Microbial Translocation and Cardiometabolic Risk Factors in HIV Infection

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Abstract

The widespread access to antiretroviral treatment during the past decades has transformed HIV infection from a lethal disease to a chronic condition, in which the relative burden of non-AIDS-related chronic disorders such as cardiovascular disease, malignancy, renal, liver, and bone disease has increased. The adjusted relative risk for myocardial infarction is reported to be around 2-fold compared to that of the general population, which over time is likely to translate into increased absolute risk in an aging population. Thus, delineating potentially HIV-specific pathogenetic mechanisms is crucial in order to tailor novel strategies for prophylaxis and treatment. This review will focus on advances in the field that possibly link HIV-induced alterations of the gut mucosa and consequent microbial translocation to cardiometabolic risk factors in HIV infection. Recent work suggests that markers of microbial translocation are closely associated with several cardiovascular risk factors such as dyslipidemia, insulin resistance, hypertension, coagulation abnormalities, endothelial dysfunction, and carotid atherosclerosis. Future studies should investigate whether associations between microbial translocation and cardiovascular risk factors will translate into increased risk of acute events, and whether strategies to target gut microbiota and microbial translocation might reduce such a risk.

Introduction

THE WIDESPREAD ACCESS TO antiretroviral treatment (ART) during the past decades has transformed HIV infection from a lethal disease to a chronic condition. In the same period, the relative burden of non-AIDS-related chronic disorders such as cardiovascular disease (CVD), malignancy, renal, liver, and bone disease has increased.¹ Today, non-AIDS-related mortality exceeds AIDS-related mortality in populations with access to ART.²

The extent to which HIV infection contributes to cardiovascular risk in the era of ART is debated. HIV infection has been associated with signs of subclinical atherosclerosis, such as measures of endothelial dysfunction,^{3–6} increased arterial stiffness,^{7–10} and increased carotid intima media thickness.^{11,12} Moreover, compared to the HIV-uninfected population, HIV-infected individuals have increased rates of CVD, including coronary heart disease,^{13–15} acute myocardial infarction,^{15–17} cerebrovascular disease,¹⁸ and peripheral vascular disease,¹⁹ even after adjustment for cardiovascular risk factors. The adjusted relative risk for myocardial

infarction is reported to be around 1.5- to 2-fold compared to that of the general population.^{15,16}

Despite an increased relative risk of CVD in the HIV-infected population, the absolute rates of CVD disease in the HIV-infected population are still low, and the incidence of cardiovascular events and mortality has in fact been reported to be stable or declining over the past years.^{14,20,21} Because 50% of those living with HIV will be older than 50 years by 2015,²² an increased relative risk is likely to translate into increased absolute risk in an aging population.

From a global perspective, HIV-associated cardiomyopathy and pulmonary hypertension are still the leading cardiac manifestations in developing countries with incomplete access to ART.²³ However, increased ART coverage in combination with rapid demographic transitions is about to change this picture, as exemplified by Brazil, in which a shift from AIDS to non-AIDS-related mortality is already evident.²⁴

Thus, delineating potentially HIV-specific pathophysiological mechanisms is crucial in order to tailor novel strategies for prophylaxis and treatment in a growing population at

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risk. This review will focus on recent advances in the field that possibly link HIV-induced alterations of the gut mucosa and consequent microbial translocation to cardiometabolic risk factors in HIV infection.

Traditional and HIV-Specific Risk Factors for CVD

As in the general population, established cardiovascular risk factors such as family history, age, male sex, hypertension, hyperlipidemia, and smoking are leading causes of CVD in the HIV-infected population.^{15,16,25–27} Certain established risk factors are more prevalent in the HIV-infected population than in the general population, in particular smoking.^{28–33} Notably, HIV-infected smokers seem to have excess mortality rates compared to HIV-uninfected smokers.³⁴

Furthermore, the use of ART has an unfavorable effect on the lipid profile,^{16,31,32} at least with earlier regimens, and is associated with increased risk of diabetes mellitus.^{35–37} Moreover, unhealthy diet, low socioeconomic status, and excessive alcohol intake are likely to be more common in HIV-infected populations,³⁸ as suggested by a Danish study reporting that mothers of HIV-infected patients have an increased risk of myocardial infarction.³⁹

In addition to traditional risk factors, several HIV-specific factors have been proposed to contribute to the increased burden of non-AIDS-related disorders, including consequences of persistent inflammation, immune activation, and immune dysfunction.¹ Importantly, incomplete immune recovery in patients on ART is a predictor of both non-AIDS-related morbidity and mortality.⁴⁰ In addition, advanced immunodeficiency has been associated with an increased burden of non-AIDS morbidities.⁴¹

