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Authors
Deeks, Steven G
Tracy, Russell
Douek, Daniel C

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Systemic Effects of Inflammation on Health during Chronic HIV Infection

Steven G. Deeks[1], **Russell Tracy**[2], and **Daniel C. Douek**[3]

[1]University of California, San Francisco, San Francisco, CA, USA

[2]University of Vermont, Colchester, VT, USA

[3]Vaccine Research Center, National Institutes of Health, Bethesda, MD, USA

Abstract

Combination antiretroviral therapy for HIV infection improves immune function and eliminates the risk of AIDS-related complications, but does not restore full health. HIV-infected adults have excess risk of cardiovascular, liver, kidney, bone and neurologic diseases. Many markers of inflammation are elevated in HIV disease and strongly predictive of the risk of morbidity and mortality. A conceptual model has emerged to explain this syndrome of diseases where HIV-mediated destruction of gut mucosa leads to local and systemic inflammation. Translocated microbial products then pass through the liver, contributing to hepatic damage, impaired microbial clearance and impaired protein synthesis. Chronic activation of monocytes and altered liver protein synthesis subsequently contribute to a hypercoagulable state. The combined effect of systemic inflammation and excess clotting on tissue function leads to end-organ disease. Multiple therapeutic interventions designed to reverse these pathways are now being tested in the clinic. It is likely that knowledge gained on how inflammation affect health in HIV disease could have implications for our understanding of other chronic inflammatory diseases and the biology of aging.

INTRODUCTION

The natural history of both untreated and treated HIV infection is well known. In the absence of antiretroviral drugs, persistent high-level HIV replication causes progressive decline in CD4+ T cell counts, immunodeficiency and AIDS. When the right combination antiretroviral treatment regimen is given to a motivated patient, HIV replication is essentially completely inhibited, leading over time to improved immune function and the near elimination of any risk for developing an AIDS-defining complication. However his

Correspondence to: Steven G. Deeks, University of California, San Francisco, School of Medicine, Department of Medicine, San Francisco General Hospital Bldg 80, 1001 Potrero Avenue, San Francisco, CA 94110, sdeeks@php.ucsf.edu.

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does not mean that health is fully restored. For reasons that are now the focus of intense research, effectively-treated HIV-infected adults have a greater risk of non-AIDS-related overall morbidity and perhaps mortality than age-matched HIV-uninfected adults. Cardiovascular disease, neurocognitive disease, osteoporosis, liver disease, kidney disease and some cancers are more common in those with HIV than those without HIV (Freiberg et al., 2013). Because many of these problems are generally associated with aging, the concept that HIV somehow "accelerates" aging has caught the attention of many in the community and the popular press. Indeed, there are reports that frailty and other geriatric syndromes occur years earlier than expected, at least in small subset of patients (Desquilbet et al., 2007).

Several factors contribute to the excess risk of these non-AIDS events, including antiretroviral drug toxicity, a high prevalence of traditional risk factors (such as substance abuse, obesity and hypertension), and immune dysfunction and inflammation. The literature with regard to the latter risk factor is remarkably consistent. The frequency of "activated" T cells, inflammatory monocytes, and inflammatory cytokines is higher in untreated and treated HIV infected adults than that observed in age-matched uninfected adults (French et al., 2009; Hunt et al., 2003; Neuhaus et al., 2010; Sandler et al., 2011b). Biomarkers associated with a hypercoagulable state are similarly elevated in HIV-infected adults (Neuhaus et al., 2010). Importantly, subtle elevations in both inflammatory and coagulation biomarkers are associated with dramatic and sustained increases in risk of all-cause morbidity and mortality, as compared to their prognostic effects in the general population (Cushman et al., 1999a; Kuller et al., 2008; Tien et al., 2010).

In this Perspective, we discuss the mechanisms for chronic inflammation in HIV disease. We also discuss how inflammation and hypercoagulation might cause disease and summarize ongoing attempts to alter these pathways therapeutically. A testable model is presented in which HIV infection directly and indirectly causes chronic activation of both the adaptive and innate immune systems, resulting in a low-level but sustained inflammatory state that persists even after the virus is controlled with antiretroviral therapy. This sustained inflammatory state over decades causes vascular dyfunction and alterations in coagulation state, leading to end-organ disease and eventually multimorbidity (Figure 1).

HIV AS AN INFLAMMATORY DISEASE

Since the initial reports of AIDS, it has been clear that chronic inflammation plays a central role in the pathogenesis of untreated HIV infection. Acute HIV infection is associated with rapid and intense release of a variety of cytokines (including interferon-α, interferon-γ, inducible protein 10, tumor necrosis factor, IL-6, IL-10, IL-15) (Stacey et al., 2009). The frequency of activated T cells also increases dramatically during acute HIV infection, with up to 50% of certain CD8+ T subsets activated (Papagno et al., 2004). After resolution of acute infection, a T cell activation "steady-state" is achieved that is predicted in part by degree of HIV replication and innate immune responses (Chevalier et al., 2013; Deeks et al., 2004). Decades of intense research into this phenomenon has led to a number of conclusions regarding the potential root causes of inflammation: (1) HIV replication contributes directly to T cell activation, (however, the frequency of HIV-specific T cells is only a small

proportion of the activated cell population, suggesting other less direct mechanisms) (Papagno et al., 2004), (2) other pathogens—including common herpes viruses such as CMV—contribute to high level T cell activation, although why the percentage of antigen-specific T cells is dramatically elevated is not known (Doisne et al., 2004; Naeger et al., 2010; Smith et al., 2013; Wittkop et al., 2013), (3) HIV-mediated breakdown in the gut mucosa and chronic exposure to gut microbial products like lipopolysaccharide (LPS) is also a key factor driving inflammation (Brenchley et al., 2006), and (4) dysfunctional immunoregulatory factors likely contribute to persistent inflammation. This chronic inflammatory environment appears to cause fibrosis in lymphoid tissues, which in turn causes CD4+ T cell regenerative failure and disease (Figure 1) (Boulware et al., 2011; Schacker et al., 2002; Zeng et al., 2012). Antiretroviral therapy partially reverses many if not all of these pro-inflammatory pathways, but the effect is incomplete, and inflammation persists indefinitely.

