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Residual Immune Dysregulation Syndrome in Treated HIV infection

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Abstract

Antiretroviral therapy has revolutionized the course of HIV infection, improving immune function and decreasing dramatically the mortality and morbidity due to the opportunistic complications of the disease. Nonetheless, even with sustained suppression of HIV replication, many HIV-infected persons experience a syndrome characterized by increased T cell activation and evidence of heightened inflammation and coagulation. This residual immune dysregulation syndrome or RIDS is more common in persons who fail to increase circulating CD4+ T cells to normal levels and in several epidemiologic studies it has been associated with increased morbidity and mortality. These morbid and fatal events are not the typical opportunistic infections and malignancies seen in the early AIDS era but rather comprise a spectrum of cardiovascular events, liver disease, metabolic disorders, kidney disease, bone disease, and a spectrum of malignant complications distinguishable from the opportunistic malignancies that characterized the earlier days of the AIDS epidemic.

While immune activation, inflammation, and coagulopathy are characteristic of untreated HIV infection and improve with drug-induced control of HIV replication, the drivers of RIDS in treated HIV infection are incompletely understood. And while inflammation, immune activation, and coagulopathy are more common in treated persons who fail to restore circulating CD4+ T cells, it is not entirely clear how these two phenomena are linked.

1. THE ROLE OF ACTIVATION AND INFLAMMATION IN THE NATURAL HISTORY OF INFECTION

The earliest reports of AIDS were prescient in recognizing that profound depletion of circulating CD4+ T cells was central to the immune deficiency that defined the syndrome (Gottlieb et al., 1981; Masur et al., 1981). These investigators also recognized that despite

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profound immune deficiency, activation of T cells (Gottlieb et al., 1981) and B cells (Lane et al., 1983) was also characteristic of this syndrome. A number of reports linked phenotypic indices of T cell activation, primarily defined by the expression of CD38 or CD38 and HLA-DR to the risk of disease progression in natural history studies (Giorgi et al., 1999, 1993, 2002). The importance of immune activation in the pathogenesis of disease is also underscored by the recognition that African nonhuman primates that have coexisted with endemic infection with related simian immunodeficiency viruses generally tolerate high-level SIV replication without progressive immune deficiency or opportunistic infections (Silvestri, Paiardini, Pandrea, Lederman, & Sodora, 2007). In these animals, immune activation is transient after acute infection and is typically brought under control (Harris et al., 2010). In contrast, Asian rhesus macaques infected experimentally with SIV that is nonpathogenic in African animals experience a pathogenic process that is characterized by both progressive immune deficiency and sustained high levels of systemic immune activation (Silvestri et al., 2007).

Early events in both pathogenic SIV infection and HIV infection are typically associated with high levels of virus in plasma that in time diminish to a lower steady state level. This is associated with a modest decrease in numbers of circulating CD4+ T cells that in most persons progressively decline in the absence of effective antiretroviral therapy (ART). But the effects of acute HIV infection on circulating CD4+ T cell numbers are very poor reflections of pathologic events elsewhere in the body. In both pathogenic SIV infection and HIV infection of humans, acute infection is associated with “catastrophic” infection and depletion of mucosal CD4+ T cells that are typically enriched with cells coexpressing the virus chemokine receptor CCR5 that is used by the vast majority of all SIV and HIV viruses that are transmitted. This gut mucosal CD4+ T cell depletion may have a profound impact on the determinants of pathogenesis and persistent inflammation as discussed in the sections below.

As noted above, broad systemic immune activation is characteristic of untreated HIV infection. A robust activation and inflammatory state are seen during acute infection (Stacey et al., 2009), which is often reflected clinically as a “viral syndrome” with fever, rash, lymphadenopathy, and occasionally an aseptic meningitis (Schacker, Collier, Hughes, Shea, & Corey, 1996; Tindall et al., 1988). These clinical manifestations typically resolve and markers of inflammation attenuate but still remain relatively and persistently elevated. Thus, laboratory indices of T cell activation and B cell activation, activation of monocytes and dendritic cells (DCs), and natural killer cells are recognized concomitants of untreated infection. Likewise, inflammatory and coagulation indices are typically and persistently elevated during untreated infection (Funderburg et al., 2010, 2012). With application of antiretroviral therapies, and as circulating CD4+ T cell numbers rise, these markers improve; yet in many, and especially among those who fail to restore circulating CD4+ T cell numbers, persistent immune activation, inflammation, and coagulation abnormalities persist (Lederman et al., 2011) and are the subject of this review. With ART-induced suppression of HIV replication, circulating CD4+ T cell numbers typically increase in a biphasic pattern. An early first-phase increase that includes all lymphocyte subpopulations is likely the consequence of rapid redistribution of cells from lymph nodes (LNs) where they were likely sequestered in the inflammatory environment that accompanies untreated infection (Autran

