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Sex-Differences in Select Non-communicable HIV-Associated Comorbidities: Exploring the Role of Systemic Immune Activation/Inflammation

Avanthi Raghavan, MD^{1,*}, Dodie Rimmelin, MPH^{1,*}, Kathleen V. Fitch, MSN, FNP¹, and Markella V. Zanni, MD^{1,*}

¹Massachusetts General Hospital, Program in Nutritional Metabolism, Harvard Medical School

Abstract

Purpose of the Review—The goals of this review are to: 1) explore HIV-associated cardiovascular disease (CVD), neurocognitive impairment, and non-AIDS defining cancers (NADC) as heterogeneous model disease states fuelled in part by systemic immune activation/inflammation; 2) consider sex-differences in the epidemiology of these diseases in both high-resource and lower-resource settings; and 3) examine biological and environmental factors which may contribute to heightened systemic immune activation/inflammation specifically among WLHIV.

Recent findings—The observation that WLHIV have higher levels of systemic immune activation/inflammation than MLHIV may be relevant to sex-differences in select non-communicable HIV-associated comorbidities. Heightened systemic immune activation among WLHIV may be influenced by sex-specific responses to the virus and to immunomodulatory agents, as well as by behavioral choices/co-morbid conditions and perturbations in the hypothalamic-pituitary-gonadal axis.

Summary—Additional research is needed to elucidate region-specific drivers of heightened systemic immune activation/inflammation among WLHIV and to determine whether WLHIV who present with one immune-mediated HIV-associated comorbidity (e.g. cognitive impairment) may be at increased risk for another (e.g. CVD, NADC). This kind of research would facilitate improved risk prediction for non-communicable HIV-associated comorbidities among WLHIV and the development of targeted immunomodulatory prevention strategies.

Keywords

HIV; Non-Communicable Diseases; Women; Sex-Differences; Inflammation

* **Corresponding Author:** Markella V. Zanni, MD, Massachusetts General Hospital Program in Nutritional Metabolism, 55 Fruit St. Boston, MA 02114, tel: 617-724-6926, mzanni@mgh.harvard.edu.

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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INTRODUCTION

The landscape of morbidity and mortality associated with HIV is shifting in response to increasing global uptake of effective antiretroviral therapy (ART). In both high- and lower-resource regions, the proportion of individuals with HIV >50 years old is rising(1), and aging individuals with HIV are increasingly encountering morbidity and mortality related to non-communicable diseases. Cohort studies among individuals with HIV and access to ART consistently reflect a decline in the percentage of AIDS-related deaths coupled with a spike in the percentage of deaths from non-communicable diseases(2, 3). A number of non-communicable comorbidities in HIV are thought to be exacerbated by systemic immune activation/inflammation(4), which persists despite ART-induced viral suppression(5). Among women living with HIV (WLHIV), levels of key immune activation/inflammatory markers are increased, even as compared to levels among men living with HIV (MLHIV)(6). Heightened systemic immune activation/inflammation among WLHIV may contribute to sex-differences in select HIV-associated comorbidities.

In this review, we will explore HIV-associated cardiovascular disease (CVD), neurocognitive impairment, and non-AIDS defining cancers (NADC) as heterogeneous model disease states fuelled in part by systemic immune activation/inflammation. We will consider sex-differences in the epidemiology of these diseases in both high-resource and lower-resource settings. Next, we will examine biological and environmental factors which may contribute to heightened systemic immune activation/inflammation specifically among WLHIV. In closing, we will highlight avenues of research relevant to safely suppressing systemic immune activation/ inflammation in HIV and potentially preventing or mitigating the impact of non-communicable HIV-associated comorbidities in women and in men aging with HIV globally.

SYSTEMIC IMMUNE ACTIVATION/ INFLAMMATION AND HIV-ASSOCIATED COMORBIDITIES

Systemic immune activation/inflammation persists among ART-treated individuals with HIV, even when viral load is undetectable(5). Drivers of this persistent systemic immune activation in ART-treated individuals with HIV are believed to include low-level viral replication in reservoirs, enhanced microbial translocation, and viral or bacterial co-infections(7). In this section, we will discuss why heightened systemic immune activation/ inflammation would be expected to contribute to CVD, neurocognitive impairment, and select NADC. Further, we will cite specific evidence linking systemic immune activation/ inflammation to these diseases processes among men and women living with HIV.

