Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Maina et al., J AIDS Clin Res 2014, 5:12
DOI: 10.4172/2155-6113.1000395

Review Article Open Access

The Relative Balance between Th17 and Regulatory T cell subsets is Critical for Progression of HIV Infection

Maina EK[1,3], **Bukusi EA**[3], **Martha S**[4], **Lartey M**[2] **and Ampofo WK**[1]

[1]*Virology Department, Noguchi Memorial Institute for Medical Research, Ghana*

[2]*University of Ghana, Medical School, Ghana*

[3]*Centre for Microbiology Research, Kenya Medical Research Institute, Kenya*

[4]*Malaria Program, Naval Medical Research Centre, USA*

[*]**Corresponding author:** Edward Maina, Virology Department, Noguchi Memorial Institute for Medical Research, P.O. Box LG 581 Accra, Ghana, Tel: 233265154115; E-mail: emaina02@yahoo.com

Received date: September 15, 2014; **Accepted date:** October 24, 2014; **Published date:** November 28, 2014

Abstract

HIV pathogenesis is extremely complex and involves both immunodeficiency that leads to opportunistic infections and AIDS as well as excessive inflammation and systemic immune activation. Generalized chronic immune activation and the progressive loss of the balance between T-helper 17 (Th17) and T-regulatory (Treg) cells have been demonstrated as leading events in HIV pathogenesis. Recent studies have investigated interactions between Th17 and Treg cells in relation to HIV infection. Th17 cells are perturbed during HIV infection in humans and SIV infection in nonhuman primates. Studies of Th17 cells in humans and nonhuman primates has shown that depletion of these cells is associated with the dissemination of microbial products from the infected gut, increased systemic immune activation, and disease progression. Treg cells, another small sub-population of T-cells involved in preventing or inhibiting autoimmune and inflammatory disorders has also been associated with HIV infection. Treg cells have been associated with the reduced antiviral T-cell responses but not with the suppression of generalized T-cell activation. In HIV patients, a profound depletion of peripheral blood Th17 cells, contrasted with a gradual decline in Treg cells, has also been documented. Both T-cell subsets influence innate immune responses and, in doing so, may shape the progression of HIV infection. Therefore, the relative balance between these two subsets rather than the function of either alone is critical for disease progression following HIV infection. This review provides updates and discussions on the relationship between Th17 and Treg cells subsets and HIV infection and disease progression. Further, the impact of antiretroviral therapy (ART) on these cellular subsets will be reviewed. Finally, unanswered questions relating to Th17/Treg cells and HIV progression and future perspectives for achieving effective therapeutic strategies for HIV infection will be highlighted.

Keywords: T cells; HIV; Pathogenesis; Immunodeficiency; Th17 cells; Virus; Apoptosis

Introduction

The pathogenesis of Human Immunodeficiency Virus (HIV) is extremely complex. HIV infection is characterized by gradual loss of $CD4^+$ T cells, which leads to the loss of immune competence, susceptibility to opportunistic infections and persistent systemic immune activation resulting in Acquired Immune Deficiency Syndrome (AIDS) [1]. Since the recognition of this infection, considerable efforts have been made to identify the mechanism involved in its pathogenesis. Research has been focused on the immunological and clinical abnormalities that characterize HIV infection. Whether the loss of immune competence seen in HIV patients is caused by chronic immune activation or by the imposition of immune balance or both is still debated. It is on this understanding that current HIV research is focused on the immune balance and cellular interplay among helper T-cells, especially Th17 and Treg cells subsets.

Th17 and Treg cells are derived from a common progenitor, and depending upon the cytokine milieu their differentiation is modulated reciprocally in several ways [2,3]. This represents a close fundamental relationship among these cellular subsets. The role of these cell subsets are complex, and can have both detrimental and beneficial outcome during HIV infection. In vitro, HIV replication can be controlled by Th17 mediated immune responses and Treg cells may protect the host from immune mediated damage [1]. However, the unchecked proliferation of Th17 cells may contribute to systemic immune activation while the unimpeded production of Treg cells may reduce HIV specific T-cell responses and therefore facilitate the establishment and maintenance of a chronic infection. Therefore, the relative balance between these two subsets rather than the function of either alone is critical for disease progression following HIV infection.

Different studies on the contribution of these cells subsets in HIV infection have shown divergent results and their role in HIV infection is poorly understood. This paper reviews changes in Th17 and Treg cells and the possible role these cells play in disease progression during HIV infection. The article also presents a review of the effects of Antiretroviral Therapy (ART) on normalization of Th17/Treg cell balance.

IL-17 producing Th17 cells in HIV Infection

The main target of HIV is $CD4^+$ T cells which consist of multiple functional cell subsets, such as Th1, Th2, Treg, and Th17 cells [1]. Th17 cells are the most recent subset of the T- helper (Th) family defined by the secretion of IL-17, a pro-inflammatory cytokine that

mediates most of its effectors functions. TGF-β along with IL-6, IL-21 and IL-23 cytokines are responsible for differentiation, amplification and stabilization of Th17 cells respectively [4-6]. Through the potent induction of cytokines, Th17 cells can bridge innate and adaptive immunity and attract other pro-inflammatory cytokines, chemokines, metalloproteinases from various tissues and Th cells to the sites of infection [4].

