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Persistent immune activation in chronic HIV infection: do any interventions work?

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Introduction

The availability of combination antiretroviral therapy (cART) has led to substantial reduction in morbidity and mortality in HIV-infected patients; however, life expectancy remains reduced especially in HIV-infected patients who initiate cART with CD4 T-cell counts less than 200 cells/μl [1]. Increased immune activation in patients on long-term suppressive cART [2–4] has been associated with increased mortality [5,6] and both AIDS and non-AIDS-defining illnesses [7–10], suggesting that chronic immune activation may have a potential role in driving increased morbidity and mortality.

Causes of HIV-associated immune activation

The mechanisms driving systemic immune activation in chronic HIV infection are multifactorial (reviewed in [11], Fig. 1) [12] and include the translocation of microbial products from the gastrointestinal tract [13,14], low-level HIV viremia [15,16], and

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coinfections with other persistent viral pathogens including cytomegalo-virus (CMV) and hepatitis C virus (HCV) [17]. A recent study in simian immunodeficiency virus-infected macaques demonstrated a significant increase in immune activation and coagulation markers, including D-dimers, following exogenous administration of lipopolysaccharide (LPS) [18]. The excessive production of interferon alpha (IFN-α) [19–22] and pro-inflammatory cytokines leading to upregulation of pro-apoptotic molecules [23–26], lymph node fibrosis [27], dysfunction of CD4 T-regulatory cells (T-regs) [28,29], and depletion of $CD161^{++}$/(mucosal-associated invariant T cells, MAIT) [30,31] are likely to also contribute.

Strategies to reduce persistent immune activation in HIV-infected patients

Pharmacological agents

Multiple clinical trials have been completed (Table 1) [32–76], or are in development (Table 2) [27,77–86], to reduce immune activation in HIV-infected patients and have also been recently reviewed in [87]. Potential drivers of immune activation include microbial translocation which occurs due to persistent dysfunction in the gut-associated lymphoid tissue (GALT), persistent HIV infection, coinfections with cytomegalovirus (CMV) and hepatitis C virus (HCV), aberrant activation of plasmacytoid dendritic cells (pDC), and altered ratio of Tregs and Th17 cells. Immune activation, though significantly reduced, persists even in patients receiving suppressive combination anti-retroviral therapy (cART) and leads to increased lymph node fibrosis and T-cell exhaustion, which affects CD4 T-cell recovery. Chronic immune activation also activates monocytes, which drives local inflammation in tissues and leads to the development of various end-organ damage and non-AIDS-defining illnesses including cardiovascular disease (CVD). Various treatment strategies to attenuate immune activation or its effects have recently been trialed and are labeled A to F. These strategies include (A) agents that promote mucosal repair in the GALT (bovine serum colostrum, micronutrient supplementation, probiotics and prebiotics); (B) cART treatment intensification (maraviroc and raltegravir); (C) treatment of coinfections (valgancyclovir, interferon-α, and ribavirin); (D) agents that reduce pDC activation (chloroquine and hydroxychloroquine); (E) agents that reduce transforming growth factor-β1 (TGF-β1)-mediated lymph node fibrosis (pirfenidone); and (F) immunomodulators [HMG CoA reductase inhibitors, minocycline, selective cyclooxygenase-2 inhibitors, leflunomide, and intravenous immunoglobulin (IVIG)]. Modified from [12].

Statins—The use of statins in HIV-infected patients on and off cART has reported variable changes in T-cell activation and highly sensitive C-reactive protein (hsCRP) levels [32–35] but no effect on CD4 T-cell counts [32,33,36]. However, in two large observational studies of cART-treated patients, the use of statins was associated with reduced mortality [37] and reduced incidence of non-Hodgkin lymphoma (NHL) [38]. No immunological correlates were assessed in these two studies and a greater understanding of the mechanisms underlying the benefits of statins is needed.

Chloroquine and hydroxychloroquine—Chloroquine and hydroxychloroquine inhibit endosomal acidification in plasmacytoid dendritic cells (pDCs) and Toll-like receptor 7 (TLR-7) signaling by HIV-1 single stranded (ss)RNA and also inhibit IFN-α production

[88,89]. *In vitro*, chloroquine inhibited pDC activation and maturation, reduced IFN-α-mediated CD8 T-cell activation, and downmodulated indolamine 2–3 dioxygenase (IDO) and PD-L1 expression on pDCs, which are negative regulators of T-cell responses [90].

