HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2024 September 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2023 September 01; 18(5): 257–263. doi:10.1097/COH.0000000000000812.

Features of Functional and Dysfunctional CD8+ T cells to Guide HIV Vaccine Development

Shaown Bhattacharyya[1,*], **Charles R. Crain**[1,*], **Benjamin Goldberg**[1,*], **Gaurav D. Gaiha**[1,2]

[1]Ragon Institute of Mass General, MIT and Harvard, Cambridge, MA 02139

[2]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA 02115

Abstract

Purpose of Review—CD8$^+$ T cell responses are a key component of the host immune response to HIV but vary significantly across individuals with distinct clinical outcomes. These differences help inform the qualitative features of HIV-specific CD8$^+$ T cells that we should aim to induce by vaccination.

Recent Findings—We review previous and more recent findings on the features of dysfunctional and functional CD8$^+$ T cell responses that develop in individuals with uncontrolled and controlled HIV infection, with particularly emphasis on proliferation, cytotoxic effector function, epitope specificity and responses in lymph nodes. We also discuss the implications of these findings for both prophylactic and therapeutic T cell vaccine development within the context of T cell vaccine trials.

Summary—The induction of HIV specific CD8$^+$ T cell responses is an important goal of ongoing vaccine efforts. Emerging data on the key features of CD8$^+$ T cell responses that distinguish individuals who spontaneously control from those with progressive disease continues to provide key guidance.

Keywords

HIV; CD8$^+$ T cells; T cell dysfunction; epitope specificity; vaccines

Introduction

CD8$^+$ T cells play a pivotal role in the adaptive immune response to HIV infection. However, progressive HIV disease induces a dysfunctional T cell phenotype due to chronic antigen exposure. In rare instances, CD8$^+$ T cells are able to durably control HIV infection due to a combination of unique functionality, specificity and anatomic location – findings which are being actively leveraged to generate new prophylactic and therapeutic T cell vaccines. In this review, we discuss recent advances in each of these key areas of HIV T cell immunology and vaccinology.

AUTHOR OF CORRESPONDENCE: Name: Gaurav D Gaiha, Address: Ragon Institute of Mass General, Harvard and MIT, 400 Technology Square, Room 862, Cambridge, MA 02139, Telephone number: (857)268-7016, ggaiha@mgh.harvard.edu.

*indicates equal contribution

Features of Dysfunctional CD8+ T cells During Chronic HIV Infection

Functional HIV-specific $CD8^+$ T cells have the capacity to proliferate, produce cytokines and release cytotoxic effector molecules, with proliferative capacity being the single strongest predictor of an effective response [1]. However, because of the persistent nature of HIV infection, the vast majority of HIV-specific $CD8^+$ T cell responses become dysfunctional due to chronic antigen exposure, resulting in a loss of cytokine secretion, cytolytic activity and proliferative capacity [2]. Dysfunctional $CD8^+$ T cells also demonstrate increased and sustained expression of inhibitory receptors. Among these is the canonical marker programmed cell death protein 1 (PD-1), which was classically shown to be upregulated on chronic antigen-exposed HIV-specific $CD8^+$ T cells [3,4] and strongly correlated with measures of disease progression, such as viral load and low $CD4^+$ T cell count. Subsequent studies have demonstrated that PD-1 functionally impairs T cells by upregulating the transcription factor BATF, which alone is sufficient to disrupt T cell proliferation and cytokine secretion [5].

In addition to PD-1, co-expression of other surface molecules, such as T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and T cell immunoglobulin and mucin-domain containing protein-3 (TIM-3), have been linked to more severe $CD8^+$ T cell dysfunction in both mouse models of chronic viral infection (i.e. lymphocytic choriomeningitis virus; LCMV) and HIV [6–9]. Compared to HIV-specific $CD8^+$ T cells expressing PD-1 alone, those expressing a multitude of inhibitory receptors were shown to have even more reduced proliferation and secretion of cytokines IL-2 and IFN-γ [7]. In addition, $CD8^+$ T cells expressing PD-1, TIGIT and TIM-3 have been shown to have altered glucose metabolism, which is part of an emerging set of observations regarding the critical role of glycolysis and metabolic plasticity in maintaining antiviral $CD8^+$ T cell activity [10–12]. In fact, recent work has shown that restoration of HIV-specific $CD8^+$ T cell function following blockade of PD-1 and TIGIT was enhanced by utilization of pro-glycolytic drugs in combination [13].

The loss of $CD8^+$ T cell proliferative capacity is key feature of the dysfunctional cellular immune phenotype that emerges during chronic HIV infection. Prior work has demonstrated that decreased proliferation of HIV-specific $CD8^+$ T cells was associated with increased necroptotic cell death and reversed by small molecule scavengers of mitochondrial reactive oxygen species [14]. This is consistent with numerous recent studies elucidating the contribution of altered mitochondrial function to HIV-specific $CD8^+$ T cell dysfunction [15,16]. Longitudinal studies of individuals who spontaneously lose immune control of HIV (e.g. previous controllers) have further demonstrated that HIV-specific $CD8^+$ T cells develop diminished proliferative capacity prior to increases in plasma viremia [17]. Importantly, this early stage of $CD8^+$ T cell dysfunction was not characterized by increased surface expression of inhibitory molecules (e.g. PD-1, TIGIT, TIM-3). However, RNA sequencing analysis did identify transcription factor KLF2 as a putative regulator of early HIV-specific $CD8^+$ T cell dysfunction , which has previously been shown to modulate $CD8^+$ T cell proliferation [18].

While substantial progress has been made towards understanding inhibitory molecule expression and metabolic features of T cell dysfunction in chronic HIV infection, studies of the epigenetic $CD8^+$ T cell landscape have revealed additional features. In mouse models and primary HIV infection, antigen-specific $CD8^+$ T cells undergo extensive changes in chromatin accessibility that are largely irreversible and therefore reflect a stable dysfunctional state [19,20]. This epigenetic "scarring" remains fixed even when the antigenic stimulus is removed, such as following anti-retroviral therapy (ART) [21], and greatly hinders functional memory $CD8^+$ T cell differentiation resulting in compromised recall capacity [22]. This is consistent with previous reports of demethylation of the PD-1 locus in HIV-specific $CD8^+$ T cells, which also remained following initiation of ART [23]. Another recent study showed that even during early HIV infection, individuals had substantial epigenetic changes in HIV-specific CD8+ T cells, similar to those seen in chronic HIV infection, which only partially shifted with ART initiation [24]. Collectively, these findings reveal a need for therapies that can counteract this extensive epigenetic remodeling, in addition to ones aimed at blocking inhibitory receptors, in order to effectively reverse T cell dysfunction.

