Progress in Cardiovascular Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Prevention of cardiovascular disease among people living with HIV in sub-Saharan Africa

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ARTICLE INFO

Article history:
3 February 2020
3 February 2020
Available online xxxx

Keywords:
Cardiovascular risk factors
Cardiovascular disease
People living with HIV
Sub-Saharan Africa

ABSTRACT

As longevity has increased for people living with HIV (PLWH) in the United States and Europe, there has been a concomitant increase in the prevalence of cardiovascular disease (CVD) risk factors and morbidity in this population. Whereas the availability of HIV antiretroviral therapy has resulted in dramatic increases in life expectancy in sub-Saharan Africa (SSA), where over two thirds of PLWH reside, if and how these trends impact the epidemiology of CVD is less clear. In this review, we describe the current state of the science on how both HIV and its treatment impact CVD risk factors and outcomes among PLWH in sub-Saharan Africa, including regional factors (unique to SSA) likely to differentiate these relationships from the global North. We then outline how current regional guidelines address CVD prevention among PLWH and which clinical and structural interventions are best poised to confront the co-epidemics of HIV and CVD in the region. We conclude with a discussion of key research gaps that need to be addressed to optimally develop an actionable public health response.

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Abbreviations and acronyms: ACS, acute coronary syndromes; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; CAD, coronary artery disease; CD, cluster of differentiation; cIMT, carotid intimal-medial thickness; CVD, cardiovascular disease; DALYs, disability-associated life-years; DM, diabetes mellitus; EACS, European AIDS clinical society; HAP, household air pollution; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein-cholesterol; HDP, hypertensive disorders of pregnancy; HIV, human immunodeficiency virus; HTN, hypertension; LDL-c, low density lipoprotein cholesterol; MLWH, men living with HIV; PLWH, people living with HIV; PM, particulate matter; SSA, sub-Saharan Africa; WLWH, women living with HIV.

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https://doi.org/10.1016/j.pcad.2020.02.004
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Background

Approximately two thirds of the world's population of people living with HIV (PLWH) reside in sub-Saharan Africa (SSA).[1] After a lag in resource allocation and implementation of HIV control programs, the continent has seen a meteoric rise in access to HIV treatment over the past decade – with antiretroviral therapy (ART) coverage rates rising from virtually none in 1990s to 62% by 2018.[1] This massive public health commitment and implementation has resulted in significantly increased longevity for PLWH. Due to this longevity, the leading causes of mortality among PLWH are now cardiovascular disease (CVD), non-AIDS malignancies, and liver disease.[2] In the United States and Europe, there is evidence of heightened risk of myocardial infarction, stroke, heart failure,[3,4] and sudden cardiac death[5] among PLWH. Globally, the risk of CVD in PLWH is estimated to be 2.5-fold higher than HIV-uninfected persons, contributing to 2.6 million disability-associated life-years (DALYs) annually (a third of which are in SSA).[6]

In the wake of these epidemiologic shifts among PLWH, there is growing interest in measuring CVD risk factors and outcomes in the sub-Saharan African region has grown; however, most of these data have been limited to risk factor assessments, such as blood pressure (BP) and diabetes and lipids. Despite heterogeneity in unmeasured effects (genetics and environmental risk factors) and relationships between risk factors and outcomes, these data have been used to assess CVD risk, with risk prediction models derived from Western populations, such as the Framingham and Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Risk scores.[7,8]

Consequently, public health programs for HIV care are at a crucial crossroads, with parallel (or competing) priorities of ensuring all PLWH have access to care, maximizing HIV prevention efforts, and promoting health and quality of life for PLWH. Achieving these goals will require a thorough understanding of CVD epidemiology among PLWH. However, a number of critical questions remain unanswered related to CVD risk among PLWH in SSA:

1) What is the epidemiology of traditional (long-established) CVD risk factors among PLWH on chronic ART?
2) Which regionally relevant risk factors modify CVD risk among PLWH?
3) How do currently available data inform us about how HIV infection directly affects CVD risk in SSA?
4) How well do current regional guidelines account for CVD prevention through routine screening and management?
5) What CVD prevention interventions are most likely to reduce morbidity and mortality in the region?
6) What are the major research gaps that need to be addressed to ensure CVD risk is optimally minimized among PLWH in SSA?

In this systemic review, we aim to address these questions and lay the groundwork for future research and programmatic priorities for this field.

The epidemiology of traditional CVD risk factors among PLWH taking long-term ART

Hypertension (HTN)

As described globally, HTN ranks as the leading risk factor for CVD in PLWH in sub-Saharan Africa (SSA).[9] According to a recent meta-analysis, the prevalence of HTN in PLWH on ART is 35% and rising.[10] PLWH in SSA experience a high incidence of new-onset HTN, particularly in the first 1–2 years after ART initiation.[11] Some evidence suggests that PLWH who have HTN may experience an even higher risk of CVD than HIV-negative adults with HTN.[12] Though there were conflicting early reports on the burden of HTN in PLWH compared to uninfected people, recent studies from SSA demonstrate lower rates of HTN in PLWH compared to controls, and that women living with HIV have higher rates than men living with HIV.[13–16] Interestingly, while women have a higher prevalence of HTN, they are more likely to be aware, and more likely to have BP control.[17]