A recent randomized controlled trial (RCT) in cART-naive patients (n =13) found chloroquine was associated with decreased memory CD8 T-cell activation, CD4 and CD8 T-cell proliferation, and LPS levels compared to baseline but there were no changes in plasma HIV RNA [39]. In contrast, a RCTof hydroxychloroquine in cART-naive patients demonstrated no change in CD8 and CD4 T-cell activation and proliferation, an increase in HIV RNA, and decrease in CD4 T-cell counts [40]. In a small nonrandomized study (n =20), administration of hydroxychoroquine to patients receiving suppressive cARTwas associated with a reduction in multiple markers of immune activation but no significant increase in CD4 T-cell recovery [41]. Given these promising findings, numerous clinical trials are currently being conducted with choloroquine (NCT00819390) and hydroxychloroquine (NCT01232660).

Selective cyclooxygenase-2 inhibitors—Selective cyclooxygenase-2 (COX-2) inhibitors are anti-inflammatory agents that modulate T-cell activation via inhibition of prostaglandin E2 and the cyclic adenosine 3′,5′-monophosphate (cAMP)-protein kinase A pathway ([91,92], reviewed in [93]). In cART-treated patients, selective COX-2 inhibitors were associated with increased T-cell proliferation [94], a nonsignificant reduction in T-cell activation, and increased perforin-containing CD8 T cells [42]. A recent RCT of high-dose celecoxib in untreated HIV-infected patients (n = 31) reported a significant reduction in immune activation levels [43].

Leflunomide—A77 1726, the active metabolite of the antirheumatoid arthritis agent leflunomide, has anti-HIVactivity [95,96], inhibits pyrimidine synthesis [96,97], and reduces proliferation of activated T cells *in vitro* [98]. A small RCT in cART-naive patients (ALETHIA, A Study of Leflunomide to Target Immune Activation in HIV; n =16), found no significant change in CD4 and CD8 T-cell counts or HIV RNA levels in patients treated with leflunomide compared to placebo [44]. Furthermore, more grade 1 and 2 adverse events were reported with leflunomide. However, short-term leflunomide use was associated with reduced T-cell cycling and activation. It is currently unclear whether similar immunological effects will be seen in patients receiving cART.

Biological agents

Bovine colostrum, micronutrients, and prebiotics/probiotics—Multiple approaches are now being taken to directly reduce microbial load and translocation in HIV patients. These include supplementation with micronutrients, bovine colostrum, probiotics, and prebiotics, all of which have previously been shown to reduce HIV-associated diarrhea [99–101,45,46]. These strategies may also alter the composition of gut microflora, which may be important in modulating microbial translocation-driven immune activation [102,103]. Most of these studies have been in cART-naive patients and some have reported increases in CD4 T-cell counts [45,46,47–51] (Table 1). In a RCT of orally administered

hyperimmune bovine colostrum (that contains antibodies to LPS), there was no effect on immune activation or CD4 T-cell recovery in patients receiving suppressive cART [52].

Antiretroviral intensification

Chronic immune activation in patients receiving cART may also be driven by low-level HIV viremia [15,16,104,105]. In multiple observational and RCT studies, the addition of raltegravir to suppressive cART resulted in no significant immune activation reduction in plasma, cerebrospinal fluid, or tissue [52,53–58] nor any change in endothelial function, a surrogate marker of cardiovascular disease [106]. There have, however, been two studies that have shown that the addition of raltegravir led to a significant reduction in T-cell activation markers in a subset of patients and a reduction in reservoir size [59,60]. Further larger randomized studies are still needed to definitively determine the impact of raltegravir intensification on immune activation.

Several studies of maraviroc intensification have shown a reduction in immune activation [61–63]; however, one study reported an unexpected increase in immune activation [64] (Table 1). CCR5 antagonists inhibit the binding and signaling of CCR5 ligands (including CCL3, CCL4, and CCL5) leading to an increase in their plasma concentration. This increase could potentially activate monocytes/macrophages via CCR1 [62] and/or increase antigen-specific T-cell and antibody responses, which has been observed in some [107] but not all studies [108]. Further studies are needed to better characterize the immunological changes associated with maraviroc use.

