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Conceptualizing the Risks of Coronary Heart Disease and Heart Failure Among People Aging with HIV: Sex-Specific Considerations

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Abstract

Cardiovascular disease (CVD) is emerging as a major threat to healthy aging among people with HIV (PHIV). PHIV face heightened risks for coronary heart disease (CHD)/myocardial infarction (MI) and heart failure (HF), fueled by systemic immune activation and by metabolic dysregulation. Women with HIV (WHIV) evidence unique patterns of vascular and myocardial pathology as compared to men with HIV (MHIV). These patterns include a predilection to microvascular dysfunction and type II MI, as well as a penchant for diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF). Investigations are underway to understand how advanced reproductive aging among WHIV influences systemic immune activation and metabolic dysregulation *en* route to these CVD phenotypes. A key goal is to identify targeted CVD prevention strategies relevant to WHIV, particularly as efficacious treatment approaches to type II MI and HFpEF are lacking.

Introduction

Effective antiretroviral therapy (ART) has transformed HIV into a chronic disease with an extended projected lifespan [1]. The global population of people with HIV (PHIV) is aging—across all regions, but particularly in regions characterized by widespread ART access [2]. In this context, cardiovascular disease (CVD) is emerging as a major threat to healthy aging among PHIV. Epidemiologic investigations performed in high-income countries suggest PHIV (vs. controls) face an approximately 2-fold increased risk of coronary heart disease (CHD)/myocardial infarction (MI) [3, 4] and heart failure (HF) [5, 6, 7•, 8]. Parallel studies conducted in low- and middle-income countries highlight unique heart failure risks—and to a lesser extent, CHD/MI risks—associated with HIV [9, 10]. Further, several studies indicate that established CHD/MI [11, 12] or HF [6, 7•, 13] diagnoses engender worse CVD outcomes for PHIV.

Understanding the mechanisms underlying CHD/MI and HF risks among PHIV will facilitate the development and implementation of targeted CVD preventive strategies. Mechanisms may be expected to differ by CVD type and subtype as well as by region—in relation, for example, to ART access, lifestyle, endemic comorbidities, and underlying genetics. However, among PHIV across regions, two common drivers of CVD risk emerge. The first is heightened systemic immune activation, a condition which bears theoretical relevance to the pathogenesis of both CHD/MI [14] and HF [15]. HIV represents a paradoxical state of immune suppression coupled with heightened systemic immune activation [16]. ART succeeds at suppressing viremia, but importantly, even contemporary ART fails to sufficiently mitigate systemic immune activation [17, 18, 19] and arterial inflammation [20]. Among PHIV, markers of systemic monocyte activation have been linked to arterial inflammation [21], a trigger for both vascular and myocardial pathology. A second key driver of CVD risk among PHIV is metabolic dysregulation, related possibly to HIV infection itself, HIV-associated immune activation, and/or treatment with select antiretroviral therapeutics [22, 23]. In this way, HIV typifies a model disease for better understanding how immune activation and metabolic dysregulation contribute to the development of CHD/MI and HF [24].

In conceptualizing risks of CHD/MI and HF among PHIV, why factor in sex-specific considerations? General population studies have illustrated, irrefutably, that CVD risk mechanisms differ by sex [25]. Further, the manner in which HIV infection precipitates immune activation and/or metabolic dysregulation also differs by sex [26, 27]. Taken together, these two points presage sex differences in CVD risks among PHIV, as well as sex differences in HIV-attributable CVD risk (Fig. 1). In order for HIV-specific CVD preventive strategies to help women, as well as men, sex-specific considerations pertaining to HIV-associated CVD risk must be examined. Each sub-topic of the ensuing focused review is analyzed through a lens of sex-specific considerations. Of note, women with HIV (WHIV) tend to have the highest-level systemic immune activation as compared with men with HIV (MHIV), non-HIV-infected women, and non-HIV-infected men [27]. WHIV (vs. MHIV) also tend to display distinct patterns of metabolic dysregulation [28]. In parallel, general population studies suggest women are more prone than men to enhanced immune responsiveness [29] and unique patterns of metabolic dysregulation [30]. Thus, an enhanced appreciation of sex-specific mechanisms of CVD risk among WHIV may also yield clues as to sex-specific mechanisms of CVD risk among women in the general population.

