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COMPLICATIONS OF HIV AND ANTIRETROVIRAL THERAPY (GA MCCOMSEY, SECTION EDITOR)

The Opioid Epidemic: Impact on Inflammation and Cardiovascular Disease Risk in HIV

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Abstract

Purpose of Review People infected with HIV through injection drug use are more likely to experience progression to AIDS, death due to AIDS, and all-cause mortality even when controlling for access to care and antiretroviral therapy. While high-risk behavior and concurrent infections most certainly are contributors, chronic immune activation, downstream metabolic comorbidities may play an important role.

Recent Findings Altered intestinal integrity plays a major role in HIV-related immune activation and microbial translocation markers are heightened in active heroin users. Additionally, greater injection frequency drives systemic inflammation and is associated with HIV viral rebound. Finally, important systemic inflammation markers have been linked with frailty and mortality in people who inject drugs with and without concurrent HIV infection.

Summary Heroin use may work synergistically with HIV infection to cause greater immune activation than either factor alone. Further research is needed to understand the impact on downstream metabolic comorbidities including cardiovascular disease. Medication-assisted treatment for opioid use disorder with methadone or buprenorphine may ameliorate some of this risk; however, there is presently limited research in humans, including in non-HIV populations, describing changes in immune activation on these treatments which is of paramount importance for those with HIV infection.

Keywords Inflammation · HIV · Opioid use disorder · Heroin · Cardiovascular risk

Introduction

Globally, life expectancy for HIV-infected persons has increased dramatically with combination antiretroviral therapy (ART) [1, 2]. Further, we have seen a shift in the proportion of deaths from AIDS related to non-AIDS-related causes, primarily cancers and cardiovascular disease (CVD) [3]. HIV-infected adults are at increased risk of myocardial infarction (MI) and stroke, and CVD risk may accelerate faster with age than the general population [4, 5••, 6]. Beyond traditional risk factors, HIV-related immune activation is considered a key player in the pathogenesis of CVD in HIV. Indeed, activation of monocytes and the pro-inflammatory nuclear factor kappa B (NF-κB) pathway have been linked with subclinical vascular disease in HIV-infected individuals [7–18].

Men and women HIV-infected through injection drug use (IDU) are at higher risk of progression to AIDS, death due to AIDS, and all-cause mortality even when controlling for access to care and for ART [19–21]. In fact, even in those surviving for 10 years on ART, HIV-infected persons whose transmission risk was IDU are roughly two and a half times more likely to die from all causes [22]. High-risk lifestyle or death from co-morbid conditions such as bacterial infection or hepatitis C are likely contributors, but chronic inflammation and immune activation may play an important role [23, 24]. While current knowledge suggests that most exogenous opioid agonists more than endogenous opioid peptides lead to suppression of both innate and adaptive immunity [25–28],

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the increased immune response to IDU combined with that present in HIV-infected persons even despite viral suppression with ART [29] may result in excess immune activation and downstream risk of co-morbid conditions including increased CVD risk.

HIV-Related Immune Activation

Although the mechanisms of HIV-associated immune activation are incompletely understood, alteration in intestinal integrity appears to be a central factor [30, 31]. Damage to the tight epithelial barrier of the gastrointestinal tract allows microbial products, such as lipopolysaccharide (LPS), to enter the lamina propria and systemic circulation leading to immune dysfunction [30, 32–34]. Lipopolysaccharide, a component of Gram-negative bacterial cell walls and a known agonist of Toll-like receptor 4 [35], is considered an important marker of microbial translocation [36, 37]. Lipopolysaccharide interacts with LPS binding protein (LBP) which catalytically transfers LPS onto membrane or soluble CD14 (sCD14). This leads to NF-κB activation and cytokine production [38] resulting in a state of aberrant immune activation. Increased zonulin, a marker of intestinal permeability, and intestinal fatty acid-binding protein (I-FABP), a marker of enterocyte damage, are both associated with increased mortality in HIV [39]. Further, both LPS and sCD14 have been linked with progression of subclinical vascular disease in HIV-infected persons on ART [9].

While systemic levels of immune activation tend to decrease with ART, they remain higher than in uninfected individuals [40–42]. Contributors to heightened immune activation in HIV-infected persons on ART may include persistent low-level HIV replication occurring in lymph nodes or gastrointestinal tract [43–45], and inflammatory lipids such as oxidized low-density lipoprotein [46] or oxidized high-density lipoprotein. In addition, the contribution of co-infections should also not be overlooked as co-infection with hepatitis B virus, hepatitis C virus (HCV), or cytomegalovirus has been linked to heightened levels of LPS and CD8+ T cell activation, respectively [47, 48].

