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

Reena Rajasuriar[a,b,c], Gabriela Khoury[c,d,e], Adeeba Kamarulzaman[a], Martyn Andrew French[f,g], Paul Urquhart Cameron[c,d,h] and Sharon Ruth Lewin[c,d,h]

Persistent immune activation (IA) is a hallmark of chronic HIV infection. IA has been associated with poor CD4 T-cell recovery, non-AIDS defining illnesses and mortality during combination antiretroviral therapy (cART). Measures of chronic immune activation, namely T-cell activation and more recently monocyte activation and plasma inflammatory and thrombotic biomarkers, have all been shown to remain elevated despite years of suppressive cART. Here we review recent clinical trials and therapeutic approaches targeted to reduce persistent IA in HIV patients and discuss the impact of each of these approaches on clinically relevant end-points.

© 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

AIDS 2013, **27**:000–000

Keywords: chronic immune activation, combination antiretroviral therapy (cART), HIV, non-AIDS defining illness, T-cell activation

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 a CD4 T-cell counts <200 cells/μl [1]. Increased immune activation (IA) 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 IA may have a potential role in driving increased morbidity and mortality.

Causes of HIV-associated immune activation

The mechanisms driving systemic IA in chronic HIV infection are multifactorial (reviewed in [11], Fig. 1) and include the translocation of microbial products from the gastro-intestinal tract [12,13], low-level HIV viremia

[a]Centre of Excellence for Research in AIDS (CERiA), University Malaya, Kuala Lumpur, Malaysia, [b]Department of Pharmacy, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia, [c]Department of Infectious Diseases, Monash University, Melbourne, Australia, [d]Centre for Virology, Burnet Institute, Melbourne, Australia, [e]Department of Medicine, Monash University, Melbourne, Australia, [f]School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia, [g]Department of Clinical Immunology, Royal Perth Hospital and PathWest Laboratory Medicine, Perth, Australia, and [h]Infectious Diseases Unit, Alfred Hospital, Melbourne, Australia.

Correspondence to Sharon R. Lewin, Department of Infectious Diseases, 2nd Floor Burnet Institute, 85 Commercial Road, 3004 Victoria, Australia.

Tel: +61 3 976 8491

Received: 26 September 2012; revised: 8 January 2013; accepted: 9 January 2013.

