Combination antiretroviral therapy (ART) has dramatically transformed HIV infection from a death sentence to a clinically manageable chronic disease. Strict adherence to ART effectively suppresses viraemia, halts progression to acquired immune deficiency syndrome (AIDS), thwarts HIV acquisition when used as pre-exposure or post-exposure prophylaxis, and prevents transmission. However, limitations in medication access and adherence, together with emerging drug resistance, remain major obstacles to ending the epidemic with ART alone. Moreover, the risks of disease progression and virus transmission rapidly re-emerge in the vast majority of individuals upon cessation of ART due to rebound from viral reservoirs that persist during treatment, necessitating lifelong ART administration. These key limitations compel refocused efforts towards understanding the determinants of HIV immune control, and the failure of such control, in order to inform the development of preventive and therapeutic vaccine strategies.

A central challenge to immune containment and vaccine development is that HIV is among the most diverse and rapidly evolving human pathogens ever encountered. For perspective, a snapshot of HIV sequence diversity within a single individual is comparable to the global diversity of influenza virus over an entire year. Perhaps unsurprisingly in light of such variation, vaccine strategies to date have failed to provide adequate protection from HIV infection, and the path forwards to an effective neutralizing antibody-based vaccine remains uncertain. Considering the formidable challenges associated with a preventive vaccine, it is perhaps even more difficult to imagine immune-based elimination of HIV infection, which, in addition to combating viral diversity, would also need to eradicate persistent viral reservoirs. Indeed, the only two examples of apparent HIV reservoir clearance have been mediated not by immunological or pharmacological interventions but rather by HIV-resistant haematopoietic stem cell transplantation.

CD8+ T cells in HIV control, cure and prevention

David R. Collins1,2, Gaurav D. Gaiha1,3 and Bruce D. Walker1,2,4✉

Abstract | HIV infection can be effectively treated by lifelong administration of combination antiretroviral therapy, but an effective vaccine will likely be required to end the HIV epidemic. Although the majority of current vaccine strategies focus on the induction of neutralizing antibodies, there is substantial evidence that cellular immunity mediated by CD8+ T cells can sustain long-term disease-free and transmission-free HIV control and may be harnessed to induce both therapeutic and preventive antiviral effects. In this Review, we discuss the increasing evidence derived from individuals who spontaneously control infection without antiretroviral therapy as well as preclinical immunization studies that provide a clear rationale for renewed efforts to develop a CD8+ T cell-based HIV vaccine in conjunction with B cell vaccine efforts. Further, we outline the remaining challenges in translating these findings into viable HIV prevention, treatment and cure strategies.

Spontaneous control of HIV infection

Whereas most infectious agents are effectively contained or eliminated by pathogen-specific immune responses, immune failure is a hallmark of HIV pathogenesis. In the early stages of HIV infection, the window of opportunity
to mount an effective immune response is limited by profound CD4+ T cell depletion in blood and tissues, mutational escape from early HIV-specific immune responses and immune exhaustion. Consequently, most immune responses ultimately fail to contain HIV infection, resulting in progression to AIDS.

By contrast, a small subset of infected individuals, known as HIV controllers, can suppress viral replication without antiretroviral medications. These unique persons have been broadly defined by sustained levels of viraemia below 2,000 RNA copies per ml of plasma, a level at which disease progression and sexual transmission are markedly reduced, and can be subdivided into elite controllers (often defined as those with a viral load <50 RNA copies per ml) and viraemic controllers (viral load 50–2,000 RNA copies per ml). An additional category has been termed long-term non-progressors, usually defined by the ability to maintain stable CD4+ T cell counts above 500 cells per μl for 10 or more years in the absence of ART. Despite considerable clinical, genetic and phenotypical heterogeneity among these groups, common features have emerged indicating that HIV-specific CD8+ T cells mediate durable HIV control, offering critical insight for the design and implementation of approaches to induce similar immunity on a broader scale for HIV prevention and cure.

**CD8+ T cells and HIV control: clues from host genetics.** One of the early links implicating CD8+ T cells in modulating HIV control came not from studies of immune function but rather from cohort studies of host HLA class I alleles, which present viral peptides on the surface of infected cells for recognition by HIV-specific CD8+ T cells. Unlike many features assessed in comparative studies between HIV controllers and chronic progressors, genetic polymorphisms are not influenced by HIV infection. Initial studies in long-term non-progressors identified a dramatic enrichment in HLA-B*57 (Ref. 5), and subsequent genome-wide association studies encompassing over 6,000 infected individuals across multiple large international cohorts have confirmed that the major genetic polymorphisms modulating HIV control reside almost entirely within the HLA-B and HLA-C loci on chromosome six. In particular, these studies identified strong associations between HIV control and polymorphic amino acids lining the HLA class I peptide-binding groove, which likely influence the viral peptides that are presented for CD8+ T cell recognition of virally infected cells. Variation at these amino acid positions define specific class I HLA alleles that previous studies have repeatedly shown to be associated with increased likelihood of control (for example, HLA-B*57, HLA-B*27, HLA-B*52 and HLA-B*14) and others with risk of progression (for example, HLA-B*07, HLA-B*08 and HLA-B*35).

