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Serious Non-AIDS Events: Therapeutic Targets of Immune Activation and Chronic Inflammation in HIV infection

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Abstract

In the ART era, serious non-AIDS events (SNAEs) have become the major causes of morbidity and mortality in HIV-infected persons. Early ART initiation has the strongest evidence for reducing SNAEs and mortality. Biomarkers of immune activation, inflammation and coagulopathy do not fully normalize despite virologic suppression and persistent immune activation is an important contributor to SNAEs. A number of strategies aimed to reduce persistent immune activation including ART intensification to reduce residual viremia; treatment of co-infections to reduce chronic antigen stimulation; the use of anti-inflammatory agents, reducing microbial translocation as well as interventions to improve immune recovery through cytokine administration and reducing lymphoid tissue fibrosis have been investigated. To date, there is little conclusive evidence on which strategies beyond treatment of hepatitis B and C co-infections and reducing cardiovascular risk factors will result in clinical benefits in patients already on ART with viral suppression. The use of statins seems to show early promise and larger clinical trials are underway to confirm their efficacy. At this stage, clinical care of HIV-infected patients should therefore focus on early diagnosis and prompt ART initiation, treatment of active co-infections and the aggressive management of co-morbidities until further data are available.

1. Introduction

Even though combination antiretroviral therapy (ART) has resulted in dramatic reduction in morbidity and mortality, differences in life expectancy persist between HIV-infected and uninfected individuals [1–3]. Serious non-AIDS events (SNAEs), including non-AIDS malignancies, cardiovascular events, renal and hepatic diseases, bone disorders and neurocognitive impairment, are the major causes of morbidity and mortality in the ART era [4–6]. The pathogenesis of SNAEs is multifactorial and complex. The direct effect of HIV, the impact of immunodeficiency, underlying co-morbidities and co-infections, chronic immune activation and ART toxicities all contribute to SNAEs and are considered in this review (Fig 1).

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Conflict of interest

The authors declare no conflict of interest.

2 Pathogenesis of SNAEs

2a. The direct effect of HIV

HIV infection is associated with immune activation, progressive CD4 T cell depletion and immunodeficiency (discussed below). HIV can also directly contribute to dysfunction in various organs. HIV transgenes can impact on tubular and glomerular epithelial cells and podocytes proliferation, differentiation and apoptosis, leading to HIV associated nephropathy [7]. HIV proteins can induce hepatic fibrosis by promoting hepatic stellate cell activation and collagen expression [8] and render hepatocytes more susceptible to apoptosis through increased sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [9].

2b. The impact of immunodeficiency

The risk of SNAEs is associated with the extent of immunodeficiency, both in terms of pre-ART and on treatment CD4 T cell counts [10–12]. In a cohort of 52 278 individuals in France, those with latest CD4 T cell count of 200–349 cells/ μ L have 2.2, 3.4 and 4.1 folds higher risk of Hodgkin's lymphoma, lung and liver cancers when compared to those with CD4 T cell count >500 cells/ μ L [13]. Data from the D:A:D cohort found that CD4 T cell count <100 cells/ μ L was associated 2.3 and 1.1 fold higher risks of stroke and cardiovascular disease [14].

2c. The role of underlying co-morbidities

Due to common routes of transmission, HIV-infected individuals have higher rates of hepatitis B and C infection than the general population with a prevalence of 6–14% and 25–30%, respectively [15]. Co-infection with hepatitis C virus (HCV) is associated with increased risk of renal disease (1.5 folds) [16], CVD (1.5 folds) [17], cirrhosis (19 folds) [18], hepatocellular carcinoma (5 folds) [18] and overall mortality (1.4 folds) [19], when compared to HIV mono-infected individuals.

HIV-infected individuals are also more likely to have cardiovascular risk factors including higher rates of smoking, hypertension, diabetes, dyslipidemia and renal impairment than the general population [20–22]. However, even after adjusting for traditional cardiovascular risk factors and HCV co-infection, HIV-infected individuals still have elevated risks of myocardial infarction, end stage renal disease and non-AIDS cancers [23].

