Published in final edited form as:
*Curr Opin HIV AIDS*. 2011 May ; 6(3): 221–227. doi:10.1097/COH.0b013e32834577b3.

# Th17 cells and regulatory T cells in elite control over HIV and SIV

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## Abstract

**Purpose of review—**We present current findings about two subsets of $CD4^+$ T cells that play an important part in the initial host response to infection with the human immunodeficiency virus type 1 (HIV): those producing IL-17 (Th17 cells) and those with immunosuppressive function ($CD25^+FoxP3^+$ regulatory T cells, or T-reg). The role of these cells in control of viral infection and immune activation as well as in prevention of immune deficiency in HIV-infected elite controllers will be examined. We will also discuss the use of the simian immunodeficiency virus (SIV)-infected macaque model of AIDS to study the interplay between these cells and lentiviral infection *in vivo*.

**Recent Findings—**Study of Th17 cells in humans and non-human primates (NHP) has shown that depletion of these cells is associated with dissemination of microbial products from the infected gut, increased systemic immune activation, and disease progression. Most impressively, having a smaller Th17 cell compartment has been found to predict these outcomes. T-reg have been associated with reduced antiviral T cell responses but not with suppression of generalized T cell activation. Both cell subsets influence innate immune responses and, in so doing, may shape the inflammatory milieu of the host at infection.

**Summary—**Interactions between Th17 cells, T-reg, and cells of the innate immune system influence the course of HIV and SIV infection from its earliest stages, even before the appearance of adaptive immunity. Such interactions may be pivotal for elite control over disease progression.

### Keywords

HIV; SIV; Th17; regulatory T cells; T-reg; elite

## Introduction

After infection with HIV, a small fraction of subjects (called elite controllers, or EC) demonstrate low to undetectable viral loads in peripheral blood, maintain normal $CD4^+$ T

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cell numbers, and remain clinically asymptomatic in the absence of therapy [1]. Similarly, long-term survival and viral control have been well documented in a small number of SIV-infected NHP in the absence of therapy [2]. However, the mechanisms responsible for the suppression of viral replication in these cases have not been clearly defined, for several reasons. First, it appears that human EC comprise a heterogeneous group in which multiple pathways can sustain varying degrees of viral control. Second, by the time human EC have been identified, the events that led to viral control within them may have already occurred and no longer be detectable. It is accordingly important to devise experimental conditions in which host control of viral replication can be studied from the onset of viral infection. Should certain mechanisms prove to be critical for and predictive of subsequent viral control, the prevalence of these mechanisms in the larger population of humans and NHP could be ascertained. More to the point, it would be possible to test the ability of such mechanisms to reverse disease progression and/or to prevent infection altogether.

To identify mechanisms of elite control that are operative in early infection, several approaches could be taken in tandem. On the one hand, genetic studies of candidate determinants of viral control have great potential [3•], since they do not suffer from the difficulties inherent to studying infected immune systems. On the other hand, studies of NHP are uniquely informative: the immune system can be prospectively altered and monitored prior to and following viral infection, and causal relationships between mechanisms of protection and lower viral load can be assigned with confidence. Finally, it seems important to focus more attention on innate immune mechanisms that might be able to set the stage at the time of infection and to confer the most rapid and effective antiviral defense.

Here, we focus on two $CD4^+$ T cell populations, Th17 cells and $FoxP3^+$ T-reg, that share a reciprocal maturation pathway and that appear to be pivotal in the establishment of an effective immune response at the time of infection. We place significant emphasis on studies of NHP that facilitate direct investigation of the mechanisms by which such cells may influence disease.