Current evidence shows that during HIV infection Th17 cells are preferentially depleted as compared to other Th subsets [7]. Given the pivotal role of these cells in the defence against pathogens and in mucosal homeostasis, their depletion impacts the outcome of HIV infection. The characteristic depletion of Th17 cell in the gut may result in increased microbial translocation and consequentially in systemic immune activation, one hallmark of HIV infection [2]. Contradictory findings have however been reported on the role of Th17 cells in HIV infection, and expression of Th17 related cytokines have been linked to HIV disease progression [8-12].

Selective depletion of this T-cell subset has been reported in the gut-associated lymphoid tissue as well as in peripheral blood of HIV-infected individuals [9,13-16]. In fact, severe depletion of $CD4^+$ T-cells has been shown to occur in the *gut* mucosa during *primary* HIV infection [16]. These observations suggest that HIV targets Th17 cells for destruction from the onset of infection for its subsequent establishment in the host. It also pinpoints to a possible target for treatment during early HIV infection aimed at increasing the population of Th17 cells in the gut, which could be an important factor in limiting HIV growth in cells throughout the body. In SIV infection models, monkey species with both non-pathogenic infection and those with pathogenic infection but good control of SIV replication, are able to maintain normal Th17 cell levels in the gut mucosa and blood, compared to animals with progressive infection or HIV infected patients [9,17]. This demonstrates the importance of these cells in the progression of HIV infection, making them possible therapeutic target during HIV infection. HIV specific Th17 cells have also been demonstrated in peripheral blood of HIV patients, suggesting a possible role of these cells in host defence against HIV infection [8,11]. On the contrary, another study reported preferential loss of Th17 cells from gut mucosa, but could not detect such loss in the peripheral blood [9]. It has been reported that IL-17 inhibits virus-induced apoptosis and this could potentially enhance viral persistence [12]. Such protection of virus-infected cells could represent a powerful means for viral evasion of the immune system. These reports points to a lack of consensus on the impact of HIV infection on these cellular subset. There is therefore a major gap in our understanding of the immune competency of Th17 cells in HIV infection which requires further investigations.

Recently, a study group examined frequency and functionality of Th17 cells in HIV-1 subtype 'C' infected and uninfected individuals [18]. In this study, the authors reported that in healthy individuals, virus specific Th17 cells were significantly induced in peripheral blood at early stage of HIV-1 infection, but were considerably reduced in the late stage subjects. It can therefore be speculated that HIV either infects and destroys Th17 cells during the early stages of infection or employs mechanisms to alter Th17 cells production. Systematic studies to address this hypothesis are however yet to be undertaken. It has also been reported that HIV-1 Gag specific peripheral blood Th17 cells are significantly depleted in late HIV infected subjects, compared to early infected subjects and slow progressors [18]. A loss of Th17 cells in peripheral blood during late stage of HIV-1 infection could render the subjects more prone to opportunistic infections. Furthermore, early and enhanced emergence of IL-17 cytokine could contribute to local tissue damage and favour viral dissemination in HIV infection. These findings provide further evidence for a role of IL-17 as important mediators of host response during viral infection.

Although efforts have been made in studying the relationship between Th17 cells and HIV infection, more areas remain unexplored. Of note, as preferential Th17 cells depletion occurs quite quickly, for example, in a matter of days after acute infection in nonhuman primates, it seems more likely that destruction of existing Th17 cells must also occur. Current literature does not provide clear information on whether these cells are preferentially infected by virus or, instead, indirectly destroyed as bystanders. Studies are also limited to clearly define mechanisms of selective Th17 cells depletion.

Regulatory T cells in HIV Infection

The importance of Treg cells contribution in HIV pathogenesis is increasingly recognized. Significant research has been conducted on the role of these cells in HIV infection. To date, however, the role of Treg cells during HIV infection remains controversial [19-21]. It is not clear whether Treg cells play a detrimental role or a beneficial role in the pathogenesis of HIV infection, as two opposing hypotheses have been proposed. A detrimental role of Treg cells during HIV infection was suggested based on the evidence that Treg cells suppress virus-specific immune responses [21]. Conversely, Treg cells could be beneficial by limiting immune activation, thus controlling the availability of HIV targets as well as preventing immune-based pathologies.

Primary HIV infection is characterized by high levels of viral replication followed by induction of HIV-specific $CD4^+$ and $CD8^+$ T-cell immune responses [22]. Studies have shown that the magnitude of those immune responses determines the subsequent course of infection. It has been reported that regulatory $CD4^+$ and $CD25^+$ T-cells could suppress HIV-specific effector $CD4^+$ and $CD8^+$ T-cell responses in chronically HIV-infected patients [23]. Authors in this study [23], found that in chronically infected patients, HIV antigens triggered the proliferation of virus-specific Treg cells [23]. Indeed, Treg cells appear to contribute to the control of viral replication during the short phase of primary infection while appearing to have a deleterious impact in the chronic phase of infection by inhibition of HIV specific immune responses. A number of studies have investigated Treg cells in HIV infection by assessing their frequency and numbers in peripheral blood, mucosa and lymphoid tissue and results have not been consistent. Treg cells numbers have been reported to be decreased [24-27], increased [28-31], or unchanged [32] during HIV-1/SIV infection [33]. Results with the SIV model show an increased frequency of Treg cells in lymphoid tissues together with the preferential depletion of Th17 cells [9]. This leads to a loss of balance between these two T-cell subsets.