2d. The consequences of immune activation

In the general population, immune activation and inflammation play a major role in cancer [24, 25], atherosclerosis [26, 27] and liver fibrosis [28, 29]. High levels of markers of inflammation including C-Reactive Protein (CRP) and interleukin (IL)-6 and markers of coagulopathy (D-dimer and fibrinogen) have been associated with increased cancer risk [30–32], cardiovascular disease [33–36] and mortality [37–39]. In HIV-infected individuals higher levels of CRP, IL-6, D-dimer and soluble (s) CD14 (marker of monocyte activation [40]) are also associated with increased risk of malignancy [41], CVD [42, 43], cardiovascular death [44] and overall mortality [45–47].

2e. The drivers of immune activation

HIV infection leads to activation of both innate and adaptive immune responses. HIV RNA can stimulate plasmacytoid dendritic cells through binding to pattern recognition receptors (PRR) such as Toll-like receptor (TLR) 7 [48]. Reverse transcribed HIV DNA can also be sensed in the cytosol by interferon gamma-inducible factor 16 (IFI16) and cyclic GMP-AMP synthase (cGAS) [49]. These lead to the induction of type-I interferons that can activate dendritic cells to enhance antigen presentation, amplify NK and T cells cytotoxic responses and promote antibody production by B cells [50]. HIV also causes immune activation through antigenic stimulation of HIV-specific CD8 and CD4 T cells [51]. Abortive HIV infection in CD4 T cells can also trigger pyroptosis, a form of caspase-1 mediated cell death that is associated with inflammatory cytokine and danger signals release, inducing further inflammation [52, 53]

Microbial translocation may also contribute to immune activation in HIV infection [54]. CD4 T cells in gut-associated lymphoid tissue (GALT) are major targets for HIV infection, due to their activated state and high expression of CCR5 [55–57]. TH17 cells are also preferentially lost [58]. TH17 cells secrete IL17 and IL22, promote neutrophil recruitment and are important in the defense against bacterial and fungal infections and the maintenance of epithelial barrier function [59, 60]. Furthermore, HIV also leads to disruption of intestinal tight junctions and increased mucosal permeability [61]. The translocation of bacterial and fungal products then elicits further inflammatory responses through binding to PRR on monocytes, macrophages and plasmacytoid dendritic cells.

In chronic HIV infection, the microbiome composition is altered (dysbiosis), with decreased levels of beneficial gut microbiota including lactobacilli and bifidobacteria and elevated levels of potentially pathogenic microbiota including those from the enterobacteriaceae family (*Salmonella*, *Escherichia*, *Serratia*, *Shigella*, *Klebsiella*), *Pseudomonas* and *Campylobacter species* [62–64]. Dysbiosis was associated with higher plasma IL-6 and Kynurenine/tryptophan (Kyn/Trp) ratio, which was also associated with lower frequency of TH17 cells [64]. Thus, dysbiosis may further contribute to impairment in mucosal immunity and microbial translocation.

Evaluating the extent that microbial translocation contributes to immune activation is difficult given the lack of a reliable biomarker [65, 66]. Commonly measured markers include plasma lipopolysaccharide (LPS), bacterial 16s rDNA, sCD14, LPS binding protein (LBP) and anti-endotoxin core antigen immunoglobulin (EndoCab). Of these, only LPS and bacterial 16s rDNA are direct measurements of microbial translocation. Both assays, however, suffer from inconsistencies and are sensitive to contamination [65, 66]. sCD14 is secreted by monocytes and macrophages and can bind to LPS and gram positive cell wall components. It is not a specific marker of microbial translocation, however, as it can also be induced by monocyte activation and produced by hepatocytes as acute phase reactant [40, 67]. Intestinal fatty acid binding protein (I-FABP), a biomarker of enterocyte turnover has also been measured and found to correlate with plasma LPS and sCD14 in some [68, 69] but not all studies [70], further obscuring the relationships between intestinal damage, microbial translocation and immune activation. Nonetheless, higher levels of plasma I-FABP and Kyn/Trp ratio have been associated with mortality in treated HIV infection [69].