Special considerations pertaining to CVD risk among cisgender WHIV are explored through this review. Few studies have examined unique CVD risks among transgender WHIV [31, 32], although additional research is underway to address this critical knowledge gap.

CHD/MI risks and subtype presentations among PHIV

Sex-stratified analyses of CHD/MI incidence rates among individuals with vs. without HIV in high-income countries reveal a greater HIV-attributable CHD/MI risk among women. Triant et al. analyzed data from the US Partners Healthcare System on MI rates among 3851 PHIV (30% women) and 1,044,598 control subjects (59% women) followed from 1996 to 2004 [3]. Unadjusted MI incidence rates per 1000 person-years were 12.71 among WHIV, 10.48 among MHIV, 4.88 among non-HIV-infected women, and 11.44 among non-HIV-infected men [3]. After adjustment for traditional CVD risk factors, the relative risk for MI among women with vs. without HIV was 2.98 (95% CI 2.33–3.75) whereas the relative risk for MI among men with vs. without HIV was 1.40 (95% CI 1.16–1.67) [3]. Sex-stratified analyses from a French cohort yielded analogous findings, confirming increased HIV-attributable CHD/MI risk among women [33].

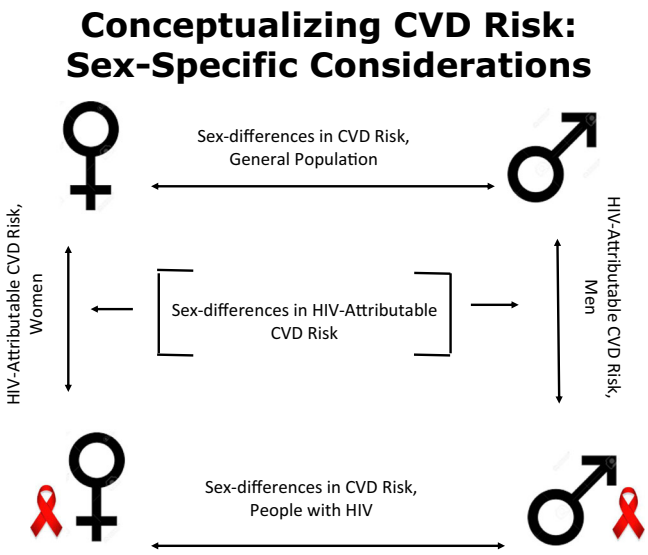

Fig. 1. Conceptualizing CVD risk: sex-specific considerations.

Recent work by Crane et al. highlights sex differences in MI subtype presentations among PHIV in a high-income country [34••]. Analyzing data from 26,909 PHIV evaluated between 1996 and 2014 at one of six US medical centers, Crane's team adjudicated all possible clinical MI events. Overall, in the full cohort, 362 such events were deemed to be definite/probable type I MIs and 288 were deemed definite/probable type II MIs. Among WHIV who presented with an MI, the MI subtype breakdown was 46% (69/150) type I vs. 54% (81/150) type II, yielding a modest type II predominance. By contrast, among MHIV who presented with an MI, the MI subtype breakdown was 59% (293/500) type I vs. 41% (207/500) type II, reflecting a modest type I predominance. Of relevance, a large-scale general population study led by Gaggin et al. revealed that type II MIs predict subsequent major adverse cardiovascular events, CV death, and all-cause mortality at rates comparable to the rates following upon type I MIs [35]. The poor prognosis of type II MI—intertwined with an absence of efficacious therapeutic strategies for this disease—highlights a public-health imperative to identify preventive strategies tailored to at-risk groups. Such strategies will need to be rooted in an understanding of sex-specific, population-specific physiology.

Subclinical CHD among PHIV: insights from physiology studies employing advanced non-invasive imaging

Synthesized observations from studies employing coronary CT angiography (CCTA) among asymptomatic US individuals with and without HIV have yielded the following insights: (1) Men with vs. without HIV evidence an increased prevalence and burden of subclinical coronary atherosclerotic plaque—including non-calcified plaque and plaque with high-risk morphology (HRM) features [36, 37, 38, 39]. (2) Women with vs. without HIV have a comparable overall prevalence and burden of subclinical coronary atherosclerotic plaque. Among those WHIV with subclinical plaque, a shift towards a non-calcified plaque phenotype is observed [40, 41]. (3) WHIV have a lower prevalence and burden of both any plaque and HRM plaque as compared with MHIV, even after controlling for CVD risk factors. WHIV (vs. MHIV) also exhibit a lower prevalence of obstructive plaque [41]. Importantly, a large-scale study led by Siedner et al. is underway to evaluate by CCTA subclinical coronary atherosclerotic plaque among women and men with HIV living in rural Uganda. Sex-stratified analyses are planned, and region-specific risk factors contributing to subclinical coronary atherosclerotic plaque presence will be assessed (http://projectreporter.nih.gov/reporter.cfm).

