Unravelling the mechanisms of durable control of HIV-1

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Abstract | Untreated HIV-1 infection typically progresses to AIDS within 10 years, but less than 1% of infected individuals remain healthy and have normal CD4$^+$ T cell counts and undetectable viral loads; some individuals have remained this way for 35 years and counting. Through a combination of large population studies of cohorts of these 'HIV-1 controllers' and detailed studies of individual patients, a heterogeneous picture has emerged regarding the basis for this remarkable resistance to AIDS progression. In this Review, we highlight the host genetic factors, the viral genetic factors and the immunological factors that are associated with the controller phenotype, we discuss emerging methodological approaches that could facilitate a better understanding of spontaneous HIV-1 immune control in the future, and we delineate implications for a 'functional cure' of HIV-1 infection.

CD4$^+$ T cell counts
A normal CD4$^+$ T cell count is 1,000 cells per microlitre (μl) of plasma, with a range of 600 to 1,400 cells per μl. The count falls during primary infection with HIV-1, then returns nearly to, or to lower than, normal levels. It then slowly falls, taking many years to reach the level of 200 cells per μl that characterizes the development of AIDS.

HIV-1 controllers
HIV-1-infected patients who spontaneously maintain very low levels of viral replication in the absence of antiretroviral therapy.

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Most of our initial understanding of host immune responses to chronic viral infections has come from studies using inbred mice. Such models have provided spectacular insights, particularly through the study of two closely related strains of lymphocytic choriomeningitis virus (LCMV; reviewed in REF. 1). In a particular genetic background of mice, infection with the parental Armstrong strain of LCMV results in an acute infection that is rapidly cleared; however, a single amino acid substitution in LCMV clone 13 leads to a persistent uncontrolled infection with a markedly altered tissue tropism and disease course[2,3]. Infection of mice with LCMV therefore provides a highly controlled system to dissect the immune responses that are associated with viral control versus viral persistence. Indeed, the study of LCMV has been a major guide in our understanding of the immunopathogenesis of chronic viral diseases.

In contrast to this LCMV model in mice, HIV-1 infection in humans is an ongoing pandemic that has infected more than 60 million individuals worldwide and has led to more than 30 million deaths[4]. If left untreated, HIV-1 infection is associated with considerably different disease outcomes in different individuals; some individuals develop AIDS — the end stage of HIV-1 infection — in less than 1 year, whereas other individuals (albeit a very small minority) maintain spontaneous control of viraemia and normal CD4$^+$ T cell counts for more than 35 years and counting (reviewed in REF. 5). Notably, these differences in outcome occur in the context of enormous genetic heterogeneity in both the virus and its host population. Therefore, human HIV-1 infection overshadows the highly controlled LCMV model system in terms of its complexity. Such observations highlight the difficulties in dissecting the crucial components of effective immunity to HIV-1 in humans given such tremendous variability in the virus and its host.

In this Review, we address the advances in this area of research that have come from outbred studies of HIV-1 infection in humans, focusing in particular on large population-based studies that have shed light on the mechanisms of control (and lack of control) of this chronic viral infection. To this end, we review the results of multiple cohort studies of HIV-1 controllers, including those individuals known as elite controllers, in whom plasma viraemia is controlled to levels that are undetectable using currently available assays[6] (BOX 1). The data that have been gathered from these diverse studies indicate that elite controllers are a heterogeneous population and, although virus-specific CD8$^+$ T cell responses are a dominant feature of durable immune control, there are multiple additional host genetic, immunological and virological factors among different HIV-1 elite controllers that probably contribute to this remarkable outcome. Here, we review recent progress in delineating the factors that contribute to spontaneous HIV-1 immune control, we outline specific methodological advances that are relevant for the study of HIV-1 controllers, and we summarize ideas for translating these studies into clinical strategies to induce a 'functional cure' or a long-term drug-free remission in individuals with HIV-1 infection.

Box 1 | **HIV-1 controllers**

The ability of a small number of HIV-1-positive patients to resist normal disease progression and to remain disease-free for prolonged periods of time was first recognized approximately 10 years into the HIV-1 pandemic. Such patients — referred to as 'long-term non-progressors' — were initially categorized on the basis of the absence of HIV-1-associated disease manifestations[125]. When tests for viral load became available, the heterogeneity of these patients and their ability to spontaneously control HIV-1 replication became evident. At least two subgroups of HIV-1-positive patients with non-progressive disease courses have been identified so far. Elite controllers (also known as 'elite suppressors') are a small number of untreated HIV-1-positive patients (estimated to be about 1 in 300 infected people) who have undetectable viral loads in commercial PCR assays. Most definitions[6,24] require HIV-1 replication to be below the level of detection on at least three separate occasions during a 12-month period. By contrast, viraemic controllers consist of patients who maintain low-level viraemia in the absence of treatment and typically have less than 2,000 copies of viral RNA per millilitre of plasma; these individuals represent up to 7% of all HIV-1-positive patients. The durability of HIV-1 control in elite controllers and viraemic controllers varies, but several epidemiological studies have shown that the spontaneous control of HIV-1 replication can last for extremely long periods of time (more than 30 years), although loss of immune control is observed in some of these individuals. Importantly, this definition of HIV-1 controllers is based solely on virological criteria, which do not exclude individuals who, despite having undetectable or minimally detectable HIV-1 replication, develop progressive loss of $CD4^+$ T cells and AIDS-defining clinical events. This progression to AIDS in the presence of low or undetectable HIV-1 replication is one of the most perplexing findings in HIV-1 controllers and its aetiology remains unclear. Recent studies suggest that despite the spontaneous control of HIV-1 replication, these individuals have abnormal levels of immune activation and/or defects in haematopoietic and thymic tissue regeneration[126,127], which might be associated with other disease sequelae such as increased carotid atherosclerosis[128]. The extent to which HIV-1 controllers who have progressive $CD4^+$ T cell loss will benefit from antiretroviral therapy has been analysed in a recent pilot study[129] and is now being investigated in a multicentre clinical study carried out by the AIDS Clinical Trials Group (ACTG Study A5308). Despite the absence of detectable HIV-1 replication in elite controllers, functional reservoirs of latently infected $CD4^+$ T cells are detectable in the majority of these individuals, although at lower levels than in individuals with highly active antiretroviral therapy (HAART)-mediated viral suppression[13,130]. The extremely low levels of latently infected $CD4^+$ T cells in elite controllers might make these patients attractive candidates for future clinical investigations that aim to reactivate and to eradicate latent viral reservoirs using novel pharmaceutical and/or immunological strategies[131].