The presence of co-infections significantly contributes to immune activation and in some cases, end organ injury. Higher CD8 T cell activation has been documented in individuals with HCV co-infection when compared with HIV mono-infected individuals [71, 72]. Immunodeficiency associated with HIV infection also leads to the reactivation and replication of co-infection pathogens such as *M. tuberculosis* (TB) [73, 74], *Cytomegalovirus* (CMV) [75, 76] and *Epstein Barr Virus* (EBV) [77]. HIV-infected individuals with latent or active TB have higher CD4 T cell activation and those with active disease also have elevated levels of plasma sCD14, CRP, IL-6, and IP-10 [78]. In a study of 191 individuals on ART with virologic suppression, the presence of CMV specific CD4 and CD8 responses was associated with CD8 T cell activation [79].

Finally, CD4 T cell depletion in HIV infection may stimulate physiologic homeostatic mechanisms e.g. IL-7 secretion [80], leading to lymphocyte proliferation [81]. This may further lead to the differentiation and the generation of effector T cells that are pro-inflammatory, thereby contributing to immune activation [82].

Immune activation is detrimental in HIV infection. Firstly it can cause activation induced cell death [83, 84], leading to CD4 T cell depletion and progressive restriction in T cell repertoire in both CD4 and CD8 T cells [85]. Secondly, it may promote HIV infectivity as activated T cells are targets for HIV. Thirdly, ongoing immune activation is associated with increased numbers of regulatory T cells (Tregs) in the lymphoid tissues [86]. Tregs secrete Transforming Growth Factor- β (TGF- β), triggering collagen production and deposition by fibroblasts; resulting in structural damage and fibrosis of the lymph node, disrupting access to IL-7 and reduces the regeneration and survival of CD4 T cells [87, 88]. Thus, immune activation leads to CD4 depletion through both increased losses and decreased production and survival of CD4 T cells.

Immune activation has also been associated with coagulopathy. Activated monocyte, macrophages and platelets express increased levels of tissue factor (TF), potentially activating the coagulation cascade [89, 90]. These, together with the coagulopathy (increased pro-coagulants and reduced anticoagulants) associated with HIV-infection [91] may contribute to thrombus formation and atherosclerosis.

Chronic immune activation driven by persistent viral infections such as HIV and CMV can lead to immunosenescence [92, 93]. This is characterized by cells with shortened telomere, impaired proliferative capacity and the presence of CD28⁻CD57⁺ terminally differentiated T cell [94, 95]. Senescent T cell phenotypes have been associated with atherosclerosis and acute coronary syndromes [96–98]. Whether the serious non-AIDs conditions affecting HIV-infected individuals is a manifestation of accelerated aging is still contentious. A study with 2854 HIV-infected individuals and 8562 controls found that 40-year-old HIV-infected individuals' risk of multiple comorbidities is similar to 55-year-old controls [99]. However, in another study involving >450,000 person years of follow-up, though HIV-infected individuals have a higher risk of age associated morbidities, these occurred at similar ages to HIV uninfected individuals [23].

2f. Effect of ART on Immune Activation and SNAEs

ART leads to virologic suppression and reduction in immune activation [100–102]. Despite virologic suppression, levels of markers of immune activation do not fully normalize in all individuals on ART. When compared with the general population, the levels of hsCRP, IL-6, D-dimer, sCD14 and CD38+HLA-DR+ expression on T cells remain elevated in HIV-infected persons despite ART and virologic suppression [103–105, 102].

Sources of persistent immune activation in treated HIV infection were discussed previously and may include intermittent low-level HIV viremia, repeated stimulation and activation of the immune system by persistent co-infections, microbial translocation and ongoing homeostatic drive secondary to impaired CD4 T cell recovery.

ART can also be associated with adverse effects and SNAEs. Exposure to older generation protease inhibitors [106] and thymidine analogs nucleoside reverse transcriptase inhibitors (NRTIs) including stavudine and zidovudine [107, 108] leads to the development of lipodystrophy, characterized by abnormal fat distribution, insulin resistance and dyslipidemia [109–111]. ART exposure has also been associated with increases in cardiovascular risk factors including elevation in blood pressure [112, 113], insulin resistance and diabetes [114, 115] and dyslipidemia [116–118].