Treg cells plays a beneficial role during HIV infection by controlling HIV replication in conventional T-cells [34] during early stages of HIV infection, through a direct transfer of cAMP to conventional T cells via gap junctions. Treg cells can have a beneficial role by protecting HIV infected patients either at the primary or chronic phase of infection from the deleterious effects of HIV-induced chronic immune activation [35]. In HIV controllers, low frequencies of Treg cells have been associated with effective adaptive immune responses, and also with generalized immune activation and $CD4^+$ T-cell

depletion [36]. Treg cells activity could have a beneficial effect through suppression of generalized chronic immune activation, and also through inhibition of activated $CD4^+$ T-cells proliferation, inflammation, cytokine production and subsequent control of viral replication [21]. Although mechanisms underlying the increased frequency of Treg cells during HIV infection are not yet well defined, increased cell proliferation and/or lower cell death have been suggested. This is based on several important studies where the correlation of Treg cells proliferation was associated with lower $CD4^+$ T-cell counts [37-39]. A different study suggested that the HIV-Treg cell interaction may contribute to the up regulated levels of Treg cells observed in lymphoid and mucosal compartments of the HIV patients [31]. In direct contrast however, several previous studies reported decreased levels of Treg cells in HIV-infected individuals [23-27], and in one study, depletion of Treg cells in HIV infection was found to be associated with immune activation [23].

Treg cells may also play a detrimental role through inhibition of anti-HIV immune responses [35,40-42], thus promoting HIV persistence at the host's expense. One study demonstrated expansion of Treg cells during HIV infection positively correlating with $CD4^+$ T-cell activation and rapid disease progression, indicating a detrimental role of Treg cells in the immune control of HIV infection [21,40]. Treg cells frequency has been reported to be higher in mucosal tissues than in the peripheral blood of untreated HIV-infected individuals, [43]. The observation that Treg cells frequency is higher in mucosal tissues than in the peripheral blood of untreated HIV-infected individuals suggests that Treg cells could reduce the availability of HIV target cells for HIV replication in these tissues. Recent studies have shown that dendritic cells (DCs) can induce peripheral conversion of conventional T-cells into Treg cells. DCs are amongst the first target cells to encounter the virus at mucosal surfaces. It is well established that DCs facilitate HIV dissemination to the lymphoid organs by enabling HIV infection of $CD4^+$ T-cells. Treg cells have been shown to accumulate during HIV infection [29] and to alter DC-T cells interactions [44]. This Treg cells accrual could thus control DC-mediated transmission of HIV to $CD4^+$ T-cells, similar to their effect on HIV infection in macrophages and conventional $CD4^+$ T-cell [34]. A recent study showed that naive Treg cells numbers were essentially preserved, whereas effectors Treg cells were consistently affected during HIV infection. Of particular interest, the effector but not total or naive Treg cells numbers negatively correlated with the magnitude of HIV-specific $CD8^+$ T-cell responses [45], suggesting a deleterious role of Treg cells in HIV-pathogenesis by diminishing HIV immunity. In HIV-exposed uninfected people, low levels of immune activation are associated with an increase in Treg cells frequency, suggesting that Treg cells may contribute to HIV resistance by controlling levels of T-cell activation and consequently by minimizing the pool of cells that are susceptible to infection [46].

Owing to these controversial findings, there remain unanswered questions of the immune competency of Treg cells in HIV infection which demand further investigations. The conflicting results from various Treg cells studies in HIV infection highlights the complex interactions that are involved in the immuno-pathogenesis of HIV infection. Further understanding of Treg cells dynamics will greatly facilitate the investigation of the role of these cells during HIV infection that will be critical for the design of potential immunotherapeutic strategies targeting Treg cells. Of particular interest, some Treg cells can also produce the inflammatory cytokine IL-17A, and recent studies suggest that IL-17^+ Treg cells may also have pathogenic potential [3], emphasizing the need for a better understanding of Treg cells in HIV infection. To date, no study that has investigated whether the altered Treg cells during pathogenic HIV is discriminative of only a subset of Treg cells that secretes IL-17 or the entire Treg cells. Studies in this area could lead to a clear reporting of specific Treg cells subset that are altered rather than reporting a blanket alteration of Treg cells, and subsequent Th17/Treg balance in HIV infection, which could also inform targeted treatment of HIV infection.

Importance of Th17/Treg cells balance in HIV Infection

Th17/Treg cells balance could explain why disease progresses fast in some people as compared to others. A significant and progressive loss in Th17 and gain in Treg cellular frequency has been observed as disease progress from early to late stage of HIV infection [18]. This observation could indicate slow progressors' capacity to develop strong HIV specific Th17 cell responses contrasted with a faint Treg cellular performance, which could explain the importance of these cellular subsets in progressive versus non-progressive HIV infection. A significant gradual loss of Th17/Treg cells balance is found to be associated with disease state, plasma viral load and immune activation [47]. Significantly elevated production of HIV specific Th17 cells was found in slow progressors [47], which indicate that the predominance of these cells in peripheral blood may contribute to their natural resistance to HIV disease progression. An increased number of Th17 cells in the long term non-progressors could result in a more preserved immune response against opportunistic infections and therefore explain the reduced immune activation and slower disease progression. In this respect, treatment aimed at increasing Th17 cells may improve the control of HIV growth by promoting an environment in which T-cells having more anti-viral capabilities are produced. On the other hand, the unchecked proliferation of Th17 cells may contribute to systemic immune activation while the unimpeded production of Treg cells will reduce HIV specific T-cell responses and may therefore facilitate the establishment and maintenance of a chronic infection. Therefore, the relative balance between these subsets rather than the function of either alone is critical for disease progression following HIV infection.