As the population of PLWH in SSA is aging, HTN may provide a valuable and easy-to-measure indicator and target of escalating overall risk for CVD. Data from large cohorts in the United States and Europe have demonstrated that over half of PLWH have HTN and those with HTN usually have multiple CVD risk factors.[18,19] A modeling-based study from Zimbabwe predicts that a similar trend will occur in the next 20 years in SSA.[20] HTN is often the first harbinger of metabolic syndrome, which is a major CVD risk factor in PLWH.[21] Even younger

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PLWH have high lifetime CVD risk scores, and this is largely driven by HTN.[22]

Notably, risk factors and treatment implications for HTN in PLWH in SSA may differ from other populations due to several factors. First, modest drug-drug interactions between ART and BP lowering drugs may affect the choice of medications for PLWH with HTN, although these drug interactions generally do not prevent titration to the highest doses.[23] Second, growing evidence suggests that the potency of BP lowering drugs for people in SSA may differ from other populations with better response to combinations, including calcium channel blockers.[24] Third, the best method for measuring BP and the optimal threshold for starting medications for HTN for PLWH has not yet been determined.[25] Finally, the pathophysiology of HTN in PLWH in SSA may not be the same as the mechanisms in HIV-uninfected adults.[26] The complex interplay between traditional risk factors, HIV viral tropism, ART, HIV-related chronic inflammation, rapid changes in adiposity and other factors leading to HTN in PLWH may require new strategies for HTN prevention and treatment in this population.[27–29]

Despite the growing knowledge of HTN among PLWH, the HIV health system in SSA is ill-equipped to handle the rising tide of HTN in PLWH with most HIV clinical care services lacking basic equipment such as BP cuffs and sphygmomanometers and front-line healthcare workers with limited basic knowledge about HTN.[30] This is compounded by fragmented clinical care for HIV and for HTN, frequent stock outs of BP lowering drugs, as such PLWH with HTN often face severe physical and financial barriers to obtaining treatment for both HIV and HTN.[31] Integration of HIV clinical care with HTN care provides a unique opportunity to improve awareness, treatment and control for HTN in PLWH.[32,33]

Diabetes mellitus (DM)

In SSA, DM is predicted to increase by 160% by 2030, partly owing to urbanization and unhealthy lifestyles.[34] Abnormal glucose regulation associated with HIV per se[35] and ART[36] may lead to a rise in DM.[37] Limited cross sectional evidence describe up to a four-fold higher risk of DM in PLWH taking ART compared to uninfected counterparts.[38,39] In the context of the rollout of the HIV treat all campaign, and the increased availability of ART, the number of PLWH on ART with an increased risk of dysglycemia and DM will escalate.

However, in western countries the positive association between HIV and prevalent DM correlates with traditional risk factors, such as increasing age and obesity,[40,41] suggesting that these factors, rather than ART play a major role in the development of DM among PLWH. Fortunately, the use of older generations of ART drugs such as indinavir, zidovudine, saquinavir, stavudine, and didanosine, which have been associated with a higher prevalence of DM,[42,43] has been curtailed in SSA and thus a reduction in ART-induced DM.

Disparities by regional settings notwithstanding, health care providers should follow existing DM screening guidelines for PLWH before and after starting ART.[44] In addition, the increased prevalence of DM among younger and non-obese PLWH, suggests modification of DM screening guidelines might help address this. Moreover, improved diagnostics for DM diagnosis and monitoring among PLWH are needed, based on studies demonstrating lower hemoglobin levels in PLWH raise limitations about HbA1c accuracy among PLWH.[41,45,46] Similar reductions in HbA1c validity have been shown in those with sickle cell trait, which is highly prevalent in much of SSA.[47] Outstanding gaps to identify optimal DM management strategies among PLWH abound. Traditional strategies to improve insulin sensitivity, such as weight loss and medical therapy have been shown to be less effective.[48] For example, drug-drug interactions of metformin and dolutegravir, a cost-effective integrase-strand transfer inhibitor used in first-line ART regimens in most national HIV care programs in SSA, should be evaluated for optimal glycemic control in PLWH in the era of test and treat.[49,50]

Obesity

Overweight and obesity are the fifth leading risk factors for global deaths[51] and the risk of mortality increases with morbid obesity (body mass index (BMI) > 40 kg/m^2).[52] In addition, 44% of the DM burden, 23% of the ischemic heart disease burden, and between 7% and 41% burdens of prostate, colon, and breast cancers are attributable to being overweight and obese.[53,54]

Obesity is increasingly common among PLWH in SSA with prevalence rates ranging from 5% in Nigeria[55] to 23% in South Africa[56] representing a remarkable transformation from the epoch when HIV was defined by “wasting” and “slimming”.[57] In SSA, PLWH have low pre-ART BMI with subsequent weight gain following ART initiation.[58] However, the ART associated weight gain is disproportionate resulting in central/visceral adiposity and eventually lipodystrophy that is believed to drive subsequent dysglycemia.[59] Further still, newer first-line ART regimens that include dolutegravir have been documented to result in significant weight gain compared to previously favored, efavirenz-based ART regimens.[60] These increases appear to be greatest in women, and appear to primarily affect the truncal areas of the body.[60]

Among PLWH, women have higher prevalence of obesity and overweight than men[16,56,61,62] though associated factors do not differ from those for the general population.[56] Modifiable factors associated with obesity include physical inactivity from increased urbanization, intake of energy dense diets that include high-fat, carbohydrate-rich foods, sugars and salt.[53,54,63]

Finally, additional data are needed to clarify optimal thresholds of BMI risk stratification among PLWH in SSA. Data from SSA, where traditionally-defined elevated BMI, particularly in women, is often seen in approximately 50% of the population, are needed to develop locally-relevant thresholds that predict downstream health outcomes.[56]