As general population studies reveal unique hazards of non-obstructive, non-calcified plaque [42], the presence of non-calcified plaque may signal significant risk for WHIV—even when such plaque does not result in significant epicardial artery stenosis. Moreover, among WHIV, the absence of coronary artery calcium (CAC), obstructive plaque, or HRM plaque should not necessarily provide reassurance. That is, even WHIV who do not manifest the aforementioned pre-clinical CHD phenotypes may face significant risk for MI, particularly type II MI.

Thus, epidemiologic studies and physiologic studies suggest that among many WHIV, mechanisms other than gradual epicardial artery occlusion or acute plaque rupture may underlie MI risk. Reinforcing this notion, Knudsen et al. recently published findings suggesting a strikingly high prevalence of coronary microvascular dysfunction among WHIV with very low traditional CVD risk scores. In this Danish study, 94 asymptomatic PHIV on ART (53% men, 47% women) were recruited to undergo 82Rb positron emission tomography/computed tomography at rest and during adenosine-induced stress. Compared with MHIV, WHIV in this cohort were younger (45 ± 1 vs. 53 ± 1, $P \leq 0.001$) and harbored a significantly lower Framingham Risk Score (2.7 ± 0.4 vs. 10.3 ± 0.8, $P < 0.001$). Nevertheless, myocardial flow reserve (MFR) was most impaired among WHIV (2.13 ± 0.10 vs 2.57 ± 0.11, $P = 0.003$) and a greater percentage of WHIV vs. MHIV exhibited a pathologic MFR < 2 (45% vs 24%, $P = 0.03$) [43••].

Taken together, CV physiology studies including WHIV imply that traditional CVD risk scoring algorithms—and even CT-based evaluation of epicardial artery disease—may not adequately capture MI risk in this population. If so, alternate approaches will need to be identified for clinical CVD risk stratification among WHIV and for selection as surrogate endpoints in sex-inclusive research studies focused on CVD prevention. Notably, a study is underway comparing coronary flow reserve among US women with vs. without HIV and assessing parameters related to coronary microvascular dysfunction among WHIV. Identification of pathways predisposing to coronary microvascular dysfunction among WHIV may facilitate the development of targeted strategies for preventing type II MI in this population.

HF risks and subtype presentations among PHIV

Large-scale epidemiologic studies furnishing sex-stratified analyses of incident HF among individuals with vs. without HIV are lacking. However, inferences may be gleaned through the juxtaposition of studies focused on men and studies focused on women. Butt et al. first analyzed incident HF in a US Veterans database including 2391 MHIV and 6095 male controls followed from 2000 through 2007. Findings suggested an approximately 80% increased risk of HF for MHIV vs. controls (adjusted hazard ratio 1.81, 95% CI 1.39–2.36) [5]. Building on these findings, Freiberg et al. subsequently analyzed incident HF by subtype among participants in the US Veterans Aging Cohort Study Virtual Cohort (98, 015 participants, 97% men, 32.2% with HIV) followed from 2003 to 2012 [6]. Among MHIV who developed HF, 34.6% exhibited heart failure with preserved ejection fraction (HFpEF), 15.5% borderline HFpEF, 37.1% heart failure with reduced ejection fraction (HFrEF), and 12.8% HF of unknown type. Across each HF subtype, the relative risk among PHIV (vs. controls) was increased 20–60% [6]. Recently, Janjua et al. published findings analyzing incident HF by subtype among women receiving care in the US Partners HealthCare System (1388 WHIV and 13,781 women without HIV). In this study, among WHIV vs. controls, HF incidence was four times as high (2.5% cumulative/0.27%/year vs. 0.74% cumulative/0.07%/year). Among WHIV who developed HF, a striking 71% developed HFpEF while only 29% developed HFrEF [7]. Of relevance to HF risk, previous studies from high-income countries have also demonstrated increased risks for atrial fibrillation and pulmonary arterial hypertension (PAH) among individuals with vs. without HIV [44, 45]. Moreover, at least one study has suggested sex-based differences in PAH predilection among PHIV, with women's sex predisposing to PAH [46].