However, genetic associations offer an incomplete explanation, as no HLA class I allele is necessary or sufficient for viral control and genetic associations defined by genome-wide association studies account for less than 25% of observed variance in host control. Thus, additional non-genetic factors must influence control in individuals without protective alleles and progression in individuals with protective alleles. The HLA associations indicate a critical role for CD8+ T cell-mediated immunity in spontaneous HIV control, an inference that is most strongly supported by CD8+ T cell depletion studies leading to loss of simian immunodeficiency virus (SIV) control in a non-human primate (NHP) model. The characteristics that define effective CD8+ T cell responses in infected persons are coming into ever greater focus, as are outlined below.

**CD8+ T cell function in spontaneous HIV control.** Nearly all individuals infected by HIV mount high-magnitude, virus-specific CD8+ T cell responses, including the vast majority who fail to control infection. Interferon-γ (IFNγ) secretion by CD8+ T cells exposed to HIV antigens, a widely used metric for identifying antigen-specific responses, does not correlate with HIV control. Additionally, the limitations of IFNγ assays are underscored by a study showing that HIV-specific CD8+ T cells that secrete IFNγ are rarely the same cells that kill infected target cells. The ability of antigen-stimulated cells to secrete combinations of cytokines and effecter molecules, termed polyfunctionality, is greater in controllers than progressors. Whether this enhanced functionality is a cause or consequence of lower viral load has been difficult to discern. Importantly, polyfunctionality is lowest in those with the lowest viral loads by ultrasensitive assays, the smallest viral reservoirs and the least culturable virus.

In contrast to assays measuring IFNγ secretion or polyfunctionality, assays measuring in vitro expansion of HIV-specific CD8+ T cells following stimulation with HIV antigens revealed properties of these cells that consistently distinguished controllers from progressors. HIV-specific CD8+ T cells from controllers, compared with those from progressors, have greater capacity to proliferate and develop cytolytic potential upon in vitro antigen stimulation; this is also the case for HIV-specific CD8+ T cells from elite controllers with undetectable responses following ex vivo antigen stimulation, as described above. By contrast, CD8+ T cells from progressors often exhibit strong ex vivo activation but fail to proliferate or acquire cytolytic capacity due to exhaustion and necroptotic cell death, and these deficiencies are not restored despite prolonged ART. Moreover, the ability of in vitro-expanded CD8+ T cell populations to suppress HIV replication also distinguishes elite controllers from progressors, further implicating the role of CD8+ T cell function in HIV control.

Given that the functional ability of CD8+ T cells to proliferate differentiates controllers from progressors, the lack of detectable IFNγ responses or CD8+ T cell polyfunctionality by direct ex vivo assays in some elite controllers likely reflects differential in vivo antigen exposure rather than being evidence for alternative CD8+ T cell-independent mechanisms of control. Thus, combined analysis of both ex vivo and expanded CD8+ T cell responses in the context of antigen exposure provides a more accurate perspective on which qualities of CD8+ T cells are associated with spontaneous viral control. In comparison with progressors, CD8+ T cell responses in HIV controllers show an overall...
increased ability to maintain long-term memory and effector potential, with the ability to kill infected cells before progeny virions are produced\(^{80-84}\), providing a clear rationale for exploiting these features for treatment, prevention and cure.

**CD8+ T cell specificity in spontaneous HIV control.** In addition to the importance of functional features of HIV-specific CD8+ T cells in viral control, evidence also points to the importance of the specificity of these responses. Antigenic specificity of CD8+ T cell responses is influenced by the unique binding properties of expressed HLA class I alleles, each of which presents a restricted set of HIV-derived peptides 8–11 amino acids in length\(^{52}\). Polymorphic positions within the HLA peptide-binding groove determine differential peptide binding constraints among HLA alleles, including anchor residue preference and orientation of peptide presentation to T cell receptors (TCRs). Despite the strong association between certain HLA alleles and disease outcome, specific alleles are neither necessary nor sufficient for durable HIV control. The majority of infected individuals with protective HLA alleles are progressors and a significant proportion of HIV controllers lack protective HLA alleles\(^{66}\).

Comprehensive assessment of CD8+ T cell specificity in viral control is complicated by HIV diversity, as assays are typically confined to recognition of a single reference strain of the virus and longitudinal samples spanning from acute to chronic phases of infection are limited. The magnitude and breadth of CD8+ T cell responses measured by IFNγ ELISPOT targeting the relatively conserved HIV structural protein Gag but not the highly variable surface protein Env are associated with a lower viral load and preserved CD4+ T cell counts irrespective of HLA allele and epitope sequence conservation\(^{53–55}\). Moreover, comparative analysis of sequence conservation of targeted epitopes does not distinguish HLA-B*57/HLA-B*27-negative controllers and progressors\(^{66}\).