Viral genetics

Initial reports showed the presence of defective or attenuated viral species in some individuals with long-term non-progressive infection and suggested that viral genetic deletions, particularly in the *nef* gene, might be responsible for the low levels of HIV-1 replication in these patients[7–9]. However, more recent whole-virus sequencing studies failed to show gross sequence alterations in viral strains that were isolated from elite controllers. Moreover, they documented that, on a population level, large viral deletions (for example, in *nef)* probably account for only a minority of cases of HIV-1 control[10]. Correspondingly, accumulating data indicate that many elite controllers are infected with a replication-competent form of virus that is predominantly controlled by host factors. Most importantly, viral outgrowth assays have enabled the *ex vivo* isolation of replication-competent viruses from a substantial number of elite controllers[11–13]. The transmission of replication-competent viruses from elite controllers to other patients who then developed progressive disease has also been documented[14,15]. Moreover, several investigations of viral sequences from elite controllers have indicated that archived provirus that has integrated in chromosomal DNA differs from HIV-1 RNA in the plasma[16,17], which has been frequently shown to harbour specific cytotoxic T cell (CTL) escape mutations that are typically associated with decreased viral fitness[18,19]. This indicates that, in elite controllers, there is likely to be ongoing low-level viral replication controlled by $CD8^+$ T cell-mediated immune pressure, and it corresponds to the attenuated viral replicative fitness that is observed after the insertion of viral *gag*, *pol* or *nef* genes from elite controllers into standardized viral reporter constructs[19,20]. As CTL escape mutations and attenuated viral fitness typically evolve later during the disease process, they are more likely to be a consequence of $CD8^+$ T cell-mediated immune pressure than a direct cause of the undetectable viraemia.

However, decreased viral fitness that is associated with increased numbers of CTL escape mutations and drug resistance mutations has also been noted during acute and early HIV-1 infection in some individuals who later developed a controller phenotype[21]. This makes it tempting to hypothesize that transmitted viral mutations could facilitate the natural control of HIV-1 replication by reducing viral replicative fitness during acute infection before the development of adaptive antiviral immunity. Thus, a refined research focus on the effects of viral sequence alterations during the earliest stages of infection might help us to better understand the viral factors that contribute to HIV-1 immune control.

In summary, investigations of viral sequence evolution in HIV-1 controllers have so far failed to provide clear evidence that infection with attenuated viral strains, as opposed to immune-induced mutations that attenuate viral functions, is the major reason for spontaneous HIV-1 immune control. This indicates that host factors are likely to be the main mechanism for the development of the HIV-1 controller phenotype. In the remainder of this article, we systematically describe the various host factors that apparently contribute to HIV-1 immune control.

Elite controllers
HIV-1-infected patients who have undetectable levels of viral replication in the absence of antiretroviral therapy.

Box 2 | **Analysis of genetic traits associated with HIV-1 immune control**

In recent years, novel high-throughput technologies have become available that enable the dissection of genetic patterns that are associated with distinct clinical outcomes of specific disease entities. Genome-wide association studies (GWASs) typically rely on automated, chip-based analysis of previously identified single-nucleotide polymorphisms (SNPs), and for the first time they have enabled genome-wide assessments of genetic variations that are associated with a given disease outcome. In the context of HIV-1 infection, multiple GWASs have been carried out to identify genetic elements that are associated with spontaneous HIV-1 immune control or accelerated progression of HIV-1 infection[6,26,28]. However, chip-based GWAS data are limited to previously defined genetic variations and they are intrinsically insufficient for the discovery of novel, previously unrecognized genetic mutations that might affect HIV-1 disease progression. Exome sequencing — a more recently introduced technology — uses DNA enrichment methods and massively parallel nucleotide sequencing to comprehensively identify and type protein-coding variants throughout the genome. Coupled with the use of growing databases that contain known variants, exome sequencing is likely to facilitate the discovery of novel genetic mutations that can influence HIV-1 disease progression. However, exome sequencing covers only about 1% of the entire genome and it limits investigations to coding variants in identified genes while missing genetic variations in non-coding regions that might have a regulatory influence on gene expression or function. Personalized whole-genome sequencing is an emerging technology that covers all genetic and genomic variations and that can be completed within weeks for individual patients. This technique is still prohibitively costly to be used for large-scale investigations of genetic correlates of HIV-1 immune control, but the development of transformative technology in this field seems imminent and might soon enable investigators to use this approach to unravel the genetic basis of HIV-1 immune control in more detail.

Host genetics

Evidence supporting the influence of host genetic factors on the course of HIV-1 infection was first noted in population studies of homosexual men in the United States, before the advent of potent combination antiretroviral therapy, through the identification of associations between specific HLA class I alleles and HIV-1 progression[22,23]. Investigations of HIV-1 controllers that have been carried out since then have confirmed that there is an over-representation of certain 'protective' HLA class I alleles in this group — including HLA-B*57, HLA-B*27, HLA-B*13 and HLA-B*58:01 — compared with HIV-1 progressors[24,25]. Large population studies show that protective HLA alleles are expressed in 67% of elite controllers but are only present at a frequency of 37% in HIV-1 progressors or in HIV-1-negative populations[24]. By contrast, certain HLA alleles are highly enriched in HIV-1 progressors, particularly subtypes of HLA-B*35 and HLA-B*07.

A better understanding of the role of HLA class I alleles in host genetic control of HIV-1 has been facilitated by genome-wide association studies (GWASs) of large populations (BOX 2). Several GWASs have now shown that single-nucleotide polymorphisms (SNPs) in the HLA class I locus, in particular in the region of HLA-B and HLA-C, are the major host genetic factors that are associated with HIV-1 disease outcome[6,26–28]. However, out of more than 90 other genetic variations that have previously been reported to influence HIV-1 disease outcome (reviewed in REFS 29,30), only polymorphisms in CC-chemokine receptor 5 (CCR5) and CCR2 have nominal statistical significance in GWASs. This highlights the need for population stratification and for sufficient statistical power when drawing inferences on genetic influences[6]. However, these data do not eliminate the possibility that there might be other genetic factors that are not identified in GWASs.

A GWAS measures less than 10% of common SNPs in the human genome and imputes other SNPs by linkage disequilibrium; therefore, even a positive GWAS signal cannot define the actual genetic loci involved in the observed associations. Using a novel imputation method to define signature polymorphisms in the HLA region that, on the basis of SNP data, underpin protective versus non-protective HLA genotypes, further insight into the mechanistic basis of the association between HLA alleles and HIV-1 disease progression has been obtained. In Caucasians, four HLA class I polymorphisms involving amino acids in the HLA-B binding groove were shown to be associated with HIV-1 control and, importantly, they were still significantly associated with control even when the effects of HLA-B*27 and HLA-B*57 were controlled as much as is possible[6]. Moreover, polymorphisms at the same HLA-B amino acid positions are also associated with lack of control in HIV-1 progressors. The mechanisms that account for such a dominant effect of single amino acids are still unclear, but the data indicate that the nature of peptide binding in the HLA-B binding pocket might be a determining feature for HIV-1 disease outcome. Additional studies will be required to verify or to refute this hypothesis[6]. For example, protective HLA class I alleles such as HLA-B*57 might have structural peptide-binding characteristics that facilitate the thymic selection of T cell clones with improved cross-recognition of viral epitope variants[31]. Such a T cell repertoire might exert more effective immune pressure on HIV-1 while simultaneously enhancing the risk of immune-mediated hypersensitivity reactions (such as those that can occur in HLA-B*57:01-expressing individuals as an adverse reaction to the HIV-1 drug abacavir)[32].