et al., 1997; Biancotto et al., 2007; Bucy et al., 1999). It is plausible to attribute much of the activation/inflammation and coagulation abnormalities in untreated infection directly to HIV replication, especially as therapy-induced control of HIV replication improves (but typically does not normalize) these activation and coagulation abnormalities. Viral elements are recognized by innate immune sensors (Beignon et al., 2005; Heil et al., 2004) and *in vitro*, ligation of these sensors by viral elements can drive innate immune cell activation directly and T cell activation indirectly (Funderburg et al., 2008; Meier et al., 2007). How much of this activation is mediated by cognate peptide recognition is less clear. On the one hand, chronic HIV infection is characterized by profound and persistent expansion of circulating CD8 T cell numbers, yet few of these cells can be shown to be HIV reactive (Betts et al., 2001). Proportionally more are demonstrably reactive with peptides derived from cytomegalovirus (Naeger et al., 2010) and it can be argued that sustained replication of this and other intracellular pathogens promoted by a failure of host defenses may underlie the dramatic expansion of CD8 T cells seen in chronic HIV infection. On the other hand, the relative expansion of these cells persists long after ART controls HIV replication and risk for opportunistic infections subsides. The mechanisms underlying this sustained CD8 T cell expansion are not understood.

2. INFLAMMATORY AND COAGULATION INDICES PREDICT MORBIDITY IN TREATED HIV INFECTION

Despite dramatic improvements in the modern treatment era, HIV-infected persons maintaining ART-mediated viral suppression continue to have increased mortality compared to the general population, particularly if ART is delayed until late in the disease course (Lewden et al., 2012, 2007; The Antiretroviral Therapy Cohort Collaboration, 2008; Lohse et al., 2007; van Sighem, Gras, Reiss, Brinkman, & de Wolf, 2010). These morbidities include cardiovascular disease (Freiberg et al., 2013; Triant, Lee, Hadigan, & Grinspoon, 2007; Tseng et al., 2012), cancer (Deeken et al., 2012; Grulich, van Leeuwen, Falster, & Vajdic, 2007; Patel et al., 2008; Silverberg et al., 2009), osteoporosis (Brown & Qaqish, 2006; Triant, Brown, Lee, & Grinspoon, 2008), neurocognitive dysfunction (Heaton et al., 2010), type II diabetes (Brown et al., 2005), thromboembolic disease (Copur, Smith, Gomez, Bergman, & Homel, 2002; Fultz, McGinnis, Skanderson, Ragni, & Justice, 2004; Sullivan, Dworkin, Jones, & Hooper, 2000), and even frailty (Desquilbet et al., 2007, 2009), a syndrome of multimorbidity typically only seen in geriatric populations. While health-related behaviors and toxicities of antiretroviral drugs may both contribute to these risks, several recent studies highlight the contribution of immune dysfunction and inflammation to morbidity and mortality in this setting.

3. PERSISTENT CD41+ T CELL LYMPHOPENIA PREDICTS CLINICAL OUTCOMES DURING ART

As discussed above, many HIV-infected individuals fail to recover normal CD4+ T cell counts (i.e., >500 cells/mm^3) despite over a decade of sustained ART-mediated viral suppression (Kelley et al., 2009). These persons appear to be at highest risk for subsequent mortality in several large multicenter cohort studies (Lewden et al., 2012; The Antiretroviral

Therapy Cohort Collaboration, 2008). Persistently low CD4+ T cell counts despite ART has been consistently associated with an increased risk for combined non-AIDS morbidity and mortality in several large cohort studies and clinical trials in North America and Europe (Achhra et al., 2010; Baker et al., 2008; Marin et al., 2009; Mocroft et al., 2010; Smurzynski et al., 2010). Interestingly, there continues to be an incremental decrease in mortality risk with increasing CD4+ T cell counts even among those with CD4+ T cell counts >500 cells/mm^3, suggesting that continued CD4+ T cell recovery—even after recovering "normal" levels—may continue to confer clinical benefit (Young et al., 2012). Several studies have also linked persistent CD4+ T cell lymphopenia to an increased risk of specific non-AIDS morbidities including cardiovascular disease (Lichtenstein et al., 2010; Triant et al., 2010), osteoporosis, and fracture risk (Yong, Elliott, Woolley, & Hoy, 2011). Persistently low CD4+ T cell counts despite ART also appear to predict several infection-related cancers (Grulich et al., 2007; Silverberg et al., 2009). While all of these chronic morbidities appear to be linked to poor ART-mediated CD4+ T cell recovery, HIV-associated neurocognitive disorders and thromboembolic disease appear to be predicted by lower pre-ART nadir—but not current—CD4+ T cell counts, suggesting that the degree or pre-ART immunodeficiency might be a more important determinant of certain morbidities than the degree of ART-mediated CD4+ T cell restoration (Ellis et al., 2011; Musselwhite et al., 2011). Collectively, these studies suggest that the degree of pre-ART immunodeficiency and the extent of CD4+ T cell recovery during ART are important predictors of morbidity and mortality in treated HIV disease.

4. IMMUNE ACTIVATION/INFLAMMATION PREDICTS MORBIDITY AND MORTALITY DURING ART

While the degree of CD4+ T cell lymphopenia is an important predictor of morbidity and mortality in treated HIV infection, the extent of persistent immune activation and inflammation have emerged as perhaps even stronger—and independent—predictors of morbidity and mortality in this setting. For example, in a recent nested case-control study within the Strategies for Management of Antiretroviral Therapy (SMART) trial, higher plasma levels of the inflammatory cytokines IL-6 and C-reactive protein (CRP) and the coagulation marker D-dimer strongly predicted higher overall mortality and cardiovascular events (Duprez et al., 2009; Kuller et al., 2008). A key finding from this study was that the degree to which these inflammatory markers predicted mortality in treated HIV infection was much stronger than that observed in older HIV-uninfected individuals (Harris et al., 1999; Reuben et al., 2002; Volpato et al., 2001; Wikby et al., 2006), consistent with the hypothesis that chronic inflammation is a much more important determinant of mortality in the context of HIV infection than it is for the general population.