Features of $CD8^+$ T cell Responses During Spontaneous HIV Control

While most untreated individuals infected with HIV experience uncontrolled viral replication and develop progressive HIV-specific $CD8^+$ T cell dysfunction, approximately 1 in 300 individuals control viral replication below the thresholds associated with transmission and disease progression [25]. These spontaneous controllers have provided insights into the features of $CD8^+$ T cell responses that are able to control viral replication and provide guidance on the types of T cell responses that we should aim to achieve through vaccination for prevention of progressive HIV disease or therapeutic HIV cure strategies.

Studies of HIV-specific $CD8^+$ T cells in spontaneous controllers have consistently revealed that they have highly advanced functional properties, which include the ability to secrete multiple cytokines, robustly proliferate in response to HIV antigen, upregulate cytotoxic effector molecules within lytic granules and suppress autologous viral replication [1,26–30]. These polyfunctional and proliferative characteristics are observed not only in controllers with robust effector HIV-specific $CD8^+$ T cells, but also in those with low to absent effector $CD8^+$ T cell responses of a largely central memory phenotype that rapidly expand upon exposure to *ex vivo* HIV antigen [31], putatively due to increased expression of transcription factor TCF-1 [32]. This potentially explains why some studies have suggested that spontaneous controllers lack functional and cytotoxic $CD8^+$ T cell responses, when it is likely the lack of recent *in vivo* antigen exposure in these extraordinarily virally suppressed individuals which leads to poorly detected circulating HIV-specific $CD8^+$ T cells in the absence of antigenic stimulation.

In addition to the functionality of HIV-specific $CD8^+$ T cells, epitope specificity is another key determinant of spontaneous HIV control [33]. This was initially suggested by the observation that specific HLA class I alleles (e.g. HLA-B*57), which present a set of HIV epitopes distinct from other HLA alleles, were consistently enriched in cohorts of spontaneous HIV controllers [34–36]. This influence of HLA class I, with some alleles

conferring protection and others conferring risk, was confirmed in several independent genome-wide association studies [37–41]. Moreover, these studies found that specific amino acid positions within the HLA-B peptide binding groove that facilitates epitope binding and presentation (amino acids 67, 70 and 97) were critical for defining protective (HLA-B*57, HLA-B*27, HLA-B*52, HLA-B*14) and risk HLA class I alleles [40,42]. A more recent GWAS, which analyzed a larger and more diverse multi-ancestry population, identified HLA-B residue 156 as also being independently implicated in HIV control, in addition to residues at positions 67 and 97 [43]. Collectively, these studies suggested that the distinct epitope presentation by HLA class I alleles for recognition by HIV-specific $CD8^+$ T cells is a major genetic determinant of spontaneous HIV control.

Given the immense range of intra-host viral sequence diversity, it was initially hypothesized that targeting of epitopes with a high degree of sequence conservation could explain spontaneous control. However, no such association was observed when comparing the sequence entropy of epitopes targeted by spontaneous controllers and individuals with progressive disease [44], which may be attributable to the lack of clear association between residue conservation and mutational constraint that has been observed for HIV and other model proteins [45–47]. In a subsequent study, application of network theory to protein structure led to the development of a new method – structure-based network analysis – which outperformed sequence conservation in its ability to identify mutation constrained residues [48]. The structure-based network analysis approach was then applied to the HIV proteome and identified both mutation-constrained residues and $CD8^+$ T cell epitopes (i.e. ‘highly networked’ epitopes), which were among the list of optimal A-list epitopes that have established immunogenicity [49]. Highly networked epitopes were preferentially targeted by the functional and proliferative $CD8^+$ T cell responses in spontaneous controllers, although this was not observed in HIV progressors. These highly networked epitopes are presented by a diverse array of HLA class I alleles, but have been demonstrated to preferentially stabilize protective HLA class I alleles [50] as identified by GWAS [40], providing a molecular rationale for the observed genetic associations between HLA alleles and HIV control. A recent study of a specific highly networked epitope (QW9, Gag $p24_{176–184}$) demonstrated that cross-reactive HIV-specific $CD8^+$ T cells of the wild-type epitope and a naturally arising variant (S3T) in spontaneous controllers were only present when the epitope was presented by a protective HLA class I allele (B*5701), but not a non-protective allele (B*5301) [51]. This suggests an additional potential advantage ascribed to protective HLA class I alleles that facilitates durable immune control. Importantly though, a distinct HIV-specific $CD8^+$ T cell response that recognized the variant QW9 S3T epitope was present in both HLA class I allele backgrounds, as has previously been described [52], indicating that the QW9 S3T networked epitope mutation does not lead to immune escape.

Recent studies of the latent viral reservoir in spontaneous controllers have revealed an enrichment of genomes present in transcriptionally repressed sites [53], with emerging evidence suggesting that this is the result of ongoing immune selection pressure [54]. These data suggest that HIV-specific immune responses may be able to achieve a possible cure of HIV infection, which has been suggested in a small number of distinct individuals [55,56]. Among the barriers to this level of immune-mediated HIV clearance however, are follicular $CD4^+$ T cells, which are a major cellular harbor of the HIV reservoir in both

HIV progressors and controllers [57–59]. While CXCR5$^+$ follicular CD8$^+$ T cells have been shown to be important for control of viral infections within lymph nodes for a number of pathogens, including SIV [60–63], the immune-privileged status of the lymph node follicle has raised questions as to the mechanism and extent that CD8$^+$ T cells can suppress HIV replication in lymphoid tissue [64,65].