Given that CD4+ T cells are the main target for HIV infection, it has long been assumed that abnormalities of the adaptive immune system would dominate in any study of disease pathogenesis. Indeed, the best characterized biomarkers of immune function in untreated HIV infection are the absolute CD4+ T cell count and the frequency of activated T cells. This assumption may not be valid in the context of treated HIV infection, where a growing number of studies have implicated monocyte and macrophage-related inflammation rather that T cell activation as a predictor and presumably cause of disease progression.

IL-6 is a broadly acting pro-inflammatory cytokine that is released from a variety of cells, particularly monocytes and macrophages. Antiretroviral-treated adults have on average about 40 to 60% higher concentrations of IL-6 than well-matched uninfected adults (Neuhaus et al., 2010). IL-6 amounts were strongly associated with all-cause mortality in the INSIGHT Strategies for Management of Antiretroviral Therapy (SMART) study (odds ratio for fourth versus first quartile of 8.3, $P < 0.0001$) (Kuller et al., 2008). These findings have been confirmed in many other studies, including the large ESPIRIT and SILCAAT cohorts (odds ratio fourth/first quartile 5.6).

Soluble CD14 (sCD14) and sCD163 are also markers of monocyte and macrophage activation. Both are elevated in HIV disease and predictive of morbidity and mortality (Burdo et al., 2011b; Kelesidis et al., 2012; Sandler et al., 2011b). CD14 is expressed on circulating monocytes and many tissue macrophages (although not those in the gut) and is the co-receptor, along with TLR4, for LPS. LPS binding results in cleavage of the GPI anchor of cell-surface CD14, the production of non-GPI-linked CD14, and the release of both into the circulation as soluble CD14 (sCD14). sCD14 can bind LPS and deliver it to a variety of cell types, including vascular endothelial cells, thus allowing for their activation by LPS. sCD14 is elevated in other diseases characterized or exacerbated by endotoxemia, such as hepatitis, rheumatoid arthritis, and systemic lupus erythematosus. CD163 is the hemoglobin scavenger receptor expressed on the surface of monocytes and macrophages, particularly those which are more inflammatory (CD14+CD16+). It is released as a soluble form (sCD163) in response to a number of inflammatory signals, including binding of LPS to TLR4.

Abnormalities of the indoleamine 2,3-dioxygenase (IDO) pathway also exist in HIV disease, and are only partially reversed by antiretroviral therapy. The ratio of kynurenine to tryptophan, which reflects IDO activity, is elevated in untreated and treated disease, is correlated with other inflammatory biomarkers, and predicts disease progression independent of other pathways (Boasso et al., 2007; Favre et al., 2010; Hunt et al., 2011b).

Monoctye turnover and activation have been directly linked to SIV and HIV pathogenesis. SIV infection is associated with increased turnover of circulating monoctyes, and the frequency of these proliferating cells is correlated with sCD163, T cell activation and risk of disease progression (Burdo et al., 2010; Hasegawa et al., 2009). The frequency of activated (CD14+CD16+) monocytes is elevated in untreated and treated HIV disease (Burdo et al., 2011a), while the frequency of pro-inflammatory CD16+ monocytes in a largely treated cohort of HIV-infected adults was independently associated with greater risk of coronary artery calcium progression (Baker et al.).

Collectively, these data strongly implicate chronic activation of innate immunity contributes to morbidity and mortality in HIV-infected adults. Indeed, in those studies in which both innate and T cell markers were measured, the former tended to dominate in terms of the prognostic capacity (Hunt et al., 2012; Tenorio et al., 2013). A critical task for the field is to determine why chronic upregulation of these pathways cause disease. Several possibilities exist. Given that monocyte and macrophage-related inflammation is central to formation of atherosclerosis in the general population, much of the attention in the HIV research community has shifted toward understanding how these cells affect vascular health. Inflammation, altered blood flow dynamics, circulating bacterial products, pro-atherogenic lipids, and other factors associated with HIV infection can cause damage to the endothelium and upregulation of adhesion factors. Monocytes are recruited, take up “residence” in blood vessel walls, phagocytize lipids and other toxins, form foam cells, and contribute to the formation of atherosclerotic plaques. When plaques become unstable or rupture, the coagulation process is activated, and thrombotic occlusion of the vessels occurs, leading to tissue damage. This process is clearly not unique to those with HIV infection (Libby et al., 2011; Woollard and Geissmann, 2010), but may be accelerated by the chronic inflammatory nature of the disease. Chronic activation of the innate immune system could also cause a potentially harmful hypercoagulable state, as outlined below.

UNIQUE ROLE OF GUT MUCOSA IN HIV DISEASE PATHOGENESIS

The gut mucosa contains a high concentration of HIV-susceptible, CCR5-expressing CD4+ T cells. During acute HIV infection, the virus rapidly spreads throughout the gut-associated lymphoid tissue (GALT), leading directly to the loss of CD4+ T cells and indirectly to epithelial injury (Brenchley et al., 2004; Li et al., 2005; Sankaran et al., 2008). The resulting loss of mucosal integrity results in sustained exposure within the gut mucosa to pro-inflammatory microbial products (Figure 2). With acute disease progression, microbial product translocation and its inflammatory effects becomes systemic (Brenchley et al., 2006; Burdo et al., 2011a; Hunt et al., 2012; Mehandru et al., 2004). Effective antiretroviral therapy might temper this process, particularly if initiated early, but the effect is incomplete (Jiang et al., 2009; Mavigner et al., 2012; Mehandru et al., 2006). In multiple observational

studies of untreated and treated HIV disease, plasma measures of microbial translocation such as LPS, sCD14 (the LPS co-receptor), intestinal fatty acid binding protein (I-FABP, a marker of gut epithelial cell apoptosis), and zonulin (which declines in response to barrier disruption) have been associated with disease progression (Ancuta et al., 2008; French et al., 2013; Hunt et al., 2012; Kelesidis et al., 2012; Marchetti et al., 2011; Sandler et al., 2011b). The role of microbial translocation in disease pathogenesis has been confirmed in experimental models of pathogenic SIV infection (Estes et al., 2010).