Dyslipidemia

To-date, few studies have examined the impact of dyslipidemia on cardiovascular health in SSA, and locally validated thresholds are lacking. Recently, an elevation of the ratio of total cholesterol to high density lipoprotein-cholesterol (HDL-c) - a validated measure of dyslipidemia - was shown to predict short-term all-cause mortality among PLWH in Malawi.[64]

Though dyslipidemia is common in the general adult population, PLWH taking ART have a higher burden compared to their HIV-uninfected counterparts.[65] A meta-analysis by Noubiap et al.[66] of 177 facility- and population-based studies of dyslipidemia across Africa reported a prevalence for elevated total cholesterol of 26.2% in PLWH compared to 25.5% in the general population, and more than two-fold higher prevalence for elevated low density lipoprotein (LDL)-cholesterol (45.6% *vs* 21.4%).[66]

A study from Malawi described population attributable fraction for stroke by hypercholesterolemia (total cholesterol ≥ 6.2 mmol/L) was 3% among adults younger than 45 years and 1% among those older than 45 years,[67] demonstrating the comparatively minimal role of dyslipidemia in CVD morbidity and mortality compared to other risk factors. Nonetheless, hypercholesterolemia's contribution to CVD burden among PLWH receiving ART in SSA might be considerably higher as demonstrated in USA and Europe.

As with obesity and diabetes mellitus discussed above, newer ART regimens with fewer dyslipidemic effects are increasingly available; however, continued research is needed to delineate the metabolic effects of newer ART, and particularly so for dolutegravir, which is now

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a first-line agent in much of the region and which preliminary studies implicate in significant weight gain.[68,69]

Smoking

Smoking is the leading behavioral cause of CVD worldwide.[70] Though smoking rates are decreasing worldwide in the wake of tightened regulations such as the World Health Organization's Framework Convention on Tobacco Control, progress has lagged across much of SSA,[71–73] likely driven by differences in tobacco taxation and policies regarding advertising and public smoking.[73]

Similar to trends in high-income settings, PLWH in SSA are more likely to smoke than their HIV-uninfected counterparts. In a meta-analysis of nationally-representative studies from 28 low and middle income countries, Mdege et al.[74] found that 24% of men with HIV and 1% of women with HIV in SSA smoke tobacco products. Compared to the HIV-uninfected population, this translates to a 47% higher risk of smoking among men and 87% higher risk of smoking among women with HIV. Reasons why PLWH may smoke more than the general population include self-treatment of the comorbid anxiety and depression that is prevalent among PLWH, risky behaviors driven by the perception that life expectancy is too short to experience tobacco-related health effects, and self-management of HIV-associated symptoms.[75,76]

In high income settings, smoking decreases life expectancy more than HIV infection itself for PLWH taking ART,[77] though it is unknown whether this relationship holds for PLWH in SSA. Though smoking and HIV infection each independently increase the risk for CVD, whether PLWH have increased susceptibility to smoking-associated CVD compared to HIV-uninfected smokers remains unknown. Furthermore, the types and forms of tobacco use in SSA differ from that found in other settings, but little is known regarding whether the unique sources of tobacco have different influences on cardiovascular health. PLWH require concerted smoking cessation efforts, but further work is needed to characterize the most effective cessation strategies in this population.

Regionally relevant risk factors modify CVD risk among PLWH in sub-Saharan Africa

Sex

Women living with HIV (WLWH) in North America and Europe are estimated to have 2 to 4 times higher risk of myocardial infarction, stroke and heart failure as compared to women without HIV infection and approximately equivalent risk compared to men living with HIV (MLWH).[78–81] The reasons behind this elevated risk are multifactorial, including 1) increased levels of systemic inflammation and interaction with sex-specific hormones,[82] 2) sub-optimal implementation of guideline-directed preventive therapy for traditional cardiometabolic risk factors,[83] and 3) heightened levels of behavioral and psychosocial risk factors as compared to the general population.[84]

Whether relationships between sex and CVD risk are similar in SSA as elsewhere is unknown. Large-scale comparative data assessing the links between sex and subsequent development of CVD are lacking in the region. As discussed above, cross-sectional studies have demonstrated increased prevalence of a variety of CVD risk factors (obesity, dyslipidemia and HTN) among women in SSA compared to men, with significant variation depending on the population that is studied.[85,86] One potential contributor to sex-determined CVD risk is pregnancy-related physiologic changes and its' downstream effects on chronic health. Hypertensive disorders of pregnancy (HDP), are a major cause of mortality and morbidity worldwide, complicating 5%–10% of all pregnancies.[87] The impact of HIV and its treatment on HDP has yet to be fully elucidated. In several studies, WLWH have been found to carry similar risks for HDP compared to uninfected counterparts; however, the influence of ART on this risk remains unclear.[88–91] In some studies, pregnant women living with HIV taking ART have been shown to have higher rates of HDP compared to those not taking ART or uninfected.[92–95] However, the role ART and or HIV in increasing the risk of HDP and gestational DM are yet to be fully elucidated.

