Trafficking to
7 the gut was associated with upregulation of $\alpha 4\beta 7$ on NK cells and pDCs and blocking of
8 $\alpha 4\beta 7$ could reduce viral loads in this tissue [34].

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12 Macaques infected with SIVmac exhibit all the different disease progression profiles
13 described in HIV-1-infected humans, from rapid to slow progression. Spontaneous control
14 of viral replication has been observed in at least two macaque species (rhesus and
15 cynomolgus) with specific MHC or TRIM5 α alleles [35-37]. Some SIVagm strains
16 (SIVagm.ver90 and SIVagm.sab92018) induce AIDS in pig-tailed macaques, but not in
17 rhesus macaques [38-40]. Infection of rhesus macaques with SIVagm.sab92018 is
18 characterised by high levels of viremia and dramatic mucosal CD4⁺ T cell depletion during
19 acute infection followed by complete control of SIVagm replication defined as follows:
20 undetectable viral load in the blood and tissues beginning at three months post-inoculation
21 (pi) and continuing for at least 4 years; sero-reversion; complete recovery of mucosal CD4⁺
22 T cells by 4 years pi; normal levels of immune activation; and no disease progression [39].
23 Virus control was independent of MHC, APOBEC and Trim5 genotypes. This “functional
24 cure” of SIVagm infection in rhesus macaques could be reverted by depleting CD8⁺ cells,
25 which resulted in a transient rebound in viral load, suggesting that control may be at least
26 partly immune mediated. This represents a new animal model of controlled lentiviral
27 infection, and other, complementary models are currently under development.

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Macaque models are being used to examine the effect of short-term cART initiated at
different stages during acute infection on viral dissemination and replication. The
Zidovudine (AZT)/Lamivudine (3TC) and Indinavir (IDV) combination efficiently reduced
viral replication in all tissues when treatment was initiated before peak viremia. When the
same treatment was initiated after peak viremia, the effect of treatment was stronger in the
gut than in the secondary lymphoid tissues [41]. Studies are currently being conducted to
evaluate pre-exposure prophylaxis (PrEP) strategies, such as rectal application of drug
combinations before challenge [42].

Complete cART-associated suppression of SIVmac in rhesus macaques, even after several
weeks and months of treatment, has been rarely achieved thus far. Without complete
suppression, testing of strategies to reduce viral reservoirs is confounded by ongoing cycles of
viral replication that can replenish such reservoirs. One major obstacle was the natural
resistance of SIVmac to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Efforts are
currently underway to achieve the goal of drug-induced full viral suppression in the macaque
model, by improving drug combinations and administration strategies, and early results are

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3 encouraging [43]. Alternative strategies consist of chimeric simian-human
4 immunodeficiency viruses, or SHIVs, in which the SIVmac reverse transcriptase (RT) is
5 replaced with the RT from HIV-1 (RT-SHIV). RT-SHIVs have the advantage of being as
6 susceptible to both nucleoside and non-nucleoside RT inhibitors as HIV-1. However, these
7 chimeric viruses also have limitations; for example, the physiopathology of infection is not
8 the same as with the wild-type virus. Recently, Shytai *et al.* succeeded in completely
9 suppressing viral replication by intensifying cART in SIVmac-infected rhesus macaques
10 [44]. Altogether, efficient treatment regimens in macaques will represent an essential model
11 for answering crucial questions in the HIV cure research field, such as more precise
12 insights into the nature of viral reservoirs in distinct body compartments during long-term
13 treatment, the impact of early treatment on inflammation and viral reservoirs and the exact
14 source(s) of virus during viral rebound.

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21 Fundamental clues regarding the mechanisms that protect against AIDS also reside in the
22 natural hosts of SIV, such as African green monkeys (AGMs), sooty mangabeys (SMs) and
23 mandrills [45]. In contrast to macaques, these African non-human primates are natural carriers
24 of SIV in the wild. Protection against AIDS in natural hosts occurs despite viral replication in the
25 blood and gut at levels similar to or higher than in HIV-1-infected humans and SIVmac-infected
26 macaques [46]. Protection is associated with an absence of both chronic T cell activation and
27 chronic inflammation [45, 47]. The studies in natural hosts have contributed to the increased
28 consideration of the major role of chronic immune activation in the development of AIDS. In
29 countries where cART is accessible, the nature of HIV disease has largely shifted from one of
30 immunodeficiency to one of chronic inflammation [48]. Deciphering the factors that predispose
31 the natural host to control inflammation is the subject of several current studies and may have a
32 major impact on translational research.

33 34 35 36 37 38 39 40 41 5. Insights into immune responses conferring spontaneous control of 42 viral replication

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45 HIV infection leads to a period of acute infection with vigorous viral replication, which is then
46 partially controlled and stabilises 3-6 months after infection. The pace and level of virus control
47 depends on both viral and host determinants. Innate responses are mobilised to first counteract
48 the virus and to assist in the development of adaptive cellular and humoral responses against
49 HIV. However, these defences are generally imperfect and are eventually overwhelmed by the
50 infection. Analysis of cases of immune-driven natural control of infection offers the opportunity to
51 examine the characteristics of optimal immune function.

52 53 54 55 56 57 (a) Innate responses

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NK cells

NK cells are key effectors of innate immunity. Through their capacity to mediate cytotoxicity and to produce numerous cytokines, NK cells can control the virus during the earliest stages of infection and shape the adaptive immune response. Thus, NK cells constitute one of the first lines of defence against HIV-1. Accordingly, several reports have linked enhanced basal and/or induced NK cell activity with protection from infection in groups of intravascular drug users, commercial sex workers and sero-discordant partners who remain sero-negative despite repeated exposure to HIV-1 [49-53] (Table I). Once established, HIV-1 infection is accompanied by an expansion of NK cells [54]. However, a skewed distribution of NK cell subpopulations and loss of cell functions occur as a consequence of exposure to HIV-1 [55]. NK cell dysregulation is at least partially driven by viral products, which suggests that HIV-1 may have evolved to escape NK cell-mediated control [56].