Recent studies evaluating the lymph nodes of spontaneous controllers identified an enrichment of antiviral tissue-resident HIV-specific CD8$^+$ T cells in lymphoid tissues [66], which were suggested to control viral replication within the follicle without demonstrable cytolytic activity [67]. However, similar to studies of HIV controllers with low to absent effector CD8$^+$ T cell function [31], the minimal antigenic viral load in these study participants and the absence of *ex vivo* antigen stimulation, likely contributed to a primarily memory CD8$^+$ T cell phenotype and observed low *ex vivo* cytolytic activity. Consequently, a recent study demonstrated that when HIV-specific CD8$^+$ T cells derived from the lymph nodes of spontaneous controllers were stimulated with *ex vivo* antigen, they did in fact upregulate high levels of cytotoxic effector molecules perforin and granzyme B [68], indicating the clear capacity for cytolytic function. Moreover, cytotoxic CD8$^+$ T cells could be identified near foci of active viral replication in lymph nodes and expression of perforin and granzyme B was directly correlated to their proximity to HIV-infected cells. Collectively, these findings suggest that HIV-specific CD8$^+$ T cells are a key component of immune control at relevant tissue sites that harbor the latent reservoir such as lymph nodes and that cytotoxic effector function likely maintains control of ongoing viral replication.

Implications for HIV T cell Vaccine Development

Elucidating the features of successful and unsuccessful HIV-specific CD8$^+$ T cell responses during natural HIV infection provides guidance for the development of efficacious prophylactic and therapeutic HIV T cell vaccines. These findings will be critical to move beyond the STEP and Phambili trials [69,70], which despite inducing robust HIV-specific CD8+ T cell responses in >75% of participants after vaccination with an adenovirus serotype 5 vector encoding full-length HIV Gag/Pol/Nef subtype B, failed to show evidence of protection or reduction in viral setpoint. These disappointing results led to a shift in effort towards the induction of HIV-specific broadly neutralizing antibody responses (bNab), but this has also been marked by challenges despite some recent successes inducing bNab precursors in humans [71]. In addition, insights from the Antibody Mediated Prevention (AMP) trial demonstrate that particularly high serum levels of bNabs will likely be needed to protect against HIV acquisition [72]. Consequently, there has been a growing interest in approaches that utilize T cell vaccines to bolster antibody-based approaches. A recent study demonstrated that non-human primates vaccinated with heterologous viral vectors (HVVs) expressing SIVmac239 Gag (shown to induce durable and functional CD8$^+$ T cell responses) in concert with prototype native-like trimer BG505 SOSIP.664 (shown to produce high neutralizing antibody titers) resulted in the majority of dual vaccinated macaques being protected against infection at a lower nAb titer [73]. This suggested that vaccine-induced CD8$^+$ T cells may be able to synergize with nAbs to lower the threshold needed for protection, providing support for additional investigation into combined B and T cell vaccination approaches.

A central component to these T cell vaccine efforts, as revealed by work on spontaneous controllers, will be the development of immunogens that induce functional HIV-specific $CD8^+$ T cell responses that are focused on mutationally constrained sites. Vaccines that incorporate full-length proteins, such as the one used in the STEP trial, are likely to be suboptimal as evidenced by the observed sieve effect where breakthrough infections in vaccine recipients have significant genetic distance at mutable HLA-restricted epitope sites specifically within vaccine-encoded Gag, Pol and Nef [74]. Newer immune-focusing vaccine candidates include those that specifically incorporate multivalent mosaic antigens [75,76], highly sequence conserved viral regions [77–79] or epitopes that have been statistically associated with spontaneous controllers [80]. These T cell-based vaccines have been largely tested in therapeutic vaccine trials with mixed results. The BCN02 study utilized a conserved HIV T cell immunogen [77] delivered by Modified Vaccinia Ankara (MVA) virus vaccination, followed by three doses of latency reversal agent Romidepsin [81,82] and then a second MVA boost, before ART cessation [83]. Interestingly, ~23% of individuals, who had previously been vaccinated in the BCN01 study [84] prior to enrollment in BCN02, showed sustained suppression of plasma viremia up to 32 weeks. In comparison, the AELIX002 study utilized the HIVACAT T cell immunogen (HTI) delivered by a combination of DNA, MVA and ChAdOx.1 vector [85] to perform a randomized, placebo-controlled study in early ART treated individuals to evaluate the safety, immunogenicity and therapeutic effect of this vaccine regimen on viral rebound [86]. While there was no significant difference in the percentage of participants in each study group that remained off ART, there was an apparent difference in placebo and HTI-vaccine recipients who lacked protective HLA class I alleles (although some of the alleles classified as protective, e.g. B*15, have not previously been delineated as such by GWAS) [37,40,43]. Nonetheless, this study did demonstrate significant correlations between $CD8^+$ $GzmB^+$ HTI-specific $CD8^+$ T cell responses and both time off ART and viral load at the end of the acute treatment interruption, further illustrating the importance of cytotoxic $CD8^+$ T cell responses, as was observed with spontaneous controllers.

Vaccine studies involving highly networked epitope immunogens remain in development, although an *ex vivo* DC-based priming model demonstrated a relative enhancement of $CD8^+$ T cell response induction in comparison to both full-length Gag and conserved antigens [87]. Additionally, while highly networked epitopes are derived from the optimal A-list [49], they have quite limited overlap with other epitope-based immunogens [88], indicating that they will target distinct regions of the viral proteome. The key next step is determining the optimal vaccine modality to elicit highly functional and *de novo* $CD8^+$ T cell responses, particularly in cure settings given concerns regarding the irreversible dysfunctional features of pre-existing responses [21]. A number of recent studies using neoantigen epitope-based vaccines in novel formats, such as mRNA [89,90] and heterologous simian adenovirus/self-amplifying RNA immunization [91] provide reason for optimism. Inducing tissue-resident HIV-specific $CD8^+$ T cell memory responses at relevant mucosal sites will also be another important part of future vaccine efforts [92].

Conclusion

Studies of HIV-specific $CD8^+$ T cells in progressive and controlled HIV infection have provided critical insight into their function and dysfunction, specificity and features in both blood and lymph nodes that modulate immune-mediated outcomes to HIV infection. With these findings in hand, we now collectively move forward to realize the potential and power of $CD8^+$ T cells to limit HIV acquisition and curtail pathogenesis through continued T cell vaccine development.