Microbial translocation is not unique to HIV disease. Increased intestinal permeability is a key factor in the pathogenesis of inflammatory bowel disease, pancreatitis, graft-versus-host disease, excessive alcohol consumption, as well as obesity and diabetes, and might even contribute to aging (Lassenius et al., 2011; Monte et al., 2012; Nalle and Turner, 2012; Pussinen et al., 2011; Pussinen et al., 2007; Sandler et al., 2011a; Tran and Greenwood-Van Meerveld, 2013). The proinflammatory products known to translocate in such states include LPS, peptidoglycan, lipoteichoic acid, flagellin, ribosomal DNA and unmethylated CpG-containing DNA, all derived from bacteria and fungi. These products cause both local and, after passing through the liver, systemic effects via their stimulation of innate immune cells (particularly macrophages and dendritic cells) and non-immune cells (including endothelial cells of the cardiovascular system) (Kanneganti et al., 2007; Kawai and Akira, 2010).

What sets HIV disease apart from the many other conditions of microbial translocation is that the damage to the gut mucosa is two-fold — both immunologic and structural. Massive HIV-mediated CD4+ T cell depletion is accompanied by enterocyte apoptosis and lamina propria fibrosis (Brenchley et al., 2004; Li et al., 2005; Sankaran et al., 2008). Furthermore, the preferential loss of IL-17 and IL-22-secreting CD4+ T cells, which are critical for both antimicrobial immunity and epithelial integrity at mucosal surfaces, exacerbates and perpetuates this damage (Brenchley et al., 2008; Favre et al., 2010). Inhibition of Th17 cell differentiation is further exacerbated by an upregulation of tryptophan catabolism by the interferon- and microbial product-inducible enzyme IDO. A vicious cycle has been proposed in which microbial products such as LPS stimulate tissue-resident dendritic cells to produce interferon-alpha and activate the IDO pathway, leading to shift in T cells from Th17 phenotype to T regulatory phenotype. This loss of Th17 leads to even more microbial translocation, and the cycle continues (Favre et al., 2010).

HIV disease disrupts the normal microbiota of the gut (dysbiosis) (Ellis et al., 2011; Gori et al., 2008; Vujkovic-Cvijin et al., 2013). This process is associated with an enrichment of bacterial species that can catabolize tryptophan through the kynurenine pathway, which may contribute to the loss of Th17 cells (Vujkovic-Cvijin et al., 2013), as noted above. While the effect of bacterial metabolism on the gut immune system needs to be more thoroughly characterized, it is tempting to speculate on more far-reaching consequences of dysbiosis in HIV infection. For example, recent studies have shown that metabolism of phosphatidylcholine in the diet by components of the intestinal microbiota results in the production of trimethylamine-*N*-oxide (TMAO), which has potent proatherogenic effects (Koeth et al., 2013; Tang et al., 2013). Given the increased incidence of cardiovascular disease in HIV-infected people (Freiberg et al., 2013), associations between the intestinal

microbiota and non-immunologic sequelae of HIV disease are clearly an area ripe for investigation and a possible target for therapeutic intervention.

Similar concerns have been raised regarding enteric viral communities ("virome"). Pathogenic SIV infection is associated with increased size and diversity of the enteric virome (Handley et al., 2012), while advanced HIV infection is associated with increased size of the plasma virome (Li et al., 2013). The clinical significance of these changes has yet to be reported.

Once microbial products, catabolites and metabolites have passed through the mucosa, they pass through the portal vein into the liver. Sensing of microbial products by hepatocytes, hepatic stellate cells and Kupffer cells within the liver activates pro-inflammatory and profibrotic pathways (Duffield et al., 2005; Rivera et al., 2001; Seki et al., 2007; Su, 2002). Through mechanisms yet to be defined, HIV reduces the number of Kupffer cells and impairs hepatic function, thus reducing the capacity of the liver to mitigate the consequences of microbial translocation (Balagopal et al., 2008; Balagopal et al., 2009; French et al., 2013; Sandler et al., 2011a). The combined loss of mucosal immune surveillance and hepatic impairment allows pro-inflammatory microbial products to access the peripheral circulation and the organ systems it supplies.

In summary, a unique 'local' state exists in the gut in which the virus, simply by rapidly depleting CD4+ T cells, destabilizes the immunologic and structural integrity of epithelial barrier, leading to microbial translocation, local inflammation, fibrosis, and perhaps dysbiosis. Microbial products then reach the liver, contributing to liver dysfunction and reduced clearance of these same products (described below). Although the impact of this process on inflammation in acute infection and in resource poor regions remains undefined and controversial (Chevalier et al., 2013; Redd et al., 2009), the collective data from HIV and general population literature strongly implicate this process in the development of end-organ disease, including liver fibrosis and cardiovascular disease. Once the process has been initiated, each of the events associated with local mucosal damage and microbial translocation both exacerbates and drives the other such that even when virus replication is drastically reduced by antiretroviral therapy the process persists, preventing restoration of health.

HIV ALSO CAUSES A HYPERCOAGULABLE STATE, WHICH IS LINKED TO INFLAMMATION AND RISK OF DISEASE

Abnormalities in coagulation factor levels in HIV-positive individuals have been observed for over 20 years (Bissuel et al., 1992; Lijfering et al., 2008), and a hypercoagulable state was proposed 10 years ago (Shen and Frenkel, 2004). The potential role of hypercoagulability as a cause of morbidity and mortality in HIV disease became more widely accepted after release of the results from the aforementioned SMART study. In this large clinical endpoint study, D-dimers—which are degradation products produced during clot lysis—yielded remarkably strong associations with all-cause mortality, with an initial fully-adjusted fourth quartile odds ratio of approximately 40 (Kuller et al., 2008). Follow-up in SMART and other studies have confirmed a strong association of D-dimers with mortality

and cardiovascular disease (Duprez et al., 2012). D-dimer also predicts venous thromboembolic disease (Jong et al., 2009; Musselwhite et al., 2011), which is also increased in incidence in HIV-positive individuals (Fultz et al., 2004). The association between D-dimers and thromboembolic disease in the general population (e.g., with oral contraception) is generally considered as evidence that hypercoagulation causes morbidity, and it is likely that the same causal pathway applies to HIV disease.