Immune Activation and Microbial Translocation

Importantly, the immune dysfunction of HIV infection is characterized not only by immunodeficiency and loss of CD4⁺ T cells, but also by chronic immune activation and inflammation.¹ Microbial translocation has been proposed as a major driver of the latter.⁴² During acute HIV infection the gastrointestinal mucosa is depleted of CD4⁺ T cells, especially Th17 cells. Th17 cells normally promote recruitment of neutrophils, prevent invasion of extracellular microorganisms, and promote epithelial regeneration.^{43–45} In the course of chronic infection the gastrointestinal mucosa shows evidence of local inflammation, lowered levels of IgA, abnormal enterocyte differentiation and apoptosis, and disruption of tight junctions. These factors enable shifts in the intraluminal microbial composition as well as translocation of microbial products such as lipopolysaccharide (LPS) and flagellin into the systemic circulation.^{46–50}

Translocated microbial products are recognized by Toll-like receptors (TLRs) and other receptors on cells of the innate immune system. To activate TLR4, LPS requires binding by the myeloid differentiation-2 (MD-2) complex, facilitated by CD14-mediated transfer from LPS binding protein.^{51,52} Recently, it was shown that systemic LPS levels and markers of TLR4 activation (MD-2 and soluble CD14; sCD14) in chronic HIV infection are increased.⁵³ Activated TLRs in turn activate transcription factors that lead to *de novo* production of proinflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF).^{42,54}

Enhanced microbial translocation has been associated with activated CD4⁺ and CD8⁺ T cell phenotypes,^{42,55,56} and accumulating evidence suggests that microbial translocation is a predictor of disease progression, poor immune restoration, and non-AIDS morbidity in HIV infection.^{57–59} Notably, chronic immune activation and microbial translocation decrease but persist in the course of effective ART and suppressed viral replication.^{60–64} This also seems to be true for markers of microbial translocation that decrease upon initiation of ART although they do not reach the level of healthy adults.^{42,65} Thus, abnormal and in some cases substantially enhanced translocation of microbial products may persist in HIV-infected individuals.⁶⁶

Microbial Translocation and Cardiovascular Risk in Non-HIV Populations

Several recent studies in HIV-seronegative populations suggest that crosstalk between the gut flora (microbiota) and innate immunity might be involved in the pathogenesis of obesity and cardiovascular risk.⁶⁷ The gut microbiota contains 10-fold the number of cells and 150 times the number of genes compared to the human body, and is currently being characterized in the Human Microbiome Project and in the MetaHIT program.⁶⁸ An altered gut microbiota has been linked not only to symptomatic atherosclerosis⁶⁹ but also insulin resistance, diabetes mellitus,⁷⁰ and obesity, by increasing the amount of energy harvested from the diet.⁷¹ In particular, circulating LPS has been proposed to be an early trigger of inflammation, insulin resistance, and subsequent cardiovascular risk.⁶⁷ Furthermore, links between inflammation, microbial translocation, and CVD have been reported in patients undergoing peritoneal dialysis and hemodialysis.^{72,73}

An increase in plasma LPS even occurs in HIV-seronegative healthy individuals after a high fat meal,⁷⁴ probably due to cotransportation over the gut wall together with dietary fat, by incorporation in triglyceride-rich chylomicrons. This “metabolic endotoxemia” has been shown to initiate obesity and insulin resistance.⁷⁵ Furthermore, low-grade endotoxemia is evident in patients with type 2 diabetes mellitus and the metabolic syndrome^{75,76} and may predict future atherosclerosis and cardiovascular disease.⁷⁷ Recently, it was shown that plasma LPS is increased in obese patients and is closely associated with intraabdominal fat volumes and components of the metabolic syndrome.⁷⁸ Moreover, bacterial DNA in adipose tissue surrounding the gut was found, with concentrations decreasing with increasing distance from the gut, suggesting a “microbial gradient” from mesenteric fat to omental and subcutaneous adipose tissue.⁷⁸ These findings are well in line with a previous report showing that elevated levels of LPS-binding protein are associated with obesity in otherwise healthy subjects.⁷⁹