Although delayed HIV-1 disease progression among carriers of protective HLA class I alleles has also been observed in larger epidemiological studies[33], it is important to recognize that the majority of infected individuals expressing protective alleles still develop progressive disease[34]. Moreover, in some elite controllers, undetectable viraemia is observed in the absence of the expression of protective HLA class I alleles[24]. This indicates that specific HLA-B alleles are neither a necessary nor a sufficient genetic cofactor for HIV-1 control, and it emphasizes that there is considerable genetic and immunological heterogeneity between elite controllers. In addition, as genetic studies have indicated that only about 20% of the variability in the viral load between HIV-1-infected individuals is due to genetic factors[6], there are clearly other important modulators. Specific HLA class I alleles might also be associated with the delayed loss of $CD4^+$ T cells without affecting levels of viral control[35]. Interestingly, specific MHC class I molecules have been associated with the immune control of simian immunodeficiency virus (SIV) infection in rhesus macaques, and investigations using these animals might help to clarify the functional mechanisms of MHC class I-associated immune protection (BOX 3).

Genome-wide association studies
(GWASs). Studies that assess upwards of one million single-nucleotide polymorphisms in the human genome for associations with disease outcomes. As such, they require very large numbers of individuals; the number of individuals that are required depends on the strength of the associations that are being investigated.

Box 3 | **Elite controllers in SIV-infected rhesus macaques**

The investigation of HIV-1 immune control has considerably benefited from rhesus macaque models that seem to imitate the biological and clinical characteristics of HIV-1 elite controllers. Following infection with the SIVmac239 strain of simian immunodeficiency virus (SIV), the majority of rhesus macaques develop ongoing, high-level SIV viraemia and progress to an AIDS-like clinical phenotype over the subsequent months. Similarly to human HIV-1 infection, the kinetics of disease progression in rhesus macaques are highly variable, but a small number of animals typically achieve spontaneous control of SIV replication and remain clinically healthy. This elite controller phenotype in rhesus macaques is associated with the expression of Mamu-B*00801 — an MHC class I allele that has a similar binding motif to HLA-B*2705 (which is significantly over-represented in human elite controllers)[132]. Mamu-B*00801-restricted T cell responses mediate the majority of cellular immune responses in primary SIV infection, at the time when peak levels of SIV replication decline to the viral set point level[133]; this is reminiscent of the dominant role of HLA-B*57 in restricting cellular immune responses in primary HIV-1 infection[134,135]. Moreover, spontaneous immune control was impaired following the infection of rhesus macaques with an SIVmac239 variant in which immunodominant Mamu-B*00801-restricted cytotoxic T cell epitopes are mutated. This supports the idea that cytotoxic T cells have a crucial role in SIV immune control in these animals[136]. However, it is important to recognize that only about 50% of all SIVmac239-infected Mamu*B00801-positive rhesus macaques develop elite control, whereas the others develop progressive disease; this again seems to mimic the situation in humans in whom only a minority of all HLA-B*57 or HLA-B*27 carriers achieve spontaneous HIV-1 immune control. This might partly be due to differences in the targeting of specific epitopes. Indeed, pre-infection immunization of macaques expressing the protective allele Mamu-B*08 to induce Nef-specific immune responses correlates with decreased viral loads, and escape from vaccine-induced $CD8^+$ T cell responses is associated with a loss of viral control[65]. In about 40% of all elite controller rhesus macaques, no underlying genetic trait can be identified and the mechanisms of immune control in these animals remain poorly defined. These results show that, even in a relatively well-controlled animal model in which viral and host parameters can be more easily manipulated for experimental purposes, the identification of factors that are responsible for SIV immune control is extremely difficult and will require substantial additional future investigations.

GWASs and, in some cases, subsequent sequence analysis of the host genome have indicated that HLA class I polymorphisms outside the HLA-B binding pocket are also likely to contribute to HIV-1 control. In African Americans, the non-pocket HLA-B amino acid position 246 is independently associated with HIV-1 immune control, possibly by modifying T cell receptor (TCR) binding to CD8 (REF. 36). Moreover, a polymorphism that is located 35 kilobases upstream of HLA-C is significantly linked to higher levels of HIV-1 immune control, as measured by genome-wide analysis[37], although this polymorphism is not significantly enriched in elite controllers. This polymorphism probably functions as a marker of genetic variants in the 3′ untranslated region of HLA-C, which regulates the binding of the microRNA hsa-miR-148a to its target site. HLA-C alleles that bind to this microRNA are expressed at relatively low levels at the cell surface, in contrast to the high-level expression of HLA-C alleles that escape post-transcriptional regulation by hsa-miR-148a[38]. Higher levels of HLA-C expression might increase the immune activity of HLA-C-restricted HIV-1-specific $CD8^+$ T cells. An alternative explanation is that the effect of the HLA-C polymorphism might be mediated by linkage disequilibrium with HLA-B alleles[39]. In addition, a SNP on chromosome 1 has been linked to differences in HIV-1 disease progression, but it does not meet the rigorous statistical threshold that is used to determine significance in such studies[40].

The associations between HLA class I molecules and viral regulation indicate that $CD8^+$ T cells might have a role in mediating this control, but other HLA class I-binding partners might also be involved. In addition to the restriction of antiviral $CD8^+$ T cell-mediated immune responses, polymorphisms in HLA class I alleles might affect HIV-1 immune control through interactions with HLA class I receptors that are expressed on innate immune cells, such as the killer cell immunoglobulin-like receptors (KIRs) that are expressed by natural killer (NK) cells. The expression of the activating receptor KIR3DS1 in conjunction with its ligand HLA-Bw4-80I, or specific combinations of KIR3DL1 and HLA-Bw4-80I alleles, have a marked effect on HIV-1 disease outcome[41,42], but studies have so far failed to show whether elite controllers are enriched for protective KIR–HLA combinations[43].

In addition to interactions with KIRs, HLA molecules bind to members of the leukocyte immunoglobulin-like receptor (LILR) family, which comprises a group of surface molecules expressed on dendritic cells (DCs) that regulate the functional properties of these cells[44,45]. Unique expression patterns of LILRs have been detected in elite controllers (see below), but to what extent they are genetically determined or are due to epigenetic or other modulators is unknown. It is also unknown whether these HLA–LILR interactions significantly influence clinical HIV-1 disease outcome or whether they facilitate an elite controller phenotype.