HIV replication likely causes hypercoagulation and an increase in D-dimer. The level of HIV replication is correlated with D-dimer levels in untreated disease (Calmy et al., 2009; Kuller et al., 2008) and the initiation of ART is associated with a reduction in D-dimer (Jong et al., 2010; Palella et al., 2010) although not to pre-infection levels as judged by comparison with non-infected controls. Intensification of apparently effective antiretroviral therapy with an additional potent antiretroviral drug decreases HIV replication even further and as a consequence decreases D-dimer levels (Hatano et al.). HIV-associated inflammation is also weakly associated with coagulation status in some studies. Higher levels of sCD14 and sCD163 are correlated with D-dimer levels (Funderburg et al., 2009; Jiang et al., 2009; Pandrea et al., 2012), while IL-6 and CRP are associated with D-dimer levels (Duprez et al., 2012; Justice et al., 2012a).

Perhaps the most direct experimental evidence supporting a causal link between microbial translocation, monocyte activation, hypercogulation and disease comes from a series of nonhuman primate studies. Despite comparable levels of viral replication, SIV infection of its natural host (e.g., African green monkeys) causes only transient inflammation and no hypercoagulation while SIV infection of susceptible hosts (e.g., Pigtail macaques) causes chronic inflammation and hypercoagulability (Pandrea et al., 2012). Susceptible monkeys also developed extensive *in situ* coagulopathies, with thrombi identified in the kidney, lung and brain among other organs. Infusion of LPS into SIV-infected African green monkeys causes increased macrophage activation (as defined by sCD14), increased coagulation (as defined by D-dimer) and increased SIV replication, providing a direct link between these various pathways (Pandrea et al., 2012).

A growing number of human studies have linked microbial translocation with hypercoagulation. As noted above, HIV-mediated destruction of gut mucosa leads to chronic systemic exposure to LPS. LPS binds to CD14 and TLR4, setting off a cascade of cell activation and tissue factor expression (Funderburg et al., 2010). This in turn activates the coagulation cascade, leading to increased risk of clotting. As described in the next section, microbial translocation also affects liver function, which has complex effects on coagulation system.

Given the observational nature of these studies, whether the coagulopathy reflected by D-dimer levels is a causal component of HIV pathophysiology remains unproven. Arguing in favor of causality, D-dimer levels prospectively predict the occurrence of both venous and arterial thrombosis in the general population (Cushman et al., 2003; Cushman et al., 1999b) and in HIV disease (Duprez et al., 2012; Ford et al., 2010; Jong et al., 2009; Ledwaba et al., 2012; Musselwhite et al., 2011). Among HIV-infected adults, D-dimer amounts add risk prediction to complex risk algorithms such as the VACS Index (Justice et al., 2012b). D-

dimer levels are associated with important intermediate pathophysiological mechanisms such as endothelial damage and vascular dysfunction (Baker et al., 2010; Hileman et al., 2012). Finally, D-dimer levels are associated with *in situ* clot formation in SIV infected macaques (Pandrea et al., 2012). However, the definitive answer to this question must await the gold standard of randomized clinical trials of anticoagulation in HIV.

INFLAMMATION, LIVER FUNCTION AND HYERPCOAGULATION

HIV infection may cause liver disease through several mechanisms, including direct infection of stellate and Kupffer cells, chronic inflammation, translocation of microbial products, and low-grade disseminated coagulaopathy (Balagopal et al., 2009; French et al., 2013; Peters et al., 2011b; Tuyama et al., 2010). This effect is exacerbated by chronic hepatitis C infection and alcohol abuse, both common in HIV infected adults (Weber et al., 2006) (Justice et al., 2010). Some commonly used antiretroviral drugs are potentially hepatoxic. The well-described metabolic syndrome that is associated with antiretroviral therapy likely impacts upon liver health. Biomarkers of liver fibrosis such as hyaluronic acid and clinical estimates such as the FIB-4 are elevated in untreated and treated HIV disease and associated with mortality (Justice et al., 2012a; Peters et al., 2011a, b) These observations collectively argue that hepatic function is a critical determinant of health in HIV disease, although how hepatic function influences non-liver outcomes is incomplete.

The liver produces a series of important coagulation factors. Measurements of these factors in people proven useful in modeling the potential to produce thrombin (Baker et al., 2013). Mathematical models of thrombin generation have been explored since the mid-1980s (Nesheim et al., 1984), and have demonstrated substantive associations with prothrombotic states such as coronary heart disease (Brummel-Ziedens, 2013). In a comprehensive study of pro- and anticoagulation factors within the tissue factor-mediated extrinsic pathway, we found that HIV replication leads to short-term increases in some pro-coagulants (e.g., factor VIII) and decreases both pro-coagulants (e.g., prothrombin) and anticoagulants (e.g., antithrombin, protein C). We then applied mathematical modeling to estimate thrombin generation based on the composition of extrinsic pathway factors (the “coagulome”) and demonstrated that the net effect of HIV replication was increased coagulation potential, with a magnitude similar to that seen in the context of acute coronary syndromes (Brummel-Ziedens, 2013).

There are many pathways by which chronic inflammation can cause liver dysfunction and as a consequence affect coagulation status. For example, untreated and treated HIV infection is associated with chronic interferon-alpha signaling. This signaling is presumably related to a number of factors, including HIV replication, excess loads of co-pathogens such as CMV, microbial translocation and dysbiosis. Chronic type I interferon signaling is a well-accepted property of pathogenic HIV disease (Rotger et al., 2011), and persists during effective antiretroviral therapy, where it has negative effects on immune function and reconstitution (Fernandez et al., 2011; Herbeuval and Shearer, 2007). Chronic interferon-singalling can cause upregulation of double-stranded RNA-dependent protein kinase (PKR) which is a cytosolic kinase whose activity results in the inhibition of cellular mRNA translation, with a dramatic inhibition of global protein synthesis (Pindel and Sadler, 2011; Stark et al., 1998).