Cardiovascular diseases

Monocytes/macrophages and other immune cells contribute meaningfully to atherosclerotic plaque formation and pathologic remodeling. Early in the process of atherogenesis, circulating monocytes are lured to the coronary arterial endothelial cell surface, where they adhere before migrating into the tunica intima of the affected vessel. There, monocytes-turned-macrophages engulf oxidized LDL, transitioning to foam cells that form the fatty

core of a plaque. Activated immune cells also contribute to plaque remodeling, promoting the development of high-risk morphology plaque features which predispose to atherothrombosis(8). In studies focused on MLHIV, systemic markers of monocyte activation have been related to arterial inflammation(9, 10), subclinical carotid and coronary artery atherosclerosis(11–14), and pathologically remodeled coronary atherosclerotic plaque(15, 16). Studies focused predominantly on WLHIV have revealed relationships between systemic immune markers and carotid atherosclerosis(17–19), as well as the percent of non-calcified coronary atherosclerotic plaque(6). Monocytes/macrophages also play a part in promoting myocardial edema/inflammation and fibrosis, and these structural changes predispose to diastolic dysfunction and heart failure with preserved ejection fraction(20, 21). In a small study analyzing endomyocardial biopsy samples, samples from PLHIV (vs. controls) exhibited increased myocardial fibrosis in association with myocardial infiltration of CD163+ macrophages and circulating levels of soluble CD163 (22). Moreover, cardiac MRI studies have demonstrated increased myocardial inflammation, myocardial fibrosis, and diastolic dysfunction among PLHIV vs. individuals without HIV (23–25).

Neurocognitive Impairment

Monocytes/macrophages and other immune cells also precipitate neurocognitive impairment across a variety of disease states from Alzheimer's(26, 27) to autoimmune vasculitis(28). In HIV, monocyte/macrophage-mediated neuroinflammation may trigger neuronal injury and cell death: The HIV virus crosses the blood brain barrier, both as cell-free virus as well as inside infected host monocytes and T-cells. Upon crossing, the virus may then infect microglia, astrocytes, and macrophages, stimulating the release of inflammatory cytokines. HIV viral proteins also contribute to the activation of resident immune cells and endothelial cells, prompting additional inflammatory cytokine release(29). *In vitro* studies have shown that HIV viral proteins may instigate gliosis and neuronal death, but only in the presence of macrophages, implicating macrophages as mediators of HIV-induced neurotoxicity(30). In studies among women and men with HIV, systemic markers of monocyte activation(31–34) and cerebrospinal fluid (CSF) markers of monocyte activation(33, 35) have been linked to neurocognitive impairment. Specific links between systemic immune activation markers and neurocognitive impairment have also been drawn among WLHIV, even those who are well-treated with ART and have undetectable serum viral load(36). Just as arterial inflammation and myocardial inflammation have been quantified by non-invasive imaging studies among people living with HIV (PLHIV) with CVD risk factors(9, 10, 25), neuroinflammation has also been quantified by non-invasive imaging studies among individuals with HIV and neurocognitive impairment(37).

Non-AIDS Defining Cancers

Immune activation/inflammation has also been implicated in the pathogenesis of a variety of malignancies(38). A key mechanistic link, in this regard, is the tendency of *in situ* inflammation to potentiate cellular turnover. Naturally, each cancer subtype has a distinct etiopathology and the extent to which immune activation/inflammation contributes may be variable. In HIV, predisposition to cancer is multi-factorial and cancer-subtype specific. Co-infection by oncogenic viruses and, in some regions, a heightened prevalence of behavioral

risk factors like cigarette smoking and excess alcohol consumption, are thought to contribute. However, systemic immune activation/inflammation likely also contributes to the risk of select NADC in HIV. For example, in a prospective cohort study 5,023 individuals with HIV on continuous ART, the risk of developing cancer of any type was associated with higher levels of inflammatory and coagulation markers, including interleukin-6, C-reactive protein, and d-dimer(39).

SEX-DIFFERENCES IN SELECT HIV-ASSOCIATED COMORBIDITIES

In this section, we will consider sex-differences in the epidemiology of HIV-associated CVD, neurocognitive impairment, and NADC in high-resource regions and in sub-Saharan Africa, the epicenter of the HIV pandemic. For several reasons, it cannot be assumed that HIV-associated comorbidities have the same epidemiology or the same drivers in North America and Europe as in sub-Saharan Africa or other geographically distinct regions. First, the most common culprit viral subtype differs by region, with different subtypes exhibiting distinct fingerprints of genomic diversity(40). Second, genetics governing immune responsiveness to HIV infection – as well as non-immune pathways relevant to susceptibility for different non-infectious comorbidities – may be expected to differ by region. And third, the prevalence of risk factors for non-infectious comorbidities differs markedly by region. Wherever possible, we will juxtapose North American / European studies and with African studies, highlighting differences and calling attention to the need for investment in cross-comparative HIV-associated comorbidities research that can benefit all(41).