The relationship between dyslipidemia and inflammation are closely intertwined [119]. In HIV-infected individuals, plasma oxidized low-density lipoprotein (oxLDL) levels are correlated with sCD14 levels. Furthermore, *in vitro* stimulation of monocytes with oxLDL resulted in higher frequency of inflammatory monocytes and augmentation of tissue factor expression [120]. Increased oxLDL levels are also correlated with coronary atherosclerosis, independent of traditional cardiovascular risk factors [121]. Thus ART associated increase in LDL may contribute to immune activation and SNAEs.

Nonetheless, it is important to bear in mind that the benefits of ART outweigh the risks. In the SMART study where 5,472 HIV-infected individuals with CD4 T cell counts >350 cells/ μ L were randomized to either continuous ART (viral suppression arm; VS) or CD4 T cell count-guided use of ART (drug conservation arm; DC), the hazard ratio for DC vs. VS arms were 1.8 for deaths and 1.7 for major cardiovascular, renal and hepatic disease [122].

3. Interventions to reduce SNAEs in HIV infection

3a. Early ART initiation

To date, early ART initiation is the intervention with the greatest effect in reducing SNAEs and mortality in HIV infection. In the START study, where 4685 HIV-infected individuals with CD4 T cell count >500 cells/ μ L were randomly assigned to starting ART immediately or deferred until CD4 T cell count <350 cells/ μ L, immediate ART initiation was associated with a marked reduction in serious AIDS related events (72%), SNAEs (39%), non-AIDS cancers (50%) and CVD (16%) [123]. Thus early ART initiation is critical in order to reduce SNAEs, even at high CD4 T cell counts. Unfortunately, a large number of individuals still have significant immunodeficiency (CD4 T cell count < 300cells/ μ L) at ART initiation due

to delay in diagnosis and treatment initiation [124, 125]. Therefore, utmost priority should be given to early diagnosis of HIV infection and ART initiation.

3b. Reducing metabolic dysfunction

In a study of 2921 HIV-infected individuals and 10642 controls with 14281 and 45122 person-years of follow up, smoking alone increased all cause and non-AIDS related mortality by 4.4 and 5.3 fold respectively. Furthermore, all cause and non-AIDS mortality were halved in previous vs current smokers, suggesting that smoking cessation leads to substantial benefits [126]. Regular screening and aggressive management of traditional CVD risk factors including hypertension, diabetes and dyslipidemia according to current guidelines are critical [127–129]. Meta-analysis using data from the general population showed that every 10 mmHg reduction in systolic blood pressure, every 1 mmol reduction in LDL and every 1% reduction in hemoglobin A_{1C} each reduces the risk of CVD by about 20% [130–132]. A detailed review on the management of metabolic disease in HIV infection is beyond the scope of this review. Excellent reviews on this topic have been published by Currier et al [133, 118].

Careful selection of ART regimen can reduce metabolic dysfunction. The avoidance of or switching from stavudine and zidovudine will reduce the risk of lipodystrophy [134–136]. The use of agents with more favorable lipid profiles including integrase inhibitors [137, 138], CCR5 antagonists [139] and newer generation protease inhibitors such as atazanavir and darunavir [140, 141] may reduce dyslipidemia.

PPARs (peroxisome proliferator-activated receptors) are ligand-activated nuclear receptors that control the transcription of genes involved in adipogenesis, lipid metabolism and inflammation [142]. Thiazolinediones are PPAR- γ agonists used in the treatment of diabetes and can increase insulin sensitivity, reduce triglyceride and free fatty acid levels and central adiposity [143]. A meta-analysis of 5 placebo-controlled trials of rosiglitazone for lipodystrophy found no significant change in limb fat when compared to placebo but an increase in the risk of hypercholesterolemia and hypertriglyceridemia [144]. On the other hand, pioglitazone use was associated with increase in limb fat and improved HDL without deleterious effects on triglyceride and LDL [145]. Lipodystrophy is also associated with hypoleptinemia [146]. Recombinant leptin (adipocyte-secreted protein that regulate energy homeostasis, neuroendocrine function, and metabolism) has been examined in a few small pilot studies and was associated with improved insulin sensitivity and HDL [147–149].