Evidence of a role for NK cells in the control of HIV infection comes from genetic and epidemiological studies. These studies consistently show that when linked with some HLA class I molecules carrying the Bw4-80I motif, some killer immunoglobulin-like receptor (KIR) (KIR3DS1/KIR3DL1) alleles are associated with low-level viremia and slow disease progression [57, 58]. The mechanisms underlying this control are not completely clear, but the interactions between KIR3DS1/KIR3DL1 and their Bw4 ligands may determine the expansion of specific subpopulations of NK cells [59] or the licensing of NK cells with increased responsiveness [60]. Recent studies suggest that changes in the peptides bound by HLA molecules may critically impact the way KIRs are stimulated by the HLA class I/peptide complex [61]. Interactions between KIR3DL1 and HLA class I alleles carrying the Bw4-80I motif are peptide specific [62], and some peptide residues are directly involved in the binding of KIR3DL1 to its ligand [63]. Along these lines, compelling evidence of the impact of NK cells on virus control in the context of a particular KIR background comes from the observation that HIV-1 evolves to evade NK cell-mediated immune pressure by selecting for sequence variants that specifically affect KIR binding to HLA class I ligands [64].

Natural control of HIV-1 infection appears to begin early in most HICs who usually have lower levels of viremia than do progressor patients during acute infection [22]. The HLA-B alleles B*27 and B*57, which are commonly over-represented in HICs [65-67], are members of the Bw4-80I group [68], suggesting that NK cells may contribute to establishing HIV control in these patients through direct cytolytic or non-cytolytic anti-HIV activities or by favouring the induction of an efficient CD8+ T cell response (see below) through optimal crosstalk with dendritic cells. Various reports suggest that NK cells from HICs have increased cytolytic and secretory potential [69-71], which may be associated with particular NK cell receptor profiles [69, 71]. However, it remains unclear how this impacts the control of

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3 infection *in vivo*, and NK cells from HICs exhibited only a modest capacity to suppress viral
4 replication in autologous CD4+ T cells *in vitro* [72].
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7 Plasmacytoid dendritic cells, type I interferon and intrinsic immunity

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9 PDCs are another key component of the innate immune response. These cells influence
10 HIV pathogenesis through their capacity to produce type I interferon (IFN-I) [73]. IFN-I up-
11 regulates interferon-stimulated genes (ISG), several of which possess antiviral activity.
12 During acute infection, pDCs may be a critical antiviral agent. IFN- α has long been known
13 to block HIV-1 replication *in vitro* and *in vivo* [74-77]. Several studies performed during the
14 last few years have identified a number of IFN-stimulated cellular factors (e.g., MX2, BST-
15 2/tetherin, TRIM5 α , APOBEC3G and SAMHD1) that can restrict retroviral replication [74,
16 78-81]. During acute infection, transmitted founder viruses (HIV strains that succeed in
17 establishing a persistent infection [82]) are more resistant to IFN-I than chronic-phase HIV
18 strains [83, 84]. In addition to its antiviral effect, IFN-I may also play an important role in the
19 stimulation of innate responses (NK) and the shaping of adaptive immune responses [85].
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22 In contrast, during chronic HIV infection, the continuous stimulation of pDCs may be deleterious
23 via several mechanisms. The induction of inflammatory cytokines could enhance the trafficking
24 of new target cells to sites of viral replication [86]. The IFN-mediated induction of Indoleamine-
25 pyrrole 2,3-dioxygenase (IDO) is associated with the loss of the TH17/Treg balance [87]. PDCs
26 with increased TRAIL, another ISG, on their surfaces could induce apoptosis of DR5-expressing
27 CD4+ T cells [88]. During a non-controlled HIV infection, the number of circulating pDCs
28 decreases, which is likely due to their migration to the lymph nodes and the gut where extensive
29 HIV replication occurs [89]. In contrast, pDC levels in the blood of HICs are comparable to those
30 found in normal donors and can produce high levels of IFN- α in response to HIV [90, 91]. PDCs
31 from HICs do not express TRAIL on their surfaces but carry high intracellular levels that can be
32 mobilised to the membrane upon encountering HIV [90]. These results suggest that pDCs from
33 HICs may specifically produce IFN- α and induce the apoptosis of infected cells [90, 91]. Along
34 these lines, pDCs from HICs can limit HIV replication *in vitro* when co-cultured with infected cells
35 [91].
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38 Other IFN- α -independent cellular factors can also block viral replication (e.g., p21) [92]. Host
39 cells appear to have evolved a number of restriction factors that can block infection at different
40 stages of the viral replication cycle. Many of these factors, which likely play critical roles in
41 preventing cross-species transmission [93], are counteracted by HIV-1 proteins [94]. However, it
42 is tempting to speculate that inter-individual differences in expression levels and/or
43 polymorphisms in these cellular factors may have an impact on HIV pathogenesis. Studies
44 examining this question have produced conflicting results thus far. Polymorphisms in the *Trim5a*
45 gene [95] and different expression levels of APOBEC3G [96] are associated with
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3 greater control of infection. However, this result has not been confirmed by other studies
4 [97, 98], and the expression of IFN-induced restriction factors may also be driven by viral
5 replication [99]. Nevertheless, intrinsic cellular resistance to infection [e.g. linked to lack of
6 CCR5 expression, high p21 levels] has been associated with both protection from infection
7 among HIV-exposed seronegative individuals [100, 101] and control of infection among
8 HICs [102, 103].
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12 (b) Adaptive cellular responses