DOI:10.1097/QAD.0b013e32835ecb8b

ISSN 0269-9370 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

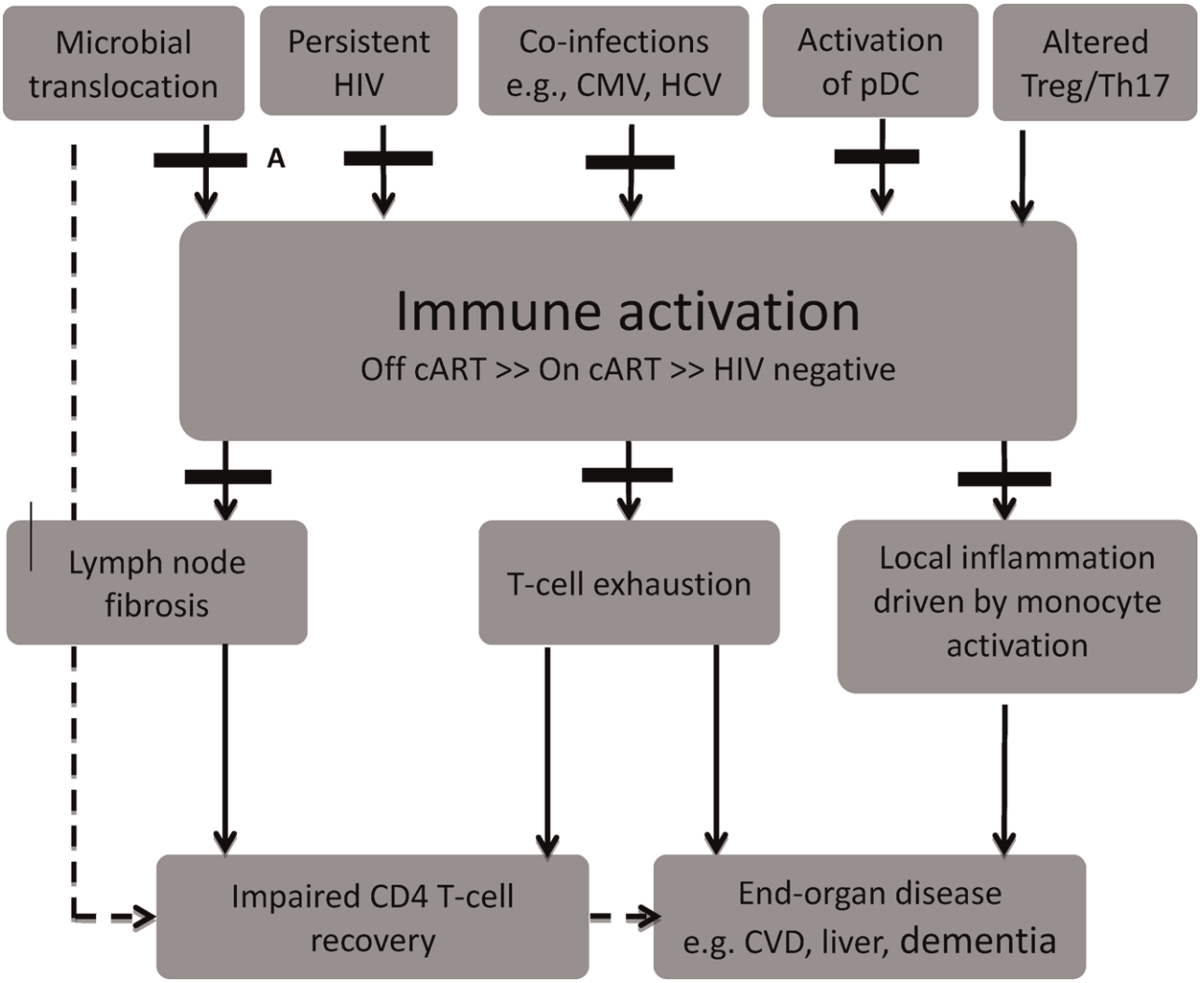

Fig. 1. Schematic representation of the potential causes of chronic immune activation in HIV-infected patients, its impact on clinical end-points and strategies of intervention tested in recent completed and on-going clinical trials. Potential drivers of immune activation include microbial translocation which occurs due to persistent dysfunction in the gut-associated lymphoid tissue (GALT), persistent HIV infection, co-infections with cytomegalovirus (CMV) and hepatitis C, aberrant activation of plasmacytoid dendritic cells (pDCs) and altered ratio of Tregs and Th17 cells. Immune activation (IA), though significantly reduced, persists even in patients receiving suppressive combination antiretroviral therapy (cART) and leads to increased lymphoid tissue fibrosis and T-cell exhaustion which affects CD4 T-cell recovery. Chronic IA also activates monocytes which drives local inflammation in tissues and leads to the development of various end-organ damage and non-AIDS defining illnesses. Various treatment strategies to attenuate immune activation or its effects have recently been trialled and are labelled A to F. These strategies include (A) agents that promote mucosal repair in the GALT (bovine serum colostrum, micronutrient supplementation, pro and pre-biotics); (B) cART treatment intensification (maraviroc and raltegravir); (C) treatment of co-infections (valgancyclovir, interferon-α and ribavirin); (D) agents that reduce pDC activation (chloroquine and hydroxychloroquine); (E) agents that reduce TGF-β1 mediated lymph node fibrosis (pirfenidone); and (F) immune-modulators (HMG CoA reductase inhibitors, minocycline, selective cyclo-oxygenase-2 inhibitors, leflunomide and IVIG). (Figure modified from [113]).

[14,15] and co-infections with other persistent viral pathogens including cytomegalovirus (CMV) and hepatitis C virus (HCV) [16]. A recent study in SIV-infected macaques demonstrated a significant increase in IA and coagulation markers, including D-dimers, following exogenous administration of LPS [17]. The excessive production of interferon-alpha (IFN-α) [18–21] and pro-inflammatory cytokines leading to up-regulation of pro-apoptotic molecules [22–25], lymph node fibrosis [26],dysfunction of CD4 T-regulatory cells (T-regs) [27,28] and depletion of CD161++/(mucosal-associated invariant T-cells, MAIT) [29,30] are likely to also contribute.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Strategies to reduce persistent immune activation in HIV-infected individuals

Pharmacological agents

Multiple clinical trials have been completed (Table 1), or are in development (Table 2), to reduce IA in HIV-infected patients and have also been reviewed in [31].

Statins

The use of statins in HIV-infected patients on and off cART have 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 TLR-7 signaling by HIV-1 single stranded (ss)RNA and also inhibit IFN-α production [39,40]. *In vitro,* chloroquine inhibited pDC activation and maturation, reduced IFN-α mediated CD8 T-cell activation and down-modulated indolamine 2–3 dioxygenase (IDO) and PD-L1 expression on pDCs, which are negative regulators of T-cell responses [41].

A recent RCT in cART-naïve 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 [42]. In contrast, a RCT of hydroxychloroquine in cART naïve 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 [43]. In a small non-randomised study ($n = 20$), administration of hydroxychoroquine to patients receiving suppressive cART was associated with a reduction in multiple markers of IA but no significant increase in CD4 T-cell recovery [44]. Given these promising findings, numerous clinical trials are currently being conducted with choloroquine (NCT00819390) and hydroxychloroquine (NCT01232660).

Selective cyclooxygenase-2 (COX-2) inhibitors

Selective COX-2 inhibitors are anti-inflammatory agents which modulate T-cell activation via inhibition of prostaglandin E2 and the cyclic adenosine 3′,5′-monophosphate (cAMP)-protein kinase A pathway ([45,46], reviewed in [47]). In cART-treated patients, selective COX-2 inhibitors were associated with increased T-cell proliferation [48], a non-significant reduction in T-cell activation and increased perforin-containing CD8+ T-cells [49]. A recent RCT of high-dose celecoxib in untreated HIV-infected patients ($n = 31$) reported a significant reduction in IA levels [50].

Leflunomide

A77 1726, the active metabolite of the anti-rheumatoid arthritis agent leflunomide, has anti-HIV activity [51,52], inhibits pyrimidine synthesis [52,53] and reduces proliferation of activated T-cells *in vitro* [54]. A small RCT in cART-naïve patients (ALETHIA; $n = 16$), found no significant change in CD4 and CD8 T-cell counts or HIV RNA levels in patients treated with leflunomide compared to placebo [55]. 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 if similar immunological effects will be seen in patients receiving cART.

Biological agents

Bovine colostrum, micronutrients and pre-/probiotics

Multiple approaches are now being taken to directly reduce microbial load and translocation in HIV patients. These include supplementation with micronutrients, bovine colostrum, pro- and prebiotics; all of which have previously been shown to reduce HIV-associated diarrhea [56–60]. These strategies may also alter the composition of gut microflora which may be important in modulating microbial translocation-driven IA [61,62]. Most of these studies have been in cART-naïve patients and some have reported increases in CD4 T-cell counts [59,60,63–67] (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 [68].

Antiretroviral treatment

Chronic IA in patients receiving cART may also be driven by low-level HIV viremia [14,15,69,70]. In multiple observational and RCT studies, the addition of raltegravir to suppressive cART resulted in no significant IA reduction in plasma, CSF or tissue [68,71–76] nor any change in endothelial function, a surrogate marker of cardiovascular disease [77]. 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 [78,79]. Further larger randomised studies are still needed to definitively determine the impact of raltegravir intensification on IA.

Several studies of maraviroc intensification have shown a reduction in IA [80–82] however one study reported an unexpected increase in IA [83] (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

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 1. Therapeutic agents/biologicals that have been evaluated in HIV-infected patients for their effects on immune activation and associated morbidities.