## T-reg and Th17 cells

T-reg and Th17 cells are subsets of the $CD4^+$ T cell compartment that are important modulators of the innate and adaptive immune systems. Interest in T-reg, originally called "suppressor" T cells [4,5], was re-kindled after experiments in the mouse revealed their presence unambiguously [6,7]. Given the demonstration that exogenously-provided T-reg both prevented and cured various autoimmune diseases [8], a large amount of ongoing work is attempting to better understand the biology and potential applications of these cells in mice and humans. Recent interest in the Th17 cell lineage was also sparked by the study of an autoimmune disease, experimental autoimmune encephalitis (EAE), in which IL-23-driven Th17 cell expansion was found to be critical for disease induction [9]. Thus, these two $CD4^+$ T cell subsets are of interest because they appear to play opposing roles in inflammation and immunity, particularly auto-immunity.

Interest in the importance of T-reg and Th17 cells in infectious disease has grown dramatically with appreciation of the importance of regulatory control over immune responses in the setting of chronic infection. In most such conditions, an appropriate balance must be established between the host immune system and the infectious agent, so that the latter can persist without inciting an excessive inflammatory response that might damage the host. In lentiviral infection, for example, hosts mounting vigorous inflammatory responses experience disease progression whereas those that do not can harbor virus with impunity [10••,11]. Likewise, in malaria infection, high levels of inflammation are associated with a more severe disease course [12].

Th17 cells, which are usually equated with the induction of inflammation, have also been shown to be important in defense against infection. For example, mice deficient in Th17 cells are more susceptible to pulmonary infection with *Klebsiella pneumoniae* [13] and to dissemination of *Salmonella typhimurium* from gut lymphoid tissue [14]. In both cases, immunity at mucosal surfaces is compromised in the absence of Th17 cells. Raffatellu and colleagues showed that Th17 cells are relevant for containment of *S. typhimurium* in the NHP: animals with Th17 cell depletion caused by SIV infection exhibited increased systemic bacterial dissemination [14]. Humans with *STAT3* mutations have hyper-IgE syndrome, a deficiency of Th17 cells, and increased susceptibility to *Candida albicans* infection, a vulnerability that is shared by mice lacking the IL-17 receptor [15,16]. In addition, acute infection with H1N1 (swine-origin) flu can be accompanied by Th17 cell depletion and elevated $CD4^+$ T cell activation [17]. Because evidence suggests that death from H1N1 infection is associated with hyperactivation of the immune system, this finding suggests the possibility that Th17 cell depletion is an important contributor to pathogenesis of severe H1N1 disease.

Given that T-reg and Th17 cells often function in opposing ways, it is fascinating that these cell populations share a common developmental link that could actively maintain "balance" between them. Thus, TGF-β is required for development of both cell types [18–21]. In the case of Th17 cells, TGF-β upregulates the retinoic acid receptor-related orphan receptor-γt (ROR-γt, encoded by *RORc* gene) [22,23], a master transcription factor required for their differentiation. In the case of T-reg, TGF-β induces FoxP3, a key regulatory gene necessary for their development [24,25]. Bettelli and colleagues were the first to demonstrate the reciprocal nature of T-reg vs. Th17 cell differentiation, showing that addition of interleukin-6 to TGF-β inhibits T-reg differentiation and induces Th17 cell differentiation, thus tilting the balance between them [26]. Retinoic acid similarly impacts development of both cell types under certain conditions, inhibiting the ROR-γt required for Th17 cell development and promoting T-reg differentiation [27,28]. Finally, IL-2 is required for generation and maintenance of T-reg but inhibits differentiation of Th17 cells [29–31].

Despite these developmental links between T-reg and Th17 cells, it is not yet clear if robust development of one compartment is normally offset by deficiency in the other. In screens of normal, uninfected macaques, for instance, no consistent inverse relationship is observed; however, treatment of the animals with IL-2 and G-CSF induces an inverse relationship (D.J.H and J.M.M, unpublished data). Perhaps this reciprocal relationship develops only

under the acute influence of high concentrations of mediators such as IL-6, retinoic acid, and/or IL-2.