13 CD8⁺ T cell responses

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16 CD8⁺ T cell responses have been consistently associated with control of infection following
17 acute HIV infection. The appearance of HIV-specific CD8⁺ T cells coincides with a decrease in
18 viremia during primary infection [104] and the selection of viral escape mutants in regions
19 targeted by these responses [105]. CD8⁺ T cell responses targeting HIV-1 Gag epitopes are
20 associated with smaller viral loads [106, 107], which may be associated with a higher fitness
21 cost for the virus to escape from Gag-restricted responses [108]. *In vivo* depletion of CD8⁺ cells
22 in macaque models of pathogenic SIV infection has demonstrated that CD8-depleted macaques
23 are unable to control infection during acute infection [109, 110]. CD8⁺ depletion also results in
24 increased viral loads in chronically infected macaques [111, 112]. CD8⁺ T cells can counteract
25 HIV by non-lytic (secretion of soluble factors such as β -chemokines or the as yet unidentified
26 cellular antiviral factor CAF) [113, 114] or lytic mechanisms (cytolysis of infected cells through
27 the Fas-Fas ligand pathway or cytotoxic granules) [115, 116]. However, CD8⁺ T cells can only
28 partially control HIV. Continuous HIV replication provokes the gradual loss of CD8⁺ T cell
29 functions associated with the expression of negative regulatory molecules, such as PD-1 [117].
30 In addition to progressive CD8⁺ T cell exhaustion, HIV infection is characterised by a skewed
31 distribution of HIV-specific CD8⁺ T cells with low frequencies of effector cells that may be
32 especially prone to apoptosis [118, 119].
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43 Due to the enrichment of protective HLA class I alleles among HICs, these individuals were
44 soon proposed as a convenient model to uncover the characteristics of efficient CD8⁺ T cell
45 responses against HIV-1. Despite the low levels of circulating virus in HICs, high frequencies of
46 HIV-specific CD8⁺ T cells have been observed in these individuals [67, 120]. These cells have
47 maintained their capacities to proliferate in the presence of HIV antigens and to secrete IL-2 and
48 other cytokines and chemokines [121, 122]. Moreover, HIV-specific CD8⁺ T cells in HICs have
49 been reported to possess or rapidly up-regulate cytotoxic granule contents [123, 124] and
50 accordingly, have a striking capacity to eliminate infected autologous CD4⁺ T cells [67]. This
51 enhanced capacity to suppress HIV infection is linked to a higher frequency of further
52 differentiated cells in association with a discordant CD38^{low}HLA-DR^{high} phenotype [67]. HIV-
53 specific CD8⁺ T cell responses in HICs preferentially target epitopes in Gag, and
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3 Gag-specific responses account for most of their capacity to suppress HIV infection [125],
4 which may be due to faster recognition of infected cells [126].
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8 Some of the characteristics of HIV-specific CD8⁺ T cells from HICs are not found in most HIV-
9 infected patients, even during primary infection [127]. Metabolic alterations in HIV-specific CD8⁺
10 T cells have been proposed to occur very early during acute infection due to hyperproliferation
11 associated with continual stimulation of the cells [128]. CD8⁺ T cells from HICs may also
12 possess particular intrinsic characteristics. For example, selection of particular high-avidity TCR
13 clonotypes associated with a broader capacity to recognise epitope variants and to orchestrate
14 enhanced cytolytic functions has been shown to distinguish HICs from viremic HIV-infected
15 patients sharing the same protective HLA class I alleles [129, 130]. Selection of such clonotypes
16 occurs very early, although the mechanisms of selection are unknown. The function of myeloid
17 dendritic cells, which are principally responsible for priming T cell responses, is altered during
18 primary infection [131] (blood). In contrast, myeloid dendritic cells from HICs have enhanced
19 antigen-presenting capacities but produce lower levels of pro-inflammatory cytokines ([132] our
20 own unpublished results). This profile may favour T cell priming and the selection of specific
21 optimal clonotypes in the context of reduced antigenemia and a weakly inflammatory
22 environment.
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32 During the chronic phase of infection, instead of a strong effector CD8⁺ T cell response,
33 many HICs present with a small number of quiescent memory CD8⁺ T cells [125, 133, 134].
34 These responses may constitute a pool of preserved CD8⁺ T cells that are highly reactive
35 to small quantities of antigen and can rapidly gain effector capacities in response to viral
36 relapses from HIV reservoirs. This hypothesis is supported by *in vitro* experiments in which
37 memory CD8⁺ T cells from these HICs were able to gain cytotoxic activities within a few
38 days of stimulation with cognate peptides [135]. These experiments are not completely
39 conclusive because cells from non-controller patients also gain anti-HIV capacities upon
40 stimulation *in vitro* [136]. Therefore, further studies are necessary to identify clear
41 distinguishable characteristics in memory CD8⁺ T cell from HICs, which may hold important
42 clues for the development of an efficient T cell-based vaccine.
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50 CD4[±] T cell responses