Drug name	Immune activation/inflammatory markers			Clinical outcomes				Ref
	T-cell activation (co-expression of HLA-DR and CD38)[##]	Soluble activation markers	Others	CD4 T-cell counts	HIV RNA levels [assay detection limit, copies/ml][§] /Markers of viral persistence	AIDS-defining illness	All-cause mortality	
HMG CoA reductase inhibitors								
Statin use	-	-	-	-	-	-	↓	[37]
	-	-	-	**-**	-	**↓(NHL)**	-	[38]
Atorvastatin	-	-	-	↔	-	-	-	[36]
	↓: CD8+	-	-	↔	↔	-	-	[32]
Pravastatin	**↓: CD8+ (CD38+)**	**↔hsCRP**	**-**	↔	-	-	-	[33]
	↑: CD8+ (CD38+)	-	-	↓	↔	-	-	[93]
Rosuvastatin	-	**↔: sTNFR** **↓: hsCRP**	-	-	-	-	-	[34]
	-	**↔: hsCRP, PAI-1**	**↔: P-selectin**	**-**	**-**	**-**	**-**	[35]
Chloroquine	↓: CD8+	-	↔: Ki-67 expression in CD4+ & CD8+ T-cells	-	↔	-	-	[42]
Hydroxychloroquine	**↓: CD4+** **↔: CD8+**	**↓: IL-6** **↔: TNF-α**	**-**	↔	**-**	**-**	**-**	[44]
	↔: CD8+, CD4+	↔: IL-6, D-dimer	↔: Ki-67 expression in CD4+ and CD8+ T-cells	↓	↑	**-**	-	[43]
Selective cyclooxygenase-2 inhibitors								
Celecoxib/rofecoxib	**↓: CD8+∗ (HLA-DR+ and CD38+)**	**-**	**-**	↑**	**-**	**-**	**-**	[49]
Celecoxib	↓: CD8+ (CD38+)	-	-	↔	-	-	-	[50]
Leflunomide	↓: CD8+	↔: D-dimer, CRP, sCD14	↓: BrDU incorporation in CD4+ T-cells	↔	↔			[55]
	↔: CD4+							
Intravenous immunoglobulin (IVIG)	↔: CD4+,CD8+	↔: CRP	↔: Ki-67 expression in CD4+ and CD8+ T-cells	↔	↔	-	-	[94]
	↔: CD4+, CD8+	**-**	**-**	**-**	**↔[<2]**	**-**	**-**	[95]
Minocycline	↔: CD8+(blood & CSF)	↔: CCL2 (CSF), neopterin (blood & CSF)	↔: CD16+ (blood & CSF)	↓	↔ (blood & CSF)	-	-	[96]
Bovine colostrum	-	-	-	↑	↔	-	-	[97]
	-	-	-	↑[#]	-	-	-	[59,63]
	↔: CD4+, CD8+	**↔: sCD14, LPS**	**↔: 16srDNA**	↔				[68]
Micronutrient supplementation	-	-	-	↔	↔	-	↓	[98]
	-	-	-	↔	-	-	↓	[99]
	-	-	-	↑	↓	-	-	[64]
	-	-	-	↑	-	-	-	[65]
Probiotics								
Bifidobacterium bifidum, Streptococcus thermophiles	-	-	-	↑	-	-	-	[66]
Lactobacillus rhamnosus	-	-	-	↑	-	-	-	[60]
	-	-	-	↔	-	-	-	[100]
Lactobacillus reuteri	-	-	-	↑	-	-	-	[67]
Prebiotics								
Oligosaccharide mixture[+]	↔: CD8+ (CD38+)	↓: sCD14	↓: CD4+CD25+ T-cells	↔	-	-	-	[101]
Raltegravir treatment intensification	**↔: CD8+, CD4+**	**-**	**-**	↑	**↔: SCA, 2-LTR, HIV DNA**	**-**	**-**	[71,102]
	↔: CD8+	**-**	**-**	↔	**↔: Usen HIV RNA, cell-associated HIV RNA, HIV DNA**	**-**	**-**	[72]
	↓: CD8+[@]	**-**	**-**	↔	**↔: SCA, HIV DNA** **↑: 2-LTR**[@]	**-**	**-**	[78]
	↔: CD8+	**↔: sCD14, LPS**	**↔: 16srDNA**	↔	**↔: Usen HIV RNA**	**-**	**-**	[68]
	↓: CD8+ (blood & GI tract)	**-**	**-**	**↑(tissue)/↔ (blood)**	**↓: US HIV RNA(tissue)** **↔: US HIV RNA, Usen HIV RNA, HIV DNA (blood & tissue)**	**-**	**-**	[73]
	↔: CD8+ (blood & CSF), CD4+ (CSF) **↑: CD4+ (blood)**	**↔: neopterin (CSF & blood)**	**-**	**-**	**↔: SCA (CSF & blood)**	**-**	**-**	[74]
	-	**-**	**-**	↔	**↔: HIV DNA (tissue & blood)**	**-**	**-**	[75]

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 1 (*continued*)

Drug name	Immune activation/inflammatory markers			Clinical outcomes				Ref
	T-cell activation (co-expression of HLA-DR and CD38)[##]	Soluble activation markers	Others	CD4 T-cell counts	HIV RNA levels [assay detection limit, copies/ml][§] /Markers of viral persistence	AIDS-defining illness	All-cause mortality	
	-	**↔: β2- microglobulin (blood & CSF), neopterin (blood & CSF)**	**-**	↔	**↔: HIV RNA [<20] (CSF & blood)**	**-**	**-**	[76]
	↓: CD8+ **↔: CD4+**	**↓: LPS** **↔: sCD14**	**-**	↔	**↓: IUPM in memory CD4+ T-cells** **↔: SCA, 2-LTR**	**-**	**-**	[79]
Maraviroc treatment intensification	**↓: CD4+, CD8+**	**↑: sCD14, LPS**	**-**	↔	**↔: SCA,2-LTR**	**-**	**-**	[80]
	↑: CD8+(blood & tissue)	**↓: LPS** **↑: sCD14**	**-**	↔	**↔SCA**	**-**	**-**	[83]
	↓: CD4+, CD8+	**-**	**↑: CD57+** **↓: caspase3+, Bcl-2**	↔	**-**	**-**	**-**	[81]
	↓: CD8+ **↔: CD4+**	**-**	**-**	↑	**↔: HIV DNA, Usen HIV RNA**			[82]
Valgancyclovir	**↓: CD8+**	**↔: hsCRP, IL-6, D-dimer, sCD14, cystatin C**	**-**	↔	↔	**-**	**-**	[90]
IFN-α + ribavirin	**↓: CD8+ (CD38+), CD4+ (CD38+)**	**-**	**-**	↓[T]	**-**	**-**	**-**	[91]

Bold fonts indicate studies that were done in cART-treated patients while normal text indicate studies that were performed in treatment-naïve HIV-infected individuals. ∗only in viremic patients, ∗∗ only in aviremic patients, [#]concomitant reduction in HIV-associated diarrhea, [+]mixture of short-chain galacto-oligosaccharides, long-chain fructo-oligosaccharides, pectin-hydrolysate-derived acidic oligosaccharides, [@]in a subset of patients, [T] transient, [§]assay detection limit <50 copies/ml unless otherwise specified. [##]T-cell activation markers represent co-expression of CD38+HLA-DR+ on T-cells unless otherwise specified. CRP, C-reactive protein; CSF, cerebrospinal fluid; LPS, lipopolysaccharide; LTR, long-terminal repeat; NHL, non-Hodgkins lymphoma; PAI-1, plasminogen activator inhibitor -1; SCA, single-copy assay; TNF, tumor necrosis factor; US, unspliced; Usen, ultra-sensitive.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 2. Therapeutic agents currently in or being considered for clinical trial to reduce immune activation levels in HIV.