## Contribution of innate and adaptive immune responses to elite control

Intestinal mucosal $CD4^+$ T cells are severely depleted within the first few weeks of HIV infection, even as circulating cell numbers are maintained [32–34]. Depletion is progressive, being greater at six to eight weeks than at four weeks post-infection. It is not clear if such early depletion of mucosal $CD4^+$ T cells is predictive of or required for disease progression. Human EC do not suffer from comparably high levels of depletion [33]; however, NHP models of non-pathogenic infection demonstrate $CD4^+$ T cell depletion without disease progression [35]. In these models, disease progression may be more closely associated with T cell activation. In either case, it is clear that disease activity begins very soon after the initial infection, probably within the first week and before adaptive T cell responses have been generated. Thus, the earliest host-pathogen interactions and first steps in pathogenesis are shaped by innate rather than adaptive immune responses.

The strong influence of T-reg on adaptive T cell responses is well described [8]. T-reg can prevent the proliferation of effector T cells through mechanisms that likely include inhibition of cytokine production and of co-stimulatory pathways [36], as well as induction of tryptophan catabolism [37]. To the extent that replication of HIV virus is accelerated by cell division, it seems reasonable that T-reg might therefore limit virus production. Somewhat less attention has been paid to the effects of T-reg on antigen presenting cells (APC) and the contribution of those effects to the innate immune environment. Although T-reg require antigen-specific activation via the T cell receptor, their suppressive effects are not antigen specific [38]. Thus, T-reg activity in lymphoid tissues establishes an anti-inflammatory environment that sets the tenor for subsequent immune responses. These bystander effects are best documented in the setting of "infectious tolerance," wherein a tolerogenic milieu established by antigen-specific T-reg either persists after disappearance of those T-reg or causes subsequent evolution of tolerance to new antigens within the tissues where T-reg were active [39,40].

IL-17 production by Th17 cells, too, has important effects on the local immune environment. Most importantly, IL-17 causes release of an impressive array of immune signaling molecules, including IL-6, G-CSF, GM-CSF, defensins, chemokines, and matrix metalloproteinases from cells as diverse as keratinocytes, endothelial cells, fibroblasts, and osteoblasts [41]. IL-6, IL-8, and CXCL1 are neutrophil chemoattractants and, indeed, pulmonary overexpression or inhalation of IL-17 leads to neutrophilia in rodents [42–44]. IL-17 has also long been known to have an important structural role in maintenance of the tight junctions between intestinal epithelial cells. IL-17 increases production of claudin and zona occludens 1 and, more convincingly, inhibition of IL-17 signaling exacerbates epithelial destruction in colonic injury disease models [45]. Epithelial destruction or, perhaps, even a low level of intestinal permeability, would be expected to dramatically alter the immunologic environment of the gut and draining lymph nodes, by increasing the prevalence of pathogen-associated molecular patterns. Thus, the presence of an insufficient number of Th17 cells within the gut mucosa at the time of infection with HIV could lead to

a dramatically altered adaptive immune response to virus and to exacerbated inflammation in acute infection.

Although we focus in this review on Th17 cells (i.e., $CD4^+$ cells), it is interesting to note that many other immune and non-immune cell types produce IL-17, including $CD8^+$ T cells (Tc17), gamma-delta T cells, lymphoid tissue inducer cells, iNKT cells, and Paneth cells [46]. Recently, there has been an increased appreciation of the contribution of $CD8^+$ T cells to the IL-17 immune response [47,48]. In contrast to cytotoxic T lymphocytes, Tc17 have less cytotoxic potential: they express less granzyme B and perforin and have been shown to provide protection in mice from an influenza challenge [49]. In SIV-infected rhesus macaques, Tc17 cells are maintained in acute infection and subsequently depleted in end-stage disease [50]. This depletion, however, is not observed in sooty mangabeys with non-pathogenic SIV infection. Further studies are required to determine whether these cells can partially compensate for the loss of Th17 cells in acute infection and what role they play in the immune response to HIV and SIV. Expression of IL-17 with Paneth cells is interesting because these cells reside at the base of intestinal crypts; accordingly, the IL-17 they produce is ideally located both to regulate the baseline level of inflammation in the gut and to modulate gut permeability.