As of yet, no large-scale, prospective cohort studies have assessed the comparative risk of developing coronary artery disease or stroke by sex with use of end-organ diagnostics, such as coronary angiogram or brain magnetic resonance imaging. Several studies have shown an increased prevalence of secondary markers of CVD in women, such as ischemic findings on ECG in Uganda, and angina symptoms as reported on the Rose Angina Questionnaire in South Africa.[85,96] Numerous studies have looked at carotid intimal-medial thickness (cIMT) as a surrogate for the prevalence of CVD, with mixed results. Ssinabuulya et al. found no difference in mean cIMT in WLWH as compared to MLWH in Uganda, whereas Schoffelen et al. found a slightly lower mean cIMT among WLWH in South Africa,[97,98] and Nonterah et al. demonstrated lower cIMT values among PLWH as compared to the HIV-negative population, with no significant difference by sex.[99] Larger-scale, prospective studies are needed for a comprehensive understanding of the relative risk of CVD in women *versus* men and to quantify the contribution of ART and HIV to that risk.

Further work building upon these findings is needed to elucidate if and how sex and traditional risk factors combine to alter CVD risk among WLWH in SSA. If the preliminary relationships are confirmed, entirely new frameworks for considering female sex as a potential risk factor for CVD, an inverse of the standard conceptualization in western settings, would be needed.

Environmental factors including air pollution

Globally, air pollution is responsible for at least one out of every four deaths from both CVD and cerebrovascular disease.[100] Air pollution results from a variety of human-related activities and natural events that include emissions from vehicles, factories and power plants; burning of biomass fuels (*e.g.*, charcoal, firewood, animal dung, crop residues) for home cooking and heating; dust storms; forest fires; and volcanic eruptions. The pollutants released from these sources include particulate matter (PM), volatile organic compounds, and gases. These affect cardiovascular health by inciting systemic inflammation, oxidative stress, coagulation, and endothelial dysfunction through both local pulmonary parenchymal damage and by crossing the lung alveolar endothelium to directly enter the bloodstream.[101,102] Air pollution exposure in SSA is among the highest in the world[103] (Fig. 1) as a result of both rapid urbanization and industrialization as well as lack of air quality regulations.[104]

Ambient air pollution

There are few studies of the cardiovascular effects of ambient pollution in SSA that directly measure pollutant concentrations, and none that focus specifically on PLWH. The Prospective Urban Rural Epidemiology (PURE) Study which included only one African country (Tanzania) estimated that increased ambient pollution exposure was associated with 3 to 8% increased risk of CVD-related death, incident CVD events, myocardial infarction, or stroke.[106] Based upon the higher ambient pollutant levels in SSA, authors suggested that ambient pollution exposure may account for the higher CVD burden. A multi-country cross-sectional study of 45,625 adults that included Ghana and South Africa showed that each 10 $\mu g/m^3$ increase in average $PM_{2.5}$ exposure over the preceding three years was associated with 13% higher odds of self-reported stroke.[107] Wichmann and Voyi demonstrated that interquartile range increases in particulate matter, nitrogen dioxide and sulfur dioxide were each associated with increased daily CVD and/or cerebrovascular mortality, particularly in the warm season, among 149,667 residents of Cape Town, South Africa from 2001 to 2006.[108] In non-African settings, ambient pollution exposure has also been associated with angina, acute myocardial infarction, heart failure hospitalizations, arrhythmias, cardiac arrest, carotid intimal thickening, aortic

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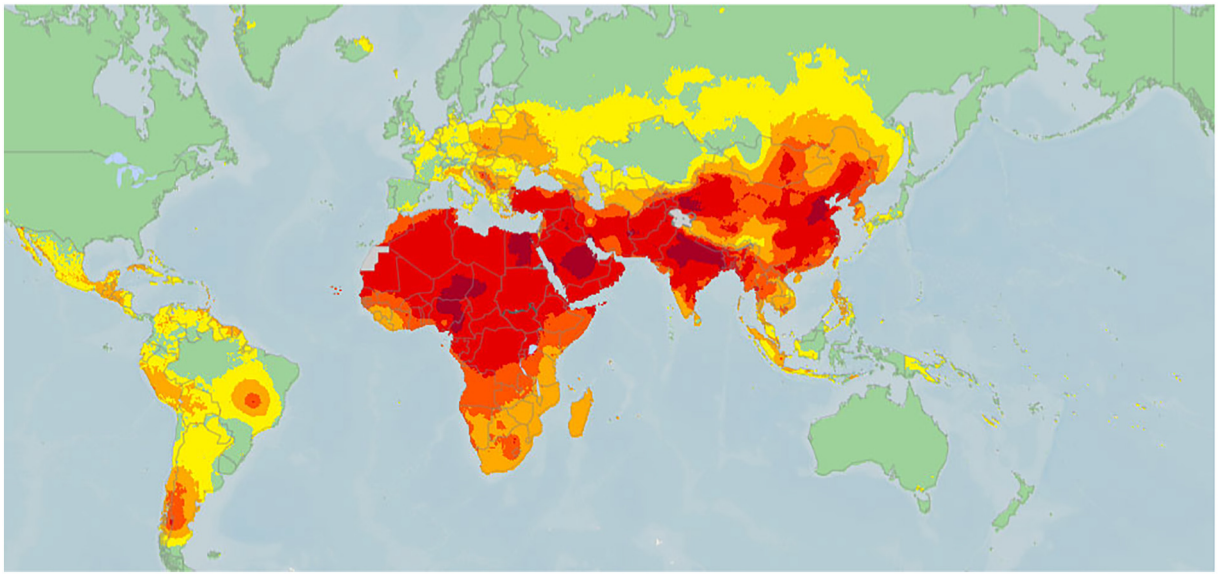

Fig. 1. Global mean concentrations (μg/m^3) of ambient particulate matter (PM) of diameter of <2.5 μm in 2016. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society.[105]

atherosclerotic plaques, coronary calcium progression, and adverse cardiac remodeling.[109] None of this work has evaluated the potential effect modification of HIV or ART.