Understanding how Th17 cells are deregulated in HIV infection is crucial to restoring its population and function and it is possible that treatments designed to increase Th17 levels may be beneficial to HIV infected patients. Furthermore, if an intervention can be developed to restore Th17/Treg cells balance, it could allow for a more effective immune response after exposure to an HIV vaccine or the virus itself. This may be particularly important in the protection against opportunistic diseases, given that Th17 cells have been well characterized to protect against bacterial, parasitic, and fungal infections [7,13,16]. Clearly, alteration in the status of Th17/Treg cells might be central to the development of therapeutic interventions that modify the consequence of cellular damage and by extension, disease progression. Also, treatment strategies designed at replenishing these cytokines during late stage of infection should be considered. More studies to definitively link changes in the Th17/Treg balance with the immunopathology of HIV infection are needed. Further attention to the balance of Th17 and Treg subsets will therefore reveal much about the immune- dynamics of Th17 and Treg cells in HIV pathogenesis.

Impact of ART on

IL-17 Producing Th17 cells

Left untreated, HIV depletes mucosal Th17 cells within the first 6 months of infection, and long-term therapy does not fully restore them [48,49]. Loss of these critical cells sets the stage for on-going immune activation in people with HIV [50]. Highly Active Antiretroviral Therapy (HAART) is currently the most effective treatment to control AIDS progression [1]. HAART treatment acts by controlling viral replication and reducing viral load, preventing worsening symptoms of immune deficiency, slowing disease progression, and ultimately decreasing opportunistic infections and tumours.

HAART has been demonstrated to alter the percentage of Th17 and Treg cells in peripheral blood and lymphoid tissue of HIV patients under treatment. In one study to determine dynamic changes in peripheral blood Th17/Treg cell balance in HAART HIV- 1/AIDS patients, it was observed that after HAART therapy for 6 or 12 months, the Th17 percentage increased while Treg cells percentage decreased. The ratio of Th17/Treg cells was significantly decreased in HIV/AIDS patients before treatment, and HAART treatment partially normalized the Th17/Treg ratio [51]. This suggests that the imbalance of peripheral blood Th17 and Treg cells may play a crucial role in the pathogenesis of AIDS. HAART can therefore restore the balance of Th17 and Treg cells as well as the IL-17 level, which may gradually rebuild the immune equilibrium in HIV/AIDS patients even if not to levels comparable to healthy individual.

Effects of Antiretroviral Therapy (ART) on inflammatory markers are generally thought to be due to suppression of viral replication and immune reconstitution rather than direct effects on the immune system. T-cell activation declines during long-term ART treatment, but immune activation remains elevated and is associated with poor $CD4^+$ T-cell reconstitution [52]. When viral load is suppressed with ART, immune activation persists and predicts progression. Although the causes of persistent immune hyper-activation remain incompletely characterized, physiological alterations of gastrointestinal tract probably play a major role. Of note, ART, which results in the complete suppression of HIV replication, is not sufficient to fully turn off immune activation, and indeed, HIV-infected individuals with poor $CD4^+$ T-cell recovery on virologically suppressive ART often exhibit higher levels of immune activation [53]. Such immune activation could be due to the loss of Th17 cells permitting microbial translocation across the gastrointestinal mucosa and thereby promoting immune activation driven by bacterial lipopolysaccharide, which is associated with disease progression. Immunologic abnormalities in Gut-Associated Lymphoid Tissues (GALT) are thought to be a major cause of microbial translocation and resulting chronic immune activation in HIV-infected patients on ART. Long-term ART may normalize Th17 cells frequency as well as the Th17/Treg ratio in GALT [54]. However, there is evidence in the literature that Th17 cells are only partially restored by ART in the GALT [55].

Timing for start of ART significantly influences the outcome of HIV infection. Starting ART in the earliest stage of acute HIV infection prevents loss of mucosal Th17 cells which are instrumental in preserving the mucosal barrier in the gut, according to results of a comparative study in Thailand [56]. Early ART use also fully reversed significant local and systemic immune activation in the gut. But starting ART just a little later did not have these effects [56]. This evidence supports earlier initiation of ART and the lack of demonstrable harm in starting therapy earlier. In addition to the benefit of earlier initiation of therapy for the health of the HIV-infected individual, the reduction in sexual transmission to HIV-uninfected individuals provides further reason for earlier initiation of ART [53]. However, future studies should establish how late in HIV infection ART can be started and still achieve normalization, the durability of the response, the effect on other biomarkers of inflammation, and assess if restoration of immune function is adequate.