A major challenge in the future will be to expand genetic studies in elite controllers to include assessments of epigenetic mechanisms that might contribute to immune control. Although specific epigenetic mechanisms — such as promoter methylation[46] and transcription factor phosphorylation[47] — have been shown to be involved in specific aspects of immune defence in elite controllers, a systematic analysis of epigenetic alterations in large cohorts of elite controllers will probably be necessary to generate a comprehensive picture of how epigenetic mechanisms can influence HIV-1 immune control. To be most informative, such a comprehensive analysis of epigenetic factors should be carried out in parallel with high-throughput investigations of gene expression profiles in individual cell subsets of elite controllers.

In conclusion, genetic polymorphisms in the human HLA class I locus are currently the strongest and best-defined predictors of HIV-1 control, but the functional mechanisms that are responsible for these associations remain an area of intense study. As HLA class I alleles can regulate both adaptive and innate cellular immune responses, such mechanisms might involve a diverse set of immunological networks. In addition, the possible roles of HLA-C, KIR and LILR polymorphisms in spontaneous HIV-1 immune control have not been investigated in dedicated studies and they should be further analysed in large cohorts of elite and viraemic controllers.

Adaptive immunity

Strong and effective HIV-1-specific CD4⁺ and CD8⁺ T cell responses are generally regarded as the backbone of antiviral immune activity in elite controllers, and they might define the biological characteristics of an effective T cell response against HIV-1. Although the T cell responses of elite controllers typically do not differ from those of non-controller patients in terms of the number of targeted epitopes, as measured by interferon-γ (IFNγ) secretion[24], they can be qualitatively differentiated using several parameters (FIG. 1).

CD8⁺ T cells. The most dominant functional characteristic that distinguishes HIV-1-specific T cells in elite controllers from those in HIV-1 progressors is their ability to effectively inhibit HIV-1 replication in *ex vivo*-infected autologous CD4⁺ T cells[48,49]. This inhibitory activity, which can be seen in many — but not all — HIV-1 controllers, seems to be mediated mostly by CD8⁺ T cells targeting the viral Gag protein, and it probably represents the net result of diverse phenotypic, functional, structural and gene expression characteristics of these T cells.

On a phenotypic and gene expression level, the expression of transcripts that are involved in lymphocyte exhaustion and senescence is lower in HIV-1-specific T cells from elite controllers than from HIV-1 progressors[50]. HIV-1-specific CD8⁺ T cells from elite controllers synthesize greater amounts of cytotoxic granule components, such as granzyme, perforin and granulysins, which enable greater cytotoxic activity and can synergistically induce apoptosis in target cells[34,51,52]. The increased expression of these cytotoxic granule components seems to be partly under the control of T-bet (also known as TBX21), which is

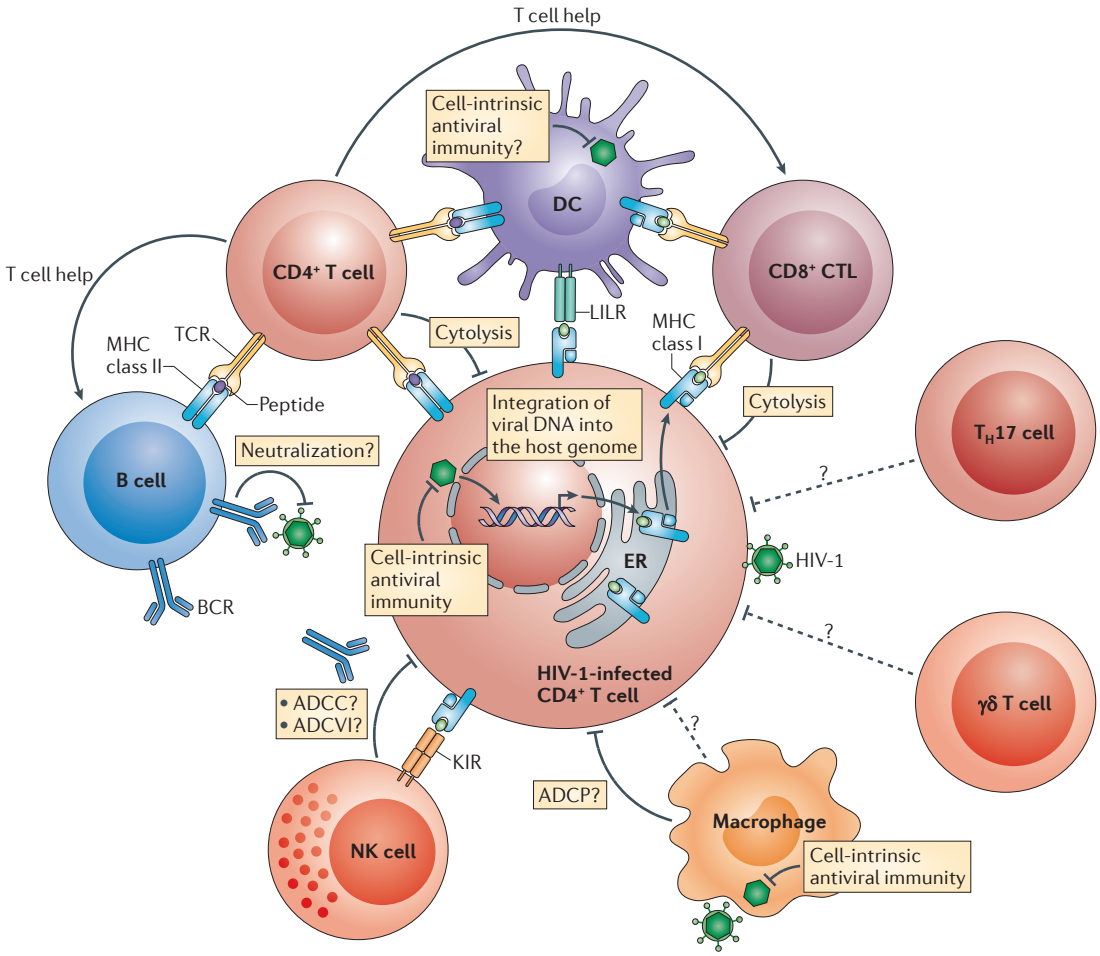

Figure 1 | **Innate and adaptive immune defence mechanisms contributing to spontaneous HIV-1 control.** HLA class I-restricted CD8⁺ cytotoxic T lymphocyte (CTL) responses are generally regarded as a central component of HIV-1 immune control. The antiviral activities of these cells might be supported by conventional dendritic cells (DCs) and CD4⁺ T helper cells, both of which seem to have unique functional activities in elite controllers compared with other patient populations. Cell-intrinsic restriction of HIV-1 replication stages has been reported in CD4⁺ T cells and macrophages from elite controllers; whether such mechanisms also occur in DCs from elite controllers is unknown. γδ T cells and natural killer (NK) cells have been suggested to participate in antiviral immune defence mechanisms in HIV-1 controllers, but this requires further investigation. Question marks on the figure indicate that the evidence is unclear. ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCVI, antibody-dependent cell-mediated viral inhibition; BCR, B cell receptor; ER, endoplasmic reticulum; KIR, killer cell immunoglobulin-like receptor; LILR, leukocyte immunoglobulin-like receptor; TCR, T cell receptor; T_H17, T helper 17.

a transcription factor from the T-box family that can directly bind to the promoter regions of perforin and granzyme B genes and that seems to be uniquely upregulated in HIV-1-specific T cells from elite controllers[53].