Cardiovascular Diseases

A number of large-scale epidemiologic studies conducted in the US and in Europe have highlighted a 1.5- to 2-fold increased risk of myocardial infarction (MI) among individuals with vs. without HIV(42–47). With respect to sex-differences in the epidemiology of HIV-associated MI in these regions: Triant et al. analyzed data from 3,851 individuals with HIV (30.4% women) and 1,044,589 individuals without HIV (59.1% women) in the US Partners HealthCare System, followed from 1996 to 2004. Among WLHIV, unadjusted MI rates were 12.71/1000 person-years (PY), as compared with 10.48/1000 PY for MLHIV, 4.88/1000 PY among women without HIV, and 11.44/1000 PY for men without HIV. In this cohort, among WLHIV vs. MLHIV, the unadjusted MI incidence rates were comparable; by contrast, in the non-HIV population, the unadjusted MI incidence rates were significantly lower among women vs. men. By extension, the *relative* risk of myocardial infarction among WLHIV vs. women without HIV was 2.98 whereas the *relative* risk of MI among MLHIV vs. men without HIV was 1.4, after adjustment for traditional CVD risk factors, which tended to be more prevalent among men(42). Data from other US/European epidemiologic studies have substantiated parallel trends – that is, a higher relative risk of MI among WLHIV vs. women without HIV as compared to that among MLHIV vs. men without HIV(43, 46–48). Large-scale epidemiologic studies focused on incident heart failure among PLHIV have not presented data stratified by sex. However, separate assessments of incident heart failure among MLHIV vs. men without HIV and among WLHIV vs. women without HIV have been performed: A study of 2391 MLHIV and 6095 men without HIV followed from 2000 to 2007 in the US Veterans Healthcare System suggested the risk of incident heart failure

was approximately 2-fold higher among the MLHIV (adjusted hazard ratio 1.81; 95% CI 1.39–2.36)(49). By contrast, a study of 1,388 WLHIV and 13,781 women without HIV based out of the US Partners Healthcare Database suggested the risk of incident heart failure was approximately 4-fold higher among WLHIV (2.5% cumulative or 0.27%/year for WLHIV vs. 0.74% cumulative or 0.07%/year for women without HIV)(50). In both studies, the predominant heart failure subtypes were those with preserved or nearly-preserved ejection fraction(49, 50).

Among PLHIV in Sub-Saharan Africa, heart disease has historically presented differently than among PLHIV in North America and Europe. In the Heart of Soweto Study, investigators prospectively collected data on cases from patients presenting from 2006 to 2008 to the cardiology unit of the Chris Hani Baragwanath Hospital, which serves >1,000,000 people living in Soweto, South Africa(51). In 2012, Sliwa et al published an influential study demonstrating that 518 of the 5,328 new heart disease cases (9.7%) were among individuals who also had HIV. Among those 518 cases, the most common primary cardiovascular problems were: 1) HIV-related cardiomyopathy (which tends to present with heart failure with *reduced* ejection fraction) (38%); 2) pericarditis/pericardial effusion (25%); and 3) HIV-associated pulmonary arterial hypertension (8.1%). Only in 14/518 cases (2.7%) was the presenting problem related to coronary artery disease(52). Sex-stratified analyses were not presented. Among PLHIV in Sub-Saharan Africa, CV diseases related to the heart muscle and pericardium may relate to inadequate access to ART with associated progression to AIDS and, in some cases, to tuberculosis co-infection(53). The relatively low burden of coronary artery disease in this population may have several explanations: First, PLWHIV in Sub-Saharan Africa (vs. North America/ Europe) tend to be younger (1) and tend to have a lower prevalence of select traditional CVD risk factors (e.g. cigarette smoking)(53, 54). However, the epidemiology of HIV-associated CVD in Sub-Saharan Africa may be expected to change over the next several years as access to ART expands and increased urban migration ushers in the adoption of a more atherogenic diet. Moving forward, the prospective Ndlovu Cohort Study (enrolling 1000 PLHIV and 1000 control subjects at a 1:1 M/F ratio in Limpopo Province, South Africa) will shed additional light on CVD risk factors and the burden of CVD among individuals aging with HIV in the region(55). Sex-stratified analyses in this study would offer considerable insight on region-specific sex-differences in HIV-associated CVD.