Although sequence conservation is a reasonable proxy for mutational constraint, immune targeting of conserved regions may be insufficient as only a subset of conserved regions exhibits fitness defects when mutated\(^{85}\). Computational modelling of HIV sequence diversity has revealed that Gag regions targeted by controller responses have a lower mutational tolerance than those targeted by progressors, implying a structural basis for the observed mutational constraints\(^{54–60}\). The importance of CD8+ T cell epitope specificity is further supported by application of network theory to HIV protein structure. Network analysis of crystallographic HIV protein structures using a novel algorithm to quantify the contribution of non-covalent amino acid side chain interactions to overall protein structure revealed that proliferative CD8+ T cell responses in HIV controllers, irrespective of expressed HLA alleles, preferentially target HIV epitopes containing amino acids derived from highly interconnected (‘networked’) regions of viral protein structure\(^{86}\). Mutation of these highly networked amino acids was also highly disruptive to viral fitness, making them ideal targets for immune pressure.

Consistent with this, robust CD8+ T cell targeting of highly networked epitopes in controllers was associated with fewer mutations, especially at HLA anchor and TCR contact sites\(^{56}\). Perhaps most importantly, elite controllers lacking protective HLA alleles were also found to target epitopes containing highly networked amino acids that are not commonly targeted, suggesting that what has been considered a genetic barrier to control can be overcome.

TCR usage may also influence differences in CD8+ T cell-mediated HIV control. Viral control has been associated with more cross-reactive public TCR clonotypes\(^{62–64}\). HLA alleles associated with HIV control impart thymic selection for TCR repertoires with increased HIV recognition and variant cross-reactivity\(^{65}\). Although differential TCR usage alone is insufficient to explain spontaneous control or confer functional differences in CD8+ T cells\(^{66–68}\), cross-reactive TCRs have been shown to limit viral escape pathways in controllers, consistent with the findings that mutations within epitopes targeted predominantly by controllers are poorly tolerated due to impaired viral replication\(^{69,70}\) and that their recognition is maintained in controllers by cross-reactive TCRs and de novo responses\(^{71–73}\).

Taken together, the combination of functional CD8+ T cell responses and targeting of mutationally constrained epitopes offers a compelling mechanism to explain the observed genetic association between HIV control and expression of certain class I HLA alleles, and how individuals without protective HLA alleles can mediate effective immune control. The data indicate that specificity and function of CD8+ T cells are necessary for durable control, yet neither alone is sufficient,
as mutational escape from functional responses and dysfunctional responses against non-mutated epitopes represent parallel pathways of immune evasion [FIG. 2]. Induction of functional CD8+ T cell responses against highly networked epitopes restricted by common HLA alleles offers an opportunity for broad translation of these findings towards preventive and curative interventions.

**CD8+ T cell localization in spontaneous HIV control.** In order to control chronic infection, HIV-specific CD8+ T cells must be able to traffic to and function at anatomical sites where HIV persists, especially mucosal and gastrointestinal lymphoid tissues where infected CD4+ T cells are present in high concentrations. Consistent with this, increased frequencies of functional CD8+ T cells have been observed in the rectal mucosa of HIV controllers. HIV-infected follicular helper CD4+ T cells, which reside within B cell follicles in lymphoid tissue and direct humoral immune responses, constitute a significant fraction of the persistent viral reservoir during chronic infection. Importantly, CD8+ T cells are largely excluded from B cell follicles, representing a significant obstacle to CD8+ T cell-mediated clearance of infected follicular helper T cell reservoirs. Recent evidence demonstrates that a population of follicular CD8+ T cells that express the follicle-homing receptor CXCR5 can traffic to or reside in lymphoid tissues under certain circumstances. Viral control is associated with a higher proportion and functionality of follicular CD8+ T cells, but viral replication within follicles cannot persist even during elite control of HIV, underscoring the need to develop strategies that promote the trafficking and function of HIV-specific follicular CD8+ T cells. Tissue-resident memory T (T<sub>RM</sub>) cells represent an additional subset of CD8+ T cells that control viral infection in various tissue sites. Relative to peripheral blood CD8+ T cells, follicular CD8+ T cells and T<sub>RM</sub> cells in lymphoid tissues have a lower expression of perforin and granzymes, potentially due to tissue-specific microenvironmental regulation of T cell function as a means to limit tissue inflammation and damage. However, their precise functional profiles and roles in HIV control remain unclear. Suppression of viral replication by lymphoid CD8+ T cells from elite controllers has been observed in the absence of detectable cytolytic activity, suggesting that non-cytolytic CD8+ T cell functions may also be important for ongoing control of HIV in lymphoid tissues. Although, as with peripheral blood responses, ex vivo function of HIV-specific follicular CD8+ T cells and T<sub>RM</sub> cells in lymphoid tissue must be carefully interpreted in the context of recent local antigen exposure, epitope specificity and viral escape from recognition. Additional studies aimed at understanding the precise role and mechanisms of action of HIV-specific follicular CD8+ T cells and T<sub>RM</sub> cells in spontaneous control will be crucial to the development of strategies that harness these cells for the cure and prevention of HIV infection.

