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# The role of T cell immunity in HIV-1 infection

C Mee Ling Munier<sup>1</sup>, Anthony D Kelleher<sup>1,2</sup>, Stephen J Kent<sup>3</sup> and Robert De Rose<sup>3</sup>

The interplay between the T cell immune response and human immunodeficiency virus (HIV)-1 largely determines the outcome of infection. Typically, the virus overcomes the immune defences leading to a gradual decline in function that permits the development of disease. In recent years, a concerted effort in comparing T cell responses between 'controllers' and 'progressors' is beginning to identify the T cell subsets and factors that affect disease progression related to the effector functions of both CD4 and CD8 T cells. These efforts are providing opportunities for development of novel therapies and vaccines.

## Addresses

<sup>1</sup> The Kirby Institute for Infection and Immunity in Society, University of NSW, Sydney, NSW, Australia

<sup>2</sup> St Vincent's Centre for Applied Medical Research, Sydney, NSW, Australia

<sup>3</sup> Department of Microbiology and Immunology, University of Melbourne, Parkville, Victoria, Australia

Corresponding author: Kent, Stephen J ([skent@unimelb.edu.au](mailto:skent@unimelb.edu.au))

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## Introduction

HIV-1 primarily infects and destroys CD4 T cells and causes dysfunction of most T cell subsets, presenting a formidable challenge to the immune system. A high rate of replication causes rapid, disseminated infection of CD4 T cells in the first few weeks and a sizeable reduction in CD4 T cell numbers. Over the long term, CD4 T cell death outnumbers the thymic output of new cells, resulting in a progressive depletion. In addition, a subset of resting memory CD4 T cells harbour latent HIV-1 DNA that cannot be cleared and are largely unaffected by drug therapies. Therefore, once established, HIV infection is life-long. This article reviews CD4 and CD8 T cell immunity to HIV-1, focusing on recent progress in the field.

## The non-protective T cell response to HIV-1

The vast majority of individuals are ultimately susceptible to HIV disease. Robust neutralising antibody

responses develop too slowly to control infection and although the T cell response is comparatively quicker, viral loads in excess of  $10^6$  copies/mL of plasma are often reached during acute infection before T cell-mediated inhibition of infected cells reduces the viral load to a typical steady-state level of  $\sim 3 \times 10^4$  copies/mL [1,2]. There are a number of factors that contribute to the failure of the T cell response to control HIV replication. Early HIV-specific CD8 T cell responses are usually narrowly focused on a few immunodominant epitopes, which facilitates viral escape [3]. Immune driven escape can lead to reductions in the replicative capacity of the virus but these fitness costs are often overcome by compensatory mutations [4]. Loss and early dysregulation of HIV-specific CD4 T cell function [5] leads to immune dysfunction. Further, although the size of the HIV-specific CD8 T cell response is often large it is usually compromised due to exhaustion [6] driven by chronic immune activation [7]. During the chronic phase of the infection the immune response becomes broader but no more effective at controlling viral replication [8].

## Features of effective T cell responses

### HLA Class I

Spontaneous resolution of HIV infection does not occur and therefore there is no natural immune correlate for complete sterilising immunity to HIV. However, there exists a small group of individuals that do not progress in the absence of antiviral therapy, these individuals are referred to as HIV controllers. They are divided into groups of individuals that maintain healthy CD4 T cell counts ( $>500$  cells/ $\mu$ L) for over 10 years without therapy and remain asymptomatic and are termed long-term non-progressors (LTNP) [9]. These have been subcategorised into individuals that control virus replication to less than 400 copies/mL for  $>5$  years (viremic controllers) or below 75 copies/mL for at least one year (elite controllers, EC) [10]. However, these definitions are somewhat arbitrary and vary between studies. Features of the immune system in these individuals may be instructive for what constitutes an effective T cell immune response.