In addition to this increased cytotoxic activity, strong proliferative properties have been defined as principal characteristics of HIV-1-specific CD8+ T cells from elite controllers[54]. These properties of HIV-1-specific CD8+ T cells seem to be closely linked to their cytotoxic activity[52] and to their autocrine secretion of specific cytokines such as interleukin-2 (IL-2)[55]. In fact, the ability to simultaneously execute multiple effector functions — now frequently referred to as 'polyfunctionality' — seems to be a key characteristic of HIV-1-specific CD8+ T cells from elite controllers[56] and might be related to a more immature phenotype, similar to that of central memory T cells[57]. By contrast, monofunctional, effector-cell-like HIV-1-specific CD8+ T cells predominate in HIV-1 progressors. The functional characteristics of HIV-1-specific CD8+ T cells from HIV-1 controllers have mostly been determined using peripheral blood cells, but any differences between HIV-1 controllers and HIV-1 progressors might be more discernible in the cells residing at mucosal sites that function as the major reservoirs for HIV-1 replication. Indeed, a series of studies in HIV-1 elite controllers has now documented the presence of strong and highly functional HIV-1-specific CD8+ T cell responses in rectal and sigmoid lymphoid tissues[58].

In tissues and peripheral blood alike, the most effective HIV-1-specific CD8+ T cells are restricted by the HLA class I alleles that are epidemiologically associated with delayed HIV-1 disease progression, such as HLA-B*57 or HLA-B*27. HIV-1-specific CD8+ T cells restricted by these HLA class I alleles seem to be less susceptible to the inhibitory effects of regulatory T (T_{Reg}) cells, possibly as a result of decreased expression of T cell immunoglobulin and mucin domain-containing protein 3 (TIM3; also known as HAVCR2)[59]. Moreover, HLA-B*57 and HLA-B*27 present several well-characterized immunodominant epitopes in Gag that might be particularly vulnerable to the antiviral effects of CD8+ T cells owing to limitations in tolerating sequence variations[60]. Although the targeting of Gag epitopes has been inversely correlated with viral load in several population studies[61–64], strong recognition of Gag epitopes by CD8+ T cells can also be observed in HIV-1 progressors, including those who express protective HLA class I alleles. In addition, studies in a rhesus macaque model of SIV infection have indicated that control of SIV can be achieved in the absence of Gag targeting[65], and not all elite controllers express protective HLA class I alleles[24,66]. This suggests the presence of additional, as yet undefined, specificities of CD8+ T cells and of modifying factors that influence the efficacy of HIV-1-specific CD8+ T cells.

A specific selection of more cytolytic TCR clonotypes has recently been identified that distinguishes between HIV-1-specific CD8+ T cells isolated from HIV-1 controllers and those isolated from HIV-1 progressors (in the presence of otherwise identical functional and phenotypic properties)[34]; this discovery indicates that specific structural interactions between the TCR and the corresponding peptide–HLA class I complex might be important factors in co-determining antiviral efficacy. Alternatively, the ability of CD8+ T cells to target particularly vulnerable regions of HIV-1 Gag may provide elite controllers with a better outcome[60]. Indeed, a recent longitudinal study of HIV-1 controllers who were followed from the time of acute infection indicated that the specific HIV-1 epitopes that are targeted by CD8+ T cells might modulate the ability of protective HLA alleles to exert a maximal effect on viral control[67].

One question that remains unanswered is whether the polyfunctional characteristics of HIV-1-specific CD8+ T cells from elite controllers represent a cause or a consequence of viral control, which is difficult to determine from cross-sectional studies. Notably, HIV-1-specific CD8+ T cells from patients with pharmacological control of HIV-1 share some of the phenotypic and functional properties of HIV-1-specific CD8+ T cells from elite controllers. This suggests that several of these characteristics might be epiphenomenons of HIV-1 immune control, instead of true correlates of HIV-1 immune defence[68]. A further longitudinal dissection of the molecular characteristics that are unique to HIV-1-specific T cell responses in elite controllers, and that distinguish them from those of HIV-1 progressors and those of individuals treated with highly active antiretroviral therapy (HAART), will be crucial in defining how spontaneous control of HIV-1 is possible. In addition, it will be important to identify the molecular signals that support the ontogeny of highly functional HIV-1-specific CD8+ T cells in elite controllers but not in other patients. Studies have been initiated to analyse the mechanisms of antigen presentation and T cell priming in elite controllers, and it is possible that specific interactions between DCs and T cells might have a crucial role in these processes.

CD4+ T cells. Our understanding of the important role of HIV-1-specific CD4+ T cells and their ability to support the antiviral effects of HIV-1-specific CD8+ T cells is improving, as is our understanding of the role of T follicular helper cells, which are required for the induction of broadly neutralizing antibodies[69]. Notably, HIV-1-specific CD4+ T cells from elite controllers seem to have higher functional avidities[70] and they secrete multiple cytokines, including IL-2 and IL-21, that increase the antiviral activities of HIV-1-specific CD8+ T cells[71,72]; however, the magnitude of these effects is small in comparison with the CD8+ T cell response. As the functional characteristics of CD4+ T cells do not strictly separate HIV-1 controllers from HAART-treated patients, it is more likely that they are a consequence of controlled viraemia[73]. The recent demonstration that there is an association between acute-phase cytolytic CD4+ T cells and viral set point control should also be investigated in elite controllers[74], preferably in mucosal tissues where the majority of functional HIV-1-specific CD4+ T cells are likely to reside[75]. Likewise, a greater understanding of the specific epitopes that are targeted by HIV-1-specific CD4+ T cells should be an important

Central memory T cells
Memory T cells that express L-selectin and CC-chemokine receptor 7 (CCR7) and that have the capacity to traffic from the blood to the secondary lymphoid organs. They have a nonpolarized differentiation state: they secrete interleukin-2 but not interferon-γ or interleukin-4. However, upon restimulation, they rapidly differentiate into cytokine-producing effector cells.