Several more recent studies have also demonstrated strong associations between inflammatory and coagulation markers and subsequent morbidity and mortality in treated HIV infection. For example, higher fibrinogen and CRP levels predicted increased mortality after adjustment for plasma HIV RNA levels and CD4+ T cell counts in a largely treated group of HIV-infected individuals in the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) cohort (Tien et al., 2010). Importantly, these bio-markers continued to

predict mortality even when restricting to HIV-infected individuals with CD4+ T cell counts >500 cells/mm^3, suggesting that inflammation may be an important driver of morbidity and mortality even for those with optimal CD4+ T cell recovery. Similarly, a nested case-control study from two AIDS Clinical Trials Group (ACTG) trials of HIV-infected individuals starting ART assessed the impact of pre-ART immune activation and inflammatory markers on subsequent AIDS and death (Kalayjian et al., 2010). Similarly, a nested case-control study showed that higher pre-ART levels of IL-6, CRP, D-dimer, and the tissue fibrosis biomarker hyaluronic acid predicted subsequent mortality and AIDS events in individuals with advanced disease prior to ART (Boulware et al., 2011). A consistent finding from all of these published studies—as well as two other recently presented studies (Hunt et al., 2012; Tenorio et al., 2013)—was that inflammatory markers continued to predict subsequent mortality during treated HIV infection even after adjustment for concurrent and pre-ART nadir CD4+ T cell count, suggesting an independent role of the inflammatory state in driving mortality in this setting.

In more mechanistic work from the SMART study, Sandler and colleagues showed that higher plasma levels of the soluble monocyte activation marker sCD14 predict earlier mortality (Sandler et al., 2011), findings later replicated by several other groups (Hunt et al., 2012; Justice et al., 2012; Tenorio et al., 2013). Since CD14 is cleaved from the monocyte cell surface upon lipopolysaccharide (LPS)-mediated monocyte activation, this study provided the first evidence potentially linking microbial translocation to mortality in treated HIV infection. While some have argued that sCD14 elevations may not always reflect LPS-induced activation of monocytes, our own group has recently demonstrated that specific markers of gut epithelial barrier integrity including intestinal fatty acid-binding protein and zonulin-1 levels during ART-mediated viral suppression also independently predict subsequent mortality in individuals who initiated ART with a diagnosis of AIDS (Hunt et al., 2012). These studies support microbial translocation as an important target of interventions in subsequent clinical trials.

Persistent inflammation, monocyte activation, and coagulation during treated HIV infection have also been strongly linked to several specific morbidities in this setting. For example, higher plasma CRP, IL-6, and D-dimer levels predict cardiovascular events in ART-suppressed HIV-infected individuals (Duprez et al., 2009; Ford et al., 2010; Triant, Meigs, & Grinspoon, 2009). As has been established in HIV-uninfected persons, soluble markers of inflammation also appear to predict incident type II diabetes in the context of treated HIV infection, independent of other established risk factors (Brown, Tassiopoulos, Bosch, Shikuma, & McComsey, 2010). Similarly, in a recent nested case-control study from the Multicenter AIDS Cohort Study (MACS), higher levels of inflammatory (including IL-6 and CRP) and B cell stimulatory biomarkers predicted subsequent development of non-central nervous system Non-Hodgkin lymphoma years later, even after adjustment for CD4+ T cell count (Breen et al., 2011). Increased peripheral blood markers of monocyte activation (i.e., sCD14 and sCD163) and inflammation are also associated with HIV-associated neurocognitive dysfunction during ART-mediated viral suppression (Burdo et al., 2013; Letendre et al., 2012; Lyons et al., 2011). Interesting recent work from the Veterans Aging Cohort Study cohort also suggests that higher plasma levels of sCD14, IL-6, and D-dimer were not only independently associated with mortality but also strongly associated with

anemia as well as with greater abnormalities in surrogate markers of liver fibrosis and renal insufficiency (Justice et al., 2012). These data support a model whereby chronic inflammation causes damage to multiple organ systems, all contributing to an increased risk of morbidity and mortality. The concept that inflammation may contribute to the multiple morbidities commonly associated with the aging process was further underscored by a recent study linking inflammatory markers to frailty in treated HIV infection (Erlandson et al., 2013).

While markers of innate immune activation and inflammation strongly predict morbidity and mortality in treated HIV infection, markers of T cell activation are less strongly and consistently associated with clinical outcomes in this setting. While higher frequencies of activated (CD38+ HLA–DR+) CD8+ T cells during early ART-mediated viral suppression predicted subsequent mortality in HIV-infected Ugandans independent of CD4+ T cell count (Hunt, Cao, et al., 2011), and among HIV-infected North Americans in the Study of the Ocular Complications of AIDS (Hunt et al., 2012), these associations were much weaker than those observed for inflammatory, coagulation, and monocyte activation markers. Furthermore, other recent studies failed to identify an independent association between T cell activation and subsequent clinical outcomes during treated HIV infection (Ford et al., 2010; Tenorio et al., 2013).