Injection Drug Use and Systemic Inflammation

Several factors are linked with heightened systemic inflammation in people who inject drugs. Utilizing data from the AIDS Linked to the IntraVenous Experience (ALIVE) study, a community-based observational study in Baltimore, MD, following a large cohort of current and former people who inject drugs since 1988, the authors assessed correlates of interleukin-6 (IL-6) and high sensitivity C-reactive protein (hsCRP) levels in 1191 participants; those with HIV-monoinfection were excluded [24]. Increased frequency of IDU or injection intensity was associated with elevated hsCRP in a dose-response fashion, i.e., no injection in the past 6 months, injection less than daily, and injection every day results in incrementally increased hsCRP levels. The association between injection intensity and hsCRP remained even when adjusting for any cocaine use or any heroin use in the prior 6 months suggesting that type of drug used was not driving the association. Additionally, participants injecting at least daily had higher IL-6 levels than those who did not inject in the previous 6 months. From the same cohort in a smaller study ($N = 219$) including only heterosexual black men aged 21–49 years, frequent injecting was associated with elevated neopterin, but not beta 2-microglobulin levels, when compared with less than daily users [49]. Injection drug use and injection intensity may lead to increased inflammation through direct injection-related injury or infection [50, 51], type of heroin injected [52, 53], filler agents, injection practices such as reusing cotton filters [54, 55], other high-risk behaviors [56, 57•], or environmental factors such as low individual and community socioeconomic status [58]. From the Study to Assess Hepatitis C Risk ($N = 541$), nearly half of people who inject drugs reported ever having an abscess; these participants were significantly more likely to have a greater number of injection partners, to inject heroin daily, to share cookers, and less likely to report using new syringes with each injection [59]. In another survey of people who inject heroin in two urban US cities ($N = 145$), two-thirds reported having at least one abscess ever and 20% reported having > 2 abscesses per year; of participants specifically injecting heroin who experienced an infection, 39% waited ≥ 2 weeks to seek care and 54% had a drainage procedure by a non-medical person in the past year [60]. It follows that injection drug use likely contributes to at least intermittent increases in systemic inflammation chronically.

Inflammation and immune activation associated with IDU differs by HIV serostatus. In early studies, HIV-infected people who inject drugs had significantly lower serum granulocyte-macrophage colony-stimulating factor and higher neopterin levels than HIV-uninfected people who inject drugs while levels of interleukin-1β and soluble interleukin-2 (IL-2) receptor were elevated regardless of HIV serostatus [61]. More recently, in a small ($N = 50$), matched, cross-sectional study of viremic, HIV-infected and HIV-uninfected people who inject drugs in and viremic, HIV-infected and HIV-uninfected participants who never injected drugs matched by gender, race, and age, the proportion of T cell subsets and activation from peripheral blood mononuclear cells (PBMCs) and colonic mucosal tissue as well as soluble CD14 (sCD14) were compared [62]. CD4+ T lymphocytes were depleted in peripheral blood and colonic tissue and CD8+ lymphocytes were increased in peripheral blood and colonic tissue without regard for IDU in viremic HIV-

infected participants. Interestingly, however, both CD4+ and CD8+ activation were significantly increased in people who inject drugs regardless of HIV status although the magnitude of increase in T cell activation was greater in the HIV-infected people who inject drugs. Regarding sCD14, again, HIV-infected groups had the highest concentrations regardless of IDU. In vitro, production of tumor necrosis factor-alpha (TNF-α), IL-6, reactive oxygen species, nitric oxide, and 3-nitrotyrosine is increased in HCV-infected hepatocytes and cytokine release is augmented by HIV-1 proteins [63]. In this system, the addition of morphine causes further increase of ROS which provides evidence that morphine may exacerbate disruption of host defenses even further in those with both HCV and HIV infections concurrently.

Impact of Opioids on HIV-Related Immune Activation

It is plausible that HIV infection and heroin use together result in further activation of the immune system than that seen with either in isolation. Opioids promote HIV viral replication and infection of new cells. Peripheral blood mononuclear cells (PBMCs) from healthy donors co-cultured with PBMCs from HIV-infected individuals in the presence of morphine have significantly greater p24 antigen release than controls or than cells in the presence of interleukin-2 (IL-2) which is recognized to promote HIV proliferation [64]. Heroin use is associated with lower gene expression and levels of specific antiviral restriction factors and type 1 interferon in effect limiting antiviral activity [65]. Morphine also significantly downregulates β-chemokine production and upregulates CCR5 receptor expression resulting in enhanced R5 tropic HIV virus infection of blood monocyte-derived macrophages that is not seen with X4 strains [66].