In addition, several mechanistic studies from animal models provide evidence that an altered gut microbiota and translocation of LPS could be early triggers of obesity, insulin resistance, diabetes, and atherosclerosis. First, chronic infusion of endotoxin is sufficient to initiate obesity and insulin resistance in mice, an effect that is almost abolished in CD14 knockout mice.⁷⁵ Moreover, colonization of germ-free mice with *Escherichia coli* is sufficient to augment adipose tissue inflammation,⁸⁰ and traces of gut bacteria are present in

mesenteric adipose tissue before the onset of insulin resistance and type 2 diabetes.⁸¹ Interestingly, an LPS-producing *Enterobacter cloacae* isolate from a morbidly obese patient was recently shown to trigger obesity and insulin resistance in germ-free mice.⁸² Moreover, recurrent exposure to LPS increased mortality and induced cardiac fibrosis in mice.⁸³

Microbial Translocation and Cardiometabolic Risk Factors in HIV Infection

As mentioned above, CVD risk in HIV infection has been linked to failure of CD4⁺ T cell count reconstitution despite effective ART,⁸⁴ which, in turn, has been associated with not only a low nadir CD4⁺ T cell count,⁸⁵ but also persistent microbial translocation⁵⁵ and immune activation.⁸⁶

Data from SIV-infected nonhuman primates suggest that hypercoagulation and CVD in part may be caused by microbial translocation and excessive immune activation,⁸⁷ supporting translocation as a possible cofactor of the increased cardiovascular risk in HIV infection.⁶⁶ This is in keeping with recent studies suggesting that microbial translocation is associated with several cardiometabolic risk factors, although direct evidence has been lacking so far.

Hypertension

As in the general population, hypertension is an independent risk factor for myocardial infarction^{25,29} and cardiovascular events.⁸⁸ Based on our recent finding of an association between low nadir CD4 count and the development of sustained hypertension,⁸⁹ we hypothesized that measures of microbial translocation would predict hypertension in ART-naïve patients. Indeed, plasma levels of both LPS and sCD14 at the time of nadir were elevated in HIV-infected compared to controls, predicted sustained hypertension, and were intercorrelated in subjects who developed hypertension several years later.⁹⁰ These data indicate that HIV-related factors including immunodeficiency and microbial translocation could be involved in the development of hypertension.

Dyslipidemia

In the general population, elevated levels of fasting triglycerides and low levels of high-density lipoprotein (HDL) cholesterol are associated with the metabolic syndrome and increased cardiovascular risk. In patients receiving ART, positive associations have recently been reported between plasma LPS and triglycerides, total cholesterol, and LDL cholesterol, respectively.⁹¹ These findings are well in line with recent reports of strong correlations between LPS and both elevated fasting triglycerides and low HDL cholesterol,⁹² as well as low levels of large particle HDL cholesterol.⁹³ Several mechanisms could explain these associations. First, LPS and triglycerides are cotransported in chylomicrons from the gut to circulation⁹⁴ where LPS is scavenged by HDL cholesterol, which is often low in dyslipidemia.⁹⁵ Furthermore, LPS down-regulates lipoprotein lipase activity leading to hypertriglyceridemia.⁹⁶ Finally, plasma metabolomic analyses showed that certain clusters of lipid abnormalities were associated with LPS and LPS-binding protein in patients receiving protease inhibitors.⁹⁷

Insulin resistance and metabolic syndrome

Interestingly, increased levels of plasma LPS correlate with lower insulin sensitivity in patients on ART.⁹¹ Furthermore, in a cohort of ART-naïve patients plasma LPS and triglycerides were independently associated and both markers correlated with the development of several factors associated with the metabolic syndrome, including high blood pressure, high body mass index, high levels of glucose and uric acid, as well as low levels of HDL cholesterol.⁹⁸ However, data on the potential impact of microbial translocation on diabetes mellitus are so far lacking in HIV-infected populations.

Coagulation and platelet dysfunction

In addition to increased cardiovascular risk, HIV-infected patients have an increased risk of venous thrombosis.⁹⁹ Of note, increased levels of D-dimer, a marker of the coagulation cascade, fibrin formation, and fibrinolysis predict mortality in HIV infection.¹⁰⁰ Both LPS and flagellin have been reported to increase the expression of tissue factor, which initiates the coagulation cascade.¹⁰¹ Furthermore, HIV-infected individuals have a higher frequency of activated platelets, which correlated with tissue factor-expressing monocytes and sCD14 levels.¹⁰² We have recently found that although HIV-infected individuals had elevated levels of D-dimer, they had paradoxically functional hypocoagulability and platelet dysfunction, where platelet dysfunction was correlated with plasma levels of LPS in untreated patients.¹⁰³ Hence, we have proposed a model in which chronic endotoxemia and other microbial products over time cause low-grade coagulation and platelet activation, which ultimately leads to platelet exhaustion and dysfunction. The clinical significance of these findings warrants further investigation.