When this global inhibition occurs in hepatocytes, the production of coagulation factors would be expected to decline.

These observations collectively suggest that subtle alterations in a pre-cirrhotic liver function (due in part to chronic inflammation) leads to a hyercoagulable site and perhaps non-liver end-organ disease. This hypothesis being actively pursued in the general, non-HIV population (Tripodi and Mannucci, 2011).

CLINICAL TRIALS OF ANTI-INFLAMMATORY DRUGS

The constellation of chronic diseases that disproportionately affect the antiretroviral-treated HIV infected population are all strongly associated with inflammation in the general population. Untangling if and how inflammation causes these diseases in adults is the topic of intense research. Since many diseases can either indirectly or directly contribute to an inflammatory state (Justice et al., 2012a), defining the cause and effect relationships has been challenging. Indeed, in analysis of a large cohort of US military veterans with and without HIV disease, controlling for the presence of co-morbidities such as cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, and substance abuse attenuated the association between HIV infection and levels of IL-6, D-dimer and sCD14 (Armah et al., 2012). Even the association between clotting, inflammation and disease is complex, as clotting can have a pro-inflammatory effect, and multi-morbidity can lead to increased risk of clotting (Engelmann and Massberg, 2013).

Most experts believe that a randomized clinical endpoint study will be needed to definitively address the role of inflammation and hypercoagulation as a cause of morbidity in HIV disease. Before such expensive studies are undertaken, pilot studies demonstrating that an intervention is safe and effective in reducing inflammation are first required. Many such studies have been completed, or are ongoing; all are small and exploratory in nature. The studies performed to date have used a spectrum of endpoints, some poorly validated, which limits the ability to draw any broad conclusions on what should happen next.

An optimal way to manage inflammation would to be to address its root cause (s). Given the central role of microbial translocation in HIV disease pathogenesis, a number of studies attempting to affect the gut microbiome and mucosa have been performed. Bovine colostrum binds LPS and may prevent its translocation, but had no effect in a randomized clinical trial (Byakwaga et al., 2011). Prebiotics and probiotics, which alter the bowel flora and might reduce the quantity of potentially pathogenic bacteria, have been tested with positive early results in non-human primate models (Klatt et al., 2013a) and humans (Cahn et al., 2013; Gori et al., 2011). The combination of sulfasalazine and rifaximin in non-human primates lowered microbial translocation and inflammation, suggesting that antibiotics, if given safely, could prove beneficial. Sevelamer binds LPS, has showed promising results in non-human primates and is being studied in untreated HIV-infected adults. No one study is persuasive, but they collectively support future research in this area.

Other root causes of inflammation include excess burden of co-pathogens, persistent HIV production and replication, and lymphoid fibrosis. Our group performed an intensive pathogenesis-oriented randomized clinical study and found reducing CMV replication with

valganciclovir resulted in substantial reduction in T cell activation (Hunt et al., 2011a). Studies aimed at HSV are ongoing. One of the more unsettled areas of HIV investigation pertains to whether HIV replication persists at low levels during standard therapy. Two randomized clinical trials in which a potent drug (raltegravir) was added to standard therapy (treatment “intensification”) found evidence that even during apparently effective antiretroviral therapy the virus can continue to replicate at very low levels and cause inflammation (Buzon et al., 2010; Hatano et al.). Even in the absence of ongoing cycles of virus replication, it is clear that virions are being constantly produced and released. The strong association between reservoir size and activation during antiretroviral therapy suggests that this reservoir may indeed have an inflammatory effect (Hatano et al., 2012; Klatt et al., 2013b). Finally, as irreversible lymphoid tissue fibrosis has been implicated in causing persistent immune dysregulation (Schacker et al., 2002), drugs that reverse collagen deposition and/or reverse fibrosis are being pursued. These drugs include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Another strategy is to reduce inflammation once the process has been initiated. Again, a number of approaches have been attempted. The statins have a well-accepted anti-inflammatory effect, although the mechanism for this effect is unknown, and its role in preventing heart disease controversial. The use of statins has been associated with reduced levels of T cell activation in untreated adults (Ganesan et al., 2011) and reduced levels of activated monoctyes and sCD14 in treated adults (Baker et al.). Aspirin appears to reduce T cell activation and sCD14 in treated adults (O’Brien et al., 2013). COX-2 inhibitors may decrease inflammation in untreated adults (Pettersen et al., 2011). Studies assessing the potential benefit of methotrexate, anti-interleukin-6 antibodies, mTOR inhibitors (e.g., sirolimus) and JAK1-JAK2 inhibitors are being planned.

Given the central role that hypercoagulation appears to have in the pathogenesis of HIV disease, there is also growing interest in looking at anticoagulants, although to our knowledge no study has advanced into the clinic at this time (with the possible exception of aspirin). Possible drugs that might be considered include dabigatran (anti-thrombin) and rivaroxaban (anti-factor Xa), although drug-drug interactions and/or excess risk of bleeding might prevent their use for HIV-associated hypercoagulation. Of note, the statins, which might have unique role in HIV disease (Moore et al., 2011), have known anticoagulant effects (Undas et al., 2005), arguing for their greater use in HIV disease.

Although many of the causes and consequences of inflammation which exist in the untreated state likely apply to the treated disease stage, intervening with an anti-inflammatory drug in these two distinct clinical conditions could be profoundly different. For example, choroquine and hydroxychloroquine are broadly activating anti-inflammatory drugs that have a number of potential beneficial effects, including preventing TLR signaling in dendritic cells. Although these drugs have shown potential benefit in antiretroviral-treated adults (Piconi et al., 2011), a large randomized clinical study of adults with early, untreated HIV disease showed that they can actually increase HIV replication and accelerate the loss of peripheral CD4+ T cell counts (Paton et al., 2012), perhaps because the drug reduces the capacity of immune system to control a very pathogenic virus. These studies and theoretical

considerations suggest that when blocking inflammation, the use of drugs which can maximally suppress HIV replication may be needed.