5. FAILURE TO RESTORE CIRCULATING CD4+ T CELLS IN HIV INFECTION

While most persons treated with ART experience substantial and progressive gains in circulating CD4+ T cell numbers, a significant proportion of treated patients fails to achieve normalization of these counts (Benveniste et al., 2005; Gazzola, Tincati, Bellistri, Monforte, & Marchetti, 2009; Kelley et al., 2009). Not surprisingly, this “immunologic failure” is more common in persons who fail to effectively suppress HIV replication (Gandhi et al., 2006). Yet, even among persons whose treatment regimens decrease HIV levels in plasma below the limits of assay detection, immunologic failure occurs and as expected, is seen more often in persons who start therapy with lower CD4+ T cell numbers (Lederman et al., 2011). Immunologic failure also appears to be more common in older subjects and among men (Gandhi et al., 2006; Lederman et al., 2011). With time and sustained suppression of HIV replication, more immune failure subjects tend to normalize circulating CD4+ T cell counts (Hunt et al., 2003; Kelley et al., 2009), yet a substantial minority of treated persons (in our clinic at University Hospitals Case Medical Center as many as one in four with suppressed viral replication under treatment) will sustain circulating CD4+ T cell numbers below the lower limits of normal (B. Rodriguez and H. Myerson unpublished). In these immune failure subjects, immune activation, inflammation, and coagulation abnormalities persist and are demonstrable at levels higher than those seen in healthy subjects and among HIV-infected subjects who experience “normalization” of blood CD4 T cell numbers (Lederman et al., 2011). In these subjects, both CD4+ and CD8+ T cells coexpress activation markers such as CD38 and HLA-DR, yet even though both CD4+ and CD8+ T cells are activated, only CD4+ T cells are more often demonstrable in cell cycle and these are primarily memory-phenotype cells. An apparent failure of T cell maturation is suggested in this setting by the diminished numbers of circulating CD4+ and CD8+ naïve T cells (Lederman et al., 2011). This is likely mediated in part by diminished T cell expression of the IL-7 receptor alpha

chain CD127 (Colle et al., 2006; Marziali et al., 2006) as well as by a suggested failure of reliable T cell access to IL-7 in lymphoid tissues as a result of fibrosis and architectural distortion of the fibroblast reticular network (Zeng et al., 2011). At the same time, immune failure patients sustain high systemic levels of inflammation and coagulation with increased expression of interferon-stimulated genes (Fernandez et al., 2011) and increased plasma levels of IL-6, sCD14, and D-dimers (Lederman et al., 2011), and not surprisingly, immune failure subjects appear at increased risk for the non-AIDS morbidities now seen in treated HIV infection as discussed above. Thus, immune failure and inflammation are linked and plausibly both are the consequence of concurrent LN fibrosis and sustained damage to the gut as outlined directly below.

6. THE LN IN TREATED HIV INFECTION

LNs were identified as major sites of viral replication in HIV-infected subjects (Pantaleo et al., 1991, 1993). A number of studies in humans and nonhuman primates have reported higher frequencies of HIV/SIV-infected cells as well as higher copy numbers of viral transcripts in CD4+ T cells isolated from lymphoid tissues (GALT, LN) when compared to the peripheral blood (Chun et al., 1997; Fox, Kotler, Tierney, Wilson, & Fauci, 1989; Kiviat et al., 1998; Pantaleo et al., 1991; Zuckerman et al., 2004). Several features of lymphoid tissues provide a favorable environment for HIV replication. They include (1) a privileged tissue architecture that favors close cellular contact between immune cells, thereby promoting cell-to-cell transmission of HIV and ensuring viral dissemination; (2) a significant enrichment in the frequency of cells that are highly permissive to HIV infection, such as activated CD4+ T cells that can produce large numbers of viral particles; and (3) a proinflammatory environment (Andersson et al., 1998; Biancotto et al., 2007) that enhances viral production from infected cells and promotes new infections. These factors contribute to the high levels of HIV replication observed in lymphoid organs from HIV-infected subjects and provide an explanation for the major role played by these compartments in the pathophysiology of HIV infection. Early in infection, there is evidence that this inflammatory environment promotes the accumulation of T regulatory (Treg) cells and the induction of collagen synthesis as a result of TGFb expression (Estes et al., 2007). This increase in collagen deposition and resultant fibrosis is thought to disrupt the normal architecture of the fibroblastic reticular network that is responsible for trafficking of cells cytokines and antigen through the LN T cell zone and perhaps limiting T cell access to the homeostatic cytokine IL-7 (Zeng et al., 2011). These structural abnormalities are typically not repaired with ART-induced suppression of HIV replication and are related inversely both to the numbers of circulating CD4+ T cells and their restoration with ART (Schacker, Nguyen, Beilman, et al., 2002; Schacker, Nguyen, Martinez, et al., 2002). A biphasic restoration of circulating CD4+ T cells is typically seen with application of ART (Autran et al., 1997; Lederman et al., 1998; Pakker et al., 1998). The first rapid phase seen in the first few weeks of therapy is thought to be a consequence of systemic redistribution of sequestered lymphocytes from inflamed and activated lymphoid tissues as viral replication is halted (Bucy et al., 1999) while the second slower phase is thought to represent homeostatic CD4+ T cell restoration. We have recently found that LN T cells in untreated HIV infection have an impaired responsiveness to sphingosine-1 phosphate, the phospholipid that mediates