Neurocognitive Impairment

Individuals with HIV may experience a spectrum of neurologic impairment ranging from asymptomatic neurocognitive impairment to mild neurocognitive dysfunction to HIV-associated dementia. Epidemiologic studies related to neurocognitive impairment in HIV tend to focus on the prevalence rather than the incidence of these conditions. Reasons may include the following: 1) the conditions reside on a dynamic continuum(56–58), precluding easily characterization of a *de novo* presentation; 2) variable definitions have been used to define these conditions; and 3) the influences on these conditions of optimally-treated vs. sub-optimally-treated HIV, comorbid diseases (e.g. psychiatric), and behaviors (e.g. drug use) are difficult to disentangle(59).

Epidemiologic studies from the US have suggested that in the ART-era (vs. the pre-ART era), the prevalence of severe neurocognitive dysfunction tends to be lower while that of mild neurocognitive impairment is higher(60). With respect to ART-era prevalences of neurocognitive impairment subtypes among US PLHIV, Heaton et al. analyzed data from the CHARTER study on 1,555 individuals with HIV recruited from 6 geographically disparate US University Centers between 2003–2007. In this cohort (23% women; 71% on ART), a striking 52% of individuals with HIV evidenced some kind of neurocognitive impairment. Excluding highly confounded cases, 33% of individuals studied were noted to have asymptomatic neurocognitive impairment, 12% mild neurocognitive dysfunction, and 2% HIV-associated dementia(61). Sex-stratified analyses in the full cohort were not presented. Simioni et al. studied the prevalence of neurocognitive impairment among a smaller group of optimally treated PLHIV (n=200; 28% women; undetectable HIV-1 RNA, no history of major CNS opportunistic infection in the past 3 years, no IVDU, no depression) recruited from university centers and private clinics across Switzerland. Seventy-four percent of virally suppressed PLHIV in this cohort were noted to have some kind of neurocognitive impairment – 42% asymptomatic neurocognitive impairment, 28% mild neurocognitive dysfunction, and 4% HIV-associated dementia. In this study, individuals with HIV-associated neurocognitive disorder were more likely to be women(62). Studies from the US women's WIHS cohort comparing neurocognitive function among women with and without HIV have suggested that WLHIV women are more likely to display neurocognitive impairments, but observed deficits are often subtle(63, 64).

With respect to the prevalence of neurocognitive impairment among individuals living with HIV in Africa, Habib et al. published a very informative meta-analysis of 16 studies from 7 countries examining HIV status, ART status, and the prevalence of neurocognitive impairment. In the pre-ART era, the prevalence of neurocognitive impairment was 42.37%. In the ART-era, among individuals on ART for 6 months, the prevalence was 30.39%. Concomitant psychiatric illness increased the risk for neurocognitive impairment among PLHIV. In meta-regression analysis, there was no relationship between sex or age and neurocognitive impairment(65). By contrast, Kabuba et al. published an important study suggesting that among PLHIV in Zambia, WLHIV performed worse on neuropsychological testing than did MLHIV even after controlling for HIV characteristics(66).

Non-AIDS Defining Cancers (NADC)

Globally, and particularly in high-resource regions, the era of ART has brought about an epidemiologic transition in cancer subtypes in HIV, with a rising incidence and prevalence of NADC. In high-resource regions, among PLHIV, NADC made up 8–38% of total cancers in the pre-ART era vs. 50–58% of total cancers in the ART-era(67). The North American ACCORD study (predominantly men) showed that PLHIV vs. individuals without HIV have an increased risk of several NADC(68). In the US WIHS study, WLHIV (vs. women without HIV) faced an increased risk for NADC such as lung cancer. Further, in this study, the standardized incidence rate ratio for *all* cancers among WLHIV vs. women without HIV was 1.9(69). Valuable information on sex-differences in NADC incidence can be gleaned from a meta-analysis of 18 studies focused on NADC (17 of which are from high-resource regions). The standardized incidence rate ratios for the following cancers were lower among MLHIV

(vs. men without HIV) than those among WLHIV (vs. women without HIV): stomach (0.35 95% CI .09, 1.34); lung (0.54; 95% CI 0.27, 1.1); kidney (0.41, 95% 0.17, 1.01); leukemia (0.43 ; 95% CI 0.11, 0.58); larynx (0.26; 95% CI 0.11, 0.58); multiple myeloma (0.38; 95% CI 0.18, 0.80); colon (0.47; 95% CI 0.23, 0.94) (70). It has yet to be determined why WLHIV have a higher *relative* risk for these NADC than MLHIV.