Drug name/compounds (trial number)*	Proposed mechanism of action (references)	Target group	Primary endpoint studied
Rifaximin (NCT01466595)	Poorly absorbed antibiotic shown to reduce bacterial load in the gastrointestinal tract [103]. 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 pigtail macaques [104]	cART treated patients with sub-optimal 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 [105].	cART treated patients with sub-optimal 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 [106]	cART-naïve 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 [107].	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) [108] and inhibit TGF-β1-mediated fibrosis [109]	cART-treated patients	Change in HIV RNA (copies/ml CD4) and mean baseline GALT RNA at 24 weeks vs placebo
Methotrexate (NCT00000834)	Immuno-suppressive agent used in the treatment of auto-immune diseases including rheumatoid arthritis.	ARV (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 signalling pathway and collagen production [26].	-	-
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) [110–112].	-	-

*Active clinical studies referenced from clintrials.gov.

could potentially activate monocytes/macrophages via CCR1 [81] and/or increase antigen-specific T-cell and antibody responses which has been observed in some [84] but not all studies [85]. 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 IA. Studies of patients treated during chronic infection have demonstrated persistently elevated IA levels post-cART compared to uninfected controls [2–4]. A recent prospective study of cART initiated during acute infection demonstrated reduced IA to normal levels after 48 weeks [86]. Prospective or randomized trials need to be performed to determine the effect of early versus delayed cART on IA in patients with chronic infection.

Treatment of co-infections

Anti-CMV treatment-Valgancyclovir

Increased CMV-specific antibodies and/or T-cells have been associated with atherosclerosis [87,88] and impaired CD4 T-cell reconstitution [89] in HIV-infected patients on cART, suggesting that CMV co-infection may be a driver of persistent IA. A RCT with 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 [90]. 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-HCV treatment-interferon gamma and ribavirin

HCV-specific treatment with interferon-α and ribavirin in HIV/HCV co-infected patients receiving cART has been associated with a significant reduction in markers of T-cell activation [91] and endothelial dysfunction [92] 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 IA

There are multiple challenges in designing clinical trials to reduce chronic IA 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

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

multiple markers of IA 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 IA.

Conclusion

To date most studies aimed at reducing IA have only included a small number of patients and/or shown an effect on biomarkers of IA 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 IA biomarkers and clinical outcomes.

Acknowledgements

RR and SL wrote the manuscript. GK, AK, MF and PUC provided helpful comments and edited the manuscript.

Sources of funding: RR and AK receive funding from the HIR/MOHE grant (UM.C/625/1/HIR/MOHE/MED01) and RR from UMRG (RG377/11HTM). SRL is an Australian National Health and Medical Research Council (NHMRC) Practitioner Fellow. GK is a recipient of a NHMRC postgraduate scholarship.

Conflicts of interest

None declared.

References

1. Lewden C, May T, Rosenthal E, Burty C, Bonnet F, Costagliola D, *et al*. **Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic).** *J Acquir Immune Defic Syndr* 2008; **48**:590–598.
2. Chege D, Sheth PM, Kain T, Kim CJ, Kovacs C, Loutfy M, *et al*. **Sigmoid Th17 populations, the HIV latent reservoir, and microbial translocation in men on long-term antiretroviral therapy.** *AIDS* 2011; **25**:741–749.
3. French MA, King MS, Tschampa JM, da Silva BA, Landay AL. **Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T cells.** *J Infect Dis* 2009; **200**:1212–1215.
4. Piconi S, Trabattoni D, Gori A, Parisotto S, Magni C, Meraviglia P, *et al*. **Immune activation, apoptosis, and Treg activity are associated with persistently reduced CD4+ T-cell counts during antiretroviral therapy.** *AIDS* 2010; **24**:1991–2000.
5. Hunt PW, Cao HL, Muzoora C, Ssewanyana I, Bennett J, Emenyonu N, *et al*. **Impact of CD8+ T-cell activation on CD4+ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy.** *AIDS* 2011; **25**:2123–2131.
6. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, *et al*. **Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection.** *J Infect Dis* 2011; **203**:780–790.
7. Tincati C, Bellistri GM, Casana M, Merlini E, Comi L, Bai F, *et al*. **CD8+ hyperactivation and senescence correlate with early carotid intima-media thickness in HIV+ patients with no cardiovascular disease.** *J Acquir Immune Defic Syndr* 2009; **51**:642–644.
8. Carsenti-Dellamonica H, Vassallo M, Pradier C, Durant J, Harvey-Langton A, Lebrun-Frenay C, *et al*. **LPS May Be a Predictive Factor Even in Mild Forms of HIV-associated Neurocognitive Impairment: Sub-analysis of the Neuradapt Study.** *18th Conference on Retroviruses and Opportunistic Infections, Boston, Feb 27-Mar 2* 2011:Paper# 404.
9. Lyons JL, Uno H, Ancuta P, Kamat A, Moore DJ, Singer EJ, *et al*. **Plasma sCD14 is a Biomarker Associated with Impaired Neurocognitive Test Performance in Attention and Learning Domains in HIV Infection.** *J Acquir Immune Defic Syndr* 2011.
10. Gazzola L, Ballistri G, Bai F, Savoldi A, Bini T, Marchetti G, *et al*. **Higher CD4+ and CD8+ T-cell activation are associated factors of impaired bone mineral density in HIV infected patients.** In: *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2012.
11. Appay V, Sauce D. **Immune activation and inflammation in HIV-1 infection: causes and consequences.** *J Pathol* 2008; **214**:231–241.
12. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, *et al*. **Microbial translocation is a cause of systemic immune activation in chronic HIV infection.** *Nat Med* 2006; **12**:1365–1371.
13. Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, *et al*. **Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection.** *J Infect Dis* 2009; **199**:1177–1185.
14. Mavigner M, Delobel P, Cazabat M, Dubois M, L'Faqihi-Olive FE, Raymond S, *et al*. **HIV-1 residual viremia correlates with persistent T-cell activation in poor immunological responders to combination antiretroviral therapy.** *PLoS One* 2009; **4**:e7658.
15. Ostrowski SR, Katzenstein TL, Pedersen BK, Gerstoft J, Ullum H. **Residual viraemia in HIV-1-infected patients with plasma viral load <or=20 copies/ml is associated with increased blood levels of soluble immune activation markers.** *Scand J Immunol* 2008; **68**:652–660.
16. Kovacs A, Al-Harthi L, Christensen S, Mack W, Cohen M, Landay A. **CD8(+) T cell activation in women coinfected with human immunodeficiency virus type 1 and hepatitis C virus.** *J Infect Dis* 2008; **197**:1402–1407.
17. Pandrea I, Cornell E, Wilson C, Ribeiro RM, Ma D, Kristoff J, *et al*. **Coagulation biomarkers predict disease progression in SIV-infected nonhuman primates.** *Blood* 2012; **120**:1357–1366.
18. Jacquelin B, Mayau V, Targat B, Liovat AS, Kunkel D, Petitjean G, *et al*. **Nonpathogenic SIV infection of African green monkeys induces a strong but rapidly controlled type I IFN response.** *J Clin Invest* 2009; **119**:3544–3555.
19. Sedaghat AR, German J, Teslovich TM, Cofrancesco J Jr, Jie CC, Talbot CC Jr, *et al*. **Chronic CD4+ T-cell activation and depletion in human immunodeficiency virus type 1 infection: type I interferon-mediated disruption of T-cell dynamics.** *J Virol* 2008; **82**:1870–1883.
20. Rempel H, Sun B, Calosing C, Pillai SK, Pulliam L. **Interferon-alpha drives monocyte gene expression in chronic unsuppressed HIV-1 infection.** *AIDS* 2010; **24**:1415–1423.
21. Fernandez S, Tanaskovic S, Helbig K, Rajasuriar R, Kramski M, Murray JM, *et al*. **CD4+ T-cell deficiency in HIV patients**