chemotactic egress of lymphocytes from lymphoid tissues (Mudd et al., 2013). This defect can be induced in vitro by both T cell receptor engagement and by exposure to type 1 interferons as well as to a variety of microbial toll-like receptor agonists (Mudd et al., 2013). Treatment with antiretroviral drugs largely (but not completely) corrects this defect thereby providing a mechanistic explanation for the rapid systemic first-phase CD4+ T cell restoration with ART.

7. THE GUT IN TREATED HIV INFECTION

The mucosal immune system is dramatically affected during HIV infection. Massive damage to the tight epithelial barrier of the GI tract is linked to microbial translocation and severe immunological dysfunction (Brenchley & Douek, 2008; Klatt, Funderburg, & Brenchley, 2013). Long-term ART partially restores this mucosal damage and dysfunction; however, complete restoration does not often occur. One of the most notable immune abnormalities during acute HIV infection is a rapid and severe depletion of CD4+ T cells from mucosal tissues (Brenchley, Price, & Douek, 2006; Brenchley et al., 2004; Mattapallil et al., 2005; Veazey et al., 1998). While long-term therapy usually induces reconstitution of CD4+ T cells in systemic circulation, depletion is typically maintained in mucosal tissues throughout treatment (Marchetti et al., 2008; Mavigner et al., 2012; Mehandru et al., 2006; Tincati et al., 2009). Initially after infection, CD4+ T cells are profoundly depleted in mucosal tissues, likely due to direct infection by HIV (Brenchley, Price, & Douek, 2006; Brenchley et al., 2004; Mattapallil et al., 2005; Picker, 2006). The selective targeting of the GI tract is likely because the majority of mucosal CD4+ T cells express the HIV coreceptor CCR5 and activated memory cells that the virus infects preferentially (Douek et al., 2002; Mattapallil et al., 2005). There is also evidence that the gut homing integrin a4b7 is also used by HIV to enhance cellular susceptibility to infection (Arthos et al., 2008). Nonetheless, and perhaps in part because of this, complete CD4+ T cell restoration in the gut rarely occurs despite clinically effective suppression of HIV replication by ART (Brenchley & Douek, 2008; Macal et al., 2008). This also may be due, in part, to incomplete suppression of virus replication in gastrointestinal tissues, permitting residual HIV replication and continued CD4+ T cell infection. Persistent damage to the gut mucosal barrier is also a likely important contributor to the failure of CD4+ T cell restoration in the GI tract during ART.

During HIV infection, there is significant damage to the tight epithelial barrier of the GI tract, leading to breaches that allow microbial products to penetrate the lamina propria (Estes et al., 2010; Klatt et al., 2010; Nazli et al., 2010). This damage not only contributes to microbial translocation but also is associated with loss of essential immunoregulatory cells such as CD103+ DCs and impaired production of immunoregulatory cytokines such as IL-17 and IL-22 by T cells and innate lymphocytes (Klatt, Estes et al., 2012). While damage to the structural barrier has not been well studied in the context of ART, it is clear that the associated immune dysfunctions persist despite treatment-induced virus suppression. Indeed, loss of IL-17 producing CD4+ T cells (Th17 cells) in the GI tract has been associated with increased immune activation and decreased CD4+ T cell restoration, despite virologic control on ART(Gordon et al., 2010; Klatt & Brenchley, 2010; Mavigner et al., 2012). Furthermore, the ratio of Th17 to Treg cells remains decreased after treatment, an imbalance

that may drive elevated indoleamine 2,3-dioxygenase (IDO) production by DCs, further potentiating immune activation, decreasing T cell proliferation, and impairing production of IL-17 and IL-22 (Favre et al., 2010; Reeves et al., 2011). Overall, antigen presenting cell dysfunction persists despite virus suppression on therapy. DCs may contribute to immune dysfunction via IDO production, via altered cytokine production, and by altered mucosal homing (Chehimi et al., 2002; Favre et al., 2010; Jasny et al., 2012; Miller et al., 2012; Reeves et al., 2012). And despite growing evidence that treated HIV infection is characterized by an increased inflammatory signature, the role of the innate immune system in mucosal immune dysfunction during ART is incompletely studied. For example, while monocytes and mucosal macrophages are clearly dysfunctional even in treated HIV infection (Klatt, Funderburg, et al., 2013; Lichtfuss et al., 2011), their role in HIV persistence and in immune activation and microbial translocation remains unclear.