Viruses with reduced replication capacities are more prevalent in HIV controllers [11]. However, the most common feature within this group of individuals is expression of a select group of HLA-B alleles, which are overrepresented compared to the broader population, strongly suggesting that T cells are associated with control. This includes HLA-B\*57, HLA-B\*58, HLA-B\*27, HLA-B\*51, HLA-B\*81, HLA-B\*44 and HLA-B\*14

[12,13]. These alleles present epitopes within Gag in structurally conserved or constrained regions of the virus [14] and are effective at constraining viral replication when induced early in infection [15]. These HLA-B alleles appear to have unusual properties. For example, presentation of peptides during thymic development by HLA\*B57 selects for a larger number of naïve B57-restricted clones. This larger repertoire of B57-restricted CD8 T cells can respond to variations in epitopes, which translates functionally into a response that is more refractory to immune-driven mutational escape [16\*\*]. However, expression of these alleles in itself does not ensure slow HIV progression, since B57 and B27 [17] heterozygotes have varying outcomes to infection. Brennan *et al.* showed that the breadth, or number, of epitopes targeted to highly conserved epitopes, especially within Gag, correlates with disease outcome [18]. A major international collaboration, called The International HIV Controllers Study, sought to identify factors associated with viral control or susceptibility. HIV controllers (VL < 2000 copies/mL blood) were compared with progressors (VL > 50 000 copies/mL) and, via SNP analysis, identified five amino acids that are important. Each of these amino acids was located to HLA-B and flank, or lies within the binding groove of the HLA molecule and directly participate in peptide binding [19\*\*]. Other HLA alleles are associated with rapid progression, such as HLA-\*B35 and HLA-\*B53 [20,21]. These are thought to present epitopes poorly or force escape mutations that impose little or no fitness cost on the virus. However, HLA associations with disease outcome can be subtype-specific, as epitope sequences differ between viruses [22].

#### HIV-specific CD8 T cells

The role of HIV-specific CD8 T cells in the control and establishment of viral set point during acute infection has been well documented. These cells appear in the blood before seroconversion [23], just before the peak in viral load, expand rapidly and then contract with decreases in viral load [24–26]. In the SIV model, depletion of CD8 T cells results in rapid progression of disease [27]. Further evidence that CD8 T cells play a role in controlling HIV is the appearance of viral escape mutations. These can occur as early as 30–54 days after peak viraemia [3] and are due to selection by HIV-specific CD8 T cells [28,29].

It has become increasingly apparent that the quality of HIV-specific CD8 T cells from HIV controllers rather than quantity is a major contributing factor in immunological control over viral replication (Figure 1a). HIV-specific CD8 T cells from controllers exhibit a wider variety of effector functions, described as ‘polyfunctional’ [30,31]. These cells proliferate more than cells from non-controllers [32] and have superior cytotoxic capabilities [33]. Recent data have shown HIV-specific CD8 T cells in controllers upregulate perforin and granzyme B (molecules essential for cell-mediated cytotoxicity) more