The increasing interest in innate immune control over HIV replication comes atop a rich background of intensive study of adaptive immune responses to the virus. A generalization of our knowledge about protective immune responses to acute viral infections would suggest that strong, antigen-specific T cell and humoral responses should be protective or at least contributory to slower disease progression. In fact, a variety of fairly simple experiments suggest that adaptive immune responses might be helpful. For example, depletion of $CD8^+$ T cells (and $CD8^+$ NK cells) from SIV-infected animals leads to an increase in viral load [51]; certain MHC alleles are associated with control of virus in macaques and humans [52,53]; and rapid disease progression is often associated with failure to make antibody responses [54]. However, it has proven surprisingly difficult to demonstrate either a quantitative relationship between adaptive T cell responses and lower viral load in viremic individuals or particularly robust T cell responses in elite controllers. In human studies, focus on rare populations of polyfunctional HIV-specific T cells has yielded some promising results [55], although it is not clear if these T cells are the cause or the result of control over viral replication. Others have emphasized qualitative differences in $CD8^+$ T cell function, including proliferative capacity [56], *in vitro* suppression of HIV replication [57], and effector molecule expression [58]. In one extraordinary macaque study, however, comprehensive immunologic analyses of Mamu-B*17-positive macaques that either achieved or did not achieve elite control yielded surprisingly few differences between groups [59]. Most disappointingly, the STEP trial failed to show that induction of adaptive immune responses yielded any benefit to humans [60]. Thus, although it would seem intuitively obvious that adaptive immune responses are beneficial, and although some experimental results appear to support that idea, it has proven surprisingly difficult to use adaptive immune responses to address the problem of HIV infection worldwide. Alteration of the innate immune environment is an alternative and perhaps a more viable approach.

## T-reg and elite control

Despite their low viral loads, elite controllers have higher levels of generalized immune activation than either HIV seronegatives or HAART-suppressed individuals [61•,62]. The mechanisms underlying this finding are not known, but an intriguing hypothesis is that T cell activation in HIV infection is caused by lower numbers or insufficient function of T-reg. Studies of T-reg in viremic individuals have generally shown that the fraction of T-reg among $CD4^+$ T cells is increased, whereas the absolute number of such cells is decreased [63–71]. This is the pattern to be expected if T-reg are either (i) depleted by HIV infection at a slower rate than other $CD4^+$ T cells or (ii) depleted at the same rate but stimulated to expand by generalized T cell activation or some other process incited by HIV. Clearly, such studies do not support the idea that a larger number of T-reg can prevent the harmful effects of immune activation. Generally, however, these studies have either not examined regulatory function or have done so in a limited fashion. Possibly, provision of T-reg in much larger numbers or with greater function could suppress T cell activation.

Studies focused on elite controllers have demonstrated both lower T cell activation than in other HIV-infected individuals and also broad and vigorous HIV-specific T cell responses [72]. It is attractive to imagine that T-reg might decrease generalized T cell activation while allowing antigen-specific responses because the latter responses are robust enough to overcome suppression. However, T-reg numbers and fractional representation among $CD4^+$ T cells are comparable in elite controllers, HIV seronegatives, and noncontrollers [72]. It remains possible that T-reg from elite controllers have abnormally high suppressive function. In a group of "asymptomatic" HIV-infected people, some of whom were treated, Kinter and colleagues observed that those with suppressive T-regs had lower viral loads than those with non-suppressive T-regs [73]. In our macaque studies, we have not observed a higher level of function among viremic controllers and greater function has also not been demonstrated among human controllers (ref. 74; D.J.H and J.M.M, unpublished data).