Subclinical myocardial pathology among PHIV: insights from physiology studies employing advanced non-invasive imaging

Synthesized observations from studies employing echocardiography, cardiac magnetic resonance imaging, and/or cardiac magnetic resonance spectroscopy among asymptomatic individuals with and without HIV across regions have yielded the following insights: (1) Diastolic dysfunction is exceedingly common among asymptomatic PHIV, with a population prevalence of up to 43% [47, 48••]. (2) Overt systolic dysfunction reflected in low ejection fraction is uncommon among asymptomatic PHIV, but a significant proportion of asymptomatic PHIV exhibit more subtle signs of systolic dysfunction [49, 50, 51]. (3) Myocardial fibrosis and myocardial steatosis represent key processes contributing to subclinical cardiac dysfunction among asymptomatic PHIV [49, 50, 52].

In low- and middle-income countries, additional parameters likely contribute to the development of subclinical and clinical myocardial pathology—for example, specific patterns of ART use, opportunistic infections, nutrient deficiencies, and pollutant exposures [53, 54]. Work by Baker, Ntsekhe et al. is underway to assess by cardiac MRI subclinical myocardial pathology among women and men with HIV (vs. controls) in South Africa, as well as region-specific drivers of such pathology (http://projectreporter.nih.gov/reporter.cfm).

To date, few studies employing advanced non-invasive imaging to characterize subclinical myocardial pathology among PHIV (vs. controls) have presented sex-stratified analyses. However, recent physiology studies focused entirely on US women highlight that among WHIV (vs. controls) myocardial fibrosis and steatosis represent pathways highly relevant to subclinical cardiac dysfunction [55•, 56].

Select drivers of CVD risk among PHIV

The ensuing discussion focuses on the potential contributions of systemic immune activation and metabolic dysregulation to risks of CHD/MI and HF among women and men with HIV.

Systemic immune activation

Both WHIV and MHIV experience heightened systemic immune activation, which persists despite effective ART [17, 18, 19]. Markers of systemic immune activation—including the monocyte activation markers sCD163 and sCD14—have been linked in all-male or predominantly male cohorts of PHIV to arterial inflammation [21, 57], subclinical coronary artery atherosclerotic plaque [36, 58], HRM plaque [38], myocardial fibrosis [59], subclinical cardiac dysfunction [50], pulmonary hypertension [60], and HF/CV mortality [61].

Women tend to have the most robust innate immune response to HIV infection [26]. There is a plausible biologic basis for heightened innate immune activation among HIV-infected women. Sex differences have been noted in the expression of toll-like receptors (TLRs) and select TLR genes are X chromosome encoded [26]. Meier et al. showed that in women (vs. men), HIV-1-mediated stimulation of plasmacytoid dendritic cells via TLR7 engenders a stronger interferon alpha (IFN-α) response [62]. Building on this observation, Laffont et al. showed in humanized mouse models that both X chromosome complement and hormonal milieu contribute to dendritic cell IFN-α production by female mice [63]. Acutely, innate immune hyper-responsiveness to HIV may enable women to better suppress the HIV virus. Over time, this sex-specific response may be maladaptive, predisposing WHIV to diverse non-communicable comorbidities including CVD [27]. Clinical studies enrolling participants from the US have shown that levels of key monocyte activation markers such as sCD163 and sCD14 are highest among WHIV (vs. MHIV, non-HIV-infected women, and non-HIV-infected men) [40]. Studies from Uganda also reveal increased levels of systemic immune activation markers among WHIV vs. non-HIV-infected women [64•]. Intriguingly, a global study conducted through the AIDS Clinical Trials Group network has suggested that ART suppresses select systemic immune indices to a lesser extent among WHIV vs. MHIV [65].