There are a number of other barriers which will need to be overcome if the field is to be advanced. Given the complexity of the human immune system, any intervention designed to affect one pathway will lead to an unpredictable effect on multiple compensatory pathways. For example, our group recently performed a limited-center, randomized, placebo-controlled study of the CCR5 antagonist maraviroc in long-term treated adults who had low CD4+ T cell counts. The primary hypothesis was that by blocking CCR5, T cell chemotaxis to areas of inflammation might be prevented, resulting in less T cell activation. However, we observed an effect opposite to that predicted, with indirect evidence from the study suggesting that compensatory increases in the ligands for CCR5 causing direct pro-inflammatory effects on macrophages (Hunt et al., 2013). This inherent complexity makes the development of immune based therapeutics far more risky that the development of drugs which directly target the pathogen, such as antiretroviral drugs.

A final barrier confronting the field is the lack of a validated surrogate marker for inflammation and/or immune dysfunction. This problem was well illustrated by the experience with interleukin-2 (IL-2) in HIV disease. Since no one questions the critical role of peripheral CD4+ T cell declines in HIV disease, interventions such as IL-2 that increase the number of these cells would expected to beneficial, but in two large and expensive clinical endpoint studies, IL-2 failed to provide any clinical benefit (it has been postulated that IL-2-mediated increase in thrombosis risk contributed to the failure of this intervention) (Abrams et al., 2009). This sobering experience has, more than any other, limited enthusiasm for developing drugs aimed at addressing the limitations of current treatment strategies for HIV-infected adults.

THE IMPACT OF INFLAMMATION ON MORBIDITY MAY BE AGE-DEPENDENT

It has been argued that humans evolved to remain robust until what is now considered “middle age”. Throughout much of recent human history, procreation and protection of the family ended by the fifth decade of life, an age at which many of the consequences of chronic inflammatory diseases start to become more readily apparent (De Martinis et al., 2005; Finch, 2007; Vasto et al., 2007). CMV infection, for example, is a chronic inflammatory infection that dramatically reshapes the adaptive immune system (Sylwester et al., 2005), but has no appreciable effect on health in the young and middle-aged. Once more advanced age is reached, the presence of CMV as a risk factor for age-associated complications such as frailty becomes more readily apparent, with CMV-associated changes to immune function being a likely mediator of disease in these at-risk individuals (Koch et al., 2007). This age effect might prove to be true in HIV disease. CD8+ T cell activation, for example, had no appreciate effect on disease progression in a large cohort of largely young adults, but had an effect in a post-hoc analysis of those over the age of 50 (Lok et al.).

The capacity of humans to compensate for many insults is a central concept in studies of healthy aging. Most organ systems exhibit some degree of redundancy, and many of the

geriatric syndromes associated with reduced function (e.g., frailty, falls, immobility, and incontinence) only emerge when several systems are affected. Isolated harm to single systems manifesting as liver disease, kidney disease, bone disease, and neuropathy has consequences in isolation, but their true effect on long-term health may only become apparent late in life when this redundancy begins to decline (Clegg et al., 2013). The fact that HIV infection and its treatment are associated with a series of biologic factors (e.g., inflammation, immune dysfunction, telomerase inhibition, mitochondria dysfunction), clinical factors (e.g., polypharmacy, multimorbidity) and social factors (e.g., social isolation, poverty) that influence aging suggest that a global population of well-treated individuals will confront unique challenges when older (Figure 3) (Deeks, 2011; Justice, 2010; Lopez-Otin et al., 2013).

The impact which chronic low-level inflammation will have on the global population of antiretroviral-treated adults who are now expected to live for decades is not known. Notably, the spectrum of inflammatory and coagulation abnormalities described in largely middle-aged HIV-infected populations (e.g.., elevated D-dimer, IL-6, T cell activation, and monocyte activation) shares a number of striking similarities with that observed in much older non-infected adults, where they are known to predict morbidity and mortality (Cesari et al., 2003; Singh and Newman, 2011; Walston et al., 2002).Prospective clinical trials aimed at defining whether anti-inflammatory interventions are beneficial will need to consider the possibility that the cumulative consequences of inflammation on health may only become apparent when participants are older.

CONCLUSION

HIV was identified as the cause of AIDS in 1983. Since that time, billions of dollars have been invested in the determining how the virus is spread and how it causes disease. We likely know more about the pathogenesis of this disease than any other chronic infection. With the advent of highly effective antiretroviral therapy, the nature of HIV disease has largely shifted from one of immunodeficiency to one of chronic inflammation, although we recognize these two phenomenon are tightly linked in both untreated and treated disease. As the cohorts of well-treated individuals become more robust, it is becoming increasingly clear that HIV infection is now a chronic inflammatory disease, and that the disease shares a remarkable similarity to a number of other inflammatory non-infectious diseases.

We believe that the disparate data spanning many disciplines reviewed here support a model that that could be used to inform future translational research. HIV replication initiates an inflammatory process during acute infection that is driven directly by viral replication and indirectly by (1) excess levels of translocated microbial products, (2) excess levels of other chronic pathogens, including CMV, (3) loss of immunoregulatory responses, and (4) potentially by hypercoagulability. Effective antiretroviral therapy reduces HIV replication to negligible levels, but the virus persists and is chronically produced at low levels. The mucosal damage brought on by HIV is incompletely reversed and microbial translocation continues indefinitely. Lymphoid damage is also only partially reversed by therapy, resulting in a state of indefinite immunodeficiency. The collective outcome of these pathways is a persistent inflammatory and/or hypercoagulable state that could in some

people persist indefinitely, even as HIV replication is largely controlled by antiretroviral therapy (Figure 3). As HIV infection is largely a disease of the young, it is possible that some people (including most concerningly the pediatric population) might be exposed to such a state for several decades. The many clinical trial and observational studies summarized here suggest but do not prove that persistent low level inflammation are causing harm to many tissues. If this harm proves to be cumulative, then even mild changes might over time lead to progressive deterioration organ function, with clinical manifestations becoming increasingly apparent as people age. Characterizing the pathogenesis of this process and identifying novel therapies to prevent or reverse inflammation and hypercoagulation will be necessary if the health of HIV-infected individuals is to be fully restored.