**Additional host and viral contributions to CD8+ T cell-mediated HIV control.** Factors that modulate the magnitude and duration of initial viraemia influence the ability of CD8+ T cells to control infection. Consistent with this, a role for natural killer cells in modulating HIV control through modest reductions in viral load has been well established by a large body of literature, including robust genetic associations. Viral factors have also been implicated in modulating HIV control; however, it is difficult to distinguish causal from consequential associations due to CD8+ T cell-associated mutations that impair viral replication capacity. Although it is clear that fully replication-competent viruses can be isolated from controllers, control has also been associated with viruses harbouring mutations that impair viral replication fitness. Studies of HIV transmission
events between controllers and progressors demonstrate that viral properties are neither necessary nor sufficient to mediate spontaneous HIV control\(^{103,104}\). Nonetheless, many transmitted viruses are pre-adapted to immune responses in their prior hosts, which may impair fitness and/or blunt the ability of CD8\(^+\) T cells to achieve spontaneous control in recipients expressing the same HLA allele\(^{105,106}\).

In contrast to cellular immunity, there is little evidence to support a role for humoral immunity in maintaining spontaneous HIV control. Antibody neutralization breadth, which requires affinity maturation against continually evolving Env antigenic variants, is associated with the duration of uncontrolled chronic viremia and is negatively correlated with spontaneous HIV control\(^{107–110}\). Moreover, broadly neutralizing monoclonal antibodies from HIV controllers rarely target autologous virus\(^{111}\). Studies of non-neutralizing antibody function in HIV controllers have not reported strong correlations with HIV control\(^{112,113}\). Although HIV-specific CD4\(^+\) T cells are required for effective adaptive immunity in HIV controllers and are affected by chronic infection, depletion of either CD4\(^+\) T cells or B cells in a NHP model of SIV control had no impact on viremia\(^{114,115}\), suggesting that neither cell type is directly involved in durable spontaneous HIV control.

**Spontaneous HIV control as a model for functional cure and vaccine development.** The demonstrated antiviral efficacy of CD8\(^+\) T cells in mediating long-term spontaneous control of infection in many individuals offers a clear rationale for harnessing cellular immunity to combat HIV; however, there remains a lack of consensus as to whether this represents a viable model for the development of preventive and therapeutic HIV vaccines. On the one hand, a small fraction (1.2% per year) of HIV controllers ultimately lose control, experiencing rebound viremia and CD4\(^+\) T cell depletion\(^{116}\). Furthermore, some controllers experience significant immune activation in the absence of detectable viremia due to persistent viral replication in tissue sites and expression of antigen from defective proviruses\(^{117–118}\), which can be reduced by ART\(^{119}\). On the other hand, a subset of elite controllers is able to maintain a stable state of undetectable viremia with no appreciable immune activation. Indeed, many elite controllers have extremely small replication-competent proviral reservoirs with low sequence diversity, suggesting functional reservoir suppression\(^{120–122}\). In some elite controllers, viral reservoirs are suppressed so profoundly that replication-competent virus cannot be detected or recovered\(^{120,124}\). Such cases of exceptional control, albeit rare, represent a natural model for immune-mediated functional cure approaches with the goal of durable remission, providing optimism that immune-mediated eradication of infection may be possible. Further research is warranted to determine whether individuals with the best reservoir containment represent an extreme on a continuum of spontaneous HIV control mediated by a common mechanism or whether additional mechanistic features distinguish this subset from other HIV controllers.

In addition to spontaneous HIV control, some individuals also control viremia after ART interruption\(^{125,126}\). These persons, termed post-treatment controllers (PTCs), have smaller HIV reservoirs and are often treated early after acute infection\(^{125–130}\). Interestingly, although protective HLA alleles have been associated with delayed viral rebound following ART interruption\(^{114}\), such alleles were not enriched in PTCs\(^{125}\), raising the possibility of distinct mechanisms of viral control in these individuals, which warrant further investigation. The translation of findings from both spontaneous controllers and PTCs to the broader population for the development of effective HIV immunization and cure strategies remains an important goal.

**Prospects for T cell-based HIV vaccines.** Vaccines seeking to elicit sterilizing humoral immunity have a strong historical precedent. However, the induction of broadly neutralizing antibodies (bNabs) against HIV has thus far proved challenging and will likely require serial immunization with a succession of variant Env immunogens to mobilize germine precursors and guide subsequent somatic hypermutation to achieve neutralization breadth\(^{132–134}\). Moreover, humoral immunity alone may be insufficient for protection against the transmission of cell-associated HIV\(^{135–137}\). By contrast, T cell-based vaccines enable targeting of viral antigens less permissive to viral escape than Env, do not require additional somatic hypermutation and may be able to augment humoral vaccine efforts. Although cellular immunity-based vaccines lack historical precedent from other infectious diseases and cells must become infected before CD8\(^+\) T cells can recognize and induce cytolysis, in vitro studies clearly show that HIV-specific CD8\(^+\) T cells can kill both activated and resting CD4\(^+\) T cells before progeny virus is produced\(^{138–140}\). This suggests the possibility that these responses may not only serve to control established infection but may also, in sufficient numbers, be able to clear the first infected cells rapidly before persistent reservoirs are established.