We studied T-reg influence on SIV disease in infants, which is a group with naturally larger numbers of more highly functional cells [75]. Despite harboring a larger population of T-reg, infant animals displayed higher levels of T cell activation among $CD4^+$ and $CD8^+$ cells, whether measured by Ki-67 expression or HLA-DR expression. Furthermore, PBMC samples from infected infants demonstrated no or very low $CD4^+$ T cell responses to SIV throughout infection. Depletion of T-reg from these samples, however, revealed proliferative and IL-2 and IFN-$\gamma$ responses among $CD4^+$ T cells that were comparable to those observed in adults. Thus, T-reg in infant animals suppressed $CD4^+$ T cell responses to virus. T-reg therefore have not been associated, in either human or NHP studies, with reduction in T cell activation or with maintenance of antiviral T cell responses.

## Th17 cells and elite control

The dynamics and consequences of Th17 cell depletion have been most carefully explored in NHP models. Initial human studies have demonstrated, however, that non-controllers with more advanced disease (CD4 < 350 cells/μl) show a decreased proportion of memory Th17 cells compared to HIV-negative subjects, and an increased proportion of memory $FoxP3^+$ T-

reg compared to controllers, HIV-positive subjects with suppressed viral loads, and HIV-negative subjects [76••]. When the frequencies of these subpopulations were compared to one another, the Th17/T-reg ratio was found to be 5- to 10-fold lower in non-controllers with advanced CD4 depletion when compared to noncontrollers with preserved CD4 counts and HIV-negative subjects, respectively. Furthermore, in the entire group under study, the Th17/T-reg ratio was inversely related to T cell activation. Most impressively, however, the presence of a larger number of Th17 cells at early time points *predicted* changes in T cell activation over the ensuing year. A higher frequency of memory Th17 cells during acute infection (three months) was an independent predictor of decreased T cell immune activation over time (-4.56 lower CD8+Ki67% per each 1 percentage point higher of CD4+Th17%, p=0.0098), whereas $CD4^+$ T cell counts or viral loads were not predictive. In HIV-infected patients with effective viral suppression and >50% $CD4^+$ T cell restoration in the gut mucosa during long-term HAART, $CD4^+$ Th17 T cells constituted a higher proportion of restoring $CD4^+$ T cells than Th1 cells, indicating their role in the mucosal immune recovery [77••].

NHP models of non-pathogenic lentivirus infection (e.g., $SIV_{agm}$ infection of African green monkeys, or AGMs) are associated with high viral loads and, in this sense, do not mirror elite control. They are instructive, however, in the analysis of parameters associated with low (or no) disease progression. Favre and colleagues demonstrated that SIV infection of the pig-tailed macaque (PT), but not the AGM, results in T cell activation and generalized CD4+ T cell depletion—and that IL-17-expressing Th17 cells are lost after SIV infection of the PT but not of the AGM [10••]. Futhermore, Th17 cell depletion was found to be selective in pig-tailed macaques, outpacing any depletion of Th1 and Th2 cells due to overall $CD4^+$ T cell loss. In this model, too, Th17 cell depletion predicted systemic and sustained T cell immune activation. Th17 cells and $CD4^+$ T cell counts were both independent predictors of T cell immune activation. In aggregate, these results demonstrated that the loss of Th17 cells was a strong and independent predictor of increased systemic immune activation during acute $SIV_{agm}$ infection of AGMs and PTs. Perhaps maintenance of Th17 cell populations is critical to prevention of disease progression in elite controllers as well.

