Published in final edited form as:

Curr Opin HIV AIDS. 2010 March ; 5(2): 189–193. doi:10.1097/COH.0b013e32833647d9.

Th17, Gut, and HIV: Therapeutic Implications

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Abstract

Purpose of Review—The purpose of this review is to discuss the apparent impact of persistent immune activation and inflammation on morbidity and mortality among treated HIV-infected individuals, to explore the potential role of Th17 T cell depletion in this process, and to discuss potential therapeutic implications.

Recent Findings—While the vast majority of HIV-infected individuals can now achieve and maintain viral suppression with modern antiretroviral therapy (ART), their life expectancy remains much shorter than the general population and they continue to be at much higher risk for non-AIDS-associated diseases commonly associated with aging (non-AIDS-associated cancer, cardiovascular disease, etc). Abnormal levels of immune activation and inflammation persist despite sustained viral suppression and may drive these clinical events. While the causes of persistent immune activation remain incompletely characterized, persistent low-level HIV replication and/or release from latently infected cells in gut-associated lymphoid tissue (GALT) and microbial translocation likely play a major role. Failure to restore Th17 cells in GALT during ART might impair both the recovery of the gut mucosal barrier and the clearance of microbial products.

Summary—Insights from recent pathogenesis studies might suggest novel therapeutic approaches designed to restore Th17 cells in GALT, thereby decreasing microbial translocation, immune activation, and ultimately morbidity and mortality during treated HIV infection.

Keywords

Th17; antiretroviral therapy; HIV; gut-associated lymphoid tissue

INTRODUCTION

The modern antiretroviral therapy (ART) era has transformed the lives of HIV-infected individuals in ways unimaginable even 15 years ago. With 23 FDA-approved antiretroviral drugs spanning 6 unique classes, the vast majority of HIV-infected individuals with access to antiretroviral therapy – even those with highly drug-resistant viruses – are now able to achieve and maintain nearly complete viral suppression [1,2]. AIDS-associated infections and malignancies are now rare events in patients who initiate ART before CD4+ T cell counts fall below 350 cells/mm³ – as is currently recommended by international guidelines – and guidelines are likely to recommend initiating ART even earlier in the near future [3–5]. ART has already saved millions of lives around the world and the greatest challenge remains getting ART to the millions of people around the world who need it but still don't have access to it [6].

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Conflicts of Interest: None

While this dramatic impact of ART cannot be overstated, it has failed to restore normal health in many HIV-infected individuals. HIV-infected individuals with access to modern ART regimens continue to have at least a 10-year shorter life expectancy than the general population, and they appear to be at higher risk for diseases commonly associated with aging including non-AIDS-associated cancers, cardiovascular disease, liver disease, renal disease, neurocognitive dysfunction, and osteoporosis [7]. Persistent inflammation and immune activation despite suppressive ART appears to strongly predict many of these non-AIDS events and has been proposed as one of the most important factors preventing the restoration of normal health in HIV-infected individuals [8]. Thus, the greatest need for most individuals with access to ART is no longer new antiretroviral medications, but interventions designed to decrease persistent immune activation and inflammation.

While our understanding of the causes of persistent inflammation and immune activation during treated HIV infection is incomplete, persistent viral replication and/or release from latently infected cells in lymphoid tissues (particularly those in the gut) and microbial translocation are likely to play a major role. The depletion of Th17 cells from the gut-associated lymphoid tissue (GALT) during HIV infection may well be an important contributor to both of these processes. The goal of this review is to discuss both why we need new interventions to decrease immune activation during treated HIV infection and how our evolving understanding of HIV-associated Th17 depletion may provide insights into novel therapeutic targets.