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

responding to antiretroviral therapy is associated with increased expression of interferon-stimulated genes in CD4+ T cells. *The Journal of infectious diseases* 2011; **204**:1927–1935.
22. Valdez H, Lederman MM. **Cytokines and cytokine therapies in HIV infection.** *AIDS Clin Rev* 1997; 187–228.
23. Biancotto A, Grivel JC, Iglehart SJ, Vanpouille C, Lisco A, Sieg SF, *et al*. **Abnormal activation and cytokine spectra in lymph nodes of people chronically infected with HIV-1.** *Blood* 2007; **109**:4272–4279.
24. Herbeuval JP, Hardy AW, Boasso A, Anderson SA, Dolan MJ, Dy M, *et al*. **Regulation of TNF-related apoptosis-inducing ligand on primary CD4+ T cells by HIV-1: role of type I IFN-producing plasmacytoid dendritic cells.** *Proc Natl Acad Sci U S A* 2005; **102**:13974–13979.
25. Katsikis PD, Wunderlich ES, Smith CA, Herzenberg LA, Herzenberg LA. **Fas antigen stimulation induces marked apoptosis of T lymphocytes in human immunodeficiency virus-infected individuals.** *J Exp Med* 1995; **181**:2029–2036.
26. Zeng M, Smith AJ, Wietgrefe SW, Southern PJ, Schacker TW, Reilly CS, *et al*. **Cumulative mechanisms of lymphoid tissue fibrosis and T cell depletion in HIV-1 and SIV infections.** *J Clin Invest* 2011; **121**:998–1008.
27. Hunt PW, Landay AL, Sinclair E, Martinson JA, Hatano H, Emu B, *et al*. **A Low T Regulatory Cell Response May Contribute to Both Viral Control and Generalized Immune Activation in HIV Controllers.** *PLoS One* 2011; **6**:e15924.
28. Eggena MP, Barugahare B, Jones N, Okello M, Mutalya S, Kityo C, *et al*. **Depletion of regulatory T cells in HIV infection is associated with immune activation.** *J Immunol* 2005; **174**:4407–4414.
29. Cosgrove C, Ussher JE, Rauch A, Gartner K, Kurioka A, Huhn MH, *et al*. **Early and non-reversible decrease of CD161++/ MAIT cells in HIV infection.** *Blood* 2012.
30. Leeansyah E, Ganesh A, Quigley MF, Sonnerborg A, Andersson J, Hunt PW, *et al*. **Activation, exhaustion and persistent decline of the anti-microbial MR1-restricted MAIT cell population in chronic HIV-1 infection.** *Blood* 2012.
31. d'Ettorre G, Paiardini M, Ceccarelli G, Silvestri G, Vullo V. **HIV-associated immune activation: from bench to bedside.** *AIDS Res Hum Retroviruses* 2011; **27**:355–364.
32. Ganesan A, Crum-Cianflone N, Higgins J, Qin J, Rehm C, Metcalf J, *et al*. **High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial.** *J Infect Dis* 2011; **203**:756–764.
33. De Wit S, Delforge M, Necsoi CV, Clumeck N. **Downregulation of CD38 activation markers by atorvastatin in HIV patients with undetectable viral load.** *AIDS* 2011; **25**:1332–1333.
34. Aslangul E, Fellahi S, Assoumou LK, Bastard JP, Capeau J, Costagliola D. **High-sensitivity C-reactive protein levels fall during statin therapy in HIV-infected patients receiving ritonavir-boosted protease inhibitors.** *AIDS* 2011; **25**:1128–1131.
35. Fichtenbaum CJ, Yeh TM, Evans SR, Aberg JA. **Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087.** *Journal of clinical lipidology* 2010; **4**:279–287.
36. Manfredi R, Calza L, Chiodo F. **Long-term statin use does not act on the temporal trend of CD4 cell count in patients on virologically effective HAART.** *AIDS* 2006; **20**:455–457.
37. Moore RD, Bartlett JG, Gallant JE. **Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients.** *PLoS ONE* 2011; **6**:e21843.
38. Chao C, Xu L, Abrams DI, Towner WJ, Horberg MA, Leyden WA, *et al*. **HMG-CoA reductase inhibitors (statins) use and risk of non-Hodgkin lymphoma in HIV-positive persons.** *AIDS* 2011; **25**:1771–1777.
39. Beignon AS, McKenna K, Skoberne M, Manches O, DaSilva I, Kavanagh DG, *et al*. **Endocytosis of HIV-1 activates plasmacytoid dendritic cells via Toll-like receptor-viral RNA interactions.** *J Clin Invest* 2005; **115**:3265–3275.
40. Schmidt B, Ashlock BM, Foster H, Fujimura SH, Levy JA. **HIV-infected cells are major inducers of plasmacytoid dendritic cell interferon production, maturation, and migration.** *Virology* 2005; **343**:256–266.
41. Martinson JA, Montoya CJ, Usuga X, Ronquillo R, Landay AL, Desai SN. **Chloroquine modulates HIV-1-induced plasmacytoid dendritic cell alpha interferon: implication for T-cell activation.** *Antimicrobial agents and chemotherapy* 2010; **54**:871–881.
