Cardiovascular disease in women living with HIV: a narrative review

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ABSTRACT

Advances in the treatment of HIV have led to a demographic shift, with increasing numbers of people living with HIV reaching older age. Age-related comorbid conditions, such as cardiovascular disease (CVD) are therefore of increasing importance in HIV clinical practice. Over half the global population of people living with HIV are female. We present a narrative literature review of 39 studies exploring CVD in women living with HIV (WLHIV), with particular reference to coronary heart disease and focusing on: (1) epidemiology, (2) pathophysiology (3) risk factors (including traditional risk factors and HIV-related risk factors), and (4) management. Although we found significant gaps in the literature on CVD in WLHIV, data suggest that HIV increases the risk of CVD in women even more than it does in men, that certain cardiometabolic risk factors (such as obesity and metabolic syndrome) are more prevalent in WLHIV than their male counterparts, and that risk factors such as hyperlipidaemia and hypertension are not optimally managed in this population. Clinicians working with WLHIV therefore need to be aware that this is a patient group at elevated cardiovascular risk, and should be familiar with relevant guidelines.

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1. INTRODUCTION

Of the estimated 34.5 million adults living with HIV globally, over half are female.[1] In the United Kingdom (UK), women represent a quarter of all newly diagnosed HIV infections, with 31,600 women estimated to be living with HIV.[2] Advances in antiretroviral therapy (ART) have resulted in HIV no longer being a life-limiting condition, but one in which those who are well-controlled on treatment can expect a near normal life expectancy.[3] This shift towards long-term survival has resulted in a significant change in the demographic profile of people living with HIV (PLWH), with increasing numbers of PLWH living into older age. In 2016 nearly 25,100 people aged 50 and over attended clinical services for HIV-related care in the UK, a five-fold increase over the past ten years; 8523 (24.5%) were female (Zheng Yin, Public Health England, personal communication, 05/10/17).

Cardiovascular disease (CVD) is an important cause of morbidity and mortality in PLWH. The association between HIV and CVD has long been documented, with studies reporting a 1.5 to 2.0-fold increase in the risk in PLWH, even in the context of virological suppression.[4,5] Furthermore, there is evidence to suggest that intervention rates in acute myocardial infarction are lower in those living with HIV when compared with their seronegative counterparts, and that mortality is higher.[6] The pathophysiology of CVD in HIV is complex, and is driven by a number of factors. These include differences in the prevalence of traditional risk factors (such as smoking, diabetes mellitus and hypertension) when compared to the general population, chronic immune activation and inflammation, effects of ART on lipid metabolism and coagulation, and the direct effects of the virus on the coronary vascular wall.[4]

The prevalence of CVD in women in Great Britain is estimated to be 9.1%, with coronary heart disease (CHD) responsible for 9% of deaths in women in the UK, three times that caused by breast cancer[7]. Oestrogen is cardioprotective, promoting vascular remodelling and having important immune-modulating activity[8]. The menopause, with its consequent oestrogen depletion, therefore significantly attenuates the gender difference in CVD rates.[9] Furthermore, early menopause is an independent predicator of CHD,[10] which may be of particular relevance in HIV given some data suggesting earlier menopause in this patient population.[11] In addition, WLHIV are known to have higher levels of systemic immune activation and inflammation when compared to men living with HIV. This is thought to be due to a combination of behavioural factors (such as cigarette smoking and recreational drug use) and biological factors (such as sex differences in both the immune response to HIV and immunomodulatory effects of ART).[12] This may offer further insight into potential sex differences in CVD among people living with HIV. Given these gender differences, it is therefore important to remember that conclusions drawn from work conducted in predominantly male study populations may not necessarily reflect the outcomes experienced by women living with HIV (WLHIV).

We present a narrative review of literature on CVD in WLHIV, with a particular focus on CHD. Our specific objectives are to summarise data on CVD in WLHIV, focusing on the following: (1) epidemiology, (2) pathophysiology, (3) risk factors (including traditional risk factors and HIV-related risk factors), and (4) management. By synthesising existing literature we aim to identify

gaps in evidence and highlight research priorities, whilst also discussing implications for clinical practice.