ART fails to completely restore normal health in many HIV-infected individuals

In recent years, several cohort studies throughout North America and Europe have confirmed that despite dramatic improvements in survival since the early 1990's [9], HIV-infected individuals living in the modern ART era continue to have at least a 10-year shorter life expectancy than the general population [10–13]. While much of this excess mortality may be explained by confounding risk factors including injection drug use and hepatitis C virus co-infection, a large multinational seroconverter cohort recently confirmed that HIV-infected patients initiating ART continue to have higher long-term death rates than the general population even when restricting to non-injection drug users [14]. While none of these large epidemiologic studies have been capable of adequately adjusting for all potential confounders (i.e. smoking, other recreational drug use, etc.), the consistency of these observations is compelling and has suggested that HIV itself may be contributing to premature mortality even in the setting of suppressive antiretroviral therapy. Interestingly, the premature deaths among HIV-infected individuals in the modern ART era are less commonly explained by classically AIDS-defining diagnoses. For example, a recent French cohort study found that nearly 2/3 of all deaths among HIV-infected patients are now due to non-AIDS associated causes including malignancies, cardiovascular disease, renal disease, and liver disease [15]. Many of these complications are typically associated with aging in HIV-uninfected individuals, but are occurring at much earlier ages in the HIV-infected population. For example, despite precipitous declines in AIDS-associated malignancies, HIV-infected individuals remain at much higher risk than the general population for a variety of non-AIDS-associated cancers [16]. Similarly, while cardiovascular disease event rates may be declining in recent years as a consequence of improved management of traditional risk factors [17], several recent large cohort studies have reported that HIV-infected individuals have a 1.5- to 2.0-fold higher risk of cardiovascular disease events than the general population after adjustment for traditional cardiovascular risk factors [18,19]. HIV-infected individuals receiving antiretroviral therapy also remain at much higher risk of hospitalization for community-acquired pneumonia [20], osteoporosis and fracture [21], and neurocognitive dysfunction than the general population [22,23], often despite recovery of CD4⁺ T cells to near normal levels.

Persistent immune activation and inflammation may drive non-AIDS-associated morbidity and mortality in treated HIV infection

While specific antiretroviral medication toxicity and other lifestyle factors like smoking and injection drug use may each play a role, persistent immune activation and inflammation has emerged as a key potential determinant of non-AIDS associated morbidity and mortality during treated HIV infection. For example, while suppressive ART markedly reduces immune activation, T cell activation levels and soluble markers of inflammation remain abnormally high despite years of treatment-mediated viral suppression and higher immune activation levels have been associated with blunted CD4+ T cell recovery [24–28]. Furthermore, elevations in soluble markers of inflammation like IL-6 and the coagulation marker d-Dimer have been strongly associated with subsequent all-cause mortality and cardiovascular events in treated individuals [8]. A role of chronic immune activation in driving non-AIDS-associated morbidity and mortality is further suggested by the high risk of many of these same complications in individuals with other chronic inflammatory diseases like systemic lupus erythematosus and rheumatoid arthritis [29–33].

Microbial translocation and Th17 depletion likely persist during treated HIV infection and may drive persistent immune activation and non-AIDS morbidity

The underlying causes of persistent immune activation and inflammation during treated HIV infection remain unclear, but are likely to include continued release of HIV from latently infected cells, co-infections associated with HIV, and microbial translocation. While the gut-associated lymphoid tissue (GALT) is a major site of HIV replication and CD4+ T cell loss during acute and early HIV and SIV infections [34–37], epithelial cell apoptosis and loss of mucosal integrity occur as well, which results in abnormal levels of microbial translocation, driving systemic immune activation [38,39]. As reviewed elsewhere in this edition, Th17 cells are key defenders against microbial translocation by stimulating epithelial cell proliferation and antibacterial defensin expression and by recruiting neutrophils to the GALT to clear microbial products [40–42]. Thus, the early and massive loss of Th17 cells from the GALT during pathogenic SIV and HIV infections is likely to be a key determinant of microbial translocation [43–45]. The increase in microbial translocation during early HIV disease has also been associated with significant alterations in the normal bacterial flora of the gut, which appears to be associated with increases in mucosal inflammation [46]. However, it remains unclear whether bacterial flora alterations are a cause or consequence of mucosal inflammation and microbial translocation. While markers of microbial translocation (i.e., plasma lipopolysaccharide (LPS), soluble CD14, and bacterial 16S ribosomal DNA levels) decline during suppressive ART, they remain persistently abnormal compared to HIV-uninfected individuals, even after several years of viral suppression [47,48]. While it remains unclear whether GALT Th17 depletion also persists during suppressive ART, recovery of CD4+ T cells in GALT is much slower than that in peripheral blood [35,36], so persistent Th17 depletion from GALT during suppressive ART is likely.

Persistent microbial translocation during treated HIV infection appears to be clinically significant. For example, higher levels of persistent microbial translocation are associated with both systemic T cell activation and poor CD4+ T cell recovery [47,48]. Provocative recent work from Funderburg et al also suggests a mechanistic link between microbial translocation and cardiovascular disease in HIV-infected individuals. For example, LPS and other bacterial products drive tissue factor expression by monocytes in vitro, and abnormal elevations in microbial translocation are strongly correlated with in vivo tissue factor expression among both untreated and ART-suppressed HIV-infected individuals [49]. Tissue factor expression in vivo activates the coagulation cascade and contributes to thrombus formation, potentially increasing the risk of thrombotic vascular diseases like myocardial infarction and stroke. Indeed, abnormal elevations in monocyte tissue factor

expression in ART-suppressed HIV-infected individuals is associated with higher plasma d-Dimer levels [49], a coagulation marker associated with subsequent death and cardiovascular disease in this setting [8].