42. Murray SM, Down CM, Boulware DR, Stauffer WM, Cavert WP, Schacker TW, *et al*. **Reduction of immune activation with chloroquine therapy during chronic HIV infection.** *Journal of virology* 2010; **84**:12082–12086.
43. Paton NI, Goodall RL, Dunn DT, Franzen S, Collaco-Moraes Y, Gazzard BG, *et al*. **Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial.** *JAMA* 2012; **308**:353–361.
44. Piconi S, Parisotto S, Rizzardini G, Passerini S, Terzi R, Argenteri B, *et al*. **Hydroxychloroquine drastically reduces immune activation in HIV-infected, antiretroviral therapy-treated immunologic nonresponders.** *Blood* 2011; **118**:3263–3272.
45. Aandahl EM, Aukrust P, Skalhegg BS, Muller F, Froland SS, Hansson V, *et al*. **Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients.** *FASEB J* 1998; **12**:855–862.
46. Torgersen KM, Vang T, Abrahamsen H, Yaqub S, Tasken K. **Molecular mechanisms for protein kinase A-mediated modulation of immune function.** *Cell Signal* 2002; **14**:1–9.
47. Brudvik KW, Tasken K. **Modulation of T cell immune functions by the prostaglandin E(2) - cAMP pathway in chronic inflammatory states.** *Br J Pharmacol* 2012; **166**:411–419.
48. Johansson CC, Bryn T, Aandahl EM, Areklett MA, Aukrust P, Tasken K, *et al*. **Treatment with type-2 selective and non-selective cyclooxygenase inhibitors improves T-cell proliferation in HIV-infected patients on highly active antiretroviral therapy.** *AIDS* 2004; **18**:951–952.
49. Kvale D, Ormaasen V, Kran AM, Johansson CC, Aukrust P, Aandahl EM, *et al*. **Immune modulatory effects of cyclooxygenase type 2 inhibitors in HIV patients on combination antiretroviral treatment.** *AIDS* 2006; **20**:813–820.
50. Pettersen FO, Torheim EA, Dahm AEA, Aaberge IS, Lind A, Holm M, *et al*. **An Exploratory Trial of Cyclooxygenase Type 2 Inhibitor in HIV-1 Infection: Downregulated Immune Activation and Improved T Cell-Dependent Vaccine Responses.** *J Virol* 2011; **85**:6557–6566.
51. Hossain MM, Margolis DM. **Inhibition of HIV replication by A77 1726, the active metabolite of leflunomide, in combination with pyrimidine nucleoside reverse transcriptase inhibitors.** *J Acquir Immune Defic Syndr* 2001; **28**:199–201.
52. Schlapfer E, Fischer M, Ott P, Speck RF. **Anti-HIV-1 activity of leflunomide: a comparison with mycophenolic acid and hydroxyurea.** *AIDS* 2003; **17**:1613–1620.
53. Davis JP, Cain GA, Pitts WJ, Magolda RL, Copeland RA. **The immunosuppressive metabolite of leflunomide is a potent inhibitor of human dihydroorotate dehydrogenase.** *Biochemistry* 1996; **35**:1270–1273.
54. Cherwinski HM, Cohn RG, Cheung P, Webster DJ, Xu YZ, Caulfield JP, *et al*. **The immunosuppressant leflunomide inhibits lymphocyte proliferation by inhibiting pyrimidine biosynthesis.** *J Pharmacol Exp Ther* 1995; **275**:1043–1049.
55. Read SW, DeGrezia M, Ciccone EJ, DerSimonian R, Higgins J, Adelsberger JW, *et al*. **The effect of leflunomide on cycling and activation of T-cells in HIV-1-infected participants.** *PLoS ONE* 2010; **5**:e11937.
56. Attili SV, Gulati AK, Singh VP, Varma DV, Rai M, Sundar S. **Diarrhea, CD4 counts and enteric infections in a hospital - based cohort of HIV-infected patients around Varanasi, India.** *BMC Infect Dis* 2006; **6**:39.
57. Lazzerini M, Ronfani L. **Oral zinc for treating diarrhoea in children.** *Cochrane Database Syst Rev* 2008:CD005436.
58. Plettenberg A, Stoehr A, Stellbrink HJ, Albrecht H, Meigel W. **A preparation from bovine colostrum in the treatment of HIV-positive patients with chronic diarrhea.** *Clin Investig* 1993; **71**:42–45.
59. Floren CH, Chinenye S, Elfstrand L, Hagman C, Ihse I. **Colo-Plus, a new product based on bovine colostrum, alleviates HIV-associated diarrhoea.** *Scandinavian journal of gastroenterology* 2006; **41**:682–686.
60. Anukam KC, Osazuwa EO, Osadolor HB, Bruce AW, Reid G. **Yogurt containing probiotic Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 helps resolve moderate diarrhea and increases CD4 count in HIV/AIDS patients.** *J Clin Gastroenterol* 2008; **42**:239–243.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