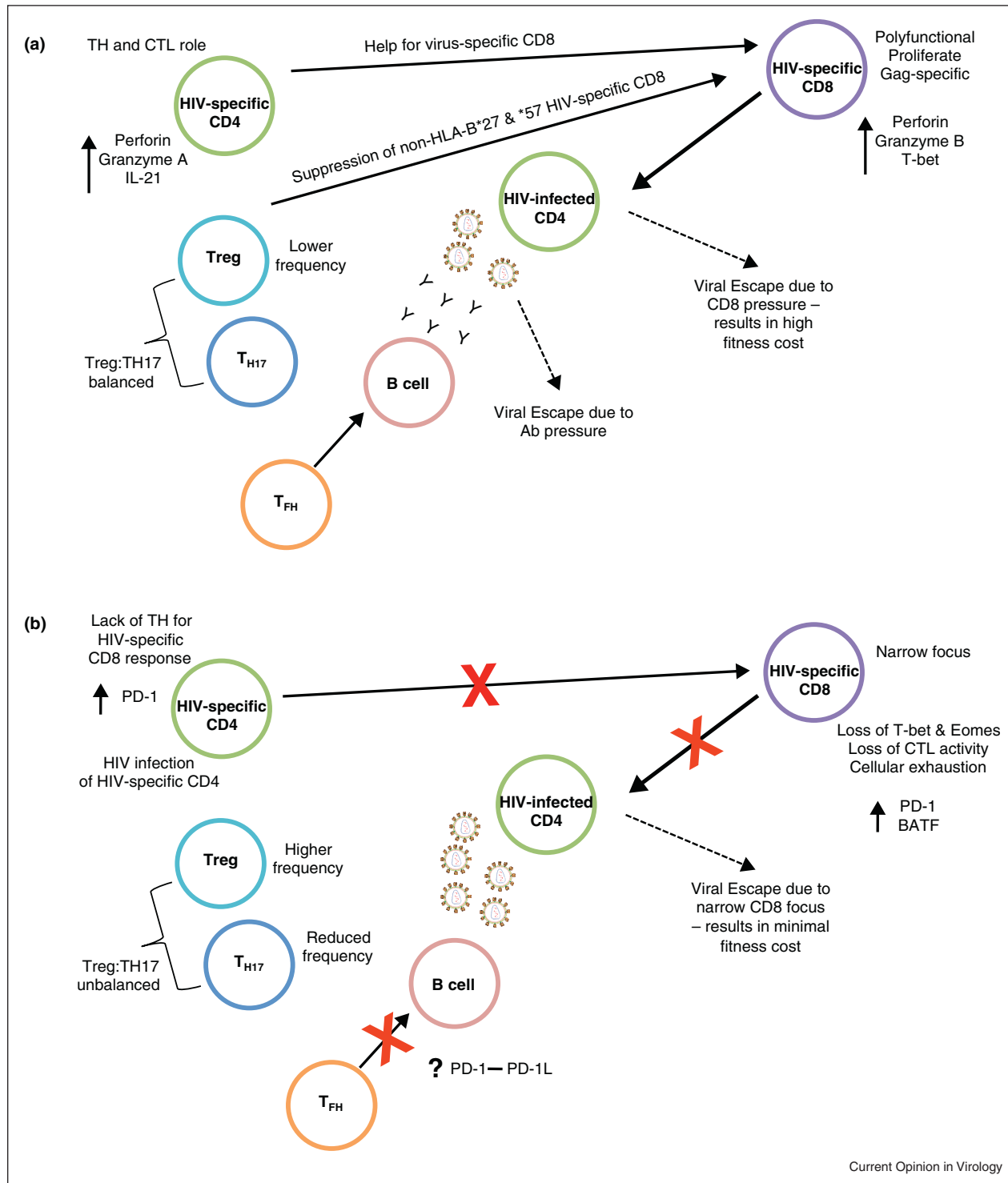
readily than non-controllers [34,35\*]. Polyfunctional CD8 T cells reside in mucosal tissues of HIV controllers, the primary site of CD4 T cell destruction during acute HIV infection and these responses were stronger and more complex than in peripheral blood [36]. Subsequent studies showed that CD8 T cell responses were dominated by responses to Gag rather than other HIV proteins in HIV controllers [37]. The timing of the CD8 T cell response is critical; early responses are associated with improved outcome and retention of CD4 T cells [38]. However, these studies are correlative and make it difficult to attribute causality or to know whether a lower viral load allows the generation of these apparently advantageous responses or if these responses result in the lower viral load. Intervention studies will ultimately go part of the way to answering this conundrum.

A number of factors contribute to HIV-specific CD8 T cell dysfunction that is observed in HIV non-controllers (Figure 1b). Recent data suggest that defects in the expression of transcription factors that control the development, differentiation and function of these cells may be responsible. Higher levels of the transcription factor T-bet are present in HIV-specific CD8 T cells from controllers, which positively correlate with perforin and granzyme B expression [35\*]. By contrast, HIV-specific CD8 T cells from individuals with chronic HIV infection lose expression of both T-bet and eomesodermin [39], with a resultant loss of CD8 cytotoxic activity [40]. Chronic antigen stimulation results in cellular exhaustion, loss of function and a consequently ineffective response. This is characterised by expression of the negative regulatory molecule, programmed-death 1 (PD-1) [41,42]. Blockade of PD-1 results in improved proliferative ability and expression of cytokines and effector molecules [41,43]. A recent study revealed that PD-1 expression on HIV-specific CD8 T cells inhibited cell function by upregulation of the transcription factor BATF. Silencing BATF rescued the function of HIV-specific T cells from individuals with chronic infection [44\*\*].