3C. Suppressing chronic antigen stimulation

Suppression of Residual Viremia—Intermittent HIV viremia can occur in 20–30% of individuals on ART [150]. The presence of viremia whilst on ART is associated with greater CD8 T cell activation [151], higher IL-6, D-dimer and sCD14 levels [103, 152] and SNAEs [12]. Even viremia below the limit of detection of conventional assays has been associated with immune activation [153, 154].

A number of intensification studies have been performed to assess the impact of adding antiretroviral agents to a suppressive ART regimen (as measured by conventional assays).

None of the raltegravir intensification studies were able to demonstrate reduction in ultra-sensitive plasma HIV-RNA levels [155–165]. In addition, the majority of studies found no reduction in markers of T cell [155–158, 161, 162] or monocyte activation [161, 162]. Some studies have however noted a reduction in D-dimer levels [163], T cell activation [159, 160, 164] as well as an early transient increase in 2-LTR circles post raltegravir intensification [163, 165], suggesting that residual viremia was occurring prior to raltegravir intensification and was contributing to immune activation in some individuals.

Maraviroc intensification studies have also been performed and yielded conflicting data. Some found reduction in T cell activation [166–168], others found no change [169] or even an increase in CD4 and CD8 T cell activation both in peripheral blood and rectal mucosa [170] as well as an increase in sCD14 after maraviroc intensification [170, 168]. Hunt et al postulated that the binding of maraviroc to CCR5 prevented the interaction between CCR5 and its natural ligands. Excess CCR5 ligands might then bind to other chemokine receptor such as CCR3 and CCR4 on T cells, leading to T cell activation [170]. Therefore, the beneficial effect of adding antiretroviral agents to an already suppressive ART regimen is uncertain based on currently available data.

Treatment of co-infections—Eradication of other persistent viral infections could likely reduce immune activation. HCV treatment and suppression of HCV viremia is associated with a reduction in CD4 and CD8 T cell activation [72] and plasma levels of type 1 interferon, sICAM-1 (soluble intercellular adhesion molecule-1) and sCD163 [171, 172]. Sustained virologic response (SVR) is associated with reduced liver-related complications as well as both liver-related and non liver-related mortality in co-infected individuals [173, 174]. The newer interferon-free regimens such as sofosbuvir plus ribavirin or ledipasvir have higher efficacy (>80% SVR), shorter duration of treatment and better side effect profiles [175–177], however, the cost may be prohibitory for many at this stage [178].

Eight weeks of valganciclovir therapy in CMV seropositive individuals on ART led to a significant reduction of CMV viremia as well as a reduction in CD8 T cell activation [179]. The study was too short and small to observe for effects on CD4 T cell count or clinical outcome measures, however, the results suggest that residual CMV replication may be a significant contributor to immune activation in individuals on ART.

3d. Anti-inflammatory agents

Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors. Not only do statins reduce serum cholesterol [180], they also have anti-inflammatory properties [181]. Statin use is associated with reduced sCD14 [182, 183] and hsCRP levels [184] as well as reduced T cell activation in individuals on ART [185, 183]. In a small randomized, placebo controlled trial of 40 virologically suppressed individuals on ART, statin use was associated with reduced non-calcified plaque volume and high-risk coronary plaque [186]. In retrospective studies of individuals on ART, statin use has also been associated with reduction in mortality [187, 188]. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE, NCT02344290), involving 6500 individuals will shed further light on the effect of statin therapy on CVD and mortality in individuals on ART.

Hydroxychloroquine (HCQ) and its analogue chloroquine (CQ) have immunomodulatory, anti-inflammatory and anti-HIV properties [189–191]. A non-randomized study of HCQ in 20 individuals on ART showed decline in plasma LPS, IL-6 and reduced T cell and monocyte activation [192]. However, another non-randomized study of CQ in 19 individuals on ART observed no change in lymphoid and myeloid immune activation or inflammatory biomarkers [193]. Thus findings are inconclusive at this stage.

Aspirin is a cornerstone in the secondary prevention of vascular disease [194]. In a pilot study, 1 week of aspirin use in individuals on ART was associated with reductions in platelet aggregation, CD4 and CD8 T cell activation and plasma sCD14 levels. There was no change in IL-6, D-dimer and hsCRP levels [195]. An aspirin study (NCT02155985) with larger number of participants is in development with the AIDS Clinical Trials Group (ACTG) and will provide further data.