Further, heroin use may lead to increased translocation of bacterial products across a leaky gut which is especially relevant with concurrent HIV infection as HIV causes the same pathologic result. In a cross-sectional study ($N = 119$), circulating bacterial LPS was higher in HIV-infected people who inject drugs compared with HIV-infected participants with no substance use [67]. Interestingly, users of intravenous heroin, but not intravenous cocaine, had higher plasma LPS compared with those without substance use despite lower HIV-1 RNA levels and higher CD4+ lymphocyte counts in the heroin users. Last, LBP was correlated with LPS and was also higher in those with active intravenous heroin use compared with those with no substance use. In this study, the investigators did not adjust for cigarette smoking and alcohol use which are limitations. Indeed, continued heroin injection with concurrent HIV infection could theoretically result in greater activation of the immune system than seen with either factor alone.

Chronic Immune Activation Contributes to the Pathogenesis of Metabolic Comorbidities in HIV

Despite improvements with ART, HIV-infected persons continue to have increased risk for morbidity and mortality compared with the general population often due to non-AIDS-related events [68–70]. These include CVD, insulin resistance and type II diabetes, osteoporosis, neurocognitive dysfunction, cancer, and frailty among others [5••, 71–75]. Many of these comorbidities have overlapping etiologies. Understanding the pathogenesis is complex; traditional risk factors, ART, and chronic immune activation most likely contribute to each of these comorbidities in HIV. Using CVD as an example, HIV-infected persons have a disproportionately high prevalence of important CVD risk factors including low HDL cholesterol, increased obesity, and cigarette smoking when compared with the general population [76–78]. These and other traditional risk factors have been associated with the presence and progression of subclinical vascular disease in HIV-infected adults on ART [79–81]. Further, certain antiretroviral drugs, including PIs [82] and abacavir [83, 84], have been associated with higher risk of MI. However, beyond traditional risk factors and ART, the role of persistent inflammation and immune activation, specifically monocyte activation, has recently received much attention [7–18]. Strikingly, results from the SMART trial have shown that patients who had intermittent interruption of ART and resultant viral rebound had an increased risk of developing CVD compared with those who were on continuous therapy [16]. Subsequent studies revealed that D-Dimer and IL-6 levels were strongly associated with all-cause mortality in the SMART study participants [13]. In the Multicenter AIDS Cohort Study (MACS) for every standard deviation increase in log-IL-6 and log-intercellular adhesion molecule-1 (ICAM-1), there was a 30 and 60% increase in the prevalence of coronary stenosis ≥ 50%, higher soluble tumor necrosis factor-α receptors 1 and 2 (sTNF-RI and II) were associated with coronary stenosis ≥ 70%, and higher levels of IL-6, sTNF-RI, and II were associated with greater coronary artery calcium (CAC) score in HIV-infected men [17]. In HIV-infected adults virologically suppressed on ART, IL-6 levels were associated with both carotid intima media thickness (CIMT) and mortality [7]. We and others have shown that hsCRP is associated with subclinical vascular disease and CVD events in HIV as well [18, 85]. Monocytes from HIV-infected persons have impaired cholesterol efflux and increased foam cell formation after transendothelial migration in vitro, a process which is blocked by TNF-α receptor antibodies [86]. Additionally, exosomes from monocytes activated with LPS significantly increase ICAM-1, chemokine ligand (CCL)-2 and IL-6 micro RNAs (mRNAs), and proteins from endothelial cells [8]. It is clear that systemic inflammation and monocyte activation play an important role in the pathogenesis of CVD in HIV.

Chronic Immune Activation and Metabolic Comorbidities in People who Inject Drugs

Presently, there is limited data on how inflammation in people who inject drugs contributes to comorbidities. From the ACCESS study, a prospective cohort of HIV-infected period who use ilicit drugs in Vancouver, Canada, high intensity heroin use, i.e., ≥ daily heroin injection, was a risk factor for HIV viral rebound [87•]. Drawing from what we learned from the SMART study [16], this could result in heightened risk for non-AIDS related events through enhanced systemic inflammation. In the ALIVE cohort, an aggregate inflammatory index constructed from serum IL-6 and sTNF-RI levels was associated with frailty and increased mortality in both HIV-infected and HIV-uninfected groups [23]. Recognizing that IDU results in heightened levels of markers in the same inflammatory pathways and are at high risk of viral rebound, it follows that similar associations with CVD and other metabolic comorbidities may be present in this population, but more studies are needed.