Household air pollution (HAP)

A leading source of air pollution in SSA is HAP, which results from indoor biomass burning and disproportionately influences the health of women and children.[110] Agarwal et al. measured HAP exposure and cardiac function in 44 Kenyan women and found that higher HAP exposure was associated with lower left ventricular ejection fraction and higher pulmonary artery diastolic pressure. In this same cohort, decreasing HAP exposure through a clean cookstove intervention led to reductions in both systolic and diastolic BP over 6 months.[111] Similarly, HAP was associated with higher systolic and diastolic blood pressure among 44 Ghanaian women,[112] and both diastolic pressure and hypertension prevalence decreased among 324 pregnant Nigerian women randomized to cook with cleaner as compared to traditional fuel sources.[113] In non-African settings, HAP exposure has been associated with ST segment changes, cIMT, right ventricular systolic pressure, and decreased right and left ventricular function.[109] There are no studies of the influence of HAP on CVD among PLWH.

Early and mechanistic data suggest that the impact of air pollution on CVD might be particularly problematic in SSA and among PLWH.[114] Yet, comprehensive exposure metrics exclusive of household-only studies are largely lacking, and those that do exist focus predominantly on urban settings. Additionally, the effects of air pollution are influenced by pollutant source.[115–118] Much of the global knowledge regarding the health effects of air pollution originates from high income settings, where traffic and industry-related activities drive air pollution, while air pollution in SSA is driven largely by biomass fuel burning.[119] Based upon similarities in the systemic inflammatory influences of both air pollution and chronic HIV infection, the potential for interactive effects on cardiovascular health is high. However, it is not yet known whether PLWH are exposed to higher levels of air pollution or whether they are more susceptible to air pollution-related cardiovascular effects.

How do currently available data inform us about how HIV infection directly affects CVD risk in SSA?

Much of the data from western settings strongly support relationships between HIV infection and risks of both pre-clinical CVD[120–127] and CVD events.[78,81,128–130] As discussed above, this relationship is primarily driven by a combination of traditional CVD risk factor profiles in PLWH[81,127,131] and an inflammatory profile, which persists despite suppressive ART.[132,133] However, critical differences exist between western and SSA populations relating to traditional risk factor profiles, regional risk factors, and clinical infrastructures for addressing CVD risk. Thus, investigation of relationships between HIV and risk of pre-clinical, clinical, and fatal CVD events in SSA remains a crucial priority.

Arteriosclerosis and pre-clinical atherosclerosis

Like in the United States, early studies assessing relationships between HIV and atherosclerosis largely focused on use of non-invasive, surrogate markers of disease, namely ankle brachial index, pulse wave velocity and cIMT. Data on arteriosclerosis, which is predictive of future CVD events, but not a marker itself, have generally demonstrated increased arterial stiffness in PLWH than HIV-uninfected comparators. For example, cohort studies from Cameroon and South Africa demonstrated increased pulse-wave velocity among ART-naïve PLWH compared to HIV-uninfected comparators, which was most pronounced in people older than 50 years.[134,135] Similarly, a study in Uganda of people over 45 years old found significantly increased arterial stiffness as measured by ankle-brachial index in PLWH on long-term ART therapy compared to community-based HIV-uninfected comparators, which remained significant after adjustment for CVD risk factors.[136]

However, there is conflicting evidence for a similar, if not decreased burden of pre-clinical carotid atherosclerosis among PLWH compared to HIV-uninfected counterparts in SSA. For example, early studies in South Africa and Uganda, found no difference in cIMT between ART-naïve, ART-treated, and HIV-uninfected comparators, before or after adjustment of CVD risk factors.[98,137,138] Interestingly, these findings were despite PLWH having higher inflammatory markers, including intracellular adhesion molecule and vascular cell adhesion molecule in South Africa, and soluble CD14, high sensitivity C-reactive protein, and fatty acid binding protein-2 in Uganda.[139] Similar results suggesting no difference in cIMT between PLWH taking ART and uninfected comparators, have since been replicated in urban populations in South Africa.[140] On the contrary, a large meta-analysis across sub-Saharan Africa including nearly 9000 individuals from four countries (Burkina Faso, Kenya, Ghana, and South Africa),[99] showed that although traditional CVD risk factors, such as BP, LDL, and age were associated with increased cIMT, HIV serostatus was notably associated with a decreased cIMT (−8.86 μm, 95% confidence interval: −15.7, −2.0). The combined

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sample appeared strongly representative of older individuals in the region (median age 50 years), with nearly 85% of PLWH on ART. The first study in the region to move beyond cIMT to assess more strongly predictive measures of CVD outcomes also found similar rates of coronary artery calcium (CAC) between PLWH on ART and HIV-uninfected comparators in an urban Kampala cohort.[141] That study, which compared CAC between individuals in Uganda with age and sex-matched individuals in the United States found remarkably lower prevalence of any CAC in Uganda (9% *versus* 48%, $P < 0.01$). These data are all limited by a number of factors, including cross-sectional designs, the possibility of residual confounding, and perhaps most importantly, limited correlation with downstream CVD events.