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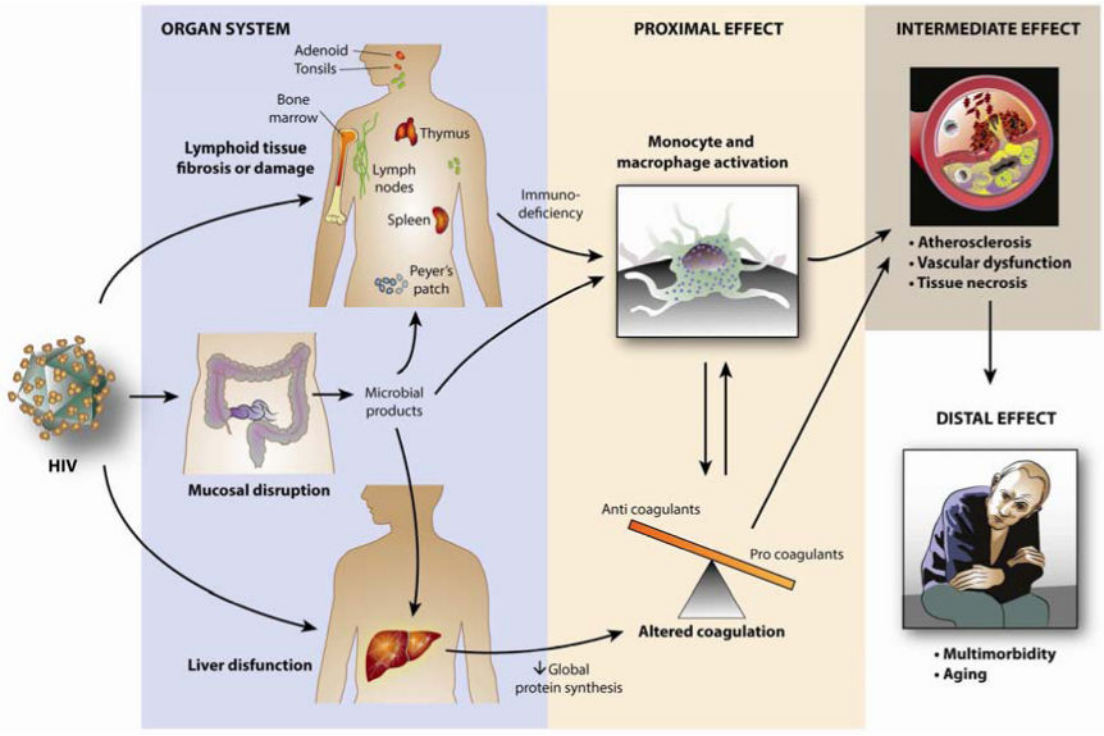

Figure 1. Pathogenesis of inflammation-associated disease in HIV-infected adults

HIV infection causes damage to lymphoid and mucosa tissues, leading to progressive immunodeficiency, excess levels of pathogens (including HIV) and inflammation, HIV also damages the mucosa of the gut, leading to microbial translocation. HIV and its treatment also affects liver function through a variety of mechanisms. The collective effect of these initial insults is chronic monocyte and macrophage activation and hypercoagulation. These processes lead directly to vascular harm, end-organ tissue damage, and multi-moribidity, all of which theoretically may manifest later in life with onset of a variety of geriatric syndromes.