51 CD4⁺ T cells play a multifaceted role in HIV infection. CD4⁺ T cells provide crucial help to
52 dendritic cells and B cells for the induction of HIV-specific CD8⁺ T cells and antibodies.
53 Furthermore, CD4⁺ T cells are the main cellular target of HIV, and HIV-specific CD4⁺ T cells are
54 preferentially infected by the virus [137]. Induction of activated HIV-specific CD4⁺ T cells in
55 vaccine trials has been associated with a higher risk of HIV infection [138] or with faster
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3 viral rebound in HIV-infected individuals upon interruption of treatment [139]. In contrast,
4 induction of HIV-specific CD4⁺ T cell responses was not associated with an increased risk
5 of infection in the RV144 vaccine trial [140], and higher frequencies of HIV-specific CD4⁺ T
6 cell responses during primary infection have been associated with higher CD4⁺ T cell
7 counts and lower viral loads after short-course antiretroviral treatment [141]. Moreover,
8 several studies have shown that some HIV-specific CD4⁺ T cells develop cytolytic potential
9 and carry high levels of granzyme A [142, 143]. These cells may be able to eliminate
10 infected macrophages and to a lesser extent, activated CD4⁺ T cells expressing high levels
11 of HLA class II molecules [142]. A recent study linked high levels of cytotoxic HIV-specific
12 CD4⁺ T cells during acute infection with lower set-point viremia, supporting a direct effector
13 activity for this subset of HIV-specific CD4⁺ T cells [144].
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21 In general, primary HIV infection is accompanied by the depletion of HIV-specific CD4⁺ T
22 cells and impaired cell functionality, particularly the capacity to proliferate and produce IL-2
23 [145]. As was the case for CD8⁺ T cells, in HICs, HIV-specific memory CD4⁺ T cells
24 maintain their functionality [146-148]. High-quality memory CD4⁺ T cells in HICs have been
25 associated with reduced expression of the negative immunoregulatory molecule cytotoxic T
26 lymphocyte-associated antigen 4 (CTLA-4) [149] and lower levels of FoxO3a-mediated pro-
27 apoptotic transcriptional activity [150]. HIV-specific CD4⁺ T cells from HICs also exhibit high
28 avidity for immunodominant Gag peptides, which may allow them to react to low levels of
29 antigens [151]. The class II HLA alleles HLA-DRB1*13 and HLA-DQB1*06 have been
30 associated with strong HIV-specific CD4⁺ T cell responses in HICs [152].
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38 CD4⁺ follicular T helper (T_{FH}) cells, which regulate the development of antigen-specific B
39 cell immunity, have received special attention in the last couple of years. T_{FH} cells are
40 highly susceptible to HIV-1 infection *in vitro* and are a major site of viral replication and a
41 viral reservoir [153, 154]. T_{FH} cells are infected at higher frequencies in macaques and
42 humans than in SMs [155]. In contrast to most other CD4⁺ T cells, this subset is expanded
43 and accumulates in lymph node germinal centers during HIV and SIVmac infections [153,
44 156-158]. Whether T_{FH} in HIV infection show an altered function that could impact anti-HIV
45 antibody development is unclear.
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51 Regulatory CD4⁺ T cells (Tregs) may play a dual role in HIV pathogenesis. Tregs may
52 contribute to reduce pathogenesis by controlling chronic immune inflammation but may facilitate
53 infection by suppressing the activation of effector T cells [159]. During HIV infection, Tregs
54 accumulate in the gut [160]. The ratio of Treg:TH17 cells decreases, and this imbalance may
55 have a deleterious effect on the integrity of the gut mucosa [161]. In contrast
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3 to other effector CD4+ T cell subsets, Tregs preserve their suppressive capacity despite HIV-1
4 infection [162]. HICs appear to maintain similar or lower levels of Tregs than do healthy
5 individuals [162-165], and their CD8+ T cells may evade Treg-mediated suppression [166]. This
6 mitigated regulatory response in HICs may help to maintain a robust and efficient T cell
7 response but may also explain the relatively high immune activation observed in these
8 individuals [163], which is associated with some loss of CD4+ T cells (see chapter 6).
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12 (c) Humoral responses

13 HIV infection elicits an antibody response that targets HIV envelope protein and is non-
14 neutralising during the early stages of infection. Neutralising antibodies are only generated
15 months after infection is established and usually lag behind viral escape mutants [167]. A
16 blunted antibody response during HIV infection is associated with B cell dysfunction. Some
17 individuals, elite neutralisers, can elicit broadly neutralising antibodies that recognise
18 conserved regions of the virus envelope protein [168]. The presence of these broadly
19 neutralising antibodies is not associated with a dramatic control of viremia *in vivo* but has
20 been shown to strongly decrease viremia when administered to SHIV-infected macaques
21 [169]. Neutralising IgA has been found in the genital tract of different cohorts of highly
22 exposed but sero-negative females [170, 171], suggesting that these antibodies contribute
23 to protection from AIDS acquisition in these subjects.
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33 High levels of IgG2 antibodies targeting gp41 were reported as a strong correlate of slow
34 progression to AIDS [172], and these antibodies are also found at high levels in HICs [173, 174].
35 The mechanism through which these antibodies contribute to HIV control is unknown, although
36 it seems to be unrelated to direct neutralisation. In general, HICs possess heterogeneous but
37 low levels of neutralising antibodies, suggesting that they are not a major determinant of virus
38 control [134, 175]. In contrast, greater antibody-dependent cell-mediated cytotoxicity (ADCC)
39 potential associated with both the quality of non-neutralising antibodies and the levels of Fcγ
40 receptors on the surface of effector cells has been observed in HICs [17, 175-177]. The
41 induction of ADCC-mediating antibodies was observed in vaccinated volunteers in the RV144
42 vaccine trial [178], showing marginally significant protection from HIV infection [179] and further
43 reinforcing the potential therapeutic utility of ADCC.
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52 Additional antibody-related activities may impact HIV infection. Non-neutralising antibodies
53 form immune complexes with soluble HIV antigens that stimulate Fcγ receptors expressed
54 by myeloid cells, particularly macrophages. Fcγ receptor aggregation provokes a blockade
55 of viral replication through the induction of p21 and the alteration of the *de novo* synthesis
56 pathway of dNTPs, which are necessary for the reverse transcription step of viral replication
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3 [92, 180]. In contrast, anti-HIV antibodies may compete with complement to opsonise viral
4 particles. The complement system is part of the innate immune response that is activated
5 immediately upon HIV-1 infection. Among other activities [181], complement opsonisation of
6 viral particles has been shown to favour HIV-1 capture and uptake by dendritic cells [182], which
7 is associated with enhanced intracellular co-localisation of HIV antigens with HLA class I
8 molecules and effective CD8⁺ T cell priming by dendritic cells. This effect is gradually lost with
9 the deposition of HIV IgG on viral particles [183]. In summary, further studies need to be
10 conducted to understand the impact of non-neutralising antibodies *in vivo*.
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17 6. Spontaneous control of chronic inflammation in HIV/SIV infections

18 The proportion of infected CD4⁺ T cells is too small to fully account for the extent of CD4⁺ T cell
19 decline. Many data point towards systemic immune activation as the factor responsible for HIV-
20 induced immunodeficiency [12]. Indeed, studies on HIV-2 infection and in natural hosts indicate
21 that viral replication alone is not sufficient to induce AIDS. Many studies have demonstrated that
22 inflammation is even more closely associated with mortality in HIV-infected patients than T cell
23 activation. Therefore, inflammatory and coagulation biomarkers (highly sensitive C-Reactive
24 Protein (hsCRP), IL-6 and D-Dimers) are associated with immunological failure, clinical events
25 and AIDS- and non-AIDS-related mortality [11].
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32 (a) Natural control of inflammation in the context of high-level viremia