2. METHODS

2.1 Data extraction

Two authors (DS and ST) undertook a systematic search of the following electronic library databases in July 2017: PubMed, Embase, and CINAHL. Our aim was to identify original research papers that examined CVD in WLHIV. The search strategy was developed by all authors. The search was restricted to publications in English from 2000 onwards, corresponding to the modern combination active antiretroviral therapy (cART) era and therefore more likely to yield data relevant to contemporary clinical practice. Search terms used to identify literature included: cardiovascular, atherosclero*, heart, angina, coronary, "ischemic heart", "ischaemic heart", myocardial infarction, AMI, MI and ACS, all in combination with HIV or AIDS. We applied these search terms to titles in all databases, and restricted all searches to studies in human adults only.

We selected studies conducted in women where at least one of the study populations was HIV-positive, or studies in HIV-positive populations in which sex-disaggregated data were presented. We attempted to restrict this review to cis-gender women in view of the important differences in sex hormone profile and healthcare access amongst transgender WLHIV, however many studies did not discuss the gender identity of their study populations. All study designs were eligible for inclusion but we excluded studies whose sole focus was novel biomarkers due to limited relevance to current clinical practice. Final selection was discussed by DS and ST until consensus was reached.

Our initial database search identified 1818 documents, reduced to 972 after removing duplicates. On reviewing these abstracts, 70 were selected for full text review, of which 39 presented data on CVD in WLHIV and are included in this review.

3. RESULTS

3.1 Epidemiology of CVD in women living with HIV

Numerous studies have reported a link between HIV infection and CVD, however many papers do not disaggregate data by gender. Among those that do, the effect of gender on the epidemiology of CVD is complex, and dependent on the outcome being measured (Table 1).

One study, a 2014 subgroup analysis of the US Veteran's Aging Cohort Study, compared CVD prevalence in WLHIV and HIV-negative women. The study found that HIV infection was associated with a higher incidence of cardiovascular events (acute MI, unstable angina, heart failure or ischemic stroke), and that WLHIV experienced these events earlier within the follow-up period.[13] Seven studies investigating CVD incidence and prevalence in mixed-sex cohorts, all found increased cardiovascular events in HIV-positive men when compared to WLHIV.[14–20]

However, the three that compared these data to data from HIV-negative populations (one using an HIV-negative comparison group, the other two referring to general population data) found that the increased prevalence of cardiovascular events seen among PLWH was more pronounced in female study participants, suggesting that the increased risk of CVD conferred by HIV may be even higher in women.[15,17,19]

3.2 Pathogenesis of CVD in women living with HIV

In studies directly comparing HIV-positive men and women, men have been found to be at greater risk of increased carotid intimal thickness (cIMT) and coronary artery stenosis (Table 2).[21,22] Data on the association between HIV and markers of pre-clinical atherosclerosis in WLHIV are somewhat conflicting. One study found an association between HIV infection and increased coronary plaque,[23] while three others report the opposite [24–26], with one analysis of South-African data finding carotid intimal media thickness to be associated with traditional, rather than HIV-related, risk factors.[25] An analysis of a US mixed cohort (comparing HIV-positive people to HIV-negative controls) found HIV to be associated with similarly increased rates of plaque formation in men and women.[27] In addition, a subgroup analysis of the US Women's Interagency HIV Study (WIHS)—an ongoing, twenty-year, prospective cohort analysis of nearly four thousand HIV-positive women and HIV-negative 'at risk' women — found the association between hyperlipidemia and atherosclerosis to be strongest in women taking cART.[28] Although few data exist on microvascular disease in WLHIV, a 2013 study found higher levels of microvascular endothelial dysfunction and microvascular tension in WLHIV compared to age- and ethnicity-matched HIV-negative controls. [29]

Circulating markers of inflammation have been reported to be higher in WLHIV than in their HIV-negative counterparts (as is also the case in HIV-positive men), potentially indicating a mechanism for the observed increase in cardiovascular risk [23,30,31]. Looking specifically at sex steroid hormone profile, a subgroup analysis of WIHS found pre-menopausal WLHIV to have significantly lower levels of serum testosterone and oestradiol than HIV-negative women, both correlating with markers of arterial disease.[32] However, a more recent US study reports comparable oestradiol and anti-Mullerian hormone levels in HIV-negative and HIV-positive women.[33] There were no studies that linked any of these biological markers to clinical endpoints in women living with HIV.