Although HAART generally suppresses HIV replication to undetectable plasma levels for prolonged periods of time, it fails to eradicate the virus. Interruption of HAART almost invariably leads to rebound viral replication. This raises the question of the importance of depleted Th17 cells in establishment of latent HIV reservoir, an area that has not been addressed. Therefore, studies to establish whether or not depletion of Th17 cells impacts establishment of latent HIV reservoir, especially in resting Treg cells, should be pursued. It is possible that depletion of Th17 during pathogenic HIV infection corresponds to viral persistence in resting Treg cells and therefore normalizing Th17 cells subsets balance could be important in reducing the number of latent HIV in resting Treg cells.

Regulatory T cells

The increased frequency of peripheral and mucosal Treg cells, which seems to be a characteristic feature of untreated HIV infection, triggers various effects that are either beneficial or detrimental. Recently, it has been shown in chronic Hepatitis B (HBV) that inhibition of viral replication by anti-HBV drugs is associated with diminished Treg cells expression [57]. An inverse relationship between the frequency of Treg cells and the qualitative and quantitative response to the Hepatitis B Virus (HBV) vaccine in HIVinfected subjects has been reported [58].

However, the impact of ART on Treg cells frequency in HIV-infected patients remains controversial and few studies have investigated the effect of ART on Treg cells levels.

Results

Results regarding the influence of ART on percentage and counts of Treg cells are not consistent among studies [28] and longitudinal effects of ART on Treg cells are rarely reported. Another important aspect of Treg cells in HIV patients is the modulation of this population with antiretroviral treatment and successful control of viral replication. Based on the hypothesis that Treg cells levels are modulated by HIV replication, one may expect that control of viral replication will induce opposite changes. Two research groups have analysed the effect of HAART on the levels of Treg cells and both found a decrease when viral load was controlled with treatment [28,59]. In the first study, levels of Treg cells were increased in lymphoid tissue and decreased in peripheral blood of untreated patients. Control of viral replication with HAART induced a decrease of these cells in lymphoid tissue and an increase in peripheral blood. The authors conclude that Treg cells migrate from peripheral blood to lymphoid tissue during periods of active HIV replication, and that this is reversed when viral replication is controlled with treatment. Similar results were obtained when levels of Treg cells in gastrointestinal mucosa was analysed [28]. However, in contrast to the work of

Andersson [59], they found a slight increase in peripheral blood Treg cells that normalize after treatment.

Most studies suggest that treatment is able to significantly decrease or even normalize Treg cells frequency at levels similar to that of healthy donors, at least in patients with successful ART [60]. Hence, successful ART might reduce Treg cells expansion associated with HIV infection. Moreover, in most cross-sectional studies, peripheral Treg cells frequency was reported to be lower in ART-treated patients compared with untreated, chronically infected patients [36]. Studies on whether Treg cells frequencies are reduced during short or long period of treatment have found no difference in the frequency of these cells during the course of ART. It is reported that maraviroc, the first ART drug to target a human protein, the CCR5 co-receptor, significantly reduced Treg cells both in the shorter term and after one year of treatment [61]. This observation explains ART associated immuno-modulatory effects and open new therapeutic expectations for the development of Treg depleting immunotherapies. A recent longitudinal study showed that Treg cells frequencies were normalized by ART [62] and that the proportion of Treg cells increased as a result of immune activation following ART interruption [63]. The authors reported that patients undergoing structured treatment interruption, showed an increase in Treg cells frequency following ART interruption [63]. Another study has further demonstrated a percentage increase in Treg cells before ART and normalization after ART [64], suggesting that low Treg cells percentage may benefit antiviral immune responses in HIV infection.

Other studies reported that levels of Treg cells frequency in ART-treated HIV patients remained significantly higher compared to those in healthy subjects [65,66]. Combined antiretroviral therapy has been reported to have an impact on Treg cells, but there are contradictory results about its capacity to normalize Treg cells levels [64]. In addition to ART, new HIV immunotherapy investigations have shown that the frequency of Treg cells may be influenced by immunotherapeutic interventions. A study has demonstrated that long-term IL-2 therapy leads to the expansion of naive CD25loFoxP3$^+$ and activated CD25hiFoxP3$^+$hinTreg [67]. Specifically, this study showed that IL-2 therapy preferentially expands Treg cells in infected individuals and that individuals with the greatest expansion are more likely to progress to disease.

Taken together, these studies show that depending on the phase of infection and the level of immune activation Treg cells may play a dual role in HIV infection in which there is a fragile balance between reducing immune activation and inhibiting HIV-specific T-cell functions. Owing to the split personality of Treg cells, information regarding their dynamics during ART treatment needs further investigation. However, the knowledge gained from previous studies provides a great deal to our understanding of the role of these cells in HIV infection and their dynamics during ART treatment. Most studies suggest that normalizing Th17/Treg cells balance is the key to successful treatment of HIV infection. Studies to explore why the current ART regimen fails to normalize Th17/Treg cells balance are therefore crucial to inform future design of ant-viral therapy.

Conclusions

Although there is ample evidence regarding the involvement of Th17 cells in various disease models, their function in HIV infection is not fully characterized. HIV infection is characterized by selective depletion of Th17 cells and loss of the balance between Th17 and Treg cells corresponding to the altered cytokine induction. These findings emphasize that strategies to preserve or to more rapidly restore altered Th17/Treg cells balance may have important therapeutic benefit to HIV infected patients. Despite previous studies, the relative impact of HIV infection on Th17 and Treg cells subsets remains poorly understood. This call for studies to elucidate further the different immuno-regulatory networks in HIV infection in order to determine the specific cellular or molecular pathways that can be altered to boost the body's immune control of HIV. Clearly, the current literature demonstrates the need to examine further the role and immune-homeostasis of Th17/Treg cells balance in the immuno-pathogenesis of HIV infection. More studies in the areas listed below could enhance our understanding of Th17/Treg balance in the context of HIV infection.