Cyclooxygenase type 2 (COX-2) inhibitors reduce prostaglandin E2 production, thereby reducing T cell activation through the cyclic adenosine monophosphate (cAMP) pathway [196]. Studies on COX-2 inhibitors have been small and reduction in T cell activation tended to occur in HIV viremic individuals [197, 198]. It is important, however, to bear in mind that COX-2 inhibitors are associated with increased cardiovascular risk, as a direct pharmacologic consequence of inhibition of COX-2 [199]. Therefore the risks of COX-2 inhibitors may outweigh potential benefits.

Prednisone at 0.5mg/kg/day in individuals on ART was associated with a reduction in CD8 T cell activation and TNF levels as well as a transient decrease in IL-6 [200]. In another study using prednisone at 40mg/day, no reduction in CD4 or CD8 T cell activation, plasma IL6 or TNF levels was found [201]. Furthermore, long-term prednisone use, especially at doses >7.5mg/day is associated with significant adverse effects such as osteoporosis, impaired glucose tolerance, dyslipidemia, weight gain, cataract formation and increased risk of infections [202]. In addition, even short courses have been associated with increased risk of osteonecrosis in HIV-infected individuals [203]. Therefore the numerous adverse effects of prednisone may outweigh its potential benefits in reducing immune activation and SNAEs.

3e. Targeting microbial translocation

Markers of microbial translocation e.g. LPS [204] and bacterial 16s rDNA [205] do not always normalize with ART. Persistent microbial translocation may lead to repeated stimulation of mucosal innate and adaptive immune cells, contributing to immune activation. LPS can also induce tissue factor expression on monocytes [89]. Tissue factor is the initiator of the coagulation cascade [206] and its expression on monocytes is correlated with D-dimer levels [89]; suggesting that on-going microbial translocation may contribute to coagulopathy and increased CVD in individuals on ART [89].

Targets to reduce the impact of microbial translocation include reducing pathogenic microbes and microbial products, enhancing mucosal recovery and reducing mucosal inflammation.

Correcting dysbiosis—A range of prebiotics (selectively fermented ingredients that change the growth and/or activity of certain gut microflora, resulting in health benefits [207]), probiotics (live microorganisms that when consumed, confer a health benefit [208]) and synbiotics (a combination of pre and probiotics) are currently under investigation on their effects on modifying gut microbiome and immune activation.

A prebiotic oligosaccharide mixture has been associated with improvement in microbiota composition and reduction in sCD14 in untreated HIV-infected individuals [209]. A randomized placebo-controlled trial on the use of probiotics (*Saccharomyces boulardii*) for 12 weeks in individuals on ART showed reduction in plasma IL-6 and LPS-Binding protein [210]. However, a study on a synbiotic agent (containing 4 strains of probiotic bacteria plus 4 non-digestible, fermentable dietary fibers) in women on ART found no change in biomarkers of microbial translocation or immune activation despite improvement in the levels of probiotic species [211]. The discrepancies may be secondary to the different strains of probiotic used and study participant characteristics. Thus, more data from randomized controlled trials are needed.

Bovine colostrum contains oligosaccharides, growth factors, immunoglobulins and antimicrobial peptides and has some activity in alleviating HIV-associated diarrhoea in single arm studies [212–214]. A randomized controlled trial on the addition of bovine colostrum to suppressive ART found no change in CD4 T cell count, markers of microbial translocation or T cell activation [161].

Rifaximin is a minimally absorbed oral rifamycin antibiotic that has activity against both gram-positive and gram-negative enteric bacteria [215]. It is effective in the treatment of hepatic encephalopathy, by reducing ammonia-producing enteric bacteria [216, 217]. A randomized, open-label study of 4 weeks of treatment with rifaximin versus no treatment in 65 individuals on ART, however, found no significant change in biomarkers of microbial translocation or immune activation within the rifaximin arm [218].