Highly active antiretroviral therapy
(HAART). An aggressive combination therapy against HIV-1 infection that typically includes three or more protease and reverse-transcriptase inhibitors.

aspect of future studies[76], particularly as there are now data suggesting that specific restricting MHC class II molecules influence HIV-1 immune control[77].

Antibodies. In contrast to the important role of HIV-1-specific CD8$^+$ and CD4$^+$ T cells in elite controllers, several studies have shown that neutralizing antibodies are less frequently found in elite controllers than in viraemic progressors[24,78–80]. This finding corresponds to studies showing that a broader range of neutralizing antibody specificities is typically observed in conjunction with higher contemporaneous viral loads[81,82] but that this is not associated with protection against spontaneous HIV-1 disease progression[83]. However, progressive *env* evolution under an antibody-mediated immune selection pressure has been documented in some elite controllers[84]. Together, these data suggest that neutralizing antibody diversity is primarily driven by increased antigenic stimulation, and they indicate that neutralizing antibodies might have a limited role in the durable control of HIV-1 replication in the context of natural infection. Nevertheless, a very small group of HIV-1 controllers does seem to produce broadly neutralizing antibodies against HIV-1 in the setting of low levels of viraemia[85] or even in the absence of detectable levels of HIV-1 replication (G. Alter and F. Pereyra, personal communication). Understanding the ontogeny of these B cell responses in elite controllers might provide crucial new information that could be used to induce broadly neutralizing HIV-1-specific antibodies for prophylactic purposes.

Whether non-neutralizing HIV-1-specific antibodies can exert significant antiviral activity in elite controllers is an area of renewed interest and is being actively investigated. Some studies have shown that antibody-dependent cell-mediated cytotoxicity (ADCC) might be increased in elite controllers who have lower levels of neutralizing antibodies[79] — a finding that is of interest given the studies in monkeys showing that an SIV vaccine can induce ADCC[86] and that vaccine-induced ADCC can lower viraemia following challenge[87]. However, recent studies have failed to confirm enhanced ADCC in HIV-1 controllers[88] and it remains controversial whether ADCC-based immune defence mechanisms contribute to the natural control of HIV-1 replication.

In conclusion, the adaptive immune response in elite controllers consists of both CD4$^+$ and CD8$^+$ T cell responses, and the idea that HIV-1-specific CD8$^+$ T cells have a dominant role in HIV-1 immune control has been supported by a large number of functional immunological studies. However, it is evident that HIV-1-specific CD8$^+$ T cell responses alone are an insufficient explanation for the immune control observed, and a specific functional property of HIV-1-specific CD8$^+$ T cells does not seem to correspond to durable control of HIV-1 infection. How the evolution of HIV-1-specific T cells in elite controllers is modulated by alternative immune defence mechanisms represents a high-priority area of current investigation and is highly relevant to vaccine and eradication strategies.

Innate immunity

Although innate immunity has long been perceived as being less relevant to HIV-1 immune control than adaptive immunity, unique properties of innate immune defence mechanisms have recently been identified in elite controllers (FIG. 1).

Dendritic cells. The evidence that is available indicates that the antigen-presenting properties of myeloid DCs are increased in elite controllers, whereas the Toll-like receptor (TLR)-dependent secretion of pro-inflammatory cytokines by myeloid DCs in these patients seems to be decreased[89]. These functional characteristics of myeloid DCs in elite controllers are associated with the selective upregulation of immunoregulatory receptors from the LILR family and have been postulated to facilitate the generation of potent effector cell responses against HIV-1 without enhancing the overall levels of immune activation. Plasmacytoid DCs, which exert antiviral activities through the secretion of high levels of IFNα, are maintained at higher levels in elite controllers than in HIV-1 progressors[90], but neither the quantities nor the functional properties of plasmacytoid DCs differ between elite controllers and HIV-1-negative individuals, which indicates that plasmacytoid DCs are unlikely to significantly contribute to HIV-1 immune control[90,91].

Innate effector cells. NK cells can rapidly kill HIV-1-infected cells using their cytolytic activities or through the secretion of cytotoxic cytokines (reviewed in REF. 92). By killing HIV-1-infected cells, NK cells can exert immune pressure on HIV-1 and influence viral sequence evolution[93]. During HIV-1 infection, various phenotypic and functional perturbations of NK cells have been identified, most of which are probably due to ongoing high-level viraemia and to the associated immune activation[94,95]. Importantly, the antiviral activities of NK cells from elite controllers — as determined using viral inhibition assays — were found to be relatively weak, which indicates that the contribution of NK cells to antiviral immune defence mechanisms in elite controllers might be limited[43]. By contrast, γδ T cells might be a distinguishing feature of elite controllers. Typically, the number of γδ T cells expressing the Vγ2Vδ2 TCR is decreased early in the HIV-1 disease process; however, elite controllers maintain supranormal levels of fully functional Vγ2Vδ2 T cells in the peripheral blood[96]. The stimuli responsible for the expansion of this γδ T cell population and for its possible involvement in HIV-1 immune regulation in elite controllers need to be further investigated.

Cell-intrinsic immune defence mechanisms. In addition to the immune protection that is provided by innate effector cells, cell-intrinsic innate mechanisms of HIV-1 immune defence seem to be functional in elite controllers. Some studies have shown that activated CD4$^+$ T cells from elite controllers can support viral replication[11,13,97], but — using slightly different methods — two further studies of two geographically distinct cohorts from the United States and France have shown that CD4$^+$

T cells from many elite controllers are less susceptible to HIV-1 infection[98,99]. This innate blockade of HIV-1 replication was associated with the upregulation of the host protein p21 (also known as CDKN1A)[98,99], which is a cyclin-dependent kinase inhibitor that might indirectly inhibit HIV-1 replication through the restriction of the host cyclin-dependent kinases that are required for effective HIV-1 transcriptional elongation[98,100]. However, p21 upregulation did not seem to be the cause of the observed blockade of HIV-1 replication in one of the two studies[99]; alternative host restriction factors are therefore also likely to be involved. Macrophages from elite controllers were also found to be less effective at supporting HIV-1 replication for reasons that remain undefined[99]. Although early studies suggested that human cells are unable to respond to HIV-1 infection by secreting type I IFNs[101], recent findings indicate that $CD4^+$ T cells, macrophages and DCs can mount strong cell-intrinsic type I IFN responses against HIV-1 when the accumulation of early HIV-1 replication products (which are substrates for intracellular sensors of microbial DNA or RNA) is not inhibited by host proteins[102,103]. It is not known whether cell-intrinsic type I IFN responses are active in elite controllers or whether they might contribute to antiviral immune defence in these patients.