Endothelial dysfunction

Endothelial dysfunction represents early stages of atherosclerosis. The endothelium is normally intact, but might become dysfunctional and leaky by hypertension, hyperglycemia, modified lipids, and free radicals from smoking.^{104,105} Important in this context is that endothelial cells often express TLR4 as a response to proatherogenic stimuli, and a link between LPS-induced TLR4 activation of endothelial cells and coronary artery disease has been reported.¹⁰⁶

Hence, it could be hypothesized that TLR4 stimulation and subsequent endothelial dysfunction might explain the close association between microbial translocation and hypertension previously reported.⁹⁰ In support of this hypothesis, strong and significant correlations were found between plasma LPS levels and asymmetric dimethylarginine (ADMA), a marker of nitric oxide-dependent endothelial dysfunction and its structural isomer symmetric dimethylarginine (SDMA), a novel biomarker of vascular and renal diseases.¹⁰⁷

Endothelial dysfunction can be directly assessed by flow-mediated dilatation (FMD). Interestingly, nadir CD4 count and ADMA were independently associated with impaired FMD in untreated patients.¹⁰⁸ In addition, it was recently shown that FMD of the brachial artery was independently associated with plasma LPS levels in patients receiving ART.¹⁰⁹ Taken together, these findings suggest that microbial translocation might indeed contribute to endothelial dysfunction in both treated and untreated HIV infection.

FIG. 1. Gut microbiota, microbial translocation, and cardiovascular disease. Proposed model, in which an altered gut microbiota is translocated across a damaged gut wall, triggering Toll-like receptors in macrophages, adipocytes, and endothelial cells, with consequent immune activation in relevant end organs. In addition, alterations of gut microbiota, as well as microbiota-dependent metabolites, e.g., resulting from dietary carnitine/phosphatidylcholine¹¹⁶ or increased tryptophan catabolism,¹¹⁹ should be investigated in relation to cardiovascular risk.

Atherosclerosis

Atherosclerotic lesions are asymmetrical focal thickenings of the two innermost layers of the arterial wall, the tunica intima and tunica media, and consist of cells, connective-tissue elements, lipids, and debris.¹¹⁰ The thickness of these two layers of the vessel wall can be measured by ultrasound, and the carotid intima media thickness (CIMT) is an established measurement of subclinical atherosclerosis. In the HIV-infected population, plasma LPS and sCD14 have been related to progression of subclinical atherosclerosis, as measured by yearly change of CIMT.¹¹¹ Furthermore, HIV-infected individuals receiving ART with pathologically increased CIMT had elevated levels of sCD14 as compared to individuals with normal CIMT.¹¹²

Risk of cardiovascular events

Due to the significant associations between LPS levels and different cardiometabolic risk factors in recent studies, we hypothesized that elevated LPS levels would be associated with an increased Framingham risk score, which is a global assessment of the 10-year risk of myocardial infarction and

CVD. Indeed, HIV-infected patients within the highest LPS level strata had a significantly higher 10-year predicted risk of myocardial infarction and CVD⁹¹.

However, it remains to be demonstrated in prospective studies whether markers of microbial translocation predict the risk of cardiovascular events, and whether a reduction in microbial translocation would reduce such a risk. In the SMART study, which mostly involved patients on ART, sCD14 but not LPS was predictive of all-cause mortality.⁵⁷ Importantly, sCD14 is a marker of monocyte activation, which is shed upon several stimuli, including peptidoglycan from Gram-positive bacteria.¹¹³ Hence, microbial products beyond LPS might contribute to cardiovascular risk in HIV infection.

Future Perspectives

Gut microbiota-related metabolites

Whereas the gut microbiota has been intensively studied in diseases such as obesity and diabetes,^{114,115} little work has been done on the potential role of gut microbiota on acute cardiovascular events¹¹⁶ (Fig. 1). Interestingly, recent data

show that a gut microbiota-dependent metabolite from dietary carnitine¹¹⁷ and phosphatidylcholine, trimethylamine-*N*-oxide, strongly predicted cardiovascular events, and was markedly reduced after a short course of antibiotics.¹¹⁶

Recent data suggest that the gut microbiota often changes during HIV infection,¹¹⁸ and that dysbiotic alterations are associated with disease progression and tryptophan catabolism as measured by the kynurenine-to-tryptophan ratio in plasma.¹¹⁹ In this context it is noteworthy that the kynurenine-to-tryptophan ratio in urine was recently shown to be strongly associated with an adverse prognosis in HIV-seronegative patients with stable coronary artery disease.¹²⁰ Hence, microbiota-related factors other than direct triggers of inflammation such as LPS should be investigated in relation to cardiovascular risk both in populations with and without HIV.