Physiology studies focused on women highlight markers of systemic immune activation which are influenced by HIV status and which relate to HIV-associated subclinical vascular [40] and myocardial [55•] pathology. For example, in a recent study, asymptomatic US WHIV and non-HIV-infected women were recruited to undergo cardiac MRI and detailed systemic immune phenotyping. WHIV, as compared with vs. non-HIV-infected women, were found to have increased myocardial fibrosis and decreased diastolic function. Additionally, novel immune indices relating to myocardial fibrosis and/or diastolic dysfunction among WHIV were identified. Namely, among WHIV, increased levels of sCD163 were found to relate to myocardial fibrosis, while increased expression of the cell-surface receptor CCR2 on circulating inflammatory $CD14^{+}CD16^{+}$ monocytes was noted to relate both to myocardial fibrosis and to diastolic dysfunction [55•]. Intriguingly, CCR2 represents a homing receptor expressed on the cell surface of monocytes, and monocyte CCR2 expression has been shown among PHIV to promote transmigration into select target tissues [66]. Thus, monocyte expression of CCR2 may represent a mechanism by which monocytes are more robustly recruited to the myocardial structural space among WHIV. Animal studies and general population human studies suggest that monocytes thus recruited may transform, in situ, to inflammatory macrophages, engendering a local fibrotic response [67, 68]. Identification of immune markers predisposing to myocardial fibrosis and diastolic dysfunction among WHIV may facilitate the development of targeted strategies for preventing HFpEF in this population.

Metabolic dysregulation

Patterns of metabolic dysregulation exhibited by women and men with HIV have evolved over time. Select early ART regimens induced a lipodystrophy syndrome characterized by peripheral lipoatrophy and/or central lipohypertrophy [23]. While contemporary ART regimens are increasingly well-tolerated, PHIV initiating contemporary ART gain weight [69], accumulate excess adiposity [70], and often deposit fat ectopically [22]—all trends associated with the development of cardiometabolic risk factors such as hypertension (HTN), dyslipidemia, and

dysglycemia. In this context, PHIV worldwide are increasingly crossing over into overt obesity and attendant metabolic syndrome [71, 72, 73]. Among ART-treated PHIV, metabolic dysregulation may relate to HIV infection itself, HIV-associated immune activation, and/or treatment with select antiretroviral therapeutics [22, 23].

WHIV may be uniquely susceptible to ART-induced weight gain and metabolic sequelae as compared to MHIV [74]. Moreover, studies suggest sex differences in fat accumulation after ART, with women aggregating larger increases in trunk and leg fat mass [75]. A recent study by Brand et al. analyzing nationally representative data from 7436 US PHIV showed that WHIV age 50–65 were more likely than MHIV to be obese and have HTN or dyslipidemia and WHIV age > 65 were more likely than MHIV to have diabetes [76•]. Hypertension, dyslipidemia, and dysglycemia are well-known risk factors for both CHD/MI and HF. Of relevance to HIV-attributable HF risk among women, a recent physiology study suggests that WHIV may deposit fat ectopically in the heart at a lower BMI set point than non-HIV-infected women. In this study, US WHIV and non-HIV-infected women well-matched on age and BMI underwent cardiac magnetic resonance spectroscopy and metabolic phenotyping. WHIV (vs. non-HIV-infected women) exhibited a three-fold increase in myocardial steatosis in relation to diastolic dysfunction [56]. In parallel, findings from a large general population study suggest that obesity and associated cardiometabolic traits predispose to HFpEF more than HFrEF and that differential risks of HFpEF with obesity appear more pronounced among women [77]. By inference, unique patterns of metabolic dysregulation among WHIV may help explain the observed predilection to HFpEF in this group.

Interrelationships between reproductive aging, immune activation, and metabolic dysregulation among WHIV

WHIV may experience accelerated reproductive aging as compared with non-HIV-infected women. Early studies comparing the age of menopause among women with vs. without HIV have yielded conflicting results [78]. Contradictory findings reflect inherent challenges of defining menopause among WHIV—a population prone to prolonged amenorrhea absent ovarian failure [79]. Advancing the debate about HIV and reproductive aging, subsequent studies revealed that WHIV (vs. non-HIV-infected women) have lower age-adjusted levels of anti-Mullerian hormone (AMH) [80, 81]—a biomarker of ovarian reserve. Levels of this hormone, which is produced by ovarian granulosa cells, decline to undetectable prior to menopause [82], and predict age at menopause [83].