Chronic mucosal dysfunction and immune activation may be a result of persistent microbial translocation despite ART. During HIV infection, mucosal damage allows microbial products to translocate across the tight epithelial barrier of the gut into the lamina propria and eventually into circulation (Brenchley, Price, Schacker, et al., 2006; Klatt, Funderburg, et al., 2013). Although most work to date is correlative, we suspect that persistent microbial translocation is an important driver of chronic, pathological immune activation in HIV infection (Brenchley & Douek, 2008, 2012; Brenchley, Price, Schacker, et al., 2006; Klatt, Funderburg, et al., 2013). Recent work in the nonhuman primate model indicates that during acute SIV infection, blockade of microbial translocation with the LPS-binding resin sevelamer decreases both systemic microbial translocation as well as systemic indices of both T cell activation and inflammation (Pandrea, 2013). And while microbial translocation is reduced with suppressive ART, most studies find elevated levels of these products in circulation in these subjects when compared to levels found in uninfected persons (Chege et al., 2011; Klatt, Funderburg, et al., 2013; Lederman et al., 2011; Lichtfuss et al., 2011; Merlini et al., 2011; Pilakka-Kanthikeel et al., 2012). This enduring microbial translocation may well underlie the persistent immune activation and inflammatory sequeale that occur despite treatment and are associated with increased morbidity and mortality in treated patients (Kuller et al., 2008; Lichtfuss et al., 2011; Rodger et al., 2009; Sandler et al., 2011).

The mechanisms that underlie mucosal immune barrier dysfunction are still poorly understood. While virus replication likely plays a role, particularly early in infection, the persistent mucosal dysfunction during ART when virus replication is effectively suppressed suggests that factors distinguishable from viral replication underlie the persistence of gut lesions (Klatt, Funderburg, et al., 2013). Furthermore, lack of mucosal dysfunction, including an absence of microbial translocation or loss of Th17 cells, in non-progressive SIV infection of naturally adapted nonhuman primates, which have high virus replication but do not progress to AIDS, further indicates that mucosal damage is not solely due to the virus (Brenchley, Price, Schacker, et al., 2006; Brenchley et al., 2008; Klatt, Silvestri, & Hirsch, 2012). We suspect that virus replication and CD4+ T cell depletion results in immune activation and inflammation, damaging the gut epithelial barrier permitting microbial translocation, that may perpetuate mucosal and systemic immune activation ultimately contributing to CD4+ T cell restoration failure. As is seen in systemic lymphoid tissues during pathogenic infection, and as a consequence of inflammation (Estes, Baker, et

al., 2008), there is also collagen deposition and fibrosis of lymphoid follicles of the GI tract that alters their architecture and appears to limit CD4+ T cell restoration at these sites (Estes, Haase, & Schacker, 2008). Interplay between gut mucosal immune defenses and the microbiota is likely as in ART-treated SIV-infected macaques, prebiotic/probiotic treatment enhanced CD4+ T cell restoration in the gut possibly by decreasing fibrosis (Klatt, Canary, et al., 2013).

8. OTHER POSSIBLE DRIVERS OF RESIDUAL IMMUNE DYSREGULATION IN TREATED HIV INFECTION

As noted earlier, several recent studies have identified markers of immune activation, inflammation, and coagulation as robust predictors of morbidity and mortality in treated HIV infection (Gray et al., 1999; Kalayjian et al., 2010; Kuller et al., 2008; Sandler et al., 2011); it remains unclear, however, which of these elements are directly driving pathogenesis and which are just markers of the persistent inflammatory environment that characterizes this setting. It is likely that morbidities are multifactorial in origin, with risks driven in part by age, in part by exposures such as cigarettes, and in part by this inflammatory environment. And if, as suspected, multiple factors acting in concert are driving pathogenesis and disease course, unraveling the contributions of each will be challenging. What is more, the underlying drivers of sustained inflammation and coagulation in the setting of treated virologically controlled infection are not clearly defined and may include any of the drivers below alone or in combination.

8.1. Microbial translocation

As noted earlier, microbial translocation has been linked strongly to both immune activation and the pathogenesis of disease in treated HIV infection (Klatt, Funderburg, et al., 2013). And while ART reduces plasma levels of microbial products, plasma levels most typically remain elevated when compared to levels in uninfected controls (Brenchley, Price, & Douek, 2006; Jiang et al., 2009; Lederman et al., 2011; Marchetti et al., 2008). Bacterial products can drive monocyte expression of inflammatory cytokines and coagulation factors (Funderburg et al., 2010, 2012; Pasare & Medzhitov, 2004) that have both been linked to morbidity and mortality in treated infection (Duprez et al., 2009; Kuller et al., 2008). Moreover, in vitro exposure of peripheral blood cells to these products can drive activation and cycling of memory CD4+ T cells (but not so much for CD8+ T cells) (Funderburg et al., 2008), inducing an activation signature that is similar to that seen among treated patients with immune failure (Lederman et al., 2011).