Is HIV any different?

It remains to be determined whether the potential impact of microbial products on cardiometabolic risk factors is any different in HIV infection compared to other chronic states of inflammation such as diabetes mellitus type 2 and obesity. Whereas the massive Th17 loss in the gut mucosa is probably a relatively HIV-specific event,⁵⁰ downregulation of tight junction proteins and increased gut permeability also occur in obesity.¹²¹ Whatever the cause, this disruption of the gut barrier is likely to contribute to low-grade endotoxemia and possibly cardiometabolic complications in these chronic conditions, yet with substantial individual variation. Thus, comparative studies of microbiota-related factors including microbial translocation and cardiometabolic risk factors in combined conditions such as HIV with and without diabetes or in diabetics with and without HIV could delineate the contribution of HIV per se in these chronic conditions.

Therapeutic options

Given that microbial translocation, and in particular low-grade endotoxemia, could contribute to cardiovascular risk, strategies targeted at reducing microbial translocation or eliminating endotoxins could in theory be prophylactic. These therapeutic options were recently reviewed in detail,⁶⁶ and we will give a short overview and update.

Sevelamer, which is used to treat hyperphosphatemia in patients with advanced chronic kidney disease, has been found to bind LPS and reduce systemic LPS levels.¹²² *Chloroquine* and *hydroxychloroquine* exert broad inhibition of TLR systems, and have been shown to reduce LPS levels and immune activation in HIV-infected patients on and off ART.^{123,124} *Rifaximin* is an orally administered, nonabsorbable antibiotic targeting Gram-negative and Gram-positive bacteria, which has been shown to reduce systemic LPS levels in patients with alcoholic cirrhosis.¹²⁵ Orally administered *bovine immunoglobulin* was recently reported to improve intestinal immune reconstitution and absorption in patients with severe HIV enteropathy.¹²⁶ *Prebiotic supplementation* with an oligosaccharide mixture has been shown to increase the percentage of bifidobacteria and to decrease sCD14 levels, although LPS levels remained unchanged.¹²⁷

It should be noted that during CROI 2014, several interventions including Rifaximin, Sevelamer and probiotics failed to show reduction in LPS-levels, although other

potentially beneficial effects were reported (poster session # P-E1, posters 337, 339 and 342).

Other ways of targeting the gut microbiota could also be potential therapeutic options in high-risk patients to reduce microbial translocation and thereby cardiovascular risk. It was recently shown that transplantation of healthy gut microbiota from lean donors improved insulin sensitivity in subjects with the metabolic syndrome.¹²⁸ Given that an altered gut microbiota plays a role in HIV infection, similar strategies could be evaluated to target microbial translocation, cardiovascular risk factors, and immune restoration in HIV-infected individuals.

Finally, the potentially interacting effect of lipids and LPS should be explored in future studies. We recently showed that reduced levels of triglycerides and trunk fat after strength training were associated with a reduction in LPS levels in HIV-infected individuals, most likely mediated through a reduction in triglycerides.¹²⁹ Notably, 75–97% of circulating endotoxin is bound to lipoproteins, in particular HDL and very-low-density lipoprotein (VLDL).¹³⁰ Interestingly, LPS promotes VLDL uptake in macrophages to promote foam cell formation *in vitro*,¹³¹ and VLDL-associated LPS activity was recently reported to be associated with systemic inflammation and expression of CD14 on macrophages in patients with periodontitis.¹³² Hence, delineating to what extent free LPS or lipoprotein-associated LPS has proatherogenic properties will be of interest. In this setting, interventions with lipid-lowering therapies such as statins, fibrates, nicotinic acid, and omega-3 fatty acid supplementation could be applied to investigate the potential effects on total LPS, lipoprotein-bound LPS, and other microbiota-related metabolites. Interestingly, rosuvastatin has been shown to reduce sCD14 levels in HIV-infected individuals on ART independent of its lipid-lowering effect.¹³¹

Conclusions

A growing body of evidence suggests that microbiota-related factors including microbial translocation might play a role not only in the pathogenesis of HIV, but possibly even in the development of long-term cardiovascular complications. Prospective studies should investigate whether associations between microbial translocation and cardiometabolic risk factors will translate into an increased risk of cardiovascular events. Finally, clinical trials should be encouraged to test whether strategies that target gut microbiota and microbial translocation might reduce such a risk. Careful selection of high-risk patients into such studies might provide more rapid and definite data.

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