Future research focus areas

- Increased research to fully characterize the involvement/functions of Th17 cells and complex cytokine interaction in HIV infection
- Elucidation of the mechanisms responsible for selective depletion of Th17 cells during pathogenic HIV infection
- Clarify whether Th17 cells are preferentially infected by virus or instead indirectly destroyed as bystanders during HIV infection
- Clarify whether Treg cells play a detrimental role or a beneficial role in the pathogenesis of HIV infection and the impact of altered Th17/ Treg cell subsets ratio in HIV infection
- Establishing how late in HIV infection ART can be started and still achieve normalization, the durability of the response, the effect on other biomarkers of inflammation, and assess if restoration of immune function is adequate

References

1. Stevenson M (2003) HIV-1 pathogenesis. Nat Med 9: 853-860.
2. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, et al. (2006) Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 441: 235-238.
3. Kryczek I, Wu K, Zhao E, Wei S, Vatan L, et al. (2011) IL-17+ regulatory T cells in the microenvironments of chronic inflammation and cancer. J Immunol 186: 4388-4395.
4. Awasthi A, Kuchroo VK (2009) Th17 cells: from precursors to players in inflammation and infection. Int Immunol 21: 489-498.
5. Bettelli E, Korn T, Kuchroo VK (2007) Th17: the third member of the effector T cell trilogy. Curr Opin Immunol 19: 652-657.
6. Ancuta P, Monteiro P, Sekaly RP (2010) Th17 lineage commitment and HIV-1 pathogenesis. Curr Opin HIV AIDS 5: 158-165.
7. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, et al. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 12: 1365-1371.
8. Maek-A-Nantawat W, Buranapraditkun S, Klaewsongkram J, Ruxrungtham K (2007) Increased interleukin-17 production both in helper T cell subset Th17 and CD4-negative T cells in human immunodeficiency virus infection. Viral Immunol 20: 66-75.
9. Brenchley JM Paiardini M, Knox KS, Asher AI, Cervasi B, et al. (2008) Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood 112: 2826-2835.
10. Ndhlovu LC, Chapman JM, Jha AR, Snyder-Cappione JE, Pagán M, et al. (2008) Suppression of HIV-1 plasma viral load below detection preserves IL-17 producing T cells in HIV-1 infection. AIDS 22: 990-992.
11. Yue FY, Merchant A, Kovacs CM, Loutfy M, Persad D, et al. (2008) Virus-specific interleukin-17-producing CD4+ T cells are detectable in

early human immunodeficiency virus type 1 infection. J Virol 82: 6767-6771.