61. Ellis CL, Ma ZM, Mann SK, Li CS, Wu J, Knight TH, *et al*. **Molecular characterization of stool microbiota in HIV-infected subjects by panbacterial and order-level 16S ribosomal DNA (rDNA) quantification and correlations with immune activation.** *J Acquir Immune Defic Syndr* 2011; **57**:363–370.
62. Merlini E, Bai F, Bellistri GM, Tincati C, d'Arminio Monforte A, Marchetti G. **Evidence for polymicrobic flora translocating in peripheral blood of HIV-infected patients with poor immune response to antiretroviral therapy.** *PLoS ONE* 2011; **6**:e18580.
63. Kaducu FO, Okia SA, Upenytho G, Elfstrand L, Floren CH. **Effect of bovine colostrum-based food supplement in the treatment of HIV-associated diarrhea in Northern Uganda: a randomized controlled trial.** *Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology* 2011; **30**:270–276.
64. Fawzi WW, Msamanga GI, Spiegelman D, Wei R, Kapiga S, Villamor E, *et al*. **A randomized trial of multivitamin supplements and HIV disease progression and mortality.** *N Engl J Med* 2004; **351**:23–32.
65. Kaiser JD, Campa AM, Ondercin JP, Leoung GS, Pless RF, Baum MK. **Micronutrient supplementation increases CD4 count in HIV-infected individuals on highly active antiretroviral therapy: a prospective, double-blinded, placebo-controlled trial.** *J Acquir Immune Defic Syndr* 2006; **42**:523–528.
66. Trois L, Cardoso EM, Miura E. **Use of probiotics in HIV-infected children: a randomized double-blind controlled study.** *Journal of tropical pediatrics* 2008; **54**:19–24.
67. Irvine SL, Hummelen R, Hekmat S, Looman CW, Habbema JD, Reid G. **Probiotic yogurt consumption is associated with an increase of CD4 count among people living with HIV/AIDS.** *J Clin Gastroenterol* 2010; **44**:e201–e205.
68. Byakwaga H, Kelly M, Purcell DF, French MA, Amin J, Lewin SR, *et al*. **Intensification of antiretroviral therapy with raltegravir or addition of hyperimmune bovine colostrum in HIV-infected patients with suboptimal CD4+ T-cell response: a randomized controlled trial.** *J Infect Dis* 2011; **204**:1532–1540.
69. Bastard JP, Soulie C, Fellahi S, Haim-Boukobza S, Simon A, Katlama C, *et al*. **Circulating interleukin-6 levels correlate with residual HIV viraemia and markers of immune dysfunction in treatment-controlled HIV-infected patients.** *Antiviral therapy* 2012.
70. Steel A, Cox AE, Shamji MH, John L, Nelson M, Henderson DC, *et al*. **HIV-1 viral replication below 50 copies/ml in patients on antiretroviral therapy is not associated with CD8+ T-cell activation.** *Antivir Ther* 2007; **12**:971–975.
71. Gandhi RT, Zheng L, Bosch RJ, Chan ES, Margolis DM, Read S, *et al*. **The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial.** *PLoS Med* 2010; **7**.
72. Hatano H, Hayes TL, Dahl V, Sinclair E, Lee TH, Hoh R, *et al*. **A randomized, controlled trial of raltegravir intensification in antiretroviral-treated, HIV-infected patients with a suboptimal CD4+ T cell response.** *J Infect Dis* 2011; **203**:960–968.
73. Yukl SA, Shergill AK, McQuaid K, Gianella S, Lampiris H, Hare CB, *et al*. **Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy.** *AIDS* 2010; **24**:2451–2460.
74. Dahl V, Lee E, Peterson J, Spudich SS, Leppla I, Sinclair E, *et al*. **Raltegravir treatment intensification does not alter cerebrospinal fluid HIV-1 infection or immunoactivation in subjects on suppressive therapy.** *J Infect Dis* 2011; **204**:1936–1945.
75. Chege D, Kovacs C, la Porte C, Ostrowski M, Raboud J, Su D, *et al*. **Effect of raltegravir intensification on HIV proviral DNA in the blood and gut mucosa of men on long-term therapy: a randomized controlled trial.** *AIDS* 2012; **26**:167–174.
76. Yilmaz A, Verhofstede C, D'Avolio A, Watson V, Hagberg L, Fuchs D, *et al*. **Treatment intensification has no effect on the HIV-1 central nervous system infection in patients on suppressive antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2010; **55**:590–596.
77. Hatano H, Scherzer R, Wu Y, Harvill K, Maka K, Hoh R, *et al*. **A randomized controlled trial assessing the effects of raltegravir intensification on endothelial function in treated HIV infection.** *J Acquir Immune Defic Syndr* 2012; **61**:317–325.
78. Buzon MJ, Massanella M, Llibre JM, Esteve A, Dahl V, Puertas MC, *et al*. **HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects.** *Nat Med* 2010; **16**:460–465.
79. Vallejo A, Gutierrez C, Hernandez-Novoa B, Diaz L, Madrid N, Abad-Fernandez M, *et al*. **The effect of intensification with raltegravir on the HIV-1 reservoir of latently infected memory CD4 T cells in suppressed patients.** *AIDS* 2012; **26**:1885–1894.
80. Gutierrez C, Diaz L, Vallejo A, Hernandez-Novoa B, Abad M, Madrid N, *et al*. **Intensification of antiretroviral therapy with a CCR5 antagonist in patients with chronic HIV-1 infection: effect on T cells latently infected.** *PLoS ONE* 2011; **6**:e27864.
81. Wilkin TJ, Lalama CM, McKinnon J, Gandhi RT, Lin N, Landay A, *et al*. **A Pilot Trial of Adding Maraviroc to Suppressive Antiretroviral Therapy for Suboptimal CD4+ T-Cell Recovery Despite Sustained Virologic Suppression: ACTG A5256.** *J Infect Dis* 2012; **206**:534–542.
82. Cuzin L, Trabelsi S, Delobel P, Barbuat C, Reynes J, Allavena C, *et al*. **Maraviroc Intensification of Stable Antiviral Therapy in HIV-1-Infected Patients With Poor Immune Restoration: MARIMUNO-ANRS 145 Study.** *J Acquir Immune Defic Syndr* 2012; **61**:557–564.
83. Hunt P, Shulman N, Hayes TL, Dahl V, Funderburg N, Adeyemi O, *et al*. **Immunomodulatory Effects of MVC Intensification in HIV-infected Individuals with Incomplete CD4+ T Cell Recovery during Suppressive ART.** In: *18th Conference on Retroviruses and Opportunistic Infections*. Boston, Massachusetts; 2011.
84. Westrop SJ, Moyle G, Jackson A, Nelson M, Mandalia S, Imami N. **CCR5 antagonism impacts vaccination response and immune profile in HIV-1 infection.** *Mol Med* 2012.
85. Canestri A, Krivine A, Assoumou L, Le Corre M, Rozenberg F, Marcelin AG, *et al*. **Maraviroc does not affect humoral response to the pandemic influenza A-H1N1v 2009 adjuvanted vaccine in HIV-1-infected patients.** *AIDS* 2010; **24**:2887–2889.
86. Markowitz M, Evering T, Figueroa K, Rodriguez M, La Mar M, Garmon D, *et al*. **Very early initiation of combination antiretroviral therapy results in normal levels of markers of immune activation.** In: *XIX International AIDS Conference*. Washington DC, USA; 2012.
87. Hsue PY, Hunt PW, Sinclair E, Bredt B, Franklin A, Killian M, *et al*. **Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses.** *AIDS* 2006; **20**:2275–2283.
88. Parrinello CM, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, *et al*. **Cytomegalovirus immunoglobulin G antibody is associated with subclinical carotid artery disease among HIV-infected women.** *J Infect Dis* 2012; **205**:1788–1796.
89. Appay V, Fastenackels S, Katlama C, Ait-Mohand H, Schneider L, Guihot A, *et al*. **Old age and anti-cytomegalovirus immunity are associated with altered T-cell reconstitution in HIV-1-infected patients.** *AIDS* 2011; **25**:1813–1822.
90. Hunt PW, Martin JN, Sinclair E, Epling L, Teague J, Jacobson MA, *et al*. **Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy.** *J Infect Dis* 2011; **203**:1474–1483.
91. Gonzalez VD, Falconer K, Blom KG, Reichard O, Morn B, Laursen AL, *et al*. **High Levels of Chronic Immune Activation in the T-Cell Compartments of Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus Type 1 and on Highly Active Antiretroviral Therapy Are Reverted by Alpha Interferon and Ribavirin Treatment.** *J Virol* 2009; **83**:11407–11411.
92. Guzman-Fulgencio M, Berenguer J, de Castro IF, Micheloud D, Lopez JC, Cosin J, *et al*. **Sustained virological response to interferon-alpha plus ribavirin decreases inflammation and endothelial dysfunction markers in HIV/HCV co-infected patients.** *J Antimicrob Chemother* 2011; **66**:645–649.
93. Negredo E, Clotet B, Puig J, Perez-Alvarez N, Ruiz L, Romeu J, *et al*. **The effect of atorvastatin treatment on HIV-1-infected patients interrupting antiretroviral therapy.** *AIDS* 2006; **20**:619–621.
94. Vermeulen JN, Prins JM, Bunnik E, Hack CE, Jurriaans S, Miedema F, *et al*. **Intravenous immunoglobulin (IVIG) treatment for modulation of immune activation in human immunodeficiency virus type 1 infected therapy-naive individuals.** *AIDS Res Hum Retroviruses* 2007; **23**:1348–1353.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