General population studies suggest that after menopause, CVD risk increases markedly [84]. Moreover, early menopause represents a well-recognized risk factor for both MI [85] and HF [86]. Physiology studies among WHIV have synthesized historical and hormonal data to explore potential mechanisms by which reproductive aging may increase CVD risk in this population. For example, Looby et al. used menstrual cycle history and AMH levels to group asymptomatic, aging US WHIV into a continuum of reproductive aging sub-groups—premenopausal, premenopausal with reduced ovarian reserve, and post-menopausal. Of interest, select markers of systemic monocyte activation—including sCD163 and sCD14—increased across the reproductive aging spectrum among WHIV. The prevalence of subclinical coronary atherosclerotic plaque also increased across this spectrum. Finally, among WHIV, reduced ovarian reserve related to subclinical coronary atherosclerotic plaque even when controlling for CVD risk scores encompassing chronological age. The latter finding suggests a potential contribution of reproductive aging to atherogenesis among WHIV [87]. Most recently, a new study among WHIV has shown an inverse relationship between AMH levels and body mass index [88]. Building on this work, studies are underway to assess how reproductive aging relates to ectopic cardiac fat deposition among WHIV.

Physiology study findings thus suggest two key points relevant to reproductive aging and CVD risk in WHIV. First, WHIV appear to have evidence of advanced reproductive aging. Second, reproductive aging may predispose WHIV to immune activation and metabolic dysregulation—processes highly relevant to population-specific risks for CHD/MI and HF.

Future directions: potential strategies for CVD risk reduction

Current knowledge about mechanisms underlying CVD risk among PHIV suggests prevention strategies across several categories. First, immediate and continuous ART [89] [90]. Second, lifestyle modification emphasizing healthy diet, exercise, abstinence from cigarettes, and illicit drugs, and promotion of mental health [91]. Third, medication-based management of persistent traditional metabolic risk factors [92]. In the post-CANTOS era [93, 94], a purely immune modulatory HIV-CVD preventive strategy also holds potential appeal [95]. Among PHIV, the balance will entail dampening the immune responses that threaten vascular and

myocardial health while preserving the immune responses essential to controlling viremia.

The REPRIEVE Trial—Randomized Trial to Prevent Vascular Events in HIV—is testing whether statin therapy prevents CVD events among PHIV in whom traditional CVD risk is not significantly increased [96••]. Among PHIV, statin therapy not only improves lipid homeostasis [97] but also lowers levels of several key immune/inflammatory markers [98, 99]. REPRIEVE has enrolled > 7500 PHIV from 116 research sites globally, rendering this the largest international, randomized placebo-controlled trial in the field of HIV [96••]. Embedded in REPRIEVE are objectives to explore systemic immune activation in relation to CVD risk and risk reduction among WHIV across the reproductive aging spectrum. In order that the study be powered to answer important questions relevant to women's CV health, an evidence-based educational awareness campaign—Follow YOUR Heart—was launched to augment enrollment of WHIV in REPRIEVE [100]. While the focus of REPRIEVE is on atherosclerotic CV events (e.g., MI, stroke), heart failure events are also being adjudicated. Additionally, a physiology study ancillary to REPRIEVE is testing whether statin therapy forestalls the progression of myocardial fibrosis and myocardial steatosis among PHIV.

Summary and Conclusions

Cardiovascular disease is emerging as a major threat to healthy aging among PHIV. PHIV face heightened risks for CHD/MI and HF, fueled by systemic immune activation and by metabolic dysregulation. WHIV evidence unique patterns of vascular and myocardial pathology as compared to MHIV. These patterns include a predilection to microvascular dysfunction and type II MI, as well as a penchant for diastolic dysfunction and HFpEF. Investigations are underway to understand how advanced reproductive aging among WHIV influences systemic immune activation and metabolic dysregulation *en* route to these CVD phenotypes. A key goal is to identify targeted CVD prevention strategies relevant to WHIV, particularly, as efficacious treatment approaches to type II MI and HFpEF are lacking. Work on sex-specific mechanisms of CVD risk among WHIV may inform efforts to understand such risk among women in the general population and vice versa.

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Compliance with Ethical Standards

Conflict of Interest

Rebecca A. Abelman and Brian M. Mugo each declare no potential conflicts of interest. Markella V. Zanni is the principal investigator of an investigator-initiated research grant support from Gilead Sciences to her institution (Massachusetts General Hospital).

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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