Human trials of T cell-based HIV vaccines to date have been disappointing. However, accumulating preclinical evidence demonstrates that emerging approaches for vaccine-induced CD8\(^+\) T cell-mediated immunity can provide sterilizing protection from retroviral infection and establish durable remission upon therapeutic vaccination (fig. 3). Moreover, clear evidence in some persons of the ability of HLA class I-restricted HIV-specific CD8\(^+\) T cells to provide durable control following infection represents an important means to potentially enhance the impact of vaccine-induced humoral immunity that is not fully protective. Although efforts to induce protective T cell responses in clinical trials have not been successful, they have revealed the need for the rational design and selection of immunogens and vectors for improved next-generation T cell-based immunogens (BOX 1).

**CD8\(^+\) T cells in prophylactic immunization: moving beyond STEP and HVTN505.** Much of the scepticism of CD8\(^+\) T cell-based vaccines for HIV prevention emerged from the disappointing results of the STEP
and HVTN505 trials\textsuperscript{4,10}. In STEP, a recombinant adenovirus serotype 5 (Ad5) vector encoding HIV Gag, Pol and Nef induced HIV-specific CD8\textsuperscript{+} T cell responses over time. In natural HIV infection (top panel), incomplete natural CD8\textsuperscript{+} T cell-mediated control of VL eventually leads to disease progression, marked by CD4\textsuperscript{+} T cell decline and uncontrolled VLs. Therapeutic vaccines that elicit effective vaccine-induced CD8\textsuperscript{+} T cell-mediated control of viraemia aim to protect against disease progression, lower VLs to below the transmission threshold and contain and reduce the residual HIV reservoir in the absence of antiretroviral therapy. Preventive CD8\textsuperscript{+} T cell-mediated vaccines aim to induce a rapid memory-recall, vaccine-induced CD8\textsuperscript{+} T cell response and clear the first infected cells to prevent reservoir establishment as well as to control and ideally clear residual infected cells.

![Diagram](https://example.com/diagram.png)

**Fig. 3 | HIV-specific CD8\textsuperscript{+} T cell responses in natural infection as well as following therapeutic and preventive vaccination.** Diagram representing relative HIV viral load (VL, green), relative total CD4\textsuperscript{+} T cell count (CD4, violet), and relative natural (nCD8) or vaccine-induced (vCD8) HIV-specific CD8\textsuperscript{+} T cell responses over time. In natural HIV infection (top panel), incomplete natural CD8\textsuperscript{+} T cell-mediated control of VL eventually leads to disease progression, marked by CD4\textsuperscript{+} T cell decline and uncontrolled VLs. Therapeutic vaccines that elicit effective vaccine-induced CD8\textsuperscript{+} T cell-mediated control of viraemia aim to protect against disease progression, lower VLs to below the transmission threshold and contain and reduce the residual HIV reservoir in the absence of antiretroviral therapy. Preventive CD8\textsuperscript{+} T cell-mediated vaccines aim to induce a rapid memory-recall, vaccine-induced CD8\textsuperscript{+} T cell response and clear the first infected cells to prevent reservoir establishment as well as to control and ideally clear residual infected cells.

and HVTN505 trials\textsuperscript{4,10}. In STEP, a recombinant adenovirus serotype 5 (Ad5) vector encoding HIV Gag, Pol and Nef induced HIV-specific CD8\textsuperscript{+} T cells and showed evidence of T cell selection pressure, although responses were of low magnitude, targeted few epitopes, and did not improve the prevention of HIV acquisition or control of subsequent HIV infection\textsuperscript{1}. Moreover, there was an increased risk of HIV acquisition in males lacking circumcision and with pre-existing anti-Ad5 antibodies. In HVTN505, these at-risk groups were excluded and a DNA prime/Ad5 boost was used to elicit antiviral T cell responses but, again, no protection from HIV infection was afforded\textsuperscript{10}. Consequently, major concerns about the viability of CD8\textsuperscript{+} T cell-based vaccines for HIV prevention have persisted.

Upon further examination of both trials, an important consideration may be the use of full-length HIV antigens. These immunogens largely give rise to CD8\textsuperscript{+} T cell responses specific for immunodominant viral epitopes that are similar to those targeted in natural infection, where the majority of individuals fail to control infection due to the emergence of viral variants that evade immune recognition. Consistent with this, viral sequence analysis from STEP trial participants revealed a ‘sieving’ effect, whereby vaccine-induced CD8\textsuperscript{+} T cell responses led to an enrichment of viral species with mutations at common HLA class I restricted T cell epitope sites\textsuperscript{10}. This also occurred in HVTN505, where CD8\textsuperscript{+} T cell responses were primarily directed against Env\textsuperscript{14}, which is among the most variable viral proteins and whose targeting by CD8\textsuperscript{+} T cells is associated with higher viral loads\textsuperscript{53}.