T_{Reg} cells and T_H17 cells. Innate immune defence mechanisms might also contribute to the spontaneous control of HIV-1 by altering the systemic levels of immune activation in T cells; immune activation is a crucial factor in HIV-1 immune pathogenesis and influences HIV-1 disease outcome independently of the extent of viral replication. Indeed, decreased levels of immune activation have been associated with immune protection against HIV-1 acquisition in individuals who remained HIV-1-negative despite repetitive exposure to HIV-1 in high endemic areas[104]. In contrast to such 'exposed but uninfected' individuals, lymphocyte immune activation — which is typically measured by phenotypic assessments of HLA-DR and CD38 — seems to be abnormally increased in some elite controllers[48,105,106], possibly as a result of the ongoing viral replication that can be detected in these patients by ultra-sensitive assays with single-copy resolution[52,107,108] or by investigations of viral sequence evolution[109]. T_{Reg} cells can decrease immune activation in other situations, but T_{Reg} cell frequency and functions seem unaltered or even slightly decreased in elite controllers compared with HIV-1-negative individuals[110,111]. T helper 17 (T_H17) cells — that is, $CD4^+$ T cells that have important functions in maintaining immune surveillance at mucosal surfaces — have been prospectively associated with decreased levels of HIV-1-associated immune activation[112], possibly owing to T_H17 cell-mediated reduction of microbial translocation in intestinal tissues. Whether and how T_H17 cells might contribute to HIV-1 immune defence in elite controllers remains uncertain.

Taken together, there is now an increasing number of studies indicating that innate immune defence mechanisms have a contributory or additive role in mediating spontaneous HIV-1 immune control; however, findings that have been reported so far are limited by relatively small sample sizes and need to be confirmed in larger populations of HIV-1 controllers. Nevertheless, the innate mechanisms that can modulate or cooperate with adaptive immune activity are likely to be an important component of antiviral immune defence in HIV-1 controllers (FIG. 1) and should be further investigated in future studies.

An integrative view of HIV-1 immune control

A fundamental limitation of most the investigations of elite controllers is that they have focused on individual immunological aspects that were typically analysed in isolation in a relatively small number of patients. However, currently available data indicate that elite control is not due to the presence or to the absence of a single factor, and that elite controllers are generally heterogeneous and have multiple underlying mechanisms of immune defence. Indeed, the operational definition of elite controllers — as untreated HIV-1-infected individuals with undetectable HIV-1 replication in commercial PCR assays — can include patients as diverse as those who have an HIV-1 infection that is nearly cured[113,114], those who have either high or low levels of immune activation, and those who have a progressive loss of $CD4^+$ T cells and have developed AIDS[105].

The broad definition of elite control based solely on viral load and on the duration of infection might preclude the identification of more definitive correlations of immune defence, particularly if there are multiple subpopulations that are associated with different mechanisms of HIV-1 control. Moreover, there has been a trend to focus investigations of immune defence in elite controllers on specific predefined molecules or pathways; however, such an analysis strategy introduces bias and might preclude the discovery of novel, previously unrecognized elements of immune protection. Finally, a major limitation of studies that have been carried out in elite controllers is that data analysis typically focuses on single, isolated aspects of immune defence while ignoring the systemic, interconnected immunological programmes that individual immune defence mechanisms are associated with or in which they are embedded.

Together, these deficiencies might explain why we are still a long way from delineating the factors and the mechanisms that enable spontaneous immune control of HIV-1. We argue that now is the time for a shift towards research strategies that have a refined focus on comprehensive, integrative and unbiased investigations of the signals and molecular pathways that can induce spontaneous control of HIV-1 replication (FIG. 2). By adopting such a systems biology approach, the HIV-1 research community would make an investigative transition that has already been successfully implemented in other research areas and that seems to have certain intrinsic advantages over the more traditional investigative approaches.

Systems biology uses global, parallel and unbiased assessments of interconnected biological variables to develop unifying, holistic models that are associated with — and predictive of — specific disease outcomes[115,116].