With respect to cancer incidence among PLHIV in Africa, a large epidemiologic study from Uganda assessing 12,607 PLHIV (67% women) followed from 1988 to 2002 revealed among PLHIV vs. individuals in the general population an increased incidence rate of both AIDS-defining cancers and NADC. Of incident cancers, 70% were AIDS-defining. Risks of five NADC were noted to be increased among PLHIV vs. individuals without HIV: Hodgkin lymphoma (standardized incidence rate ratio 5.7; 95% CI 1.2–17) conjunctival cancer (4.0; 95% CI 1.5–8.7), kidney cancer (16; 95% CI 1.8–58), thyroid cancer (5.7; 95% CI 1.1–16), and uterine cancer (5.5; 95% CI 1.5–14). Sex-stratified analyses for risk of these NADC were not presented(71). An AIDS Malignancy Consortium will perform a contemporary assessment of cancer incidence among PLHIV in sub-Saharan Africa, shedding light on the epidemiology and pathophysiology of HIV-associated cancer in this region(72).

HEIGHTENED SYSTEMIC IMMUNE ACTIVATION/INFLAMMATION AMONG WLHIV

Levels of systemic immune activation/inflammatory markers relevant to HIV-associated comorbidities have been shown to be highest among WLHIV, as compared with levels among MLHIV and women and men without HIV(6). Further, as compared with women without HIV, WLHIV appear to experience age-associated changes in monocytes at a more rapid rate(73). In this section, we will describe factors which may influence systemic immune activation/inflammation among WLHIV, including sex-specific aspects of the body's immune response to HIV and unique considerations pertaining to reproductive aging and behavioral risk factors / co-morbid conditions.

How Sex Affects the Immune Response to HIV

Women and men respond differently to HIV infection. After seroconversion, WLHIV tend to exhibit higher CD4 counts and lower-level viremia than do MLHIV(74, 75). However, this more effective viral suppression may come at the cost of heightened systemic immune activation. There are sex-specific biological factors which potentially underlie women's heightened immune response to HIV infection(76). Expression of several key toll-like receptors (TLRs) (immune cell transmembrane proteins essential in microbial pathogen recognition/response) differs by sex(76) and several TLR genes are encoded on the X chromosome. Meier et al. demonstrated that in women (vs. men) plasmacytoid dendritic cell stimulation by HIV-1 via TLR7 results in a more robust interferon alpha (IFN- α) response and downstream IFN-stimulated gene (ISG) upregulation(77). In the short term, a hyper-acute innate immune response to HIV may permit women to better control the infection. With time, however, this sex-specific response may become less adaptive or even dysfunctional, stimulating chronic systemic immune cell activation/inflammation. An

analogous model of effective viral suppression coupled with heightened systemic immune activation may be observed among “elite controllers”(78).

How Perturbations in the Hypothalamic-Pituitary-Gonadal Axis May Influence Systemic Immune Activation/Inflammation among WLHIV

Looby et al. demonstrated that among WLHIV, reproductive aging is associated with heightened systemic immune activation(79). A series of seminal studies from the WIHS cohort have shown that WLHIV (vs. women without HIV) may experience accelerated reproductive aging. Scherzer et al. showed that among WLHIV anti-mullerian hormone – a biomarker of ovarian reserve secreted by ovarian granulosa cells(80) – declines to undetectable levels before menopause and predicts age of menopause(81). Importantly, in the WIHS cohort, WLHIV exhibited lower age-adjusted levels of AMH than did women without HIV(82). Scherzer’s findings, coupled with Looby’s, may help to explain why WLHIV appear to exhibit age-related changes in monocytes at a younger chronologic age than women without HIV(73). Additional work is needed to separate effects of reproductive and chronologic aging among WLHIV. Of note, perturbations in the hypothalamic-pituitary-gonadal axis may be expected to influence levels of systemic immune activation among WLHIV in comparison with women without HIV. Whether and the extent to which hypothalamic-pituitary-gonadal axis abnormalities influence systemic immune activation among WLHIV has yet to be determined.