The timing of cART initiation may be an important parameter that influences immune activation. Studies of patients treated during chronic infection have demonstrated persistently elevated immune activation levels post-cART compared to uninfected controls [2–4]. A recent prospective study of cART initiated during acute infection demonstrated reduced immune activation to normal levels after 48 weeks [109]. Prospective or randomized trials need to be performed to determine the effect of early versus delayed cARTon immune activation in patients with chronic infection.

Treatment of coinfections

Anti-cytomegalovirus treatment: valgancyclovir—Increased CMV-specific antibodies and/or T cells have been associated with atherosclerosis [110,111] and impaired CD4 T-cell reconstitution [112] in HIV-infected patients on cART, suggesting that CMV coinfection may be a driver of persistent immune activation. A RCTwith valgancyclovir in CMV-seropositive cART-treated patients (n = 30) found that both CMV DNA and expression of $CD38^{+}$HLA DR^{+} on T cells declined significantly during valgancyclovir therapy [65]. It is currently unclear whether this approach will translate to clinical benefits and the feasibility of prolonged administration of valgancyclovir may be limited by significant toxicities of the drug.

Anti-hepatitis C virus treatment: interferon alpha and ribavirin—HCV-specific treatment with IFN-α and ribavirin in HIV/HCV coinfected patients receiving cART has been associated with a significant reduction in markers of T-cell activation [66] and

endothelial dysfunction [113]; however, its impact on clinical end-points is currently unknown.

Other strategies including treatment with intravenous immunoglobulin (IVIG) and minocycline have also been trialed in small studies but have yielded negative results (see Table 1).

Challenges in designing clinical trials to reduce immune activation

There are multiple challenges in designing clinical trials to reduce chronic immune activation in patients receiving suppressive cART. First, these studies will require patients who are otherwise clinically well to take an additional drug(s) that may be associated with toxicities. Therefore, the risks and benefits need to be carefully assessed. Second, there are multiple markers of immune activation and inflammation that have been studied and it is currently unclear which best predicts AIDS and non-AIDS-related morbidities in patients receiving suppressive cART. Biomarkers such as IL-6, D-dimer, and sCD14 show promise as they are relatively easy to standardize from measurements in plasma but whether they are indeed robust markers for predicting clinical outcomes following specific interventions needs further evaluation. Finally, given that clinical events are rare in patients on suppressive cART, relatively large samples sizes will be required to demonstrate a clinically relevant impact of any intervention to reduce immune activation.

Conclusion

To date, most studies aimed at reducing immune activation have only included a small number of patients and/or shown an effect on biomarkers of immune activation and have not had the power to assess any effects on clinical outcomes. Given that there are several candidate approaches that have shown promise in small proof-of-concept trials, these compounds warrant evaluation in larger randomized clinical trials that systematically evaluate both immune activation biomarkers and clinical outcomes.

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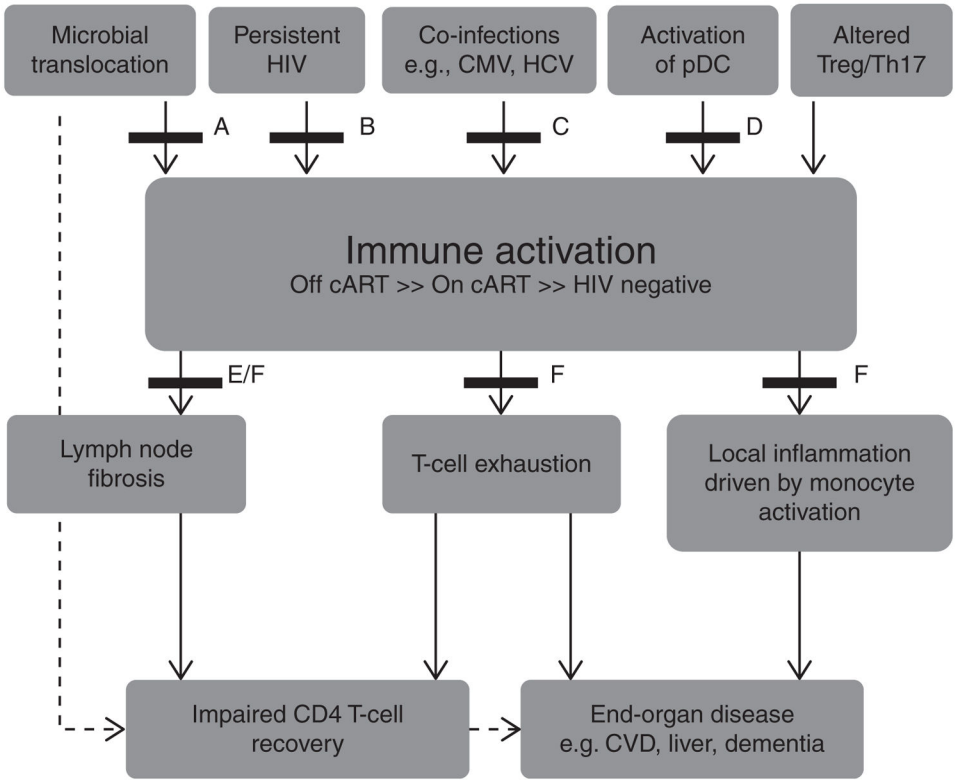