To induce immune responses that resemble those found in spontaneous HIV controllers, next-generation prophylactic T cell vaccines may benefit from the use of immunogens limited to mutationally intolerant regions within the HIV proteome. Preclinical studies of vaccine-induced CD8\textsuperscript{+} T cells targeting three epitopes presented by the protective Mamu-B*08\textsuperscript{+} allele were able to suppress viral loads to less than 1,000 RNA copies per ml in six of eight vaccinated Mamu-B*08\textsuperscript{+} rhesus macaques compared with only one of eight in a Mamu-B*08\textsuperscript{+} control arm\textsuperscript{42}, suggesting that narrowly targeted, vaccine-induced, virus-specific CD8\textsuperscript{+} T cell responses against specific epitopes can effectively control replication following SIV challenge to below the transmission threshold. Thus, new immunogens composed specifically of sequence-conserved regions of the viral proteome\textsuperscript{143,144}, regions with a relative association with viral control in large patient cohorts (HIVACAT T cell immunogen)\textsuperscript{145} or structurally constrained ‘networked’ epitopes that are mutationally intolerant\textsuperscript{141} may portend a higher probability of success in future studies. Moreover, directing T cell responses to a limited number of epitopes may reduce antigenic interference of vaccine components\textsuperscript{146} and limit the induction of strong T helper 1-biased CD4\textsuperscript{+} T cell responses, which have been shown to diminish vaccine efficacy in NHPs\textsuperscript{147}.

While immune focusing is likely to be crucial for prophylactic vaccine development, additional efforts have been dedicated to improving the breadth of T cell-based antigens in order to address possible vaccine–virus sequence mismatch between immunogen and circulating virus species. One promising strategy involves using a ‘mosaic’ of viral sequences, which are comprised of naturally occurring epitope sequences and common variants\textsuperscript{148,149}. Correlates of protection in NHPs include Env-specific antibody responses measured by ELISA and T cell responses measured by IFN\gamma\textsuperscript{19}. These antigens have been tested in human subjects and have demonstrated safety and tolerability as part of the APPROACH study\textsuperscript{150}, with clinical efficacy assessment already underway. As part of a complementary strategy, immunogen designs have also aimed to induce broad cellular immune responses solely against sequence-conserved regions of the virus (tHIVConsvX)\textsuperscript{151}, which integrates the concepts of protective specificity and breadth into a single immunogen and may afford even greater coverage of incoming viruses.
Beyond immunogen design, developments in vaccine delivery vectors have also yielded promising new directions for prophylactic T cell-based HIV vaccines. The reliance of many existing vaccine modalities on the induction of central memory CD8+ T cell responses has raised concern over whether immune recall will be sufficiently rapid to prevent the early phases of viral dissemination. Circumventing this issue are novel rhesus cytomegalovirus (RhCMV) vectors that are able to elicit persistently active effector memory CD8+ T cell responses in rhesus macaques due to the constitutive expression of SIV Gag antigen and CMV-induced memory inflation152,153. Remarkably, in numerous studies, these vectors have been able to consistently protect ~50% of animals from viral challenge154-157. Moreover, detailed evaluation at necropsy revealed that vaccinated animals lacked any detectable virus, indicating that continuous effector memory T cell responses were able to clear tissue-associated viral reservoirs and thus achieve sterilizing immunity158. This protection was also afforded by attenuated RhCMV, even when challenged 3 years post-vaccination156.

Follow-up studies of these animals have revealed that CD8+ T cell responses elicited by RhCMV vectors are exceptionally broad and restricted non-classically by HLA class II and the simian HLA-E orthologue Mamu-E159. Due to the limited polymorphism of HLA-E in humans (with only two known alleles)160, inducing such responses may be particularly advantageous for a prophylactic T cell-based HIV vaccine to broadly achieve both global coverage and sterilizing immunity. In conjunction with vector modification efforts to achieve these same kinds of responses in humans, additional studies to determine the immune parameters that differentiate protected from non-protected animals may also elucidate further improvements to this innovative vector system in order to achieve protection from infection in a larger percentage of those vaccinated. Nonetheless, an emerging spectrum of immunogens, vectors and delivery routes to improve the specificity, function and location of vaccine-induced CD8+ T cell responses highlights the promise of prophylactic T cell-based HIV vaccine approaches currently in development (TABLE 1), which are being actively pursued alongside humoral vaccines.