Financial Support

This work was supported by National Institutes of Health grants DP2AI154421, R01AI176533, DP1DA058476 and UM1AI144462. Additional support was provided by the Bill and Melinda Gates Foundation, Burroughs Wellcome Career Award for Medical Scientists, Gilead HIV Research Scholars Program and Howard Goodman Fellowship.

Conflicts of Interest

G.D. Gaiha reports research funding from Merck and is listed as a co-inventor on a patent application for networked HIV immunogen design.

References

1. Ndhlovu ZM, Chibnik LB, Proudfoot J, Vine S, McMullen A, Cesa K, Porichis F, Brad Jones R, Alvino DM, Hart MG, et al. : High-dimensional immunomonitoring models of HIV-1–specific CD8 T-cell responses accurately identify subjects achieving spontaneous viral control. Blood 2013, 121:801–811. [PubMed: 23233659]
2. Fenwick C, Joo V, Jacquier P, Noto A, Banga R, Perreau M, Pantaleo G: T-cell exhaustion in HIV infection. Immunol Rev 2019, 292:149–163. [PubMed: 31883174]
3. Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, Mackey EW, Miller JD, Leslie AJ, DePierres C, et al. : PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 2006, 443:350–354. [PubMed: 16921384]
4. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, Bessette B, Boulassel M-R, Delwart E, Sepulveda H, Balderas RS, et al. : Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. Nat Med 2006, 12:1198–1202. [PubMed: 16917489]
5. Quigley M, Pereyra F, Nilsson B, Porichis F, Fonseca C, Eichbaum Q, Julg B, Jesneck JL, Brosnahan K, Imam S, et al. : Transcriptional analysis of HIV-specific CD8+ T cells shows that PD-1 inhibits T cell function by upregulating BATF. Nat Med 2010, 16:1147–1151. [PubMed: 20890291]
6. Jin H-T, Anderson AC, Tan WG, West EE, Ha S-J, Araki K, Freeman GJ, Kuchroo VK, Ahmed R: Cooperation of Tim-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A 2010, 107:14733–14738. [PubMed: 20679213]
7. Zhang Z-N, Zhu M-L, Chen Y-H, Fu Y-J, Zhang T-W, Jiang Y-J, Chu Z-X, Shang H: Elevation of Tim-3 and PD-1 expression on T cells appears early in HIV infection, and differential Tim-3 and PD-1 expression patterns can be induced by common γ -chain cytokines. Biomed Res Int 2015, 2015:916936. [PubMed: 25685816]
8. Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, Park S, Javinal V, Chiu H, Irving B, et al. : The Immunoreceptor TIGIT Regulates Antitumor and Antiviral CD8+ T Cell Effector Function. Cancer Cell 2014, 26:923–937. [PubMed: 25465800]
9. Chew GM, Fujita T, Webb GM, Burwitz BJ, Wu HL, Reed JS, Hammond KB, Clayton KL, Ishii N, Abdel-Mohsen M, et al. : TIGIT Marks Exhausted T Cells, Correlates with Disease Progression, and Serves as a Target for Immune Restoration in HIV and SIV Infection. PLoS Pathog 2016, 12:e1005349. [PubMed: 26741490]
10. Angin M, Volant S, Passaes C, Lecuroux C, Monceaux V, Dillies M-A, Valle-Casuso JC, Pancino G, Vaslin B, Le Grand R, et al. : Metabolic plasticity of HIV-specific CD8+ T cells is associated

with enhanced antiviral potential and natural control of HIV-1 infection. Nat Metab 2019, 1:704–716. [PubMed: 32694646]

11. Rahman AN-U, Liu J, Mujib S, Kidane S, Ali A, Szep S, Han C, Bonner P, Parsons M, Benko E, et al. : Elevated glycolysis imparts functional ability to CD8+ T cells in HIV infection. Life Sci Alliance 2021, 4.
12. Trautmann L, Mbitikon-Kobo F-M, Goulet J-P, Peretz Y, Shi Y, Van Grevenynghe J, Procopio FA, Boulassel MR, Routy J-P, Chomont N, et al. : Profound metabolic, functional, and cytolytic differences characterize HIV-specific CD8 T cells in primary and chronic HIV infection. Blood 2012, 120:3466–3477. [PubMed: 22955926]
13. Calvet-Mirabent M, Sánchez-Cerrillo I, Martín-Cófreces N, Martínez-Fleta P, de la Fuente H, Tsukalov I, Delgado-Arévalo C, Calzada MJ, de Los Santos I, Sanz J, et al. : Antiretroviral therapy duration and immunometabolic state determine efficacy of ex vivo dendritic cell-based treatment restoring functional HIV-specific CD8+ T cells in people living with HIV. EBioMedicine 2022, 81:104090. [PubMed: 35665682]
14. Gaiha GD, McKim KJ, Woods M, Pertel T, Rohrbach J, Barteneva N, Chin CR, Liu D, Soghoian DZ, Cesa K, et al. : Dysfunctional HIV-specific CD8+ T cell proliferation is associated with increased caspase-8 activity and mediated by necroptosis. Immunity 2014, 41:1001–1012. [PubMed: 25526311]
15. Deguit CDT, Hough M, Hoh R, Krone M, Pilcher CD, Martin JN, Deeks SG, McCune JM, Hunt PW, Rutishauser RL: Some Aspects of CD8+ T-Cell Exhaustion Are Associated With Altered T-Cell Mitochondrial Features and ROS Content in HIV Infection. J Acquir Immune Defic Syndr 2019, 82:211–219. [PubMed: 31513075]
16. Alrubayyi A, Moreno-Cubero E, Hameiri-Bowen D, Matthews R, Rowland-Jones S, Schurich A, Peppa D: Functional Restoration of Exhausted CD8 T Cells in Chronic HIV-1 Infection by Targeting Mitochondrial Dysfunction. Front Immunol 2022, 13:908697. [PubMed: 35865519]
17. Collins DR, Urbach JM, Racenet ZJ, Arshad U, Power KA, Newman RM, Mylvaganam GH, Ly NL, Lian X, Rull A, et al. : Functional impairment of HIV-specific CD8+ T cells precedes aborted spontaneous control of viremia. Immunity 2021, 54:2372–2384.e7. [PubMed: 34496223]
18. Buckley AF, Kuo CT, Leiden JM: Transcription factor LKLF is sufficient to program T cell quiescence via a c-Myc–dependent pathway. Nat Immunol 2001, 2:698–704. [PubMed: 11477405]
19. Sen DR, Kaminski J, Barnitz RA, Kurachi M, Gerdemann U, Yates KB, Tsao H-W, Godec J, LaFleur MW, Brown FD, et al. : The epigenetic landscape of T cell exhaustion. Science 2016, 354:1165–1169. [PubMed: 27789799]
20. Pauken KE, Sammons MA, Odorizzi PM, Manne S, Godec J, Khan O, Drake AM, Chen Z, Sen DR, Kurachi M, et al. : Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. Science 2016, 354:1160–1165. [PubMed: 27789795]