Medication-Assisted Treatment and the Immune Response to HIV Infection

Given the exponential increase in opioid related deaths, targeted efforts to engage and empower persons with opioid use disorders to seek treatment are of paramount importance [88]. One option is harm reduction and diminution of cravings and withdrawal through medication-assisted treatment (MAT). While access to MAT programs is often a barrier to receipt, both methadone and buprenorphine/naloxone are established and effective medications taken by mouth for this indication [89, 90]. Randomized clinical trials have shown buprenorphine to be as effective as methadone in reducing illicit opioid use and treating opioid dependence [91–94].

Up to this point, we have discussed how increases in systemic inflammation and immune activation occur and contribute to CVD risk in persons with HIV infection and in HIV-infected and HIV-uninfected people who inject drugs. However, many exogenous opioids result in suppression of both the innate and adaptive immune systems [26–28]. In the context of HIV-associated neurocognitive disorders, it has been suggested that buprenorphine may result in better cognitive outcomes than methadone, an effect that may be attributed to the differential immunosuppressive activity of the two medications [95••]. Indeed, buprenorphine decreases several steps of CCL2-mediated transmigration of mature CD14+ CD16+ monocytes across the blood-brain barrier; these monocytes carry HIV into the CNS which is felt to be a critical mechanism promoting neuroinflammation and HIV-associated neurocognitive disorder [96•]. Whether there is a benefit to using one medication-assisted treatment over the other with regard to the effect on immune activation and downstream CVD risk is unknown and is especially important for HIV-infected persons.

There is theoretical biologic plausibility that different MAT options will result in different effects on the inflammatory pathways involved in CVD. Buprenorphine is classified as a partial agonist for the μ-receptor, i.e., it has high affinity, but low efficacy at the μ-receptor. Naloxone is antagonistic at each of the classical opioid receptors, but has the highest affinity for the μ-receptor. Naloxone has poor oral bioavailability, but is added to the sublingual form of buprenorphine to deter intravenous or intramuscular abuse. Methadone is a full opioid receptor agonist with highest affinity for the μ-receptor [97]. As buprenorphine and methadone bind opioid receptors, both have the capability of modulating immune responses. However, because buprenorphine is a partial agonist at the μ-opioid receptor and methadone is a full agonist, these two agents may have different immunomodulatory effects [98]. In a study of PBMCs derived from healthy volunteers, methadone, oxycodone, and diamorphine, but not other opioids including buprenorphine, inhibited IL-6 production by IL-2 stimulated PBMCs [99]. In this study, there was a trend towards inhibition of phagocytosis and oxidative burst by buprenorphine and other opioids, but not methadone. Methadone, among other opioids, has been shown to be a strong inducer of the anti-inflammatory cytokine interleukin-4 (IL-4) which promotes differentiation of T helper cells into the type 2 direction [98]. Interestingly, buprenorphine and morphine produced lesser induction of IL-4, a finding that supported the authors' hypothesis of biased signaling of the opioids at the μ-opioid receptor.

Studies directly comparing the two MAT strategies with regard to effects on immune activation in humans are limited. In a small, cross-sectional study comparing active heroin users, persons treated with methadone or buprenorphine for at least 6 months, and sex- and age-matched healthy controls, only active heroin users had reduced lymphoproliferative activity and production of interferon-γ (IFN-γ), TNF-α, and IL-4 from stimulated PBMCs [100]. Methadone- and buprenorphine-treated persons had levels similar to healthy controls suggesting that immune dysregulation with IV heroin use may be mitigated with MAT in the general population. Using random allocation, 62 active heroin users were given either methadone or buprenorphine and followed for a year [101]. In this study, levels of TNF-α, IL-1β, IL-2, and CD14+ monocytes were similar between groups after 12 months, and interestingly, levels of all cytokines increased in this study in both groups. Given the nature of immune activation with HIV infection, these studies cannot be generalized to HIV-infected persons.

Conclusion

While research involving active injection drug users and/or those with opioid use disorder presents complex challenges, studies evaluating the impact of heroin use as well as other illicit substances on immune activation are urgently needed and of particular importance in those with concurrent HIV infection. Further, whether there is benefit in selecting methadone, buprenorphine, or other medication-assisted treatments with regard to their differential effects on the immune system is yet to be determined. Published studies evaluating inflammation and immune activation markers are generally cross-sectional and there are limited data on associations with downstream CVD risk and other metabolic comorbidities. As the prevalence of heroin use has increased among nearly all demographic groups, understanding and addressing these factors now has the potential to ameliorate future risk for this growing population.

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Compliance with Ethical Standards

Conflict of Interest COH has served on medical advisory boards for Gilead Sciences and as site PI for Gilead Sciences sponsored clinical trials.

GAM has served as a scientific consultant for Gilead, Merck, and ViiV and had received research grants from Roche, Tetraphase, and Astellas.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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