Fig. 1.

Schematic representation of the potential causes of chronic immune activation in HIV-infected patients, its impact on clinical end-points, and strategies of interventions tested in recently completed and ongoing clinical trials.

Table 1

Therapeutic agents/biologicals that have been evaluated in HIV-infected patients for their effects on immune activation and associated morbidities.

	Immune activation/ inflammatory markers			Clinical outcomes				
Drug name	**T-cell activation (coexpression of HLA-DR and CD38)[a]**	**Soluble activation markers**	**Other markers**	**CD4 T-cell counts**	**HIV RNA levels [assay detection limit, copies/ml][b]/ markers of viral persistence**	**AIDS-defining illness**	**All-cause mortality**	**Ref**
HMG CoA reductase inhibitors								
Statin use	-	-	-	-	-	-	↓	[37]
	-	-	-	-	-	**↓(NHL)**	-	[38]
	-	-	-	↔	-	-	-	[36]
Atorvastatin	↓: $CD8^+$	-	-	↔	↔	-	-	[32]
	↓: $CD8^+$ ($CD38^+$)	**↔hsCRP**	**-**	↔	-	-	-	[33]
	↑: $CD8^+$ ($CD38^+$)	-	-	↓	↔	-	-	[67]
Rosuvastatin/Pravastatin	-	**↔: sTNFR ↓: hsCRP**	-	-	-	-	-	[34]
Pravastatin	-	**↔: hsCRP, PAI-1**	**↔: P-selectin**	-	-	-	-	[35]
Chloroquine	↓: $CD8^+$	-	↔: Ki-67 expression in $CD4^+$ and $CD8^+$ T cells	-	↔	-	-	[39]
Hydroxychloroquine	**↓: $CD4^+$**	**↓: IL-6**	-	↔	-	-	-	[41]
	↔: $CD8^+$	**↔: TNF-a**						
	↔: $CD8^+$, $CD4^+$	↔: IL-6, D-dimer	↔: Ki-67 expression in $CD4^+$ and $CD8^+$ T cells	↓	↑	-	-	[40]
Selective cyclooxygenase-2 inhibitors								
Celecoxib/rofecoxib	**↓: $CD8^{+c}$ ($HLA\text{-}DR^+$ and $CD38^+$)**	-	-	↑[d]	-	-	-	[42]
Celecoxib	↓: $CD8^+$ ($CD38^+$)	-	-	↔	-	-	-	[43]
Leflunomide	↓: $CD8^+$ ↔: $CD4^+$	↔: D-dimer, CRP, sCD14	↓: BrDU incorporation in $CD4^+$ T cells	↔	↔			[44]
Intravenous immunoglobulin (IVIG)	↔: $CD4^+$, $CD8^+$	↔: CRP	↔: Ki-67 expression in $CD4^+$ and $CD8^+$ T cells	↔	↔	-	-	[68]
	↔: $CD4^+$, $CD8^+$	-	-	-	**↔[<2]**	-	-	[69]
Minocycline	↔: $CD8^+$(blood & CSF)	↔: CCL2 (CSF), neopterin (blood & CSF)	↔: $CD16^+$ (blood & CSF)	↓	↔ (blood & CSF)	-	-	[70]