12. Hou W, Kang HS, Kim BS (2009) Th17 cells enhance viral persistence and inhibit T cell cytotoxicity in a model of chronic virus infection. J Exp Med 206: 313-328.
13. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, et al. (2008). Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. Nat. Med. 14: 421-428.
14. Favre D, Mold J, Hunt PW, Kanwar B, Loke P, et al. (2010) Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Sci Transl Med 2: 32-36.
15. Favre D, Lederer S, Kanwar B, Ma ZM, Proll S, et al. (2009) Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection. PLoS Pathog 5: e1000295.
16. Cecchinato V, Trindade CJ, Laurence A, Heraud JM, Brenchley JM, et al. (2008). Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques, Mucosal Immunol. 1: 279-288.
17. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, et al. (2001). Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med 194: 519-527.
18. Singh A Vajpayee M, Ali SA, Chauhan NK (2014) Cellular interplay among Th17, Th1, and Treg cells in HIV-1 subtype "C" infection. J Med Virol 86: 372-384.
19. Moreno-Fernandez ME, Presicce P, Chougnet CA (2012) Homeostasis and function of regulatory T cells in HIV/SIV infection. J Virol 86: 10262-10269.
20. Chevalier MF, Weiss L (2013) The split personality of regulatory T cells in HIV infection. Blood 121: 29-37.
21. Imamichi H, Lane HC (2012) Regulatory T cells in HIV-1 infection: the good, the bad, and the ugly. J Infect Dis 205: 1479-1482.
22. Pantaleo G, Demarest JF, Soudeyns H, Graziosi C, Denis F, et al. (1994) Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV. Nature 370: 463-467.
23. Weiss L, Donkova-Petrini V, Caccavelli L, Balbo M, Carbonneil C, et al. (2004) Human immunodeficiency virus-driven expansion of CD4+CD25+ regulatory T cells, which suppress HIV-specific CD4 T-cell responses in HIV-infected patients. Blood 104: 3249-3256.
24. Oswald-Richter K, Grill SM, Shariat N, Leelawong M, Sundrud MS, et al. (2004) HIV infection of naturally occurring and genetically reprogrammed human regulatory T-cells. PLoS Biol 2: E198.
25. Apoil PA, Puissant B, Roubinet F, Abbal M, Massip P, et al. (2005) FOXP3 mRNA levels are decreased in peripheral blood CD4+ lymphocytes from HIV-positive patients. J Acquir Immune Defic Syndr 39: 381-385.
26. Eggena MP, Barugahare B, Jones N, Okello M, Mutalya S, et al. (2005) Depletion of regulatory T cells in HIV infection is associated with immune activation. J Immunol 174: 4407-4414.
27. Baker CA, Clark R, Ventura F, Jones NG, Guzman D, et al. (2007) Peripheral CD4 loss of regulatory T cells is associated with persistent viraemia in chronic HIV infection. Clin Exp Immunol 147: 533-539.
28. Epple HJ, Loddenkemper C, Kunkel D, Tröger H, Maul J, et al. (2006) Mucosal but not peripheral FOXP3+ regulatory T cells are highly increased in untreated HIV infection and normalize after suppressive HAART. Blood 108: 3072-3078.
29. Montes M, Lewis DE, Sanchez C, Lopez de Castilla D, Graviss EA, et al. (2006) Foxp3+ regulatory T cells in antiretroviral-naive HIV patients. AIDS 20: 1669-1671.
30. Lim A, Tan D, Price P, Kamarulzaman A, Tan HY, et al. (2007) Proportions of circulating T cells with a regulatory cell phenotype increase with HIV-associated immune activation and remain high on antiretroviral therapy. AIDS 21: 1525-1534.
31. Mozos A, Garrido M, Carreras J, Plana M, Diaz A, et al. (2007) Redistribution of FOXP3-positive regulatory T cells from lymphoid tissues to peripheral blood in HIV-infected patients. J Acquir Immune Defic Syndr 46: 529-537.
32. Pereira LE, Villinger F, Onlamoon N, Bryan P, Cardona A, et al. (2007). Simian immunodeficiency virus (SIV) infection influences the level and function of regulatory T cells in SIV-infected rhesus macaques but not SIV-infected sooty mangabeys. J Virol 81: 4445-4456.
33. Holmes D, Knudsen G, Mackey-Cushman S, Su L (2007) FoxP3 enhances HIV-1 gene expression by modulating NFkappaB occupancy at the long terminal repeat in human T cells. J Biol Chem 282: 15973-15980.
34. Moreno-Fernandez ME1, Rueda CM, Rusie LK, Chougnet CA (2011) Regulatory T cells control HIV replication in activated T cells through a cAMP-dependent mechanism. Blood 117: 5372-5380.
35. Kared H, Lelièvre JD, Donkova-Petrini V, Aouba A, Melica G, et al. (2008) HIV-specific regulatory T cells are associated with higher CD4 cell counts in primary infection. AIDS 22: 2451-2460.
36. Hunt PW, Landay AL, Sinclair E, Martinson JA, Hatano H, et al. (2011) A low T regulatory cell response may contribute to both viral control and generalized immune activation in HIV controllers. PLoS One 6: e15924.
37. Bi X, Suzuki Y, Gatanaga H, Oka S (2009) High frequency and proliferation of CD4+ FOXP3+ Treg in HIV-1-infected patients with low CD4 counts. Eur J Immunol 39: 301-309.
38. Piconi S, Trabattoni D, Gori A, Parisotto S, Magni C, et al. (2010) Immune activation, apoptosis, and Treg activity are associated with persistently reduced CD4+ T-cell counts during antiretroviral therapy. AIDS 24: 1991-2000.
39. Xing S, Fu J, Zhang Z, Gao Y, Jiao Y, et al. (2010) Increased turnover of FoxP3high regulatory T cells is associated with hyperactivation and disease progression of chronic HIV-1 infection. J Acquir Immune Defic Syndr 54: 455-462.
40. Kinter A McNally J, Riggin L, Jackson R, Roby G, et al. (2007) Suppression of HIV-specific T cell activity by lymph node CD25+ regulatory T cells from HIV-infected individuals. Proc Natl Acad Sci U S A 104: 3390-3395.
41. Belkaid Y, Rouse BT (2005) Natural regulatory T cells in infectious disease. Nat Immunol 6: 353-360.
42. Kinter AL, Horak R, Sion M, Riggin L, McNally J, et al. (2007) CD25+ regulatory T cells isolated from HIV-infected individuals suppress the cytolytic and nonlytic antiviral activity of HIV-specific CD8+ T cells in vitro. AIDS Res Hum Retroviruses. 23: 438-450.
43. Nilsson J, Boasso A, Velilla PA, Zhang R, Vaccari M, et al. (2006) HIV-1-driven regulatory T-cell accumulation in lymphoid tissues is associated with disease progression in HIV/AIDS. Blood 108: 3808-3817.
44. Zhu T Mo H, Wang N, Nam DS, Cao Y, et al. (1993) Genotypic and phenotypic characterization of HIV-1 patients with primary infection. Science 261: 1179-1181.
45. Mendez-Lagares G, M. M. Pozo-Balado, M. Genebat, et al., (2012) "Severe immune dysregulation affects CD4+CD25hiFoxP3+ regulatory T cells in HIV-infected patients with low-level CD4 T-cell repopulation despite suppressive highly active antiretroviral therapy." Journal of Infectious Diseases. 205: 1501-1509,
46. Card CM, McLaren PJ, Wachihi C, Kimani J, Plummer FA, et al. (2009) Decreased immune activation in resistance to HIV-1 infection is associated with an elevated frequency of CD4(+)CD25(+)FOXP3(+) regulatory T cells. J Infect Dis 199: 1318-1322.
47. Salgado M, Rallón NI, Rodés B, López M, Soriano V, et al. (2011) Long-term non-progressors display a greater number of Th17 cells than HIV-infected typical progressors. Clin Immunol 139: 110-114.
48. Prendergast A, Prado JG, Kang YH, Chen F, Riddell LA, et al. (2010) HIV-1 infection is characterized by profound depletion of CD161+ Th17 cells and gradual decline in regulatory T cells. AIDS 24: 491-502.
49. Kim CJ McKinnon LR, Kovacs C, Kandel G, Huibner S, et al. (2013) Mucosal Th17 cell function is altered during HIV infection and is an independent predictor of systemic immune activation. J Immunol 191: 2164-2173.