A study of *Salmonella* dissemination in SIV-infected macaques has provided an elegant demonstration of the effect of Th17 cell depletion on gut epithelial permeability [14]. Although Th17 cell responses dominate the gene expression profile in infected gut loops, *Salmonella*-induced responses were blunted in SIV-infected animals. In addition, the mRNA levels for other genes involved in epithelial repair and maintenance were markedly upregulated in *S. typhimurium*–infected tissue from an SIV-negative macaque, and these responses were blunted by SIV infection. Decreased expression levels of genes regulating epithelial barrier maintenance have also been observed in people with HIV [32]. Furthermore, the average percentage of lamina propria $CD3^+$ T cells that was IL-17–producing and $CD4^+$ (Th17 cells) was significantly lower in SIV-infected macaques (0.12% on average) compared to control macaques (3.7% on average). These data show that SIV infection significantly lowers the number of Th17 cells in the intestinal mucosa, which is predominantly the result of the overall $CD4^+$ T cell depletion caused by the infection. The

finding that SIV-mediated memory CD4+ T cell depletion lowers the number of Th17 cells provides a plausible explanation for the blunted IL-17 response elicited by S. typhimurium in SIV-infected macaques. Most importantly, however, IL-17 deficiency accelerates *Salmonella* systemic dissemination from SIV-infected gut mucosa. SIV-infected macaques had significantly higher numbers (330-fold) of *S. typhimurium* in the mesenteric lymph node than SIV-negative macaques.

These studies show that depletion of Th17 cells is an integral part of HIV disease pathogenesis, which has important consequences for the infected host. We have more recently tested the hypothesis that individuals with a large number of Th17 cells *before* infection are protected against these consequences ((D.J.H and J.M.M, unpublished data). We screened macaques to identify rare individuals with large or small Th17 cell populations, infected the animals, and followed disease progression. We found that animals with larger Th17 cell populations had significantly lower peak and plateau viral loads. Interestingly, the effect of Th17 cells was dominant at early time points, whereas Th17 cells and MHC alleles were both influential in determining viral loads during the chronic stage of infection. The importance of MHC alleles for elite control has been repeatedly demonstrated, but immunologic correlates of protection that must mediate MHC effects have not been conclusively identified. Our findings suggest that the status of Th17 cells in the infected host may be a key determinant of whether MHC alleles can confer protection. Similarly, an adequate Th17 cell population may be important for deriving benefit from prophylactic vaccine strategies.

## Conclusion

Studies of human EC have suggested a number of immunologic differences between these patients and other HIV-infected subjects, the most consistent of which has been lower generalized T cell activation. Most interestingly, it was shown that the number of Th17 cells present in acute infection was predictive of T cell activation in the following year [76••]. Findings from NHP models have proven consistent with the idea that Th17 cells may form part of a key mechanism of resistance to disease progression; for example, these cells are only depleted during the course of pathogenic SIV infection [10••,78]. Findings from studies of T-reg in human EC and SIV-infected macaques have been less dramatic but have generally suggested that T-reg do not protect against T cell activation.

Given the developmental link between Th17 cells and T-reg, as well as their influence on innate immune cells, these two cell populations may act together to partially determine an innate tendency to an inflammatory response to infection. This tendency may determine the kinetics and magnitude of the inflammatory response to HIV infection, the intensity of resultant T cell activation, and the eventual rate of disease progression. Possibly, for example, elite control may require rapid resolution of the initial inflammatory response to infection via a mechanism that requires both mucosal integrity (enabled by Th17 cells) and a functional T-reg compartment. Th17 cells and T-reg may together play a defining role in exerting control over virus, limiting chronic inflammation and promoting long-term survival in HIV-infected patients.

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• of special interest

•• of outstanding interest


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**Key bullet points**

- Th17 cells and FoxP3$^+$ T-reg share a reciprocal maturation pathway and often function in opposing ways.
- Th17 cells and T-reg influence innate immune responses and, in so doing, may shape the inflammatory milieu of the host at infection.
- Th17 cells are depleted from humans and macaques with advanced HIV or SIV disease, but are preserved in the setting of slow disease progression, including in elite controllers.
- In some circumstances, a smaller Th17 cell compartment has been found to predict higher viral loads and greater generalized T cell activation.