**CD8+ T cells in therapeutic immunization: translating HIV control to the population at-large.** In addition to their utility for HIV prevention, CD8+ T cells that can durably suppress viral replication as demonstrated by spontaneous HIV controllers represent a promising therapeutic modality towards the development of a functional HIV cure or remission. Reversal of immune exhaustion alone is unlikely to have durable clinical benefit as many of the epitopes targeted in chronic infection have mutated to escape recognition161. Indeed, although additional studies are warranted to test immunotherapies and other strategies being developed for immune oncology162, preclinical trials of immune checkpoint blockade during ART suppression did not significantly delay or reduce rebound viremia upon treatment interruption163-165. Likewise, attempts to mobilize the latent reservoir with pharmacological interventions, such as histone deacetylase inhibitors, will require CD8+ T cell elimination of these cells, where again issues of pre-existing immune escape are prominent166,167. Together, these considerations suggest that vaccine-mediated induction of new HIV-specific CD8+ T cell responses to mutational constraints and epitopes will be required.

Early therapeutic immunization studies using antigen-pulsed dendritic cells have shown modest augmentation of immune responses and viral load reduction168, whereas other therapeutic vaccine strategies aimed at eliciting CD8+ T cell responses have yielded promising preclinical results. Delivery of rAd26 and modified vaccinia Ankara expressing full-length SIV Gag–Pol–Env along with Toll-like receptor 7 agonist GS-986 to ART-suppressed, SIV-infected rhesus macaques led to the induction of broad de novo cellular immune responses, which were strongly correlated with a reduction in median set point viral load to 1,000 SIV RNA copies per ml and a delay in viral rebound following ART cessation169. The impressive cellular immune breadth achieved by animals with more effective viral suppression is consistent with observations in HIV-infected humans, where broad and functional cellular immune responses to non-escaped CD8+ T cell epitopes have been implicated in a reduction of the latent HIV-1 reservoir170.

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**Box 1 | Comparison of humoral and cellular HIV vaccine approaches**

**Humoral**

* Advantages:
  - Strong historical precedent for prevention of other infections
  - May provide sterilizing immunity via prevention of cellular infection by non-escaped HIV variants
  - Not restricted by HLA type
  - May also provide non-neutralizing benefits via vaccinal effect and/or antibody-recruited immune cells

* Disadvantages:
  - Can only target highly variable and heavily glycosylated HIV Env
  - Broadly neutralizing antibody (bNAb) induction requires somatic hypermutation and serial immunizations
  - Escape from bNabs often requires only single mutation with compensable fitness defects
  - May be ineffective against cell-associated viral transmission

**Cellular**

* Advantages:
  - Strong basis for protection derived from spontaneous HIV controllers
  - Ability to target broad, mutationally constrained epitopes across entire viral proteome via many HLAs
  - Do not require somatic hypermutation; therefore, standard prime–boost vaccine regimens may be possible
  - Mucosal responses may protect against cell-associated HIV transmission and clear infection before reservoir establishment
  - May facilitate long-term control of established infection

* Disadvantages:
  - Limited historical precedent for the prevention of other infections
  - Previous HIV trials unsuccessful
  - Requires cellular HIV infection; cannot neutralize cell-free virus
  - Distinct immunogen design may be required to avoid mutationally tolerant immunodominant epitopes
  - Epitope-focused approaches must contend with HLA diversity, perhaps via targeting constrained epitopes presented by major HLA supertypes
Similar to T cell-based preventive vaccines, such insights emphasize the need for therapeutic immunogens that are able to direct cellular immune responses to specific invariant sites within the HIV proteome. Initial efforts to accomplish this in HIV-infected individuals have primarily focused on sequence-conserved viral regions, with one of these immunogens (tHIVConsv) having been administered in a therapeutic vaccine setting to evaluate its safety and immunogenicity (BCN01)\(^{150}\). Vaccination with a chimpanzee adenovirus vector (ChAdOx) prime and a modified vaccinia Ankara boost of tHIVConsv led to a clear shift in CD8\(^+\) T cell immunodominance patterns towards conserved segments\(^{150}\). These data provide optimism that augmentation of cellular antiviral immunity and redirection towards protective epitopes is possible via therapeutic vaccination with focused HIV immunogens.

Because sequence conservation of targeted epitopes does not clearly differentiate HIV controllers from progressors\(^{151}\), alternative approaches to therapeutic immunogen design are warranted and being pursued. Higher order HIV sequence analysis of couplings between viral mutations within the conserved Gag protein using random matrix theory\(^{152}\) and quantitative fitness landscapes\(^{153}\) has revealed multidimensional constraints on viral evolution that predict regions of vulnerability. These mutationally intolerant amino acids are likely related to structural interdependencies that are important for viral fitness, and thus represent promising targets for CD8\(^+\) T cell pressure. Recent identification of structurally constrained epitopes restricted by common HLA alleles and strongly associated with spontaneous HIV control provides an additional avenue for re-directing CD8\(^+\) T cell responses, which may further increase the probability of inducing protective immunity\(^{154}\).