21**. Yates KB, Tonnerre P, Martin GE, Gerdemann U, Al Abosy R, Comstock DE, Weiss SA, Wolski D, Tully DC, Chung RT, et al. : Epigenetic scars of CD8+ T cell exhaustion persist after cure of chronic infection in humans. Nat Immunol 2021, 22:1020–1029. [PubMed: 34312547] This study provides evidence of an epigenetic state of exhaustion in HIV-specific $CD8^+$ T cells that is largely irreversible even after fully suppressive treatment, which is an important consideration for ongoing HIV cure efforts.

22. Abdel-Hakeem MS, Manne S, Beltra J-C, Stelekati E, Chen Z, Nzingha K, Ali M-A, Johnson JL, Giles JR, Mathew D, et al. : Epigenetic scarring of exhausted T cells hinders memory differentiation upon eliminating chronic antigenic stimulation. Nat Immunol 2021, 22:1008–1019. [PubMed: 34312545]
23. Youngblood B, Noto A, Porichis F, Akondy RS, Ndhlovu ZM, Austin JW, Bordi R, Procopio FA, Miura T, Allen TM, et al. : Cutting edge: Prolonged exposure to HIV reinforces a poised epigenetic program for PD-1 expression in virus-specific CD8 T cells. J Immunol 2013, 191:540–544. [PubMed: 23772031]
24. Martin GE, Sen DR, Pace M, Robinson N, Meyerowitz J, Adland E, Thornhill JP, Jones M, Ogbe A, Parolini L, et al. : Epigenetic Features of HIV-Induced T-Cell Exhaustion Persist Despite Early Antiretroviral Therapy. Front Immunol 2021, 12:647688. [PubMed: 34149690]

25. Yang OO, Cumberland WG, Escobar R, Liao D, Chew KW: Demographics and natural history of HIV-1-infected spontaneous controllers of viremia. AIDS 2017, 31:1091–1098. [PubMed: 28301422]

26. Migueles SA, Laborico AC, Shupert WL, Sabbaghian MS, Rabin R, Hallahan CW, Van Baarle D, Kostense S, Miedema F, McLaughlin M, et al. : HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. Nat Immunol 2002, 3:1061–1068. [PubMed: 12368910]

27. Migueles SA, Osborne CM, Royce C, Compton AA, Joshi RP, Weeks KA, Rood JE, Berkley AM, Sacha JB, Cogliano-Shutta NA, et al. : Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. Immunity 2008, 29:1009–1021. [PubMed: 19062316]

28. Hersperger AR, Pereyra F, Nason M, Demers K, Sheth P, Shin LY, Kovacs CM, Rodriguez B, Sieg SF, Teixeira-Johnson L, et al. : Perforin Expression Directly Ex Vivo by HIV-Specific CD8+ T-Cells Is a Correlate of HIV Elite Control. PLoS Pathog 2010, 6:e1000917. [PubMed: 20523897]

29. Ndhlovu ZM, Stampouloglou E, Cesa K, Mavrothalassitis O, Alvino DM, Li JZ, Wilton S, Karel D, Piechocka-Trocha A, Chen H, et al. : The Breadth of Expandable Memory CD8+ T Cells Inversely Correlates with Residual Viral Loads in HIV Elite Controllers. J Virol 2015, 89:10735–10747. [PubMed: 26269189]

30. Betts MR, Nason MC, West SM, De Rosa SC, Migueles SA, Abraham J, Lederman MM, Benito JM, Goepfert PA, Connors M, et al. : HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. Blood 2006, 107:4781–4789. [PubMed: 16467198]

31. Ndhlovu ZM, Proudfoot J, Cesa K, Alvino DM, McMullen A, Vine S, Stampouloglou E, Piechocka-Trocha A, Walker BD, Pereyra F: Elite controllers with low to absent effector CD8+ T cell responses maintain highly functional, broadly directed central memory responses. J Virol 2012, 86:6959–6969. [PubMed: 22514340]

32. Rutishauser RL, Deguit CDT, Hiatt J, Blaeschke F, Roth TL, Wang L, Raymond KA, Starke CE, Mudd JC, Chen W, et al. : TCF-1 regulates HIV-specific CD8+ T cell expansion capacity. JCI Insight 2021, 6.

33. Kaseke C, Tano-Menka R, Senjobe F, Gaiha GD: The Emerging Role for CTL Epitope Specificity in HIV Cure Efforts. J Infect Dis 2021, 223:32–37. [PubMed: 33586771]

34. Kaslow RA, Carrington M, Apple R, Park L, Muñoz A, Saah AJ, Goedert JJ, Winkler C, O'Brien SJ, Rinaldo C, et al. : Influence of combinations of human major histocompatibility complex genes on the course of HIV–1 infection. Nat Med 1996, 2:405–411. [PubMed: 8597949]

35. Goulder PJ, Bunce M, Krausa P, McIntyre K, Crowley S, Morgan B, Edwards A, Giangrande P, Phillips RE, McMichael AJ: Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. AIDS Res Hum Retroviruses 1996, 12:1691–1698. [PubMed: 8959245]

36. Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, Hallahan CW, Selig SM, Schwartz D, Sullivan J, et al. : HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. Proc Natl Acad Sci U S A 2000, 97:2709–2714. [PubMed: 10694578]

37. Fellay J, Shianna KV, Ge D, Colombo S, Ledergerber B, Weale M, Zhang K, Gumbs C, Castagna A, Cossarizza A, et al. : A whole-genome association study of major determinants for host control of HIV-1. Science 2007, 317:944–947. [PubMed: 17641165]