8.2. Homeostatic proliferation

Among persons with profound lymphopenia, circulating levels of the homeostatic cytokine interleukin-7 are elevated (Fry et al., 2001; Napolitano et al., 2001). And while T cell responses to IL-7 may be impaired in HIV infection (Bazdar & Sieg, 2007; Colle et al., 2006; Kalinowska, Bazdar, Lederman, Funderburg, & Sieg, 2013; Marziali et al., 2006), the role of this cytokine in driving T cell activation and cycling in patients with immune failure and profound lymphopenia is plausible as this has been linked to cellular activation in persons with idiopathic CD4 lymphopenia (ICL; Zonios et al., 2008). On the other hand, in

ICL, plasma levels of the inflammatory cytokines IL-6 and the receptors for tumor necrosis factor that have been linked to morbidity and mortality in treated HIV infection are not elevated (I. Sereti, personal communication) suggesting that factors other than cytopenia are likely important in driving inflammation and activation in treated HIV infection. Yet after administration of IL-7 to HIV-infected patients with immune failure, selected indices of immune activation are attenuated (Sereti et al., 2012), but this could be related to IL-7-driven repopulation of the damaged gut mucosal immune system (Cimbro et al., 2012; Sereti et al., 2012). Likewise in nonhuman primates that are naturally infected with the simian immune deficiency virus, immune activation is attenuated after acute infection and CD4 lymphopenia is uncommon (Brenchley, Price, & Douek, 2006; Estes, Gordon, et al., 2008). Whether the benign course of infection is a consequence or a cause of low-level cellular activation remains an unanswered question.

8.3. HIV replication

While HIV replication is attenuated dramatically in most ART-treated patients, with sensitive enough assays, low levels of virus often can be found in plasma (Hatano et al., 2010; Maldarelli et al., 2007; Palmer et al., 2008) and HIV RNA can be found in LN and gut mucosal tissues (Cory, Schacker, Stevenson, & Fletcher, 2013; Yukl et al., 2010). Viral products can drive activation of both adaptive and innate immune responses (Beignon et al., 2005; Heil et al., 2004; Meier et al., 2007) and also can activate the procoagulant activity of circulating monocytes (Funderburg et al., 2010, 2012), potentially contributing to thrombotic risk. Yet, results of ART intensification studies have provided mixed results, with some showing no effect on T cell activation in the blood or GALT (Gandhi et al., 2011; Hatano et al., 2011) and another reporting a decrease in CD8+ T cell activation in a subset of patients (Buzon et al., 2010).

8.4. Copathogens

Coinfection with pathogens that cause chronic infection such as hepatitis C virus, cytomegalovirus, and other human herpesviruses is common in HIV-infected persons and in many regions of epidemic infection, infestation with long-lived parasites such as helminthes is also prevalent. It is reasonable to propose that these persistent infections could contribute to immune activation in treated HIV infection (Borkow, Teicher, & Bentwich, 2007; Modjarrad & Vermund, 2010) as they may serve as persistent sources of antigen that can drive T cell activation as well as other microbial elements that can activate innate immune receptors. Recently, an 8-week trial of valganciclovir, a drug used for the treatment of cytomegalovirus infection in patients dually infected with HIV and CMV reduced indices of CD8 T cell activation (Hunt et al., 2011). CMV coinfection also has been linked to the increased risk of cardiovascular disease in HIV infection (Triant et al., 2007) as those patients with more active CMV-specific T cell responses are more likely to have thickening of the carotid artery intima (Sacre et al., 2012)—a radiographic finding that is associated with increased risk of vascular morbidity, and recent data suggest that CMV-specific T cells may play a role in the endovascular inflammation of HIV infection (Sacre et al., 2012).

8.5. Inflammatory lipids

Patients with chronic HIV infection have altered lipid and metabolic profiles (Grinspoon & Carr, 2005; Rose et al., 2008). These altered lipid profiles may contribute to inflammation in HIV disease, as there is a growing appreciation that lipid subclasses, including oxidized low-density lipoprotein, may activate innate immune receptors (Stewart et al., 2010) and induce proinflammatory cytokine production through activation of the inflammasome (Erridge, 2009). Recently, in a cross-sectional study, metabolic factors (low-density LDL, apolipoprotein A) were better correlated with cardiovascular risk than were inflammatory markers (CRP, IL-6, TNF-a) in HIV-infected patients with ART-controlled viremia (Piconi et al., 2013). There is reason to suspect that certain aspects of the inflammatory lipid profile may be related to certain classes of antiretroviral therapies as the recent randomized SPIRAL study demonstrated that among patients with virologic control on ART, switching treatment from a protease inhibitor-based regimen to an integrase inhibitor-based regimen improved both the lipid profile of these subjects and diminished levels of inflammatory markers in plasma (Martinez et al., 2012) although the lipid changes and inflammatory marker changes were only weakly correlated.

9. THERAPEUTIC APPROACHES

Our evolving understanding of the possible underlying causes of persistent immune activation/inflammation/coagulation during treated HIV infection has given rise to several therapeutic approaches to decrease immune activation, inflammation, and coagulation in this setting.