Coronary artery disease (CAD) and acute coronary syndromes (ACS)

Although pre-clinical data do not suggest increased risk of CAD among PLWH in SSA, a multitude of factors have been associated with increased risk of CAD among PLWH in the USA and Europe, including: HIV-vascular dysfunction due to immune activation caused by HIV itself, metabolic derangements, including hyperglycemia and dyslipidemia related to ART, and age-related atherosclerotic CVD disease due to risk factors present in the general population.[142,143] Similarly, progression of atherosclerotic CVD into clinical coronary artery disease and acute coronary syndrome among PLWH has been observed to occur faster than that observed in the general population.[144] Finally, PLWH who present with ACS tend to be younger than their HIV-uninfected counterparts.[144] Based on these relationships, modeling studies that account for HIV prevalence and CVD risk factors have suggested an outsized effect of HIV on CAD in SSA.[6]

Unfortunately, due largely to the lack of CAD diagnostic resources in the region, primary data on CAD epidemiology outcomes in SSA are rare. Until such data become available, it will be premature to assume that predictive models for CVD risks and outcomes, which are largely based on relationships in Western populations between risk factors and outcomes, predict CVD events in the SSA region.

Stroke

In the United States, PLWH appear to have approximately 40–60% increased risk of stroke, which appears greatest in those with advanced HIV disease.[78,129,145] Studies from SSA consistently demonstrate that HIV infection is an independent risk factor for stroke.[146–148] This was best demonstrated in a large ($n = 775$) case-control study in Malawi, that noted a tripling of the odds of stroke among PLWH.[67] The same study described HIV infection as accounting for 42% of total strokes among adults younger than 45 years, 6% strokes among those older than 45 years, demonstrating that stroke in PLWH in SSA disproportionately affects the young and is associated with poor outcomes.[149]

Putative mechanisms associated with stroke in PLWH can be classified into either traditional or HIV-specific risk factors. Traditional risk factors, such as HTN, DM, dyslipidemia, CVD and physical inactivity have been consistently shown in SSA to be associated with stroke.[148,150] In addition, the burden of traditional stroke risk factors in PLWH is sharply on the rise with reports suggesting that up to 50% of PLWH in SSA have metabolic syndrome.[7,13] The role of HIV-specific risk factors in stroke is supported by the fact that stroke in PLWH is almost always due to ischemic stroke indicating an underlying propensity towards hypercoagulability and thrombosis. More than 90% of strokes in PLWH are due to ischemic stroke[149] as opposed to a reported figure of 50–60% in HIV-uninfected individuals in SSA.[151,152]

A commonly proposed HIV-specific risk factor is HIV-induced coagulopathy, which is thought to arise from deficiency of protein C and S, hyper homocysteinemia, antiphospholipid syndromes and elevated d-dimer among others.[153–155] Other HIV-specific factors include HIV-induced vasculopathy and opportunistic infections of the central nervous system. The exact mechanisms by which these factors cause stroke are yet to be elucidated; however, HIV induced vasculopathy, which is a heterogeneous term denoting HIV vasculitis, accelerated carotid atherosclerosis and small vessel disease occurring in the absence of atherosclerosis or infectious vasculitis, is the leading cause of ischemic stroke in PLWH in SSA.[156,157] Crucially, these mechanisms of HIV-specific risk are at least partially due to untreated and advanced disease. This was most notable in the Malawi case-control study, which suggested that the risk of stroke among PLWH drastically decreased after 6 months of ART and with CD4 counts over 500 cells/μL.[67]

How well do current regional guidelines account for CVD prevention through routine screening and management?

CVD risk prediction scores in SSA populations

One major strategy to promoting CVD prevention is use of risk prediction scores to identify those at high risk of CVD outcomes for cost saving interventions. Multiple studies have reported high CVD risk distributions among PLWH in SSA with a moderate to high risk among older-age groups.[159–161] However, questions exist as to whether currently available risk stratification tools, such as the Framingham and Pooled Cohort equations, have been appropriately calibrated to reflect true risk both among PLWH in general, as well as in SSA.[85] For example, studies in the United States have under-predicted CVD risk for both CAD and stroke events for PLWH,[162] more pronounced in African Americans.[163] Studies in both Botswana and Uganda have shown only modest correlations between the Framingham Risk Score, the Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score, and the Reynolds Risk Score and presence of pre-clinical atherosclerosis measured with cIMT[165] Consequently, as efforts are made to improve CVD event data collection, an important parallel effort is needed to develop CVD risk prediction models that are better suited to populations of PLWH in SSA.

Health systems and guidelines

Standardized guidelines for the primary prevention of CAD in PLWH have been suggested by a number of international and national bodies. Of the international guidelines, the European AIDS Clinical Society (2008) was among the first to provide guidelines for the prevention and treatment of CVD in PLWH.[166] Recommendations were mostly extrapolated from current general medical guidelines which included assessing CVD risk with the Framingham risk score, measuring fasting lipids regularly, and performing an electrocardiogram annually. Risk categorization into low, moderate and high-risk groups was done identically to the general population. The HIV Medicine Association of the Infectious Diseases Society of America Primary Care Guideline (2013) also addressed coronary artery disease risk specifically for PLWH.[44] In addition to applying the current CAD risk assessment as in the general population (*i.e.*, Framingham risk score), the authors alluded to HIV as an independent risk factor for CVD, leaving the option open for "more aggressive management of lipids". Smoking cessation was strongly encouraged regardless of level of CAD risk, as was annual BP checks, screening for DM, blood lipid measurement after initiation of ART, and avoidance of harmful drug-drug interactions. In 2015, the National Lipid Association conducted a thorough review and addition of HIV-specific recommendations for prevention of CVD and management of dyslipidemia. The review largely concluded that there was insufficient evidence for a unique management profile for this population, aside from ensuring risk screening for all PLWH, and potentially consideration of HIV as an independent CVD risk factor.[167]