38. Dalmasso C, Carpentier W, Meyer L, Rouzioux C, Goujard C, Chaix M-L, Lambotte O, Avettand-Fenoel V, Le Clerc S, de Senneville LD, et al. : Distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: the ANRS Genome Wide Association 01 study. PLoS One 2008, 3:e3907. [PubMed: 19107206]

39. Limou S, Le Clerc S, Coulonges C, Carpentier W, Dina C, Delaneau O, Labib T, Taing L, Sladek R, Deveau C, et al. : Genomewide association study of an AIDS-nonprogression cohort emphasizes the role played by HLA genes (ANRS Genomewide Association Study 02). J Infect Dis 2009, 199:419–426. [PubMed: 19115949]

40. International HIV Controllers Study, Pereyra F, Jia X, McLaren PJ, Telenti A, de Bakker PIW, Walker BD, Ripke S, Brumme CJ, Pulit SL, et al. : The major genetic determinants of

HIV-1 control affect HLA class I peptide presentation. Science 2010, 330:1551–1557. [PubMed: 21051598]

41. McLaren PJ, Coulonges C, Bartha I, Lenz TL, Deutsch AJ, Bashirova A, Buchbinder S, Carrington MN, Cossarizza A, Dalmau J, et al. : Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 virus load. Proc Natl Acad Sci U S A 2015, 112:14658–14663. [PubMed: 26553974]
42. Tano-Menka R, Singh N, Muzhingi I, Li X, Mandanas M, Kaseke C, Zhang A, Ogunshola F, Vecchiarello L, Piechocka-Trocha A, et al.: Residues in HLA class I that account for variation of the HIV host response distinctly modulate interactions with TCR and KIRs. 2022, doi:10.21203/rs.3.rs-2105002/v1.
43*. Luo Y, Kanai M, Choi W, Li X, Sakaue S, Yamamoto K, Ogawa K, Gutierrez-Arcelus M, Gregersen PK, Stuart PE, et al. : A high-resolution HLA reference panel capturing global population diversity enables multi-ancestry fine-mapping in HIV host response. Nat Genet 2021, 53:1504–1516. [PubMed: 34611364] The study suggests, in a large multi-ancestry population, that the conformation of peptides within the HLA class I binding groove is the major genetic determinant of HIV control.
44. Migueles SA, Mendoza D, Zimmerman MG, Martins KM, Toulmin SA, Kelly EP, Peterson BA, Johnson SA, Galson E, Poropatich KO, et al. : CD8(+) T-cell Cytotoxic Capacity Associated with Human Immunodeficiency Virus-1 Control Can Be Mediated through Various Epitopes and Human Leukocyte Antigen Types. EBioMedicine 2015, 2:46–58. [PubMed: 26137533]
45. Rolland M, Manocheewa S, Swain JV, Lanxon-Cookson EC, Kim M, Westfall DH, Larsen BB, Gilbert PB, Mullins JI: HIV-1 conserved-element vaccines: relationship between sequence conservation and replicative capacity. J Virol 2013, 87:5461–5467. [PubMed: 23468488]
46. Manocheewa S, Swain JV, Lanxon-Cookson E, Rolland M, Mullins JI: Fitness costs of mutations at the HIV-1 capsid hexamerization interface. PLoS One 2013, 8:e66065. [PubMed: 23785468]
47. Mishra P, Flynn JM, Starr TN, Bolon DNA: Systematic Mutant Analyses Elucidate General and Client-Specific Aspects of Hsp90 Function. Cell Rep 2016, 15:588–598. [PubMed: 27068472]
48. Gaiha GD, Rossin EJ, Urbach J, Landeros C, Collins DR, Nwonu C, Muzhingi I, Anahtar MN, Waring OM, Piechocka-Trocha A, et al. : Structural topology defines protective CD8+ T cell epitopes in the HIV proteome. Science 2019, 364:480–484. [PubMed: 31048489]
49. Llano A, Cedeño S, Silva-Arrieta S, Brander C, Yusim K, Korber BTM, Brander C, Barouch D, de Boer R, Haynes BF, et al.: The 2019 Optimal HIV CTL epitopes update: Growing diversity in epitope length and HLA restriction. In HIV Molecular Immunology 2018. . Los Alamos National Laboratory, Theoretical Biology and Biophysics Los …; 2019:3–27.
50. Kaseke C, Park RJ, Singh NK, Koundakjian D, Bashirova A, Garcia Beltran WF, Takou Mbah OC, Ma J, Senjobe F, Urbach JM, et al. : HLA class-I-peptide stability mediates CD8+ T cell immunodominance hierarchies and facilitates HLA-associated immune control of HIV. Cell Rep 2021, 36:109378. [PubMed: 34260940]
51. Li X, Singh NK, Collins DR, Ng R, Zhang A, Lamothe-Molina PA, Shahinian P, Xu S, Tan K, Piechocka-Trocha A, et al. : Molecular basis of differential HLA class I-restricted T cell recognition of a highly networked HIV peptide. Nat Commun 2023, 14:2929. [PubMed: 37217466]
52. Buseyne F, Chaix ML, Rouzioux C, Blanche S, Rivière Y: Patient-specific cytotoxic T-lymphocyte cross-recognition of naturally occurring variants of a human immunodeficiency virus type 1 (HIV-1) p24gag epitope by HIV-1-infected children. J Virol 2001, 75:4941–4946. [PubMed: 11312369]
53. Jiang C, Lian X, Gao C, Sun X, Einkauf KB, Chevalier JM, Chen SMY, Hua S, Rhee B, Chang K, et al. : Distinct viral reservoirs in individuals with spontaneous control of HIV-1. Nature 2020, 585:261–267. [PubMed: 32848246]
54. Lian X, Gao C, Sun X, Jiang C, Einkauf KB, Seiger KW, Chevalier JM, Yuki Y, Martin M, Hoh R, et al. : Signatures of immune selection in intact and defective proviruses distinguish HIV-1 elite controllers. Sci Transl Med 2021, 13:eabl4097. [PubMed: 34910552]
55. Turk G, Seiger K, Lian X, Sun W, Parsons EM, Gao C, Rassadkina Y, Polo ML, Czernikier A, Ghiglione Y, et al. : A possible sterilizing cure of HIV-1 infection without stem cell transplantation. Ann Intern Med 2022, 175:95–100. [PubMed: 34781719]