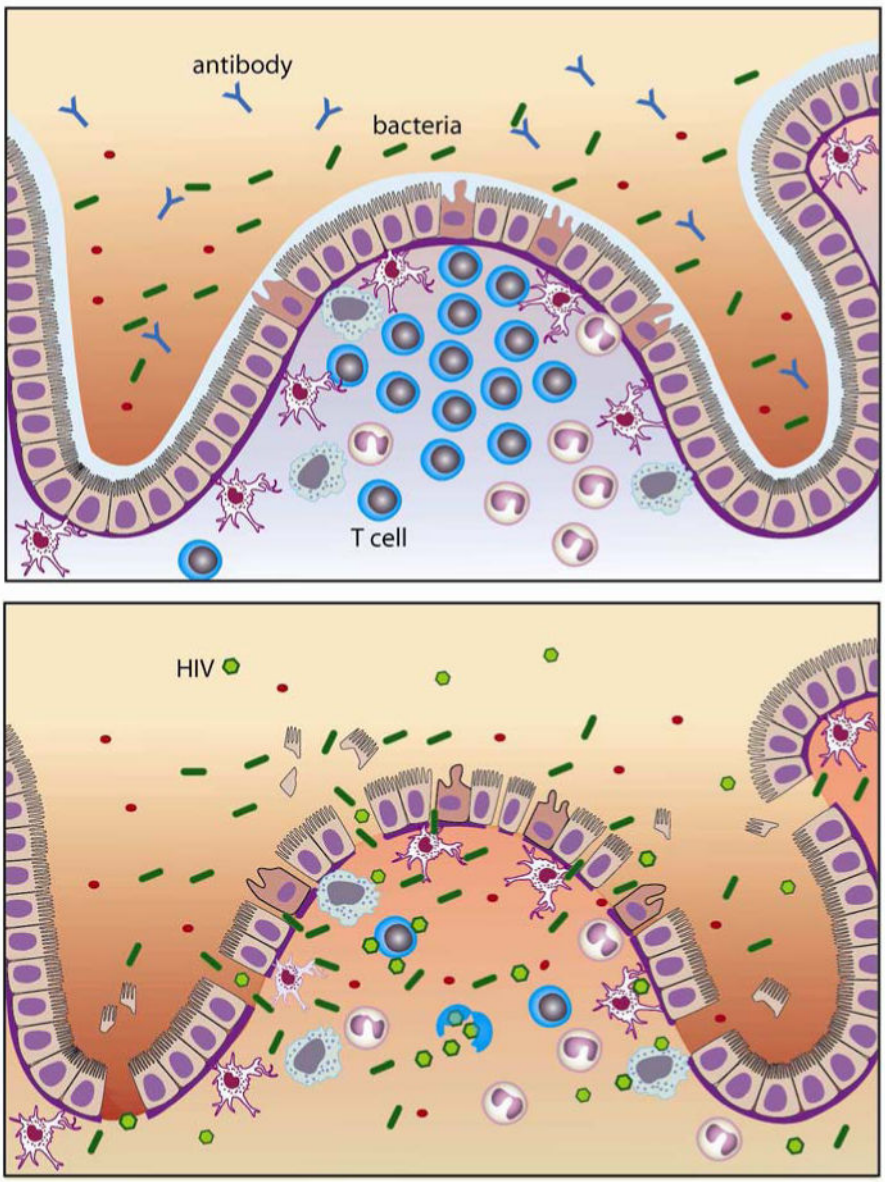

Figure 2. Impact of HIV on gut mucosa

The healthy gut mucosa is marked by functional tight epithelial junctions and a highly regulated, interrelated complex of dendritic cells, macrophages, neutrophils and T cells. This system generates protective mucus, antimicrobial peptides, and secreted antibodies. Normal gut flora is maintained and systemic exposure to microbes and microbial products limited (top). HIV infection alters most if not all aspects of gut defences, leading to breakdown in tight junctions, loss or dysregulation of resident immune cells, alterations in gut flora, and microbial translocation (bottom).

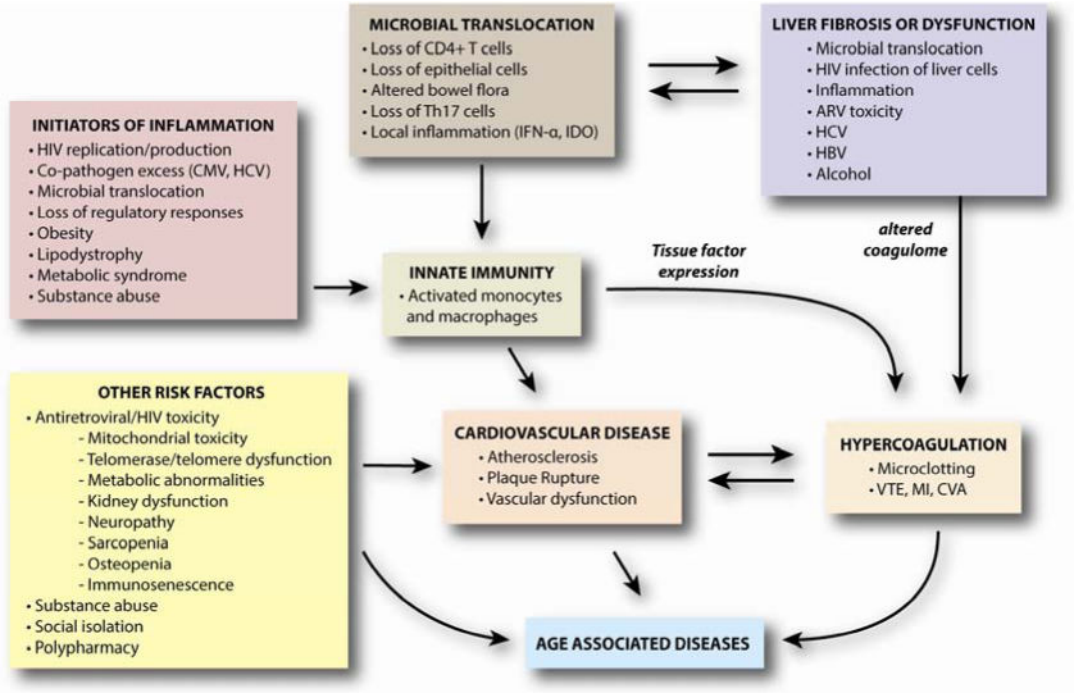

Figure 3. Impact of HIV on inflammation, coagulation and health

Root causes of inflammation in HIV disease include damage to gut mucosa and lymphoid systems, which cause exposure to microbes and high pathogen burden. Microbial translocation, inflammation, HIV replication and other factors contribute to liver dysfunction, which in turn leads to reduced clearance of microbial products and altered production of critical hepatic proteins. Liver dysfunction and chronic activation of innate immunity leads to a hypercoagulable state. Excess subclinical clotting and inflammation each contribute to end-organ tissue damage, vascular disease and a variety of diseases. The cumulative effect of these pathways in combination with other well-accepted risk factors for biologic and clinical aging is expected to affect health in older age.

Table

Anti-inflammatory agents for management of antiretroviral-treated HIV disease

Target	Drug or intervention
Residual or cryptic HIV replication	Treatment intensification, optimized antiretroviral drug tissue penetration, novel antiretroviral drugs
Excess co-pathogen burden	Valacyclovir (HSV), valganciclovir (CMV), HCV cure
Microbial translocation	Sevelamer, rifaximin, mesalamine, isotretinoin, prebiotics, probiotics, colostrum
Poor T cell function	Interleukin-7, growth hormone, anti-PD1 antibodies
Lymphoid and tissue fibrosis	Perfenidone, ACE inhibitors, angiotensin II receptor blockers
Chronic inflammation	HMG CoA reductase inhibitors (“statins”), chloroquine, hydroxycloroquine, celecoxib (COX-2 inhibitors), aspirin, methotrexate, lenalidomide, leflunomide, ruxolitinib (JAK inhibitors), sirolimus (mTOR inhibitors), IDO inhibitors, anti-interferon-alpha antibodies, anti-IL-6 antibodies, anti-IL-1-beta antibodies
Hypercoagulation	Aspirin, apixaban, dabigatran
Cellular aging	Sirtuin activators, sirolimus
Metabolic syndrome, obesity	Metformin, exercise, diet, vitamin D

Drugs aimed at reversing inflammation or its immediate consequences in antiretroviral-treated HIV infection are listed. Those drugs in more advanced stages of development (phase I/II) are listed first, followed by those which are still in development.