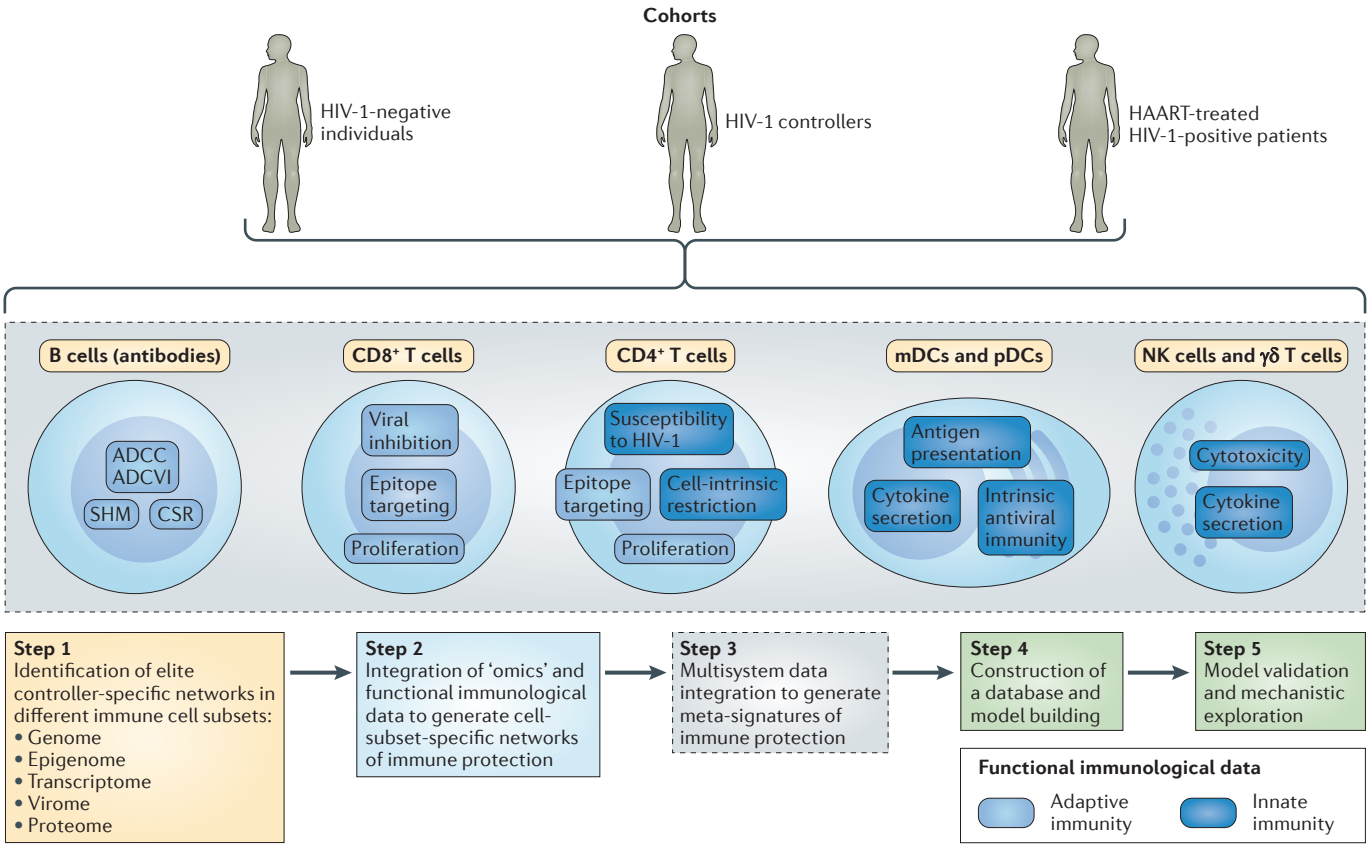

Figure 2 | **A systems biology approach to dissect immune defence mechanisms in HIV-1 controllers.** Systems biology-based investigations of HIV-1 controllers will start with comprehensive 'omics' studies in individual cell subsets from large cohorts of HIV-1 controllers, HIV-1-negative individuals and highly active antiretroviral therapy (HAART)-treated HIV-1-positive patients. Subsequently, such data can be associated with functional immunological assays and subjected to 'machine-learning' procedures to generate molecular and cellular networks defining an HIV-1 controller phenotype. Such models can then be prospectively validated in alternative HIV-1-positive patient cohorts to identify a frame of reference for what might be required in clinical intervention strategies to induce spontaneous HIV-1 immune control in larger patient populations. ADCC, antibody-dependent cell-mediated cytotoxicity; ADCVI, antibody-dependent cell-mediated viral inhibition; CSR, class-switch recombination; mDC, myeloid dendritic cell; NK, natural killer; pDC, plasmacytoid dendritic cell; SHM, somatic hypermutation.

This approach has proven to be of benefit in dissecting cellular networks in oncology[117], rheumatology[118] and transplant immunology[119], and for identifying predictable correlates of vaccine-mediated immune protection[120–122]. Systems biology-based investigations typically involve automated, large-scale, high-throughput methodologies such as genome-wide analyses of genetic polymorphisms, whole-genome transcriptional profiling and/or large-scale proteomic assessments. Although the difficulties associated with evaluating and interpreting data from such investigations should not be underestimated, we argue that a unified effort for comprehensive, parallel investigations of genetic, epigenetic, gene expression and functional immunological and virological properties from large numbers of elite controllers might be one of the most promising strategies to gain a more definitive and integrative view of the mechanisms and principles of the natural control of HIV-1 infection. Such an approach is a long way from the study of viral immunology using inbred mice and LCMV as the model virus, but it will be necessary if we are to progress from associations and correlations to identification of the determinants of immune control.

Conclusion and perspectives

HIV-1 controllers provide tangible evidence that some humans are able to effectively and durably control HIV-1 replication and to prevent HIV-1-associated disease manifestations for extended periods of time. Despite considerable heterogeneity among individuals who develop an HIV-1 controller phenotype, there is now compelling evidence from large genetic and functional immunology studies that CTL responses are the dominant component of immune defence in many of these patients, particularly in those patients expressing selected HLA class I alleles. That said, it is increasingly clear that CTL responses and their restricting HLA class I alleles only represent one piece of the puzzle and that multiple additional factors are involved that might, either independently or in conjunction with HIV-1-specific $CD8^+$ T cells, modulate the effective control of HIV-1 infection. On the basis of current

Box 4 | **Post-treatment controllers**

Whether treatment with antiretroviral therapy can facilitate spontaneous immune control of HIV-1 during the chronic phase of HIV-1 infection is a question of outstanding importance. Early studies showed that short-term treatment during primary HIV-1 infection was associated with low-level HIV-1 viraemia during a subsequent treatment interruption[137], but relative viral control was not sustained in the long term and did not protect against gradual $CD4^+$ T cell loss[138]. By contrast, more recent studies indicate that a longer treatment course started during primary infection can increase the chances of subsequent immune control. VISCONTI (Virological and Immunological Studies in Controllers after Treatment Interruption)[139] is a retrospective evaluation of patients who initiated antiretroviral therapy during primary HIV-1 infection, achieved an undetectable viral load, stayed on treatment for at least 1 year (median of 3 years) and then chose to discontinue therapy. Following treatment discontinuation, 14 patients were identified who were able to spontaneously control HIV-1 to low levels (eight of whom controlled to less than 50 copies of viral RNA per millilitre of plasma, the other six had occasional viraemia below 400 RNA copies per millilitre of plasma) for a median duration of 76 months (6 years). In comparison with classic elite controllers, these 'post-treatment controllers' were not enriched for the expression of HLA-B*57 or HLA-B*27 and had only very limited numbers of HIV-1-specific $CD8^+$ T cells. The frequency of latently infected $CD4^+$ T cells was low in these patients, probably as a result of early initiation of antiretroviral treatment. In the CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) study, 11 out of 259 patients (4%) who started treatment within 3 months of seroconversion were able to maintain spontaneous undetectable viraemia for 24 months following treatment interruption[140]. These provocative studies did not definitively show that early treatment initiation was aetiologically responsible for the increased ability of these patients to maintain drug-free HIV-1 control after treatment interruption, but future studies are warranted to investigate how long-term HIV-1 persistence and immune control can be manipulated using antiretroviral treatment during the earliest stages of HIV-1 infection.

investigations, such additional processes are likely to include a specific interplay of DCs with T cells, selected innate effector cells such as γδ T cells and cell-intrinsic immune defence mechanisms that can block individual viral replication steps in HIV-1 target cells. Whether these elite controller-specific immune defence mechanisms can ever be used to increase host immunity to HIV-1 in a broader patient population remains unclear, but we are optimistic that the lessons learned from these patients will be informative in designing novel strategies for the treatment of HIV-1. Although the immune defence strategies of elite controllers are unlikely to prevent the acquisition of HIV-1 or to provide 'sterilizing immunity' to HIV-1 infection in other individuals, their induction using vaccines or immunogens could minimize the deleterious effects of HIV-1 in infected individuals without the need for long-term antiretroviral therapy. Furthermore, in some cases, they could enable HIV-1-infected individuals to reach a condition that is phenotypically and immunologically indistinguishable from HIV-1-negative individuals. As such, investigations in elite controllers might be one of the most promising aspects of current efforts to induce a long-term, drug-free remission or a 'functional cure' of HIV-1 infection[95,123,124] (BOX 4). The observation that this natural control of HIV-1 is also achievable in the absence of specific protective HLA class I polymorphisms holds promise that, in principle, an elite controller phenotype may be therapeutically inducible in a larger number of patients, and suggests new ideas for the development of broadly applicable strategies to limit the spread of the HIV-1 pandemic.

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Competing interests statement
The authors declare no competing financial interests.

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