56. Mendoza D, Johnson SA, Peterson BA, Natarajan V, Salgado M, Dewar RL, Burbelo PD, Doria-Rose NA, Graf EH, Greenwald JH, et al. : Comprehensive analysis of unique cases with extraordinary control over HIV replication. Blood 2012, 119:4645–4655. [PubMed: 22490332]

57. Perreau M, Savoye A-L, De Crignis E, Corpataux J-M, Cubas R, Haddad EK, De Leval L, Graziosi C, Pantaleo G: Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. J Exp Med 2013, 210:143–156. [PubMed: 23254284]

58. Pantaleo G, Menzo S, Vaccarezza M, Graziosi C, Cohen OJ, Demarest JF, Montefiori D, Orenstein JM, Fox C, Schrager LK: Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. N Engl J Med 1995, 332:209–216. [PubMed: 7808486]

59. Boritz EA, Darko S, Swaszek L, Wolf G, Wells D, Wu X, Henry AR, Laboune F, Hu J, Ambrozak D, et al. : Multiple Origins of Virus Persistence during Natural Control of HIV Infection. Cell 2016, 166:1004–1015. [PubMed: 27453467]

60. Leong YA, Chen Y, Ong HS, Wu D, Man K, Deleage C, Minnich M, Meckiff BJ, Wei Y, Hou Z, et al. : CXCR5+ follicular cytotoxic T cells control viral infection in B cell follicles. Nat Immunol 2016, 17:1187–1196. [PubMed: 27487330]

61. He R, Hou S, Liu C, Zhang A, Bai Q, Han M, Yang Y, Wei G, Shen T, Yang X, et al. : Follicular CXCR5-expressing CD8+ T cells curtail chronic viral infection. Nature 2016, 537:412–416. [PubMed: 27501245]

62. Mylvaganam GH, Rios D, Abdelaal HM, Iyer S, Tharp G, Mavigner M, Hicks S, Chahroudi A, Ahmed R, Bosinger SE, et al. : Dynamics of SIV-specific CXCR5+ CD8 T cells during chronic SIV infection. Proc Natl Acad Sci U S A 2017, 114:1976–1981. [PubMed: 28159893]

63. Li S, Folkvord JM, Rakasz EG, Abdelaal HM, Wagstaff RK, Kovacs KJ, Kim HO, Sawahata R, MaWhinney S, Masopust D, et al. : Simian Immunodeficiency Virus-Producing Cells in Follicles Are Partially Suppressed by CD8+ Cells In Vivo. J Virol 2016, 90:11168–11180. [PubMed: 27707919]

64. Bronnimann MP, Skinner PJ, Connick E: The B-Cell Follicle in HIV Infection: Barrier to a Cure. Front Immunol 2018, 9:20. [PubMed: 29422894]

65. Reuter MA, Del Rio Estrada PM, Buggert M, Petrovas C, Ferrando-Martinez S, Nguyen S, Sada Japp A, Ablanedo-Terrazas Y, Rivero-Arrieta A, Kuri-Cervantes L, et al. : HIV-Specific CD8+ T Cells Exhibit Reduced and Differentially Regulated Cytolytic Activity in Lymphoid Tissue. Cell Rep 2017, 21:3458–3470. [PubMed: 29262326]

66. Buggert M, Nguyen S, Salgado-Montes de Oca G, Bengsch B, Darko S, Ransier A, Roberts ER, Del Alcazar D, Brody IB, Vella LA, et al. : Identification and characterization of HIV-specific resident memory CD8+ T cells in human lymphoid tissue. Sci Immunol 2018, 3.

67. Nguyen S, Deleage C, Darko S, Ransier A, Truong DP, Agarwal D, Japp AS, Wu VH, Kuri-Cervantes L, Abdel-Mohsen M, et al. : Elite control of HIV is associated with distinct functional and transcriptional signatures in lymphoid tissue CD8+ T cells. Sci Transl Med 2019, 11.

68**. Collins DR, Hitschfel J, Urbach JM, Mylvaganam GH, Ly NL, Arshad U, Racenet ZJ, Yanez AG, Diefenbach TJ, Walker BD: Cytolytic CD8+ T cells infiltrate germinal centers to limit ongoing HIV replication in spontaneous controller lymph nodes. Sci Immunol 2023, 8:eade5872. [PubMed: 37205767] This study demonstrates that HIV-specific $CD8^+$ T cell in spontaneous controllers that are derived from lymph nodes have elevated expression of cytotoxic effector molecules which correlates with proximity to HIV-infected cells.

69. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, Gilbert PB, Lama JR, Marmor M, Del Rio C, et al. : Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet 2008, 372:1881–1893. [PubMed: 19012954]

70. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker L-G, Nchabeleng M, Mlisana K, Metch B, De Bruyn G, Latka MH, et al. : Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis 2011, 11:507–515. [PubMed: 21570355]

71. Leggat DJ, Cohen KW, Willis JR, Fulp WJ, deCamp AC, Kalyuzhniy O, Cottrell CA, Menis S, Finak G, Ballweber-Fleming L, et al. : Vaccination induces HIV broadly neutralizing antibody precursors in humans. Science 2022, 378:eadd6502. [PubMed: 36454825]

72. Corey L, Gilbert PB, Juraska M, Montefiori DC, Morris L, Karuna ST, Edupuganti S, Mgodi NM, deCamp AC, Rudnicki E, et al. : Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition. N Engl J Med 2021, 384:1003–1014. [PubMed: 33730454]

73. Arunachalam PS, Charles TP, Joag V, Bollimpelli VS, Scott MKD, Wimmers F, Burton SL, Labranche CC, Petitdemange C, Gangadhara S, et al. : T cell-inducing vaccine durably prevents mucosal SHIV infection even with lower neutralizing antibody titers. Nat Med 2020, 26:932–940. [PubMed: 32393800]

74. Rolland M, Tovanabutra S, deCamp AC, Frahm N, Gilbert PB, Sanders-Buell E, Heath L, Magaret CA, Bose M, Bradfield A, et al. : Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. Nat Med 2011, 17:366–371. [PubMed: 21358627]