9.1. Targeting residual viral replication

While most HIV-infected patients with access to ART are able to maintain plasma HIV RNA levels below the limits of detection of current clinical assays, HIV RNA continues to be readily detectable in tissues (Anton et al., 2003), and even in plasma, using ultrasensitive methods (Maldarelli et al., 2007; Palmer et al., 2008). There has been extensive controversy over whether the detected HIV RNA in these studies represents ongoing continued productive viral replication or simply release of HIV from infected cells in the absence of new infection of target cells. While there is little evidence for viral evolution in these individuals, and most treatment-intensification studies have failed to demonstrate a reduction in low-level viremia or immune activation (Dinoso et al., 2009; Gandhi et al., 2010; Hatano et al., 2011; Hunt et al., 2013), addition of raltegravir to an apparently suppressive ART treatment regimen appeared to decrease new infection of CD4+ T cells and reduce T cell activation or D-dimer levels in two independent randomized controlled trials (Hatano et al., 2013; Massanella et al., 2012). These apparent immunologic and virologic benefits appeared to be most apparent in individuals receiving protease inhibitor-based therapy in both of these studies, and while unproven, there is some speculation that incomplete drug penetration into lymphoid tissues for some antiretroviral drugs and/or classes (Cory et al., 2013) may allow for at least some aborted rounds of viral replication—insufficient to result in viral evolution—but sufficient to contribute to immune activation. That said, the immunologic benefit of treatment intensification is marginal at best and will

likely be an insufficient strategy for managing chronic immune activation in treated HIV infection.

9.2. Targeting chronic viral coinfections

Most HIV-infected individuals are infected chronically with many other viruses including cytomegalovirus. Since CMV is responsible for at least 10% of the entire circulating memory T cell repertoire in healthy HIV-uninfected CMV-seropositive individuals, and presumably even higher levels in treated HIV infection (Naeger et al., 2010), our group recently tested the hypothesis that asymptomatic CMV (and/or other herpesvirus) replication contributes to persistent immune activation in treated HIV infection. Indeed, we found that treating asymptomatic CMV coinfection with valganciclovir significantly reduces CD8+ T cell activation in the context of treated HIV infection (Hunt, Martin, et al., 2011). While drug-related toxicities preclude the long-term use of valganciclovir, other drugs targeting CMV are in clinical development and may hold promise for future therapeutic approaches to reduce T cell activation in treated HIV infection. The contribution of other chronic viral infections to systemic immune activation in treated HIV infection is less clear but is an area of active study.

9.3. Targeting microbial translocation

Given the strong link between markers of gut epithelial barrier dysfunction, monocyte activation, and mortality, several studies are now targeting microbial translocation to reduce immune activation in treated HIV infection. While an early trial of hyperimmune bovine colostrum showed no benefit (and failed to reduce microbial translocation; Byakwaga et al., 2011), other recent pilot studies of prebiotic interventions show some promise in reducing systemic markers of monocyte activation and/or microbial translocation, though these studies need to be replicated in larger trials (Gori et al., 2011). Other ongoing studies in the NIH-funded ACTG are assessing the impact of rifaximin (an antibiotic that is not systemically absorbed) and sevelamer (which binds bacterial LPS in the gut lumen) on microbial translocation and immune activation in HIV infection.

9.4. Interventions to improve CD41 T cell recovery

While the relationship between inflammation and clinical outcomes appears independent of CD4+ T cell count, certain interventions designed to improve CD4+ T cell recovery may well help decrease microbial translocation and systemic immune activation, particularly if they restore important CD4+ T cell subsets in the gut mucosa. While IL-2 therapy failed to prevent morbidity and mortality despite raising CD4+ T cell counts (Abrams et al., 2009), IL-7 administration may prove more promising since the phenotype of the expanded cell populations appears more favorable (i.e., without Treg characteristics) and it appears to restore CD4+ T cells in the gut-associated lymphoid tissue and decrease D-dimer levels in peripheral blood (I Sereti et al., 2012).

9.5. Targeting innate immune responses

As there is substantial evidence linking innate immune activation to the pathogenesis of disease in treated HIV infection, some groups have conducted trials of weak to moderate

inhibitors of innate immune responses. For example, a small pilot trial of chloroquine appeared to have favorable immunologic effects in untreated HIV infection (Murray et al., 2010), but hydroxychloroquine appeared to increase plasma HIV RNA levels while having very little effect on T cell activation in a much larger randomized controlled trial (Paton et al., 2012). Interestingly, when hydroxychloroquine was assessed in ART-suppressed patients, it appeared to reduce T cell activation significantly (Piconi et al., 2011), suggesting that modulating the innate immune response might have qualitatively different effects when interferons are no longer needed for the control of HIV replication.

Several commonly used medications with anti-inflammatory properties decrease monocyte activation and may hold promise in treated HIV infection. For example, a recent randomized controlled trial of rosuvastatin in ART-suppressed HIV-infected individuals demonstrated significant reductions in plasma sCD14 levels and cellular markers of monocyte activation (McComsey et al., 2013). Similarly, an uncontrolled trial of aspirin in HIV-infected individuals suggested a reduction in sCD14 levels after 1 week (O'Brien et al., 2013) though this observation needs to be confirmed in a randomized controlled trial. Whether these interventions are associated with clinical benefits can only be confirmed in much larger clinical event trials.

10. SUMMARY

Despite effective control of HIV replication with combination antiretroviral therapies, there is increasing evidence that selected morbidities and mortalities are increased in treated HIV-infected persons. These outcomes appear linked to incomplete systemic CD4+ T cell restoration with therapy and also with an increased immune activation, inflammation, and coagulation profile. And while activation, inflammation, and coagulation abnormalities are greater in those with incomplete systemic immune restoration, both the determinants of these processes and their relationships to each other are incompletely understood. Defining the pathogenesis of this RIDS will help to identify targets for therapeutic intervention in treated HIV infection and may also highlight determinants of morbidities that affect the general population.

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