33 Natural hosts exhibit spontaneous protection against chronic immune activation despite
34 high levels of viremia, high mucosal replication and dramatic CD4⁺ T cell loss in the gut
35 [46]. During the chronic phase of infection, peripheral and tissue T cell activation levels are
36 not or are only modestly increased. No elevation in the expression of inflammatory
37 cytokines is observed [46]. There are no increases in coagulation markers such as D-
38 Dimers [184]. A lack of chronic immune activation is observed despite an initial transient
39 activation or mobilisation of pDCs, mDCs, NK cells and T cells [185-187]. Indeed, the acute
40 phase of SIVagm infection is characterised by the recruitment of pDCs and mDCs to the
41 lymph nodes, IFN- α production, induction of ISGs and corresponding protein expression.
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47 Early inflammation may be essential for both the virus and the host. Inflammation would be
48 beneficial to the virus because it attracts target cells to the site of infection and would allow
49 the virus to establish a persistent infection. For the host, the induction of early innate
50 antiviral responses (including IFN- α) would allow partial control of viral replication.
51 Inflammation would then be resolved before the end of acute infection. For example, most
52 ISGs are down-regulated back to normal levels in natural hosts in contrast to pathogenic
53 HIV/SIVmac infection [46]. The lack of chronic inflammation would prevent immune-
54 mediated pathology and disease progression.
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3 However, there are major differences compared with SIVmac infection in macaques: the
4 levels of several cytokines, including IFN- α , are lower than those observed during acute
5 SIVmac infection, which is not due to a functional defect in the ability of pDCs to sense the
6 virus [188, 189]. Indeed, the TLR7/TLR9/IRF7 pathway is functional [188, 189]. In addition,
7 natural hosts preserve their TH17 cells, and their epithelial barriers are not damaged and
8 consequently, they show no signs of microbial translocation. This could at least partly
9 explain the lack of systemic immune activation during the chronic phase. Finally, several
10 differences in viral reservoirs in natural hosts with respect to HIV-1 and SIVmac infections
11 have been reported: a smaller DNA reservoir (PBMC), less replication in the lymph nodes,
12 less infection of CD4⁺ T_{CM}, no infection of T_{FH}, and no or rare trapping by follicular
13 dendritic cells [46, 190]. The relevance of these observations to the lack of AIDS requires
14 further investigation, but it is interesting to notice that small reservoirs and low contribution
15 of T_{CM} cells have been associated with control of HIV infection in B57⁺ bearing-non
16 progressor patients and also in PTCs from the VISCONTI study [17, 191].
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26 Similar to natural SIV hosts, VNPs do not control viral replication but nonetheless, maintain
27 close to normal CD4⁺ T cell counts for many years in the absence of treatment. The
28 maintenance of CD4⁺ T cells is associated with a low frequency of activated (DR+CD38⁺)
29 and proliferating (Ki-67⁺) CD4⁺ and CD8⁺ T cells [192]. Therefore, attenuated infection is
30 equally associated with a lack of chronic immune activation. Obviously, a functional cure
31 such as in VNPs (or natural hosts) without control of the virus is less attractive because of
32 the risk of viral transmission. However, it is crucial to understand how VNPs avoid chronic
33 immune activation. VNPs are rare, and unfortunately only limited information on their
34 immune responses is available.
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41 (b) Inflammation and CD4⁺ T cell loss in HIV controllers

42 HICs can experience modest CD4⁺ T cell loss despite controlled viremia. Higher CD4⁺ and
43 CD8⁺ T cell activation is associated with a progressive loss of CD4⁺ cell counts in HICs [193].
44 CD8⁺ T cell activation levels in HICs are also higher than in healthy donors, efficiently treated
45 aviremic patients [193] and PTCs. Higher levels of sCD163, sCD14, IP-10, TNF- α , sTF, D-
46 dimers and hsCRP as well as an increased risk of atherosclerosis have been observed in some
47 HICs compared with healthy donors or aviremic treated patients [194-197]. HICs also seem to
48 have elevated levels of microbial translocation compared with HIV-negative and cART-
49 suppressed individuals [163]. In a recent study, the relationship between inflammatory
50 biomarkers and the CD4⁺ T cell decreases observed in some HICs has been investigated in a
51 large HIC cohort [197]. In this study, IP-10 positively correlated with activated CD8⁺ and CD4⁺
52 T cells in HICs. Moreover, IP-10 and sCD163 levels in HICs
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3 predicted the risk of CD4+ decline. Therefore, the association between inflammation and
4 disease progression is similarly present in HICs as in other HIV-infected individuals [11,
5 13]. It is unclear what drives chronic inflammation in HICs despite the control of viral
6 replication, but it could be associated with extremely low but continuous HIV replication
7 over several years. Very low plasma levels of virus can be detected by ultrasensitive RT-
8 PCR assays in HICs, revealing the persistence of viral replication despite maintaining
9 viremia close to the limit of detection by standard RT-PCR [198]. Although HICs maintain a
10 remarkable control of infection, blips in viral load levels have been observed for many of
11 these individuals [199]. In contrast, some HICs never experience blips, even over long
12 follow-up periods and when using ultrasensitive techniques that detect 1 RNA copy/ml of
13 plasma. Interestingly, these HICs are similar to healthy individuals from a transcriptomic
14 point of view [200]. HICs with blips more often exhibit CD4⁺ T cell loss. Moreover,
15 theoretically, chronic low-level inflammation in HICs could also be driven by higher viral
16 replication in a few as yet unidentified sanctuaries. Such sanctuaries could correspond to
17 immune-privileged compartments in the body, such as the brain. Recent studies in the
18 macaque model suggest that this sanctuary could also be represented by T_{FH} cells in
19 germinal centres (GC) [201]. In late-stage HIV infection, GCs are characterised by
20 infiltration of CD8+ cells [202]. However, under normal conditions, GCs are devoid of CD8+
21 T cells. Theoretically, GCs could represent a compartment in the body where HIV could
22 evade control by CD8+ T cell responses and replicate to higher levels than in the remaining
23 lymph nodes and mucosal tissue cells. Finally, because most HICs have been infected for
24 long periods, lymphoid tissues might represent some of the damage described in normal
25 progressors, such as disruption of the epithelial barrier leading to translocation of microbial
26 products. Indeed, HICs show increased levels of microbial translocation markers [197].
27 Translocation of microbial products into systemic circulation could then fuel immune
28 activation. Studies in the non-human primate model have provided the proof of concept that
29 higher systemic LPS levels lead to increased T cell activation [203], which could reactivate
30 latent virus, leading to a vicious cycle.
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47 7. Hopes and future directions for a cure