More recently, the 2018 EACS Guidelines delved further into the topic of prevention of CVD and risk assessment by specifying targets and treatment algorithms for BP, smoking, coagulation, glucose and lipid management.[168] EACS continues to recommend the Framingham risk score or regional corollary using a >10% 10-year risk threshold for initiation of primary prevention drug therapy, largely keeping

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with the idea of applying assessments and therapies as is the case in the general population. Similarly, the International Association of Providers of AIDS Care (2018) provided protocols for the management of CVD risk, specifying treatment algorithms for HTN, but did not address primary prevention of ASCVD.[169] Finally, in an effort to promote public health practice, the British HIV Association introduced auditable targets, considered to be important areas of patient care, among which includes the proportion of PLWH aged 40 or older with measured 10-year CVD risk using the QRISK2 score, a smoking history and blood pressure measurement.[170,171] In addition, annual screening for HTN, DM and dyslipidemia are recommended for those with >10%, 10-year CVD risk.

Less attention has been paid to primary prevention of CVD risk among PLWH in SSA. The World Health Organization CVD risk charts (2019) were adapted to the circumstances of 21 global regions including four WHO regions in SSA.[172] However, HIV infection was not included in the modeling approach. Most of the national CVD prevention and management guidelines that discuss CVD prevention in SSA do not deviate from the general guidance of other societies, and many countries explicitly follow recommendations from European or American societies. Of guidelines and national strategic plans that were available to review from Ethiopia, Sudan and Kenya,[173,174,175] HIV was not considered as an atherosclerotic CVD risk factor nor were CVD prevention guidelines specific to PLWH.

HIV-specific guidelines for CVD risk factor screening and management vary widely. As an example, in Kenya, guidelines for CVD screening among PLWH are thorough, and mirror those of western settings. These include BP and weight screening at each visit, lipid and fasting glucose assessment prior to ART initiation and annually, and recommendations to stop smoking.[176] In Uganda, risk factor assessment is recommended at baseline, and then at every clinic visit, though DM and HTN are the only CVD risk factors explicitly targeted.[177] By contrast, in South Africa, home to the largest population of PLWH globally, primary care guidelines lack specific recommendations for measurement of these indicators among PLWH, aside from lipid monitoring once every three months after initiation of protease inhibitors.[178] Similarly, the 2018 update to the South African dyslipidemia guideline consensus statement specifically addressed the contribution of HIV to CVD risk. Considering the relatively young age of most PLWH and the paucity of other CVD risk factors, the experts considered South African PLWH to be at low risk for CVD events and recommended lipid management and indications for lipid lowering drugs to be the same as in the general population.[178]

What CVD prevention interventions are most likely to reduce morbidity and mortality in the region?

Multi-level barriers to CVD risk prevention among PLWH in SSA

Studies on primary prevention interventions in PLWH in the region are lacking, but early efforts will first depend on developing the infrastructure necessary to implement interventions as they are shown to be effective. Currently, there are significant barriers to CVD screening and management across the patient, provider, and health systems levels. Early evidence suggests awareness alone presents a major challenge, with only about 50% of PLWH in some settings having adequate knowledge and perception of these conditions.[179] In addition to low awareness, low motivation for management of asymptomatic conditions and poor self-efficacy have been reported.[180,181] There is poor education of health care providers with gaps in initiation and intensification of CVD management.[182–184] Staffing shortages and siloed health care systems also contribute to sub-optimal health systems responses.[185,186] Moreover, complex environmental and societal factors such as transportation and urban planning, as well as food processing, distribution, and marketing impact CVD risk factors.[53] Finally, these patient, provider, and health system factors often interact to thwart CVD care in the region.[187,188] As such, it is unsurprising that large-scale assessments of health system readiness for CVD management in Tanzania and Uganda have shown significant shortages in resources.[190]

As better data on CVD risk among PLWH in SSA accrue, public health efforts to reduce CVD risk in PLWH in SSA should accentuate accomplishing three major public health priorities: 1) early identification of HIV infection and prompt initiation of ART; 2) strengthening health system-based approaches to CVD risk factor measurement at appropriate and routine intervals; and 3) empowerment of patients and health care providers to respond to those with identified risk factors.

Early ART initiation

The increased CVD risk among PLWH decreases as both CD4 nadir and population of CD4+ T cells rise.[129,191–193] This data strongly suggests that at least a proportion of the CVD risk attributable to HIV infection can be mitigated with early ART initiation. Notably, the World Health Organization guidelines and most national guidelines now recommend immediate ART initiation for all PLWH. Efforts to execute these guidelines are paramount. Nonetheless, low CD4 T cell nadirs have proved stubbornly persistent in SSA, despite public health prioritization to provide ART for all PLWH.[194–197]

Routine CVD risk screening

To promote routine screening for CVD risk factors, increased attention to CVD by national health ministries will be required. The diversity of national guidelines for CVD risk assessments described above presents a clear and actionable priority for the region to prioritize and standardize CVD risk assessment and management. Because HIV care is implemented through a public health approach in the region, which is largely determined by national guidelines, such an effort could have far-reaching effects. Moreover, because PLWH in SSA have high rates of contact with the healthcare system (typically seen once every 1–-6 months), there is a unique opportunity to integrate CVD disease screening within HIV care. Early evidence both from community-based programs and in HIV-CVD care co-implementation have demonstrated promising results[198,199], and appears to be cost effective,[200] but will require additional validation outside of academic and research-based partnerships.