#### HIV-specific CD4 T cells

Preservation of HIV-specific CD4 T cells is critical for slowing the progression of HIV infection. HIV-specific CD4 T cells support maintenance of HIV-specific CD8 T cell function and this interdependence is required for an effective T cell response (Figure 1a). Depletion of CD4 T cells in SIV infected macaques worsens disease progression, strongly suggesting that CD4 T cells play an active role in defence of this infection, not just as a victim or substrate for infection [45]. IL-21 appears to be a key cytokine [46], since Gag-specific CD4 T cells that express IL-21 are enriched, correlate strongly with lower viral load and lead to enhanced perforin expression in CD8 T cell in controllers compared to progressors [47]. Controllers also express elevated IL-21 levels

Figure 1



The current view of **(a)** 'effective' T cell immunity to HIV infection, in which HIV-specific CD4 T cells have increased expression of CTL molecules and provide help to CD8 CTLs and also in which the virus mutates due to pressure applied by HIV-specific CD8 T cell and antibody pressure. **(b)** 'Ineffective' T cell immunity to HIV Infection, where a dysfunction in CTL help from HIV-specific CD4 T cells occurs due to increased infection by the virus. There is increased expression of PD-1 on HIV-specific CD4 and CD8 T cells and reduced antibody production, all of which lead to the loss of control and an increase in detectable virus in the host.

from *in vitro* activated CD4 T cells compared to a chronically infected group (>6 m infection without HAART) [48]. These observations made in peripheral blood are intriguing given the growing realisation of the role of T<sub>FH</sub> in HIV infection (see below). However, they also need to be interpreted in the context that polyfunctional responses, especially from CD4 T cells in tissues, are correlates of slower progression [49]. Further work is required to delineate whether the observed correlations are driven by increased expression of IL-21 *per se* or whether these observations are simply a reflection of polyfunctionality.

Although the data are less extensive than for CD8 T cells, there is evidence that the loss of CD4 T cell function also correlates with PD-1 expression [50–52]. The determinants of this are unclear. Recent data suggest that BLIMP, a transcriptional repressor that governs aspects of both T and B cell differentiation (reviewed in [53]), and specifically silences IL-2 production [54], is over expressed in progressors, particularly within central memory CD4 T cells and adaptive Tregs. In addition, upregulation of BLIMP expression is most marked in PD-1+ CD4 T cells. Intriguingly the expression of BLIMP is at least partially regulated post-transcriptionally by expression of microRNA 9 (miR-9), that is in turn underexpressed in the CD4 T cells of progressors [54,55,56]. These and other recently published data [57] suggest that further insights into determinants of outcome may arise from careful studies of regulation of miR expression in T cell subsets.

Other relatively understudied aspects of CD4 T cell function have also provided possible insights into correlates of disease control. Early expansion of CD4 T cells expressing perforin and Granzyme A is associated with spontaneous control of HIV infection, suggesting direct cytolytic activity of CD4 T cells [58]. Interestingly, prior exposure to other pathogens may also prime cross-protective CD4 T cell responses against HIV that are associated with early clearance of the virus [59] and suggests that vaccines targeted to CD4 T cell responses may be useful. Overall, these studies suggest that an early CD4 T cell response to HIV, before extensive pathology of CD4 T cells, is an important factor in partial control of HIV disease progression.

### Tregs

The role of T regulatory cells in HIV infection is often conflicting (reviewed in [60]). On one hand there are data to support the hypothesis that Tregs slow disease progression by reducing chronic immune activation. However, on the contrary, there are data supporting the contention that Tregs may interfere with the anti-viral CD4 and CD8 immune responses and hence accelerate disease progression. This later hypothesis has received support from the observation of lower Treg numbers in

both peripheral blood [61] and mucosal tissues [62] of those controlling infection.

In general, the number of Tregs, relative to effector cells, increase with disease progression and increasing viral load [63]. This increase in relative numbers is reversed following HAART [64]. Further evidence suggesting a negative effect of non-specific expansion of Tregs comes from the large clinical endpoint trials of IL-2 therapy [65] in which large increases in CD4 T cell counts did not delay onset of opportunistic infections. A large proportion of the observed cell increase was from cells that had a Treg like phenotype [66], which may be one reason for the lack of clinical benefit of IL-2. Although it has been hypothesised that Treg may be relatively protected from infection, their level of CCR5 expression suggests they are capable of supporting active infection [63].