48 An HIV cure will succeed by targeting viral reservoirs, but *in vitro* and *in vivo* evidence suggests
49 that host immunity should be targeted concomitantly. Very small viral reservoirs are most likely
50 necessary but not sufficient to ensure the control of viremia off treatment, and the induction of
51 efficient responses against HIV, eventually combined with anti-inflammatory approaches, will be
52 necessary to eliminate HIV-producing cells in reservoir-purging protocols
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2 (see [204] for further information on current HIV cure strategies). Several novel treatment
3 approaches to improve host immune responses are currently under investigation.
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6 7 (a) Early treatment interventions

8 Although current antiretroviral strategies seem to have reached their limits in terms of
9 blocking HIV replication, early treatment initiation may provide further advantages. As
10 previously described, treatment initiation during primary HIV infection has been linked to
11 lasting remission of HIV infection in a group of adults [17]. Treatment initiation immediately
12 after birth also allowed a functional cure of HIV infection in a child after treatment
13 discontinuation [205]. Early treatment limits the establishment of viral reservoirs [206] and
14 severely restricts viral diversity [207]. In addition, treatment initiation during primary
15 infection has been shown to preserve CD4+ T cell homeostasis and the function of NK
16 cells, B cells and HIV-specific T cells [55, 145, 208]. Therefore, early treatment may allow
17 an optimal maturation of the anti-HIV response by reducing viremia and inflammation,
18 which may favour the control of infection after treatment interruption in some individuals
19 with low levels of infected cells. Larger studies need to be performed to identify the
20 mechanisms associated with control after treatment interruption and to uncover predictive
21 markers of post-treatment control.
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31 (b) Immunotherapies

32 Immunotherapies based on the administration of IL- 2, IL- 7 or IL-15 alone or in
33 combination with vaccine candidates aim to enhance immune function and restore T cell
34 homeostasis [209]. IL-7 has garnered some interest [210, 211], but it increases the number
35 of infected cells [210, 212], and thus far, these approaches have not shown sufficiently
36 favourable effects *in vivo*.
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40 Treatment with IFN- α has been shown to transiently decrease viral loads during chronic
41 infection [74, 213], and IFN- α monotherapy was recently shown to allow control of viremia
42 and reduction of viral reservoirs after antiretroviral treatment interruption in 48% of
43 individuals who received IFN α for several weeks in addition to their HIV-suppressive cART
44 regimens [214]. The mechanisms underlying this effect are still unclear, but as discussed
45 above, IFN α treatment may enhance the immune response in treated individuals and also
46 up-regulate HIV restriction factors, thereby rendering target cells less susceptible to HIV
47 infection. Nevertheless, IFN α therapy requires further exploration because conflicting
48 results have been obtained depending on whether it is administered in the absence or
49 presence of cART or in patients with very low CD4+ T cell nadirs [20, 215].
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3 The observation that exhaustion of HIV-specific T cells is accompanied by enhanced
4 expression of negative immunoregulatory molecules such as PD-1 has nurtured the
5 hypothesis that targeting these immunomodulatory pathways may be a promising
6 therapeutic approach in the fight against HIV (review in [216]). *In vitro*, blockage of PD-1
7 interactions with PD-1 ligands restores CD4+ and CD8+ T cell functions, particularly
8 proliferation and cytokine production. Proof of concept studies on SIV-infected macaques
9 have shown that PD-1 blockade results in the expansion of CD8+ T cells with improved
10 functionality [217], longer survival and decreased viral loads in infected animals [217] and
11 may delay viral rebound after treatment interruption [218]. Anti-exhaustion strategies may
12 not restore HIV-specific T cell functions to the levels found in HICs because some intrinsic
13 characteristics of HIC cells are determined very early during infection (see above).
14 However, the restoration of partial T cell function may act in synergy with additional effects
15 of these strategies. PD-1-expressing cells are preferential targets of HIV-1 infection [219].
16 Furthermore, the PD-1 pathway has been linked to the establishment of HIV latency, and
17 triggering PD-1 may help to purge HIV-1 reservoirs. Moreover, *in vivo* PD-1 blockade also
18 produces a reduction of the immune activation associated with chronic SIV infection [220].
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29 c) Anti-inflammatory therapies