Empowering patients and providers to respond to CVD risk

In addition to strengthening CVD guidelines and their implementation, efforts are clearly needed to empower patients and providers to translate such guidelines into health benefits. For such interventions to be sustainable and effective on a population scale, they will likely need to address barriers across the cascade of care. In high-resource settings, such interventions tend to be multi-component, including training and capacity building for health care providers, as well as measures to improve patient adherence and self-efficacy, such as home-based disease monitoring.[201] Unfortunately, early data on interventions that focus on only one strategy, such as nurse training and support, have not shown clinical benefits in the region.[202]

What are the major research gaps that need to be addressed to ensure CVD risk is optimized among PLWH in SSA?

Primary research priorities include development of observational prospective cohort studies that include collection of CVD events to enable determination of CVD epidemiology. These include which events are most common, which traditional, regional, and HIV-specific risk factors have the greatest contributions to them, and identification of intervention points. At least two active studies are specifically designed to address these needs. The Ndlovu Study is enrolling 2000 individuals in the rural Limpopo State of South Africa, mixed by HIV serostatus, into

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a perspective longitudinal cohort study with 6-monthly CVD risk factor, surrogate marker (cIMT, pulse-wave velocity) and clinical outcome data.[203] The UGANDAC study in rural Uganda is enrolling 600 individuals from the Mbarara region[204] mixed by HIV serostatus, and conducting cardiovascular disease risk profiling, local risk factor sampling (*e.g.* personal air pollution monitoring), and conducting computed tomography coronary artery angiography in an attempt to definitively assess the presence of CAD.[137] Ultimately, large, population-based cohorts similar in design, scope, and duration as the Framingham Cohort and inclusive of CVD events will be needed to truly discern the impact of HIV on CVD risk and identify preventative interventions to reduce it.

Interventional studies, including both traditional clinical randomized clinical trials and implementation science designs for health systems evaluations are needed to translate data into public health knowledge. The REPREIVE study is an ongoing randomized clinical trial of statins for primary prevention of CVD in PLWH with low CVD risk. The study includes six sites in SSA across four countries (Uganda, Zimbabwe, Botswana, and South Africa) and has the potential to provide region-specific data on the value of a low-cost and scalable primary prevention of CVD in PLWH in SSA. To translate such interventions, health systems implementation studies are also needed. Pilot studies of such interventions have been conducted, but the implementation science literature on integration of CVD services into HIV care remains under-developed and is an untapped opportunity.[205] The US National Institute of Health; National Heart, Lung, and Blood Institute recent funding opportunity announcement; Heart, Lung, and Blood ComorbiditieS Implementation Models in People Living with HIV (HLB SIMPLe)" (UG3/UH3), is one of such opportunities to implement strategies to deliver proven-effective prevention and treatment interventions for heart, lung, blood, and sleep comorbid diseases and disorders in PLWH.

Conclusions

Despite decades of accrued data on increased CVD risk among PLWH in the United States and Europe, similarly compelling data in SSA remain lacking. Data largely derived from cross-sectional studies suggest the following key points: 1) PLWH in SSA are living longer with ART, and are thus increasingly susceptible to CVD risk factors; 2) regional risk factors, such as low nadir CD4 counts, and exposure to air pollution are likely to differentiate risk factors for CVD in the SSA population; 3) PLWH have similar prevalence of CVD risk factors as people without HIV in the region, some evidence of decreased pre-clinical atherosclerosis as measured by cIMT, but appear to be at increased risk of stroke, particularly prior to ART initiation; 4) traditional CVD risk scores do not perform well (using surrogate markers as outcomes) in PLWH in SSA; and 5) there are a multitude of barriers to CVD risk screening and prevention in SSA across the patient, provider and health system levels that require urgent attention. A variety of study designs are needed to respond to the known gaps in the literature and barriers to care, including large prospective cohort studies with outcome estimation, clinical trials, and implementation science evaluations of health systems interventions. These studies must be adequately powered to demonstrate clinical benefits in SSA and are urgently needed to ensure health systems are designed accounting for regional epidemiology and health system capacities. Until the field takes such strides, optimal methods of CVD risk prevention among PLWH in SSA will remain poorly understood and largely unaddressed.

Declaration of competing interest

SO and RP are supported by a career development grant from the Fogarty International Institute of the National Institutes of Health (K43 TW010715 and K01 TW01281 respectively). MJS receives research support from the National Institutes of Health (R01 AI124718, R01 HL141053, R01 AG059504).

Acknowledgements

All individuals who contributed to this publication have been included as authors.

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Please cite this article as: S. Okello, A. Amir, G.S. Bloomfield, et al., Prevention of cardiovascular disease among people living with HIV in sub-Saharan Africa, Progress in Cardiovascular Diseases, https://doi.org/10.1016/j.pcad.2020.02.004

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Please cite this article as: S. Okello, A. Amir, G.S. Bloomfield, et al., Prevention of cardiovascular disease among people living with HIV in sub-Saharan Africa, Progress in Cardiovascular Diseases, https://doi.org/10.1016/j.pcad.2020.02.004

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Please cite this article as: S. Okello, A. Amir, G.S. Bloomfield, et al., Prevention of cardiovascular disease among people living with HIV in sub-Saharan Africa, Progress in Cardiovascular Diseases, https://doi.org/10.1016/j.pcad.2020.02.004