How Select Behavioral Risk Factors and Comorbid Conditions May Contribute to Immune Activation among WLHIV

Another possible explanation for heightened systemic immune activation/inflammation among WLHIV relates to behavioral choices and comorbid conditions. Behavioral choices (e.g. cigarette smoking, cocaine use) and the presence of comorbid conditions (e.g. obesity, depression, hepatitis C infection) may all be expected to stimulate systemic immune activation/inflammation among PLHIV(83–87). Below we will consider how cigarette smoking and obesity may affect systemic immune activation in women and men with HIV, highlighting that the prevalence of behavioral choices and comorbid conditions in these groups are rooted in regional culture.

In high-resource regions, the prevalence of cigarette smoking among WLHIV is very high. For example, a rigorously conducted US study suggests that prevalence of cigarette smoking is 34.6% among WLHIV vs. 40.9% among MLHIV, 23.3% among men without HIV, and 18% among women without HIV (67). In an analysis of data from the D:A:D cohort of PLHIV in Europe, North America, and Australia, smoking prevalence is 29% among WLHIV vs. 39% among MLHIV(88). By contrast, in Sub-Saharan Africa, the prevalence of cigarette smoking appears to be much lower among MLHIV and especially among WLHIV. A smoking prevalence study out of South Africa suggests 23.2% of MLHIV in the region and 7.4% of WLHIV in the region report active cigarette smoking (89). Among PLHIV, smoking is known to enhance systemic immune activation(83) and augment the risk of select CVD and NADC(90). It remains unknown whether cigarette smoking increases systemic immune activation to a greater extent among WLHIV vs. MLHIV.

In both high and low resource regions, WLHIV tend to have higher rates of obesity than MLHIV, and across the board, ART initiation appears to increase the prevalence of obesity. For example, in the North American-ACCORD study of 14,084 PLHIV (83% male), the percentage of obese individuals was 9% before ART and 18% after ART(91). By contrast, in a WIHS study of 1177 WLHIV, the pre-ART prevalences of overweight and obesity were 31% and 23%, respectively. ART initiation tended to shift a large percentage of normal-weight and overweight women into higher BMI categories(92). In a study of 7,901 WLHIV and 4,293 MLHIV in Western Kenya, Bloomfield et al. demonstrated that 22.6% of WLHIV vs. 11% percent of MLHIV were overweight/obese(93). ART uptake was more common among MLHIV (72%) than among WLHIV (62.8%) in this cohort. In a smaller study, Sobieszcyk et al. showed that among women in South Africa with newly diagnosed HIV, the prevalence of obesity started at 34.4% and increased to 47.7% within three years(94). Obesity appears to enhance systemic immune activation among PLHIV(85). However, whether obesity stimulates systemic immune activation more robustly among WLHIV vs. MLHIV remains to be determined.

Sex-differences in the Effects of Immunomodulatory Drugs in HIV: ART and Statins

Immunomodulatory drugs have differential effects on select indices of systemic immune activation/inflammation among WLHIV vs. MLHIV. In general, ART reduces systemic levels of immune/inflammatory markers, although not down to levels observed in individuals without HIV(95–97). There is general consensus that starting ART early prevents or mitigates the severity of select HIV-associated comorbidities(4). Importantly, the PEARLS study, conducted in resource-limited settings, revealed that ART suppresses select indices of systemic immune activation to a lesser degree among WLHIV than among MLHIV(98). This observation may be highly relevant to sex-differences in HIV-associated non-infectious comorbidities. Also of note, select statins dampen key indices of systemic immune activation more so among WLHIV than MLHIV, as was demonstrated through the recent INTREPID trial, which compared effects of pitavastatin vs. pravastatin among individuals with HIV-associated dyslipidemia(99).

CONCLUSIONS

Systemic immune activation/inflammation is implicated in the pathogenesis of a variety of non-communicable HIV-associated comorbidities including CVD, neurocognitive impairment, and NADC. There are region-specific sex-differences in the epidemiology of these diseases. The observation that WLHIV have higher levels of systemic immune activation/inflammation than MLHIV may be relevant to sex-differences in select HIV-associated comorbidities. Heightened systemic immune activation among WLHIV may be influenced by sex-specific responses to the virus and to immunomodulatory agents, as well as by behavioral choices/co-morbid conditions and perturbations in the hypothalamic-pituitary-gonadal axis. Additional research is needed to elucidate region-specific drivers of heightened systemic immune activation/inflammation among WLHIV and to determine whether WLHIV who present with one immune-mediated HIV-associated comorbidity (e.g. cognitive impairment) may be at increased risk for another (e.g. CVD, NADC). This kind of research would facilitate improved risk prediction for non-communicable HIV-associated

comorbidities among WLHIV and the development of targeted immunomodulatory prevention strategies.

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