One reason for the conflicting data regarding Tregs may be due to differences in the definition of Tregs used in various studies. Interpretation is further hampered by a lack of consensus about the critical parameters defining Treg function with various studies focusing on absolute number, relative numbers compared to effector cell number, antigenic specificity, ability to suppress, and on mechanisms of suppression (reviewed in [67]). It is unclear which of these are the most robust determinants of outcome. However, recent studies have begun to address the effect of specificity of the Tregs. Gag-specific Tregs have been identified and expanded *in vitro* using HLA-Class II tetramers [68]. An elegant study showed differential suppression of CTL by Treg depending on their restricting element: Treg from LTNP were unable to suppress CD8 CTLs restricted by the protective alleles HLA-B\*27 or HLA-B\*57, but effectively suppressed CTLs restricted by non-protective alleles within the same individual [69]. The suppression was mediated via the Tim-3-Gal-9 interaction. The evasion of suppression occurred by HLA-B27/57 restricted CTL, directly killing Tregs via a granzyme B-dependent mechanism [69].

The role of CD39, an ectonucleoside that metabolises ATP and ADP to AMP, has been suggested as a marker of a substantial subset of Treg and to play an active role in their suppressive capabilities [70]. The expression of CD39 on bulk Tregs has been shown to correlate with disease progression, extent of CD4 T cell depletion and immune activation. Further, those with a polymorphism associated with down regulation of CD39 were more likely to exhibit slower progression [71]. Somewhat counter-intuitively then, CD39 activity has been shown to mediate contact dependent suppression of HIV replication in CD4 T cells *in vitro* [72]. As both these activities appear dependent on the enzymatic activity of CD39, the exact role of CD39 expression on Treg in disease control is still to be determined.

**T<sub>FH</sub>**

A subset of memory CD4 T cells that almost exclusively reside within the germinal centres of secondary lymphoid tissues are known as T follicular helper (T<sub>FH</sub>) cells. In humans, these cells are characterised by the extracellular expression of the chemokine receptor CXCR5, high levels of PD-1 and low levels of CD127 and the intracellular expression of the transcription factor Bcl-6 and IL-21 (reviewed in [73]). T<sub>FH</sub> cells are required for germinal centre formation, are important for providing help to B cells to produce high-affinity, Ig class-switched antibodies and maturation of B cells into plasma and memory B cells (reviewed in [73,74]).

In recent studies, an expansion of T<sub>FH</sub> cells has been shown to occur in both SIV and HIV infection [75–78]. T<sub>FH</sub> cells appear to lack surface expression of CCR5, the main co-receptor for HIV and SIV [79], and hence were presumed to be protected from infection with these viruses. However, very recent data reveal that T<sub>FH</sub> cells are susceptible to infection by both SIV [77,78] and HIV [80<sup>\*</sup>] and this rate of infection appears at least equivalent to other memory T cell subsets and is established at the earliest stages of infection. Surprisingly, rates of infection of T<sub>FH</sub> with either SIV or HIV were at least as high, if not higher than other memory CD4 T cell subsets and these cells are efficient in supporting viral replication [78,80<sup>\*</sup>]. Interestingly, T<sub>FH</sub> are infected at much higher frequencies in rhesus macaques and humans than in sooty mangabeys, the natural host for SIV [81]. As these cells are PD-1 high there are intriguing parallels with the previously reported observation that the largest reservoir of infected cells are those that are PD-1+ [82]. The mechanism of T<sub>FH</sub> accumulation despite infection is unclear but may be due to trafficking and altered signalling through the IL-6R rather than an increase in proliferative or decrease in apoptotic rates of these cells [77].

The effect of infection on the function of these cells is critical to our understanding of the development of an effective antibody response to HIV. Somatically hypermutated antibodies appear critical for the generation of many neutralising antibodies to HIV. Currently, the data are somewhat conflicting. While there is general agreement that T<sub>FH</sub> from infected humans and macaques are dysfunctional, the underlying deficit is the subject of debate. One study found T<sub>FH</sub> secrete high levels of IL-21 in response to HIV antigens, with responses increasing with disease progression, as did the skewing of the B cell populations in follicles towards a germinal centre phenotype [76]. Two other studies from separate groups found low or deficient IL-21 production from T<sub>FH</sub> isolated from SIV infected macaques and HIV infected humans [77,83]. The later study showed that the deficit could be removed by blocking PD-1 signalling and suggested that compromised B cell help from T<sub>FH</sub> in

chronic HIV infection is driven by chronic ligation of PD-1 on T<sub>FH</sub> by its ligand PD-L1 on B cells [83].