30 Because immune activation is a major determinant of HIV pathogenesis, direct targeting of
31 deleterious inflammation is increasingly attracting attention. Many assays are currently under
32 investigation [221]. Chloroquine analogues are among the first anti-inflammatory molecules
33 assessed in HIV-infected patients [222, 223]. The rationale behind this approach is that
34 chloroquine can inhibit the recognition of HIV via TLR7 and TLR9 [224]. Whereas one study
35 showed that short-term chloroquine administration during chronic infection in a small group of
36 cART-naïve patients resulted in a reduction in T cell activation markers in the absence of
37 changes in plasma viremia [225], a randomised double-blind trial with a larger group of HIV-
38 infected patients demonstrated that longer hydroxychloroquine administration resulted in faster
39 CD4+ T cell decay and some increase in viral replication [226]. PD-1 blockade during chronic
40 SIV infection markedly reduced the expression of transcripts associated with type I IFN
41 signalling in the blood and colorectal tissue of rhesus macaques, even in the presence of high
42 levels of viremia [220]. Reduced type I IFN signalling was associated with a profound decrease
43 in plasma LPS levels, suggesting decreased microbial translocation into the blood. PD-1
44 blockade enhanced immunity to gut-resident pathogenic bacteria, control of gut-associated
45 opportunistic infections and survival of SIV-infected macaques. The effects of PD-1 blockade on
46 reducing hyperimmune activation could be a combination of enhanced immunity against gut-
47 resident pathogenic bacteria and repair of gut barrier permeability.
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3 Statin administration to HIV-infected patients has been shown to reduce inflammation [227]
4 and may decrease the risk of non-AIDS-defining malignancies [228] and co-morbidities
5 [229]. In contrast, statins may increase the risk of developing diabetes [230]. Studies with
6 other anti-inflammatory agents (non-steroidal anti-inflammatory drugs, pyrimidine synthesis
7 inhibitors, probiotics and Cox-2 inhibitors) have revealed similarly contrasting results. Other
8 trials with anti-inflammatory agents, such as anti-IL-6 and JAK inhibitors, are planned or are
9 underway [231]. In conclusion, clinical trials have thus far shown that identification of the
10 factors responsible for chronic inflammation is needed to be able to develop more specific,
11 better targeted approaches.
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18 Administration of cART on its own reduces inflammation, in a large part through the
19 reduction of viral replication [232]. The effect of early cART treatment on inflammation was
20 assessed more recently [233]. In a pilot study, Mega-cART initiated during acute infection
21 resulted in the reduction of viral reservoirs down to 100 copies of viral DNA per 10^6 CD4+ T
22 cells at 6 months pi (M6). In parallel with the decrease in the viral reservoir, some
23 inflammatory markers were reduced, including IP-10 and D-dimers at M6, whereas LPS
24 and sCD14 were not. In another study in which treatment was also initiated during acute
25 infection, the plasma levels of IP-10 were decreased, whereas those of 12 other cytokines
26 studied were not [234]. Therefore, early treatment seems to diminish inflammation to some
27 extent. It is not clear why the effect was only observed for some inflammatory markers but
28 could be because they are more closely associated with replication levels or earlier and
29 better markers of inflammation [13]. Intensifying treatment in cART-suppressed individuals
30 may help to further reduce residual viral replication and immune activation. Early
31 intensification of treatment with the CC chemokine receptor 5 (CCR5) antagonist maraviroc
32 may be of special interest not only because the viruses that are capable of establishing an
33 infection generally use CCR5 as a co-receptor but also because of the quick penetration
34 and sustained concentrations of maraviroc in the rectal mucosa [235]. The addition of
35 maraviroc to the antiretroviral regimen resulted in a faster reduction in newly infected cells
36 [236], a decrease in microbial translocation markers [237, 238] and a faster increase in
37 CD4 counts [236, 237]. Paradoxically, maraviroc also induced a slower decrease in plasma
38 viremia. It has been suggested that this result may be due to an immunoactivatory effect of
39 maraviroc. Indeed, MIP1b levels, CD8+ T cell counts and CD4+ T cell activation were
40 higher in the maraviroc arm of the study [236, 237]. However, higher T cell activation levels
41 were not observed in another study [238]. In an uncontrolled trial of maraviroc
42 intensification, plasma LPS levels were actually increased [237] and soluble inflammation
43 markers were similar in both arms at the end of the study [236].
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3 It has long been assumed that HICs do not need cART due to their ability to efficiently
4 control viral replication. In light of the higher levels of immune activation among HICs than
5 patients on cART, it has recently been questioned whether cART could be beneficial to HIC
6 patients. A recent pilot study comprising a small number of HICs assessed whether cART
7 leads to a reduction in inflammation in HICs [239]. Antiretroviral therapy in these HICs led
8 to statistically significant decreases in ultrasensitive plasma HIV RNA levels and rectal cell-
9 associated HIV RNA as well as decreased T cell activation levels (DR+CD38+) in both the
10 blood and gut. This pilot study suggests that even low-level replication results in immune
11 activation. Larger studies will be needed in the future to test whether the reduction in
12 immune activation observed has any clinical relevance for HICs.
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20 d) Therapeutic HIV vaccines