95. Mellberg T, Gonzalez VD, Lindkvist A, Eden A, Sonnerborg A, Sandberg JK, *et al*. **Rebound of residual plasma viremia after initial decrease following addition of intravenous immunoglobulin to effective antiretroviral treatment of HIV.** *AIDS research and therapy* 2011; **8**:21.
96. Ho EL, Spudich SS, Lee E, Fuchs D, Sinclair E, Price RW. **Minocycline fails to modulate cerebrospinal fluid HIV infection or immune activation in chronic untreated HIV-1 infection: results of a pilot study.** *AIDS research and therapy* 2011; **8**:17.
97. Lange JM, Gazzard B, Diaz R. **Reduced CD4+ Tcell decline and immune activation by NR100157: a specific multi-targeted nutritional intervention in HIV-1 positive adults not on antiretroviral therapy (BITE).** In: *49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*. San Francisco, California; 2009.
98. Jiamton S, Pepin J, Suttent R, Filteau S, Mahakkanukrauh B, Hanshaoworakul W, *et al*. **A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok.** *AIDS* 2003; **17**:2461–2469.
99. Kelly P, Katubulushi M, Todd J, Banda R, Yambayamba V, Fwoloshi M, *et al*. **Micronutrient supplementation has limited effects on intestinal infectious disease and mortality in a Zambian population of mixed HIV status: a cluster randomized trial.** *Am J Clin Nutr* 2008; **88**:1010–1017.
100. Hummelen R, Changalucha J, Butamanya NL, Koyama TE, Cook A, Habbema JD, *et al*. **Effect of 25 weeks probiotic supplementation on immune function of HIV patients.** *Gut microbes* 2011; **2**:80–85.
101. Gori A, Rizzardini G, Van't Land B, Amor KB, van Schaik J, Torti C, *et al*. **Specific prebiotics modulate gut microbiota and immune activation in HAART-naive HIV-infected adults: results of the "COPA" pilot randomized trial.** *Mucosal immunology* 2011; **4**:554–563.
102. Gandhi RT, Coombs RW, Chan ES, Bosch RJ, Zheng L, Margolis DM, *et al*. **No effect of raltegravir intensification on viral replication markers in the blood of HIV-1-infected patients receiving antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2012; **59**:229–235.
103. Eltawil KM, Laryea M, Peltekian K, Molinari M. **Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis.** *World J Gastroenterol* 2012; **18**:767–777.
104. Pandrea I, Haret-Richter G, Ma D, Ribeiro RM, Nusbaum R, Trichel A, *et al*. **Administration of Rifaximin ad Sulfasalazine during Acute SIV Infection Decreases Microbial Translocation and Coagulation Marker Levels and Significantly Impacts Viral Replication.** In: *19th Conference on Retrovirology and Opportunistic Infections*. Seattle, Washington; 2012.
105. Valdes-Ferrer SI, Crispin JC, Belaunzaran PF, Cantu-Brito CG, Sierra-Madero J, Alcocer-Varela J. **Acetylcholine-esterase inhibitor pyridostigmine decreases T cell overactivation in patients infected by HIV.** *AIDS Res Hum Retroviruses* 2009; **25**:749–755.
106. Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M, Donate-Correa J, Cazana-Perez V, Garcia-Perez J. **Effect of phosphate binders on serum inflammatory profile, soluble CD14, and endotoxin levels in hemodialysis patients.** *Clin J Am Soc Nephrol* 2011; **6**:2272–2279.
107. Rodriguez-Torres M, Rodriguez-Orengo JF, Rios-Bedoya CF, Fernandez-Carbia A, Salgado-Mercado R, Marxuach-Cuetara AM. **Double-blind pilot study of mesalamine vs. placebo for treatment of chronic diarrhea and nonspecific colitis in immunocompetent HIV patients.** *Dig Dis Sci* 2006; **51**:161–167.
108. Baker JV, Huppler Hullsiek K, Prosser R, Duprez D, Grimm R, Rhame F, *et al*. **Angiotensin Cenverting Enzyme Inhibitor (ACE-I) and/or HMG-CoA Reductase Inhibitor ('statin') Treatment as Adjunct Therapy for Persons with HIV Infection: a pilot study.** In: *19th Conference on Retroviruses and Opportunistic Infections*. Seattle, Washington; 2012.
109. Chen K, Wei Y, Sharp GC, Braley-Mullen H. **Inhibition of TGFbeta1 by anti-TGFbeta1 antibody or lisinopril reduces thyroid fibrosis in granulomatous experimental autoimmune thyroiditis.** *J Immunol* 2002; **169**:6530–6538.
110. Yao Y, Richman L, Higgs BW, Morehouse CA, de los Reyes M, Brohawn P, *et al*. **Neutralization of interferon-alpha/beta-inducible genes and downstream effect in a phase I trial of an anti-interferon-alpha monoclonal antibody in systemic lupus erythematosus.** *Arthritis Rheum* 2009; **60**:1785–1796.
111. Merrill JT, Wallace DJ, Petri M, Kirou KA, Yao Y, White WI, *et al*. **Safety profile and clinical activity of sifalimumab, a fully human anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus: a phase I, multicentre, double-blind randomised study.** *Ann Rheum Dis* 2011; **70**:1905–1913.
112. Yao Y, Higgs BW, Richman L, White B, Jallal B. **Use of type I interferon-inducible mRNAs as pharmacodynamic markers and potential diagnostic markers in trials with sifalimumab, an anti-IFNalpha antibody, in systemic lupus erythematosus.** *Arthritis Res Ther* 2010; **12 (Suppl 1)**:S6.
113. Deeks SG. **HIV infection, inflammation, immunosenescence, and aging.** *Annu Rev Med* 2011; **62**:141–155.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.