75. Fischer W, Perkins S, Theiler J, Bhattacharya T, Yusim K, Funkhouser R, Kuiken C, Haynes B, Letvin NL, Walker BD, et al. : Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. Nat Med 2007, 13:100–106. [PubMed: 17187074]

76. Theiler J, Yoon H, Yusim K, Picker LJ, Fruh K, Korber B: Epigraph: A Vaccine Design Tool Applied to an HIV Therapeutic Vaccine and a Pan-Filovirus Vaccine. Sci Rep 2016, 6:33987. [PubMed: 27703185]

77. Létourneau S, Im E-J, Mashishi T, Brereton C, Bridgeman A, Yang H, Dorrell L, Dong T, Korber B, McMichael AJ, et al. : Design and pre-clinical evaluation of a universal HIV-1 vaccine. PLoS One 2007, 2:e984. [PubMed: 17912361]

78. Rolland M, Nickle DC, Mullins JI: HIV-1 group M conserved elements vaccine. PLoS Pathog 2007, 3:e157. [PubMed: 18052528]

79. Ondondo B, Murakoshi H, Clutton G, Abdul-Jawad S, Wee EG-T, Gatanaga H, Oka S, McMichael AJ, Takiguchi M, Korber B, et al. : Novel Conserved-region T-cell Mosaic Vaccine With High Global HIV-1 Coverage Is Recognized by Protective Responses in Untreated Infection. Mol Ther 2016, 24:832–842. [PubMed: 26743582]

80. Mothe B, Hu X, Llano A, Rosati M, Olvera A, Kulkarni V, Valentin A, Alicea C, Pilkington GR, Sardesai NY, et al. : A human immune data-informed vaccine concept elicits strong and broad T-cell specificities associated with HIV-1 control in mice and macaques. J Transl Med 2015, 13:60. [PubMed: 25879820]

81. Wei DG, Chiang V, Fyne E, Balakrishnan M, Barnes T, Graupe M, Hesselgesser J, Irrinki A, Murry JP, Stepan G, et al. : Histone deacetylase inhibitor romidepsin induces HIV expression in CD4 T cells from patients on suppressive antiretroviral therapy at concentrations achieved by clinical dosing. PLoS Pathog 2014, 10:e1004071. [PubMed: 24722454]

82. Søgaard OS, Graversen ME, Leth S, Olesen R, Brinkmann CR, Nissen SK, Kjaer AS, Schleimann MH, Denton PW, Hey-Cunningham WJ, et al. : The Depsipeptide Romidepsin Reverses HIV-1 Latency In Vivo. PLoS Pathog 2015, 11:e1005142. [PubMed: 26379282]

83. Mothe B, Rosás-Umbert M, Coll P, Manzardo C, Puertas MC, Morón-López S, Llano A, Miranda C, Cedeño S, López M, et al. : HIVconsv Vaccines and Romidepsin in Early-Treated HIV-1-Infected Individuals: Safety, Immunogenicity and Effect on the Viral Reservoir (Study BCN02). Front Immunol 2020, 11:823. [PubMed: 32435247]

84. Mothe B, Manzardo C, Sanchez-Bernabeu A, Coll P, Morón-López S, Puertas MC, Rosas-Umbert M, Cobarsi P, Escrig R, Perez-Alvarez N, et al. : Therapeutic Vaccination Refocuses T-cell Responses Towards Conserved Regions of HIV-1 in Early Treated Individuals (BCN 01 study). EClinicalMedicine 2019, 11:65–80. [PubMed: 31312806]

85. Dicks MDJ, Spencer AJ, Edwards NJ, Wadell G, Bojang K, Gilbert SC, Hill AVS, Cottingham MG: A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PLoS One 2012, 7:e40385. [PubMed: 22808149]

86*. Bailón L, Llano A, Cedeño S, Escribà T, Rosás-Umbert M, Parera M, Casadellà M, Lopez M, Pérez F, Oriol-Tordera B, et al. : Safety, immunogenicity and effect on viral rebound of HTI vaccines in early treated HIV-1 infection: a randomized, placebo-controlled phase 1 trial. Nat Med 2022, 28:2611–2621. [PubMed: 36302893] This placebo-controlled trial of the immune-focusing HTI T cell vaccine demonstrated the importance of epitope-specific $CD8^+$ $GzmB^+$ T cells in extending time off ART and reducing viral load during acute treatment interruption.

87. Garcia-Bates TM, Palma ML, Anderko RR, Hsu DC, Ananworanich J, Korber BT, Gaiha GD, Phanuphak N, Thomas R, Tovanabutra S, et al. : Dendritic cells focus CTL responses toward highly conserved and topologically important HIV-1 epitopes. EBioMedicine 2021, 63:103175. [PubMed: 33450518]

88. Korber B, Fischer W: T cell-based strategies for HIV-1 vaccines. Hum Vaccin Immunother 2020, 16:713–722. [PubMed: 31584318]

89. Sahin U, Derhovanessian E, Miller M, Kloke B-P, Simon P, Löwer M, Bukur V, Tadmor AD, Luxemburger U, Schrörs B, et al. : Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017, 547:222–226. [PubMed: 28678784]

90. Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, Lihm J, Ceglia N, Guasp P, Chu A, et al. : Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. Nature 2023, 618:144–150. [PubMed: 37165196]

91. Palmer CD, Rappaport AR, Davis MJ, Hart MG, Scallan CD, Hong S-J, Gitlin L, Kraemer LD, Kounlavouth S, Yang A, et al. : Individualized, heterologous chimpanzee adenovirus and self-amplifying mRNA neoantigen vaccine for advanced metastatic solid tumors: phase 1 trial interim results. Nat Med 2022, 28:1619–1629. [PubMed: 35970920]

92. Rotrosen E, Kupper TS: Assessing the generation of tissue resident memory T cells by vaccines. Nat Rev Immunol 2023,

Key Points

- Progressive HIV disease leads to a dysfunctional HIV-specific $CD8^+$ T cell phenotype that is increasingly observed as being irreversible even with fully suppressive treatment.
- Successful T cell-mediated control of HIV infection is mediated by a highly functional and cytolytic response directed towards mutationally constrained epitopes in blood and anatomical sites that harbor foci of ongoing viral replication.
- Prophylactic and therapeutic HIV T cell vaccines are being developed to induce responses similar to those observed in spontaneous controllers.