One of the limitations of studies involving T<sub>FH</sub> is the requirement to sample lymphoid tissues to study these cells. A small subset of circulating T<sub>FH</sub>-like cells have been described [84]; however, the phenotypic definition of these cells is the subject of considerable debate. These cells appear to be more prominent following vaccination [85] and are capable of producing IL-21 [86]. Further work is needed on the significance of these cells and their relationship to lymphoid tissue T<sub>FH</sub>. Manipulation of the T<sub>FH</sub> subset could provide novel strategies for immunotherapeutic intervention and the efficient generation of neutralising antibody responses.

**T<sub>H17</sub>**

T<sub>H17</sub> cells are a subset of CD4 T cells located mainly within mucosal surfaces. These cells appear to co-ordinate protection against extra-cellular bacteria, fungi and mycobacteria [87] and may have a critical role in maintaining mucosal surface integrity [88]. Substantial depletion of T<sub>H17</sub> cells from gut and genitourinary mucosal tissue has been reported in both HIV and SIV infection with the degree of depletion correlating with progression [89–91]. This depletion is probably due to the effect of direct infection as these cells express both HIV co-receptors, are permissive for HIV-infection and harbour high levels of integrated HIV-DNA [92]. However, these cells do not appear to be simply a target of infection, as in SIV infection, macaques with greater T<sub>H17</sub> cell numbers before infection were found to have lower peak and set-point viral loads than macaques with lower T<sub>H17</sub> numbers [93<sup>\*</sup>] indicating these cells have the potential to actively contribute to defence against these retroviruses. The result of infection may not be a simple numbers game, as ratios of T<sub>H17</sub>/Treg appear to correlate with propensity for disease progression [94,95].

**Vaccines**

Only one clinical trial has evaluated the protective capacity of a T cell-based HIV vaccine. Expectations were high for a phase IIB trial, termed STEP, that tested an adenovirus serotype 5 vectored HIV vaccine expressing Gag, Pol and Nef, based on data from earlier trials and pre-clinical testing. While there was good evidence for vaccine-induced T cell selective pressure on the virus [96<sup>\*</sup>], there was no vaccine efficacy and the study was prematurely terminated. This trial was also subject to controversy surrounding whether the vaccine heightened the risk of HIV infection in subsets of individuals [97,98].

Preserving immune function in the early stages of infection appears critical in T cell mediated protection by vaccination. This is where vaccines may tip the balance in favour of the host immune system, by facilitating a rapid expansion of memory T cells in the first few days of

infection and thereby limiting CD4 T cell destruction in the gut. Perhaps the most successful example is provided by a recombinant live CMV-SIV vaccine, which restricted viral load to undetectable levels in 13 out of 24 rhesus macaques challenged with virulent SIVmac239. Protection was not quite sterilising but almost complete control of viraemia was provided and maintained by a strong SIV-specific effector memory CD8 T cell response [99\*\*]. Control of viraemia was mediated via persistent antigen expression.

## Conclusions

HIV-1 presents a formidable and unprecedented challenge to the immune system. There is no natural immunity to HIV, but there are consistent themes of the types and functions of HIV-specific CD4 and CD8 T cells that partially control HIV infection and delay disease progression. Quality rather than quantity is an important factor of these HIV-specific cells, with polyfunctionality, increased expression of cytotoxic molecules and regulation of key transcriptional factors a key to their success. In addition, there is a growing appreciation of subsets of CD4 T cells, including Tregs, T<sub>FH</sub> and T<sub>H17</sub> cells that are also linked to slow disease progression. Translating this new knowledge on HIV-specific T cells during HIV infection towards improved therapeutic or preventive HIV vaccines remains a difficult but important challenge.

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- of special interest
- of outstanding interest

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