Sevelamer is a phosphate binder that is used in individuals with end-stage renal failure [219]. It can also bind to endotoxins and reduce hsCRP, IL-6 and sCD14 in individuals on haemodialysis [220, 221]. The use of sevelamer in pigtail macaques with acute untreated SIV infection led to substantially lower markers of microbial translocation (plasma LPS), monocyte (sCD14) and T cell (CD38+HLA-DR+) activation, systemic inflammation (CRP) and coagulopathy (d-dimer) [222]. These findings were not reproduced in chronic untreated HIV infection. Sevelamer use in 36 untreated, HIV-infected individuals led to no change in markers of microbial translocation or T cell activation but there was an increase in D-dimer and a reduction in soluble tissue factor [223]. The effects of sevelamer in treated HIV infection have not yet been assessed.

Lubiprostone is a chloride channel activator that is used in the treatment of constipation [224]. It has been found to enhance recovery of mucosal barrier function in ischaemic porcine colon [225]. A pilot study of whether lubiprostone will enhance intestinal barrier integrity and reduce microbial translocation in individuals on ART with virologic suppression and CD4 T cell count <350 cells/ μ L (NCT01839734) is ongoing.

Mesalamine (5-aminosalicylic acid) is an anti-inflammatory agent used in the management of inflammatory bowel disease [226]. A randomized cross over trial using mesalamine for 12 weeks in individuals on ART with CD4 T cell count <350 cells/ μ L showed no reduction in CD4 and CD8 activation in rectal mucosa or blood and no reduction in plasma sCD14, IL-6 or D-dimer levels [227].

To date, the handful of randomized controlled trials on agents postulated to modify microbial translocation have been disappointing. One possibility may be that the correct target is still to be identified. Another possibility is that microbial translocation may not be a major contributor in persistent immune activation in individuals on ART with prolonged virologic suppression.

3f. Improving immune recovery

Given that homeostatic proliferation, depletion of TH17 cells and imbalance in TH17/Tregs ratio are possible sources of persistent immune activation, improving immune recovery may reduce persistent immune activation.

Cytokine therapies to boost immune recovery has been assessed in the following studies. Interleukin-2 (IL-2) is a cytokine secreted by activated T cells that regulates the proliferation, differentiation, and survival of T cells. Subcutaneous administration of IL-2 in concert with ART resulted in a reduction in CD4 T cell proliferation, CD4 and CD8 T cell activation [228] and was associated with sustained increase in CD4 T cell counts, however, this did not translate into measurable clinical benefits in phase III studies [229].

IL-7 plays a fundamental role in thymopoiesis and homeostasis and survival of mature T cells. Subcutaneous administration of IL-7 also led to increases in CD4 T cell counts, through increased cell cycling and proliferation [230–232]. Whether this will translate into clinical benefits, especially for individuals with poor CD4 recovery still needs to be addressed.

IL-21 is a member of the common γ -chain cytokine family, necessary in the maintenance of TH17 cells. Recombinant IL-21 administered to rhesus macaques (RM) 14 days post infection with SIV resulted in higher levels of intestinal Th17 cells, lower levels of intestinal T cell proliferation, microbial translocation and systemic activation in chronic infection [233]. The effects of IL-21 have not been assessed in individuals with chronic HIV infection yet.

Reducing fibrosis may reduce homeostatic proliferation as fibrosis of the lymphoid tissues impairs T cell regeneration. TGF- β is key to the process of lymphoid tissue fibrosis. TNF blockade with adalimumab in SIV infected RM was associated with attenuated TGF- β expression, reduced lymph node fibrosis, preservation of lymph node architecture and CD4 T cells but no reduction in T cell activation [234]. It is important to bear in mind that TNF blockade is associated with increased risk of reactivation of tuberculosis and other infections [235]. Thus its use in HIV-infected individuals with virologic suppression should be carefully assessed.

Pirfenidone is an anti-fibrotic agent that interferes with the TGF- β signalling pathway [236, 237]. Pirfenidone administered at the time of SIV infection inhibited lymph node fibrosis and preserved CD4 T cells in lymph nodes and peripheral blood. Pirfenidone administered during chronic SIV infection reversed lymph node fibrosis [238]. The effect of pirfenidone on lymph node fibrosis in HIV infection has not been studied to date.