21 The quest for an effective HIV vaccine has been unsuccessful thus far. Different vaccine
22 candidates have been evaluated in 6 phase III clinical trials. Most candidates did not show
23 any efficacy, and the STEP and HVTN503 trials showed an increased risk of HIV
24 acquisition in vaccinated individuals (<http://www.hvtn.org/media/pr/step111307.html>). The
25 HVTN 505 trial was also recently interrupted for futility
26 (<http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx>). Only
27 the RV144 trial showed marginal efficacy [179]. Although a clear correlate of protection has
28 not been identified for this trial, vaccination was associated with the induction of ADCC-
29 mediating antibodies [178]. Overall, conventional HIV vaccine development has been
30 disappointing, and an efficient therapeutic HIV vaccine will likely require innovative
31 approaches.
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40 Dendritic cell-based vaccines have garnered special attention in recent years. One approach
41 consists of vaccinating HIV-infected patients using autologous inactivated viruses to pulse
42 dendritic cells derived from autologous monocytes *in vitro*. Although this process is extremely
43 laborious, a proof of concept study has shown that the approach can significantly increase HIV-
44 specific CD8+ T cell responses and may reduce viral load set-points after treatment interruption
45 [240]. Another strategy consists of directly targeting vaccines to dendritic cells by fusing HIV
46 antigens to monoclonal antibodies recognising receptors such as DEC205, DC-SIGN or CD40,
47 which are specifically expressed by different subsets of dendritic cells [241]. These approaches
48 have shown good immunogenicity in mice and NHP animal models. A recent study suggests the
49 attractive possibility that a DNA vaccine consisting of HIV-1 Gag p24 fused to a soluble form of
50 PD-1 would not only efficiently target antigens to dendritic cells, which express PD-1 ligands but
51 also block the PD-1/PD1L pathway, which may result in enhanced priming of specific responses
52 compared with DEC205-based vaccines [242].
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4 SIV vaccines containing persistent rhesus cytomegalovirus vectors allow control of
5 pathogenic SIVmac239 in 50% of vaccinated animals [243]. Control of infection in these
6 animals is such that clearance of the virus has been reported to occur several months after
7 infection despite profound viral dissemination during primary infection [244]. Vaccination of
8 macaques with CMV vectors is accompanied by the induction of a polyfunctional SIV-
9 specific effector CD8⁺ T cell response that seems to be responsible for virus control and
10 accounts for the progressive elimination of infected cells. Interestingly, this response
11 targets a breadth of non-conventional epitopes that are mainly restricted by MHC II
12 molecules [244]. Such responses may provide specific advantages, as in the case of
13 SIV/HIV infection, by favouring the recognition of variants that escape conventional CD8⁺ T
14 cell responses and also circumventing the down-regulation of MHC class I by the virus.
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22 The observation that passive transfer of broadly neutralising antibodies allows for the control of
23 infection in chronically SIV - infected macaques [169] and delays viral rebound in acutely treated
24 patients after cART cessation [245] suggests that a therapeutic vaccine that induces broadly
25 neutralising antibodies may be effective for controlling HIV-1 in infected patients. Recent
26 knowledge of the co-evolution of the viral epitopes and neutralising antibodies [246] might prove
27 critical to anticipate the time-course that would be established between the virus and the
28 immune system after an eventual treatment interruption. However, inducing such antibodies by
29 vaccination remains a challenge. Current efforts are aimed towards identifying the structural
30 characteristics associated with the neutralising efficacy of broadly neutralising antibodies that
31 target major sites of vulnerability in the envelope protein [247], the events that lead to their
32 production [248] and the B cell clones that express their germline precursors [249, 250] as well
33 as toward designing mosaic antigens that elicit broad responses [251].
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42 In conclusion, studies of natural protection against HIV/AIDS have already provided
43 important clues about protective host determinants. Analyses of the immune responses
44 functioning in these models offer signatures or correlates of protection that will then need to
45 be validated in translational research. However, many questions remain to be investigated,
46 such as the mechanisms of residual replication, the factors driving chronic immune
47 activation and the mechanisms underlying treatment-induced protection against viral
48 replication. In the future, such insights will be helpful to design efficient, well-targeted
49 strategies for a cure and may also be of use for vaccine strategies.
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Figure captions

Figure 1: Priorities for HIV cure research based on recommendations from the International AIDS Society (IAS).

Figure 2: Schematic of the hypothetical variation in viremia, CD4+ T cell counts and inflammation in post-treatment controllers (PTC, orange) compared with HIV controllers (HIC, green), non-pathogenic infections such as SIV infection of natural hosts (NPI, pink) and viremic non progressors (blue). The orange box on the PTC curve indicates the period of cART initiation, and the dashed line indicates hypothetical levels.

Short title for page headings: Natural immune control against HIV/AIDS

Table I: Extreme profiles of natural protection against HIV/AIDS

	Protection against HIV infection	Protection against AIDS		
Type of natural protection	Highly HIV-exposed seronegative individuals	HIV controllers	Viremic non progressors	African nonhuman primates
Characteristics	<ul style="list-style-type: none"> No sign of infection despite repeated exposure to HIV 	<ul style="list-style-type: none"> <0.5% of the HIV+ population Undetectable viremia Stable CD4+ T cell counts 	<ul style="list-style-type: none"> Very rare Long-term asymptomatic High viremia Stable CD4+ T cell counts 	<ul style="list-style-type: none"> African green monkeys, sooty mangabeys, mandrills Asymptomatic High viremia Stable CD4+ T cell counts
Mechanisms potentially involved	<ul style="list-style-type: none"> Strong innate responses Humoural responses in mucosa Low levels of CD4+ T cell activation Post-virus entry blockade Host genetic polymorphism 	<ul style="list-style-type: none"> Genetic background (HLA-B27 and HLA-B57) Early control of viral replication Strong CD8+ T cell responses Enhanced ADCC activity Reduced susceptibility of CD4+ T cells to HIV infection 	<ul style="list-style-type: none"> Low levels of immune activation 	<ul style="list-style-type: none"> Early and efficient resolution of inflammation and T cell activation Less infection of TCM and TFH cells No microbial translocation
Proofs of concept or possible clinical applications	<ul style="list-style-type: none"> CCR5Δ32 homozygous bone marrow transplant B chemokines to block CCR5 Restriction factors 	<ul style="list-style-type: none"> HAART treatment during acute infection, post-treatment controllers Boosting of immune responses 	<ul style="list-style-type: none"> Design of well-targeted anti-inflammatory treatments 	

BASIC RESEARCH



TRANSLATIONAL RESEARCH



CLINICAL RESEARCH



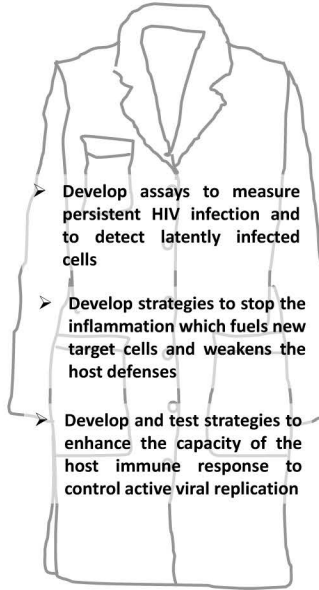
CLINICAL CARE

➤ How hosts control HIV replication in the absence of therapy?

➤ What are the mechanisms that contribute to the establishment and maintenance of latent infection, including the respective role of ongoing viral replication and/or homeostatic proliferation?

➤ What are the tissue and cellular reservoirs of HIV in individuals on long-term antiretroviral therapy?

➤ What are the origins of immune activation and inflammation in the presence of antiretroviral therapy and their consequences for HIV persistence?



- Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection or control viral reservoirs in animal models and in individuals on antiretroviral therapy

HIV CURE



HIV Remission

