# Suppression of monocyte inflammatory and coagulopathy responses in HIV infection

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The increased access globally to effective antiretroviral therapy (ART) among people living with HIV (PLHIV) has led to a change in the demographics of this population (1,2). Once considered a death sentence, HIV infection has now evolved to be a chronic disease with PLHIV achieving near normal life-expectancy (3), despite disparities that still exist between high-income and low-and-middle-income settings (4).

As PLHIV grow older, age-associated comorbidities including cardiovascular disease (CVD) have now become a clinical priority in the routine management of HIV (5). CVD risks are reported to be approximately two times higher amongst PLHIV compared to age-matched uninfected individuals, with CVD risk prediction algorithms not accurately reflecting CVD risk in PLHIV (6). Persistent immune activation is believed to be a major factor contributing to the pathogenesis of CVD-related morbidity and aging in HIV (7). Additionally, increased markers of hypercoagulation including D-dimers have been shown to independently predict mortality and CVD-related morbidity in treated HIV (8-10). In this regard, monocytes have garnered renewed attention as a number of studies examining ART treated PLHIV show associations between coagulation markers and activated monocytes (11), and indeed between monocyte activation and atherosclerosis (12). The study by Schechter *et al.* (13) provides compelling evidence that a subset of tissue factor-expressing monocytes is central to hypercoagulation and systemic inflammation in PLHIV. Tissue factor (coagulation factor III) is a cell surface glycoprotein highly expressed on monocytes in response to inflammatory stimuli such as LPS that enables the initiation of coagulation cascades. Thus, increased tissue factor expression is associated with cardiovascular complications (14).

In the study, the authors show that compared to HIV uninfected people the proportion of monocytes expressing tissue factor is elevated in both ART naïve and experienced PLHIV, with monocytes from both groups of PLHIV showing inhibition of tissue factor activity when treated *ex vivo* with Ixolaris, a tissue factor inhibitor. Tissue factor-expressing monocytes from PLHIV produced a broader array of inflammatory cytokines than monocytes lacking tissue factor. Furthermore, the authors found HIV infection was associated with a skewing of monocyte inflammatory responses towards a more polyfunctional phenotype, favouring the production of IL-6 and TNF, with this phenotype not being reversed by ART.

Both HIV and pathogenic SIV infection result in gastrointestinal mucosal barrier damage that allows for microbes and microbial products to enter the systemic circulation, a process termed microbial translocation (15).

Monocyte activation and coagulation markers are associated with translocated microbial products but a causal role has not been previously described (16). Given the well-described increase of gastrointestinal microbial translocation products that occur for both ART naïve and ART experienced PLHIV, the authors also investigated monocyte tissue factor expression and functional activity from HIV uninfected people after *in vitro* exposure to LPS, a surrogate for microbial translocated products. In these experiments, monocytes showed robust induction of tissue factor expression and activity with exposure to LPS. Monocyte tissue factor was also increased after exposure to HIV positive serum but this was partially inhibited by blocking type I interferon and TNF receptors, and completely inhibited following the addition of polymyxin B, a Gram-negative bactericidal agent that binds to LPS. In future work, it will be interesting to determine if agents that decrease microbial translocation products also decrease tissue factor expressing monocytes, and thus, limit hypercoagulation and systemic inflammation. Indeed, sevelamer was shown to limit LPS translocation and suppress inflammation in animal models, although clinical trials in HIV-positive persons were disappointing (17).

The authors extended their *in vitro* and *ex vivo* work by using non-human primate models of HIV infection, in which they exploited differences between SIV infection of natural African green monkey (AGM) hosts that do not experience disease and pigtail macaques (PTM) that experience disease similar to HIV infection. The authors show that compared to SIV-infected AGM natural hosts, PTM infected with SIV have increased tissue factor-expressing monocytes and increased polyfunctional inflammatory cytokine production. Notably, previous studies show that PTM experience increased microbial translocation during SIV infection that does not occur in natural AGM hosts (18,19).

Importantly, the authors assessed whether Ixolaris is capable of reducing inflammation and coagulation *in vivo*. Remarkably, SIV-infected PTM treated daily with Ixolaris showed substantial diminution of markers of inflammation and coagulation without significantly affecting SIV viral load. To further validate the effects of Ixolaris treatment on monocyte activation, the team evaluated glucose transporter-1 (Glut1) expression on monocytes, an important monocyte activation marker. Glut1 is a major glucose transporter on monocytes and its level is increased on activated monocytes, reflecting high glucose metabolic demands for these activated cells (20,21). Indeed, the authors demonstrated that compared to untreated controls, Ixolaris dramatically reduced monocyte Glut1 expression in SIV-infected PTM. Increased Glut1 levels on inflammatory monocytes have previously been shown to be associated with markers of CVD risk in treated HIV-infected men (22), and subclinical CVD in treated HIV-positive women (23). Thus, it remains to be determined whether some of the anti-inflammatory and anti-coagulopathy effects of Ixolaris are due to the cumulative suppression of monocyte tissue factor and Glut1. Yet, it is also unclear if the consequence of Ixolaris treatment was due solely by its action on monocytes alone or other cells that also express tissue factor and Glut1.

Taken together, the study by Schechter *et al.* provides a more detailed understanding of the linkage between microbial translocation, hypercoagulation and systemic inflammation, with tissue factor-expressing monocytes as important intermediaries. These findings also identify a novel target for therapy that may limit CVD and other age-associated diseases in PLHIV, though the feasibility of targeting tissue factor-expressing monocytes is unclear as CVD emerges over the course of many years or decades and would likely require chronic drug treatment. Probiotic restoration of healthy gastrointestinal function has emerged as a possible treatment to limit inflammation caused by microbial translocation (24,25) and would be an interesting strategy to explore in relation to tissue factor-expressing monocytes.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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