The renin-angiotensin pathway is involved in cardiac, renal and liver fibrosis. Binding of angiotensin II to the angiotensin 1 receptor on cardiac fibroblast, hepatic stellate cells or mesangial cells leads to proliferation as well as collagen and TGF- β synthesis [239, 240]. In a small pilot study of 37 individuals on ART, the use of lisinopril was associated with a small but statistically significant reduction in hsCRP and TNF levels when compared with placebo [241]. Trials on the effect of angiotensin converting enzyme (ACE) inhibitor e.g. lisinopril (ClinicalTrials.gov identifier: NCT01535235), angiotensin II receptor antagonists e.g. losartan (NCT01852942, NCT01529749) and telmisartan (NCT01928927) in modulating lymphoid tissue fibrosis are currently underway.

Conclusion

A number of studies have been performed to evaluate strategies to reduce persistent immune activation on ART (Fig 2), but there is little conclusive evidence on which strategy will result in clinical benefits. The use of statins seems to show early promise and merits confirmation in larger clinical trials. Based on currently available data, in the clinical care of HIV-infected individuals who are already on ART, the focus should be on the treatment of co-infections (HBV, HCV, TB) and the aggressive management of co-morbidities (smoking, diabetes, hypertension and hyperlipidemia) until further data are available.

The roles of inflammation, coagulopathy and tissue fibrosis in SNAEs pathogenesis are now well established. Research efforts should focus on improving current understanding and further dissecting the pathways that interlink the virus, immune activation, coagulopathy and fibrosis as well as the cascade of events leading to the development of SNAEs. This should facilitate the development of novel interventions that are safe and target critical juncture points between immune activation, coagulopathy and fibrosis, that could be integrated in the clinical care of HIV infected persons.

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Key points

- Persistent immune activation is an important contributor to SNAEs in individuals already on treatment for HIV infection.
- Potential targets to reduce persistent immune activation including elimination of residual viremia, treatment of co-infections, the use of anti-inflammatory agents, reducing microbial translocation and interventions to improve immune recovery.
- Until further data are available clinical care of HIV-infected patients should focus on early diagnosis and prompt ART initiation, treatment of active co-infections and the aggressive management of co-morbidities

Figure 1. Factors contributing to the pathogenesis of SNAES

HIV infection can lead to immune activation in a number of ways. Firstly, HIV can directly stimulate innate immune cells and HIV-specific CD4 and CD8 T cells. Secondly, HIV causes depletion of CD4 T cells in the gut as well as disruption of intestinal tight junction, allowing translocation of luminal microbial products, further exacerbating immune activation. Thirdly, the presence of and reactivation of coinfections such as HBV, HCV, CMV and EBV also contribute. Finally, HIV associated CD4 T cell depletion may stimulate physiologic homeostatic proliferation and aggravate immune activation. A vicious cycle is thus set up whereby on-going immune activation leads to further CD4 T cell depletion and thus more immune activation. Immune activation is also associated with increased numbers of regulatory T cells (Tregs) in the lymphoid tissues. Tregs secrete Transforming Growth Factor- β (TGF- β), triggering collagen production and deposition by fibroblasts; resulting in structural damage and fibrosis of the lymph node reducing the regeneration and survival of CD4 T cells thus worsening immunodeficiency. Activated monocytes and macrophages express increased levels of tissue factor (TF), potentially activating coagulation cascades, contributing to thrombus formation and atherosclerosis. The direct effect of HIV, the impact of immunodeficiency, the presence of underlying co-infections and co-morbidities, ART toxicities and persistent immune activation and coagulopathy all contribute to SNAES.

Figure 2. Potential strategies to reduce SNAEs in treated HIV infection

Early ART initiation is the most critical intervention to reduce SNAEs and mortality in HIV infection. Other potential strategies to reduce SNAEs in treated HIV infection include the selection of ART with less adverse effects; the management of cardiovascular risk factors through smoking cessation, controlling hypertension, diabetes and dyslipidemia as well as improving lipodystrophy and associated insulin resistance; reducing chronic immune activation through treatment of co-infections and residual HIV viremia, reducing microbial translocation and the use of anti-inflammatory agents; and improving immune recovery through cytokine stimulation and reduction of lymphoid tissue fibrosis. Interventions supported by evidence of reducing SNAEs are in red.