	Immune activation/ inflammatory markers			Clinical outcomes				
Drug name	**T-cell activation (coexpression of HLA-DR and CD38)[a]**	**Soluble activation markers**	**Other markers**	**CD4 T-cell counts**	**HIV RNA levels [assay detection limit, copies/ml][b]/ markers of viral persistence**	**AIDS-defining illness**	**All-cause mortality**	**Ref**
Bovine colostrum	-	-	-	↑	↔	-	-	[71]
	-	-	-	↑[e]	-	-	-	[45,47]
	↔: **CD4$^+$, CD8$^+$**	↔: **sCD14, LPS**	↔: **16srDNA**	↔				[52]
Micronutrient supplementation	-	-	-	↔	↔	-	↓	[72]
	-	-	-	↔	-	-	↓	[73]
	-	-	-	↑	↓	-	-	[48]
	-	-	-	↑	-	-	-	[49]
Probiotics								
Bifidobacterium bifidum, Streptococcus thermophiles	-	-	-	↑	-	-	-	[50]
Lactobacillus rhamnosus/Lactobacillus reuteri	-	-	-	↑	-	-	-	[46]
	-	-	-	↔	-	-	-	[74]
Lactobacillus rhamnosus	-	-	-	↑	-	-	-	[51]
Prebiotics								
Oligosaccharide mixture[f]	↔: CD8$^+$ (CD38$^+$)	↓: sCD14	↓: CD4$^+$CD25$^+$ T cells	↔	-	-	-	[75]
Raltegravir treatment intensification	↔: **CD8$^+$, CD4$^+$**	-	-	↑	↔: **SCA, 2-LTR, HIV DNA**	-	-	[53,76]
	↔: **CD8$^+$**	-	-	↔	↔: **Usen HIV RNA, cell-associated HIV RNA, HIV DNA**	-	-	[54]
	↓: **CD8$^+$**[g]	-	-	↔	↔: **SCA, HIV DNA** ↑: **2-LTR**[g]	-	-	[59]
	↔: **CD8$^+$**	↔: **sCD14, LPS**	↔: **16srDNA**	↔	↔: **Usen HIV RNA**	-	-	[52]
	↓: **CD8$^+$ (blood & GI tract)**	-	-	↑**(tissue)**/↔ **(blood)**	↓: **US HIV RNA(tissue)** ↔: **US HIV RNA, Usen HIV RNA, HIV DNA (blood & tissue)**	-	-	[55]
	↔: **CD8$^+$ (blood & CSF), CD4$^+$ (CSF)** ↑: **CD4$^+$ (blood)**	↔: **neopterin (CSF & blood)**	-	-	↔: **SCA (CSF & blood)**	-	-	[56]
	-	-	-	↔	↔: **HIV DNA (tissue & blood)**	-	-	[57]
	-	↔: **β2- microglobulin (blood & CSF), neopterin (blood & CSF)**	-	↔	↔: **HIV RNA [<20] (CSF & blood)**	-	-	[58]

	Immune activation/ inflammatory markers			Clinical outcomes				
Drug name	**T-cell activation (coexpression of HLA-DR and CD38)[a]**	**Soluble activation markers**	**Other markers**	**CD4 T-cell counts**	**HIV RNA levels [assay detection limit, copies/ml][b]/ markers of viral persistence**	**AIDS-defining illness**	**All-cause mortality**	**Ref**
	↓: CD8$^+$ ↔**: CD4$^+$**	**↓: LPS** ↔**: sCD14**	-	↔	**↓: IUPM in memory CD4$^+$ T cells** ↔**: SCA, 2-LTR**	-	-	[60]
Maraviroc treatment intensification	**↓: CD4$^+$, CD8$^+$**	**↑: sCD14, LPS**	-	↔	↔**: SCA,2-LTR**	-	-	[61]
	↑: CD8$^+$ (blood & tissue)	**↓: LPS** **↑: sCD14**	-	↔	↔**SCA**	-	-	[64]
	↓: CD4$^+$, CD8$^+$	-	**↑: CD57$^+$** **↓: caspase3$^+$, Bcl-2**	↔	-	-	-	[62]
	↓: CD8$^+$	-	-	↑	↔**: HIV DNA, Usen HIV RNA**			[63]
Valgancyclovir	↔**: CD4$^+$** **↓: CD8$^+$**	↔**: hsCRP, IL-6, D-dimer, sCD14, cystatin C**	-	↔	↔	-	-	[65]
IFN-α + ribavirin	**↓: CD8$^+$ (CD38$^+$), CD4$^+$ (CD38$^+$)**	-	-	↓[h]	-	-	-	[66]