Potential therapeutic interventions to decrease microbial translocation

Since persistent microbial translocation is likely to be a significant determinant of persistent immune activation and non-AIDS-associated morbidity during suppressive ART, several investigators are now studying interventions to either block microbial translocation or its downstream inflammatory consequences (see Table 1). For example, one recent randomized controlled trial showed that a nutritional supplement including bovine clostrums, oligosaccharides, and n2-polyunsaturated fatty acids – all agents hypothesized to either restore normal gastrointestinal flora and/or improve gut mucosal integrity – decreased the rate of CD4+ T cell decline in untreated HIV-infected individuals despite no apparent effect on plasma HIV RNA levels [50]. While a relatively high proportion of individuals receiving the active supplement discontinued therapy early due to bloating and flatulence, this trial appeared to show an immunologic benefit. It remains unclear whether this effect was mediated by a decline in microbial translocation and immune activation, but secondary analyses are underway. Other strategies to decrease microbial translocation and/or restore normal gut flora are also being studied by other groups. Several ongoing and planned trials will also test whether blocking the downstream inflammatory signaling pathways of microbial translocation have any benefit. For example, the commonly used anti-malarial agent chloroquine is effective in blocking toll like receptor signaling, has been used as an anti-inflammatory therapy in systemic lupus erythematosus, and also appears to reverse a murine model of colitis [51]. A randomized controlled trial of chloroquine is currently being conducted by the AIDS Clinical Trials group to see if this agent decreases immune activation in HIV-uninfected individuals (clinicaltrials.gov: NCT00819390).

Potential therapeutic strategies to restore GALT Th17 cells or function

Given the hypothesized role of Th17 cells in preventing microbial translocation, strategies to restore Th17 cells or function to the GALT in HIV-infected individuals might also hold some promise. While a logical experiment might be to administer IL-17 and/or IL-23 (a cytokine that induces Th17 differentiation) directly to HIV-infected individuals, this approach would likely cause significant toxicity as these cytokines cause colitis in a murine model and have been associated with inflammatory bowel disease in humans [52]. An alternative approach to restore Th17 cells in GALT might be suggested by a recent study of Th17 depletion in pathogenic and non-pathogenic SIV infections. Favre et al recently demonstrated that the early loss of Th17 cells from GALT in pathogenic SIV infections is associated with a reciprocal expansion of regulatory T cells (Tregs) [44]. Indeed, the ratio of Th17 cells to regulatory T cells to Tregs was strongly and negatively correlated with the extent of generalized immune activation. Since both Th17 cells and Tregs share a common progenitor, the inflammatory microenvironment of the gut in pathogenic SIV and HIV infections might result in shunting of progenitors down the Treg pathway, making it difficult to restore the Th17 compartment. This might set up a vicious cycle whereby local inflammation from microbial translocation and HIV may drive the expansion of regulatory T cells in the GALT, limiting the restoration of Th17 cells, and propagating more microbial translocation. Thus, interventions designed to decrease inflammation directly in the GALT might allow for better Th17 restoration, potentially interrupting the vicious cycle of microbial translocation and Th17 depletion.

CONCLUSIONS

In summary, while modern antiretroviral therapy has resulted in durable viral suppression in the vast majority of HIV-infected individuals, it has failed to restore normal health. HIV-infected individuals remain at high risk of non-AIDS-associated morbidities including cardiovascular disease, non-AIDS-associated cancers, and osteoporosis. Persistent inflammation despite suppressive ART has emerged as a key potential mediator of this risk and ongoing microbial translocation appears to be a major determinant of this persistent inflammatory state. The greatest need for HIV-infected individuals with access to antiretroviral therapy is no longer new antiretroviral medications, but new therapeutic strategies to decrease chronic inflammation. Given the probable causal role of GALT Th17 depletion in microbial translocation, interventions designed to restore Th17 cells and function in GALT or to decrease microbial translocation and its downstream inflammatory consequences may hold promise for HIV-infected individuals in the modern ART era.

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Table 1

Potential Interventions to Decrease Microbial Translocation and Th17 Depletion in HIV Infection

<u>Block Microbial Translocation Directly</u>
Luminal antibiotics
Bovine clostrum
<u>Block Inflammatory Consequences of Microbial Translocation</u>
Inhibition of toll-like receptor activation (i.e., chloroquine)
<u>Restore Th17 cells and/or function</u>
Exogenous IL-17 or IL-23 administration (significant concerns about toxicity)
Interventions to decrease inflammatory microenvironment in GALT