**Challenges facing prophylactic and therapeutic vaccine development.** Given the advantages and disadvantages of each approach, cellular and humoral HIV vaccine methods will likely be complementary in providing full protection from HIV infection (Box 1). However, eliciting each response will require different immunogens and optimization of distinct parameters, warranting separate but parallel development efforts\(^{155}\). In addition, the selection of vaccine immunogens, vectors and delivery routes will have important impacts on CD8\(^+\) T cell function, specificity and localization (Table 1). Optimal immunogen design may require an improved understanding of the effects of immunodominance and original antigenic sin on immunogenicity and protective efficacy. The selection of vectors and adjuvants to elicit the appropriate targeting of functional responses in the appropriate tissues against protective antigenic epitopes will require significant development and empirical testing, which should be derived by iterative, small-scale human immunogenicity studies before moving forwards to larger efficacy trials. The induction of CD4\(^+\) T cell help to assist the development of effective CD8\(^+\) T cell immunity will also be required, but activation of these CD4\(^+\) T cells will need to be carefully regulated given that this may cause increased susceptibility to HIV infection, diminished vaccine efficacy and more rapid disease progression\(^{147,172,173}\). The widespread availability and use of pre-exposure prophylactic ART poses unique challenges to the design of and recruitment for prophylactic vaccine efficacy trials, and the anticipated introduction of long-acting injectable ART may further complicate future studies\(^{174}\).

The development of therapeutic vaccines involves many unique challenges. Efficacy trials require monitored interruption of ART, including for individuals not receiving vaccination in controlled studies, which has raised important medical and ethical concerns\(^{175}\). Recent evidence that brief treatment interruption has no significant long-term impact on immune activation, drug resistance, reservoir size or composition indicates that such studies are safe\(^{176-178}\). Another challenge is that preventive vaccines may be ineffective in a therapeutic setting. For example, therapeutic immunization with the same RhCMV vector that afforded substantial protection and early clearance of SIV infection in a prophylactic setting was ineffective in reducing the SIV reservoir after therapeutic immunization despite early initiation of ART\(^{179}\). Pre-existing immune escape and dysfunctional immune responses in chronically infected individuals represent added challenges for therapeutic immunization approaches as immunization may preferentially expand these responses. Nonetheless, much of the preliminary clinical testing for cellular immune HIV vaccines will likely occur in a therapeutic setting owing to practical considerations in evaluating efficacy and managing risk, and where shifts in CD8\(^+\) T cell immunodominance to specific regions of the viral proteome have been previously demonstrated\(^{180,179}\). The development of optimal adjuvants, immunomodulatory agents and latency-reversing agents for coadministration with immunogens will also be important for the success of therapeutic HIV vaccines\(^{180}\). Intriguingly, the infusion

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**Table 1** | Vaccine strategies for inducing antiviral CD8\(^+\) T cells

| Vaccine component | CD8\(^+\) T cell quality | Vaccine strategy | Refs |
|------------------|-------------------------|----------------|------|
| Immunogen        | Specificity             | Broad          | Mosaic whole viral proteins | 156,158 |
|                  |                         |                | Whole viral proteins | 6,7,159,154 |
|                  |                         |                | Mosaic conserved elements | 151 |
|                  |                         |                | Conserved elements | 143,170 |
|                  |                         |                | Networked/beneficial epitopes | 61,145 |
| Vector           | Function                | Transient      | Nucleic acids | 183 |
|                  |                         |                | Dendritic cell priming | 169,150 |
|                  |                         |                | Poxvirus | 7 |
|                  |                         |                | Adenovirus | 6 |
|                  |                         |                | Cytomegalovirus | 154 |
| Delivery route   | Localization            | Systemic      | Intramuscular/subcutaneous | 6,7,150,154 |
|                  |                         |                | Intranodal | 164 |
|                  |                         |                | Intranasal | 185 |
|                  |                         |                | Oral/gastrointestinal | 186 |
|                  |                         |                | Intravaginal/prime-pull | 187,188 |

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of two potent bNAbs (38NC117 and 10-1074) early during SHIV infection led to sustained viral suppression that was lost upon subsequent delivery of a CD8β-depleting antibody, suggesting a possible vaccinal effect of these bNAbs that can improve the induction of antiviral CD8+ T cells. Although NHP models have provided clear benefits for preclinical vaccine testing, differences in viral diversity, duration of therapy, anti-vector immunity and pathogenesis may contribute towards the limited translation of efficacy from such models to humans.

Conclusions

Several remaining hurdles will need to be overcome to successfully harness T cells for prevention, treatment and cure. However, the above data provide ample support for renewed efforts to develop CD8+ T cell-based HIV vaccines in conjunction with ongoing B cell vaccine efforts. Persons with durable spontaneous control of HIV demonstrate that CD8+ T cells hold substantial promise to combat the HIV epidemic. Mechanistic studies in spontaneous HIV controllers highlight the function, specificity and localization of CD8+ T cells as important determinants of protection, and the ability to uncouple protection from specific HLA alleles represents a key step towards broad clinical translation. Preclinical and clinical vaccine trials have provided additional insights towards the development of improved T cell-based prevention and cure modalities. Further rational design of immunogens and careful selection of appropriate vectors to elicit functional effector-memory CD8+ T cell responses against protective epitopes in vulnerable viral regions represents a promising path forwards for preventive and therapeutic T cell-based HIV vaccines.

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