CRP, C-reactive protein; CSF, cerebrospinal fluid; LPS, lipopolysaccharide; LTR, long-terminal repeat; NHL, non-Hodgkin lymphoma; PAI-1, plasminogen activator inhibitor-1; SCA, single-copy assay; TNF, tumor necrosis factor; US, unspliced; Usen, ultrasensitive. Bold fonts indicate studies that were done in cART-treated patients, whereas normal text indicates studies that were performed in treatment-naive HIV-infected individuals.

[a] T-cell activation markers represent coexpression of CD38$^+$HLA-DR$^+$ on T cells, unless otherwise specified.

[b] Assay detection limit <50 copies/ml, unless otherwise specified.

[c] Only in viremic patients.

[d] Only in aviremic patients.

[e] Concomitant reduction in HIV-associated diarrhea.

[f] Mixture of short-chain galacto-oligosaccharides, long-chain fructo-oligosaccharides, pectin-hydrolysate-derived acidic oligosaccharides.

[g] In a subset of patients.

[h] Transient.

Table 2

Therapeutic agents currently in or being considered for clinical trial to reduce immune activation levels in HIV.

Drug name/compounds (trial number)[a]	Proposed mechanism of action (references)	Target group	Primary end-point studied
Rifaximin (NCT01466595)	Poorly absorbed antibiotic shown to reduce bacterial load in the gastrointestinal tract [77]. In combination with sulfasalazine (non-absorbable anti-inflammatory agent), shown to reduce markers of microbial translocation, immune activation, inflammation, and coagulation; viral load and mucosal CD4 T-cell depletion in acute SIV infection of pigtail macaques [78]	cART-treated patients with suboptimal CD4 T-cell recovery	Change in $CD8^+$ T-cell activation at 4 weeks from baseline
Pyridostigmine (NCT 00518154)	Acetylcholine esterase inhibitor shown to reduce T-cell activation, proliferation, and IFN-γ production [79].	cART-treated patients with suboptimal CD4 T-cell recovery	Change in $CD4^+$ T-cell counts at 12 weeks from baseline
Sevelemer carbonate (NCT01543958)	Non-calcium phosphate binder shown to reduce endotoxin-driven production of IL-6, hsCRP, LPS, and sCD14 levels [80]	cART-naive patients	Change in sCD14 and endotoxin levels at 8 weeks from baseline
Meselamine (NCT 01090102)	Poorly absorbed anti-inflammatory agent shown to reduce non-infectious colitis [81].	cART-treated patients	Change in $CD8^+$ T-cell activation at 12 weeks vs. placebo
Lisinopril (NCT01535235)	Angiotensin-converting enzyme inhibitor shown to reduce markers of inflammation (hsCRP, TNF-α) [82] and inhibit TGF-β1-mediated fibrosis [83]	cART-treated patients	Change in HIV RNA (copies/million CD4) and mean baseline GALT RNA at 24 weeks vs. placebo
Methotrexate (NCT00000834)	Immunosuppressive agent used in the treatment of autoimmune diseases including rheumatoid arthritis.	Antiretroviral (zidovudine and lamivudine)-treated patients	Phase I study to determine safety profile in HIV-infected patients
Pirfenidone (not in clinical trial)	Shown to reduce TGF-β1 signaling pathway and collagen production [27].	-	-
Sifalimumab (not in clinical trial)	Anti-IFN-α monoclonal antibody for the treatment of systemic lupus erythematosus (SLE) has been shown to reduce type-I IFN mRNAs (IL-10, TNF-α, IL-1β, GM-CSF) [84–86].	-	-

cART, combination antiretroviral therapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; hsCRP, highly-sensitive C-reactive protein; IFN, interferon; LPS, lipopolysaccharide; SIV, simian immunodeficiency virus; TNF, tumor necrosis factor; TGF, transforming growth factor.

[a] Active clinical studies referenced from clintrials.gov.