50. Bixler SL, Sandler NG, Douek DC, Mattapallil JJ (2013) Suppressed Th17 levels correlate with elevated PIAS3, SHP2, and SOCS3 expression in CD4 T cells during acute simian immunodeficiency virus infection. J Virol 87: 7093-7101.
51. He Y, Li J, Zheng Y, Luo Y, Zhou H, et al. (2012) A randomized case-control study of dynamic changes in peripheral blood Th17/Treg cell balance and interleukin-17 levels in highly active antiretroviral-treated HIV type 1/AIDS patients. AIDS Res Hum Retroviruses 28: 339-345.
52. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, et al. (2008) Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis 197: 126-133.
53. Schuetz A, Phuang-Ngern Y, Rerknimitr R, et al. (2014) Early ART initiation prevents disruption of the mucosal barrier and subsequent T-cell activation. CROI 2014. Conference on Retroviruses and Opportunistic Infections. Boston, USA.
54. Macal M Sankaran S, Chun TW, Reay E, Flamm J, et al. (2008) Effective CD4+ T-cell restoration in gut-associated lymphoid tissue of HIV-infected patients is associated with enhanced Th17 cells and polyfunctional HIV-specific T-cell responses. Mucosal Immunol 1: 475-488.
55. Hunt PW, Martin JN, Sinclair E, Bredt B, Hagos E, et al. (2003) T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. J. Infect. Dis. 187: 1534-1543
56. Chege D, Sheth PM, Kain T, Kim CJ, Kovacs C, et al. (2011) Sigmoid Th17 populations, the HIV latent reservoir, and microbial translocation in men on long-term antiretroviral therapy. AIDS 25: 741-749.
57. Nan XP, Zhang Y, Yu HT, Sun RL, Peng MJ, et al. (2012) Inhibition of viral replication downregulates CD4(+)CD25(high) regulatory T cells and programmed death-ligand 1 in chronic hepatitis B. Viral Immunol 25: 21-28.
58. del Pozo Balado Mdel M, Leal M, Méndez Lagares G, Mata RC, López-Cortés LF, et al. (2010) Increased regulatory T cell counts in HIV-infected nonresponders to hepatitis B virus vaccine. J Infect Dis 202: 362-369.
59. Andersson J, Boasso A, Nilsson J, Zhang R, Shire NJ, et al. (2005) The prevalence of regulatory T cells in lymphoid tissue is correlated with viral load in HIV-infected patients. J Immunol 174: 3143-3147.
60. Suchard MS, Mayne E, Green VA, Shalekoff S, Donninger SL, et al. (2010) FOXP3 expression is upregulated in CD4T cells in progressive HIV-1 infection and is a marker of disease severity. PLoS One 5: e11762.
61. Pozo-Balado MM, Martínez-Bonet M2, Rosado I1, Ruiz-Mateos E1, Méndez-Lagares G3, et al. (2014) Maraviroc reduces the regulatory T-cell frequency in antiretroviral-naive HIV-infected subjects. J Infect Dis 210: 890-898.
62. Presicce P, Orsborn K, King E, Pratt J, Fichtenbaum CJ, et al. (2011) "Frequency of circulating regulatory T cells increases during chronic HIV infection and is largely controlled by highly active antiretroviral therapy." PLoS ONE 6: e28118.
63. Weiss L, Piketty C, Assoumou L (2010) "Relationship between regulatory T cells and immune activation in human immunodeficiency virus-infected patients interrupting antiretroviral therapy," PLoS ONE. 5: e11659.
64. Zhang M, Zhang H, Zhang T, Ji Y, Jiao Y, et al. (2012) Longitudinal changes of peripheral blood DC subsets and regulatory T cells in Chinese chronic HIV-1-infected patients during antiretroviral therapy. PLoS One 7: e37966.
65. Nikolova M, Carriere M, Jenabian MA, Limou S, Younas M, et al. (2011) CD39/adenosine pathway is involved in AIDS progression. PLoS Pathog 7: e1002110.
66. ZurWiesch S, Thomssen JA, Hartjen P,et al. (2011) "Comprehensive analysis of frequency and phenotype of T regulatory cells in HIV infection: CD39 expression of FoxP3+ T regulatory cells correlates with progressive disease." Journalof Virology 85: 1287-1297.
67. Weiss L, Letimier FA, Carriere M, Maiella S, Donkova-Petrini V, et al. (2010) In vivo expansion of naive and activated CD4+CD25+FOXP3+ regulatory T cell populations in interleukin-2-treated HIV patients. Proc Natl Acad Sci U S A 107: 10632-10637.