3.3 Traditional risk factors for CVD

Eleven studies assessed the prevalence of traditional CVD risk factors (such as hypertension, diabetes mellitus and obesity) among WLHIV (Table 3).[16,34–41] Studies conducted in a variety of geographical regions found that WLHIV were significantly more likely to have a raised body mass index when compared to HIV-positive men,[37,39,41] or HIV-negative women.[30] Metabolic syndrome (MS) also appears to be more prevalent in WLHIV, with studies from Uganda and France finding an association between female gender and MS. [35,39]

Seven studies investigated the Framingham Risk Score (FRS) scores of people living with HIV, with differing results. Two studies comparing HIV-positive men and women found FRS to be significantly higher among HIV-positive men.[42,43] Similarly, analyses of the international D:A:D (Data Collection on Adverse Effects of Anti HIV Drugs) Study cohort report a higher FRS in HIV-positive men,[43] and that the increase in prevalence of CVD risk factors amongst D:A:D participants between 1999 and 2006 (seen in both men and women) was significantly greater in men.[44] In contrast, data from Brazil found female sex to be highly predictive of intermediate to high FRS,[36] while analysis of a US cohort found no difference in cardiovascular risk between genders.[45] A 2012 cross-sectional study amongst African-American WLHIV report a 10-year Framingham risk score comparable to previously published scores for HIV-negative African-American women,[46] however a comparison of postmenopausal HIV-positive and HIV-negative female cohorts found that HIV had no effect on FRS. [47]

3.4 HIV-related factors and CVD risk

Five studies focused on the contribution of HIV-related factors to CVD risk in WLHIV (Table 4).[27,41,47–49] Three explored the association between CVD risk and CD4 count (a marker of immunosuppression in HIV), reporting conflicting findings.[27,41,48] Investigation of a gender mixed Kenyan cohort, found CD4 count>200 cells/mm^3 to be associated with an increase in cardiovascular risk [41], while two US cohort studies, both combined analyses of the WIHS and MACS (a thirty-year, prospective cohort analysis of nearly seven thousand HIV-positive men and HIV-negative 'at risk' men) cohort studies found higher CVD risk in people with a CD4 count of <200 cells/mm^3.[27,48] No studies report HIV-related factors impacting on CVD risk differentially in WLHIV and HIV-positive men, although older age at HIV diagnosis has been found to be associated with increased CVD risk in post-menopausal WLHIV.[47] Only one study has specifically investigated the association of ART regimen with CVD risk factors in WLHIV. A multicentre cohort study in WLHIV in Sub-Saharan Africa found that nevirapine-based ART was associated with an increase in high density lipoprotein (HDL) cholesterol and triglycerides —both of which increase CVD risk — while lopinavir/ritonavir-based ART was associated with an increase in diastolic blood pressure.[49]

3.5 Management of CVD in WLHIV

There are very little data on the management of CVD in women living with HIV (Table 5). Two studies that compared WLHIV with HIV-positive men concluded that women are undertreated for CVD risk factors such as dyslipidaemia and hypertension, [44,47] despite one study finding that understanding of CVD risk among people living with HIV did not differ by gender.[50] This under-treatment includes lower rates of invasive cardiovascular procedures, and decreased initiation of lipid-lowering drugs and anti-hypertensives.[44,47] When comparing WLHIV with HIV-negative women, a 2016 analysis of the WIHS cohort found that hypertensive and glycaemic control were better among WLHIV but that improvements in prevention were needed in both groups, particularly for behavioural factors such as smoking cessation (which did not differ by serostatus).[51]

CONCLUSION

Improvements in the treatment of HIV, and consequently life expectancy, mean that people living with HIV are now living into middle and older age. The future of HIV care will therefore increasingly involve the management of age-related comorbidities such as cardiovascular disease.

In the general population, cardiovascular disease is often under-recognised and under-treated in women. This is of particular concern for women ageing with HIV, given the recognised association of HIV with cardiovascular disease. Although the existing body of evidence is somewhat conflicting, data suggest that HIV increases the risk of CVD in women even more than it does in men, that certain cardiometabolic risk factors (such as obesity and metabolic syndrome) are more prevalent in women living with HIV than their male counterparts, and that risk factors such as dyslipidaemia and hypertension are not optimally managed in women living with HIV (as is often also the case in HIV-negative women). It is also important to note that the presentation of CVD may be up to a decade later in women than men.[52] This may artificially inflate differences in reported prevalence and perceived risk of CVD between men and women, particularly when examining cohorts of PLWH who tend to be younger than the general population.

This review highlights the paucity of data on the pathogenesis, risk factors and management of CVD in women living with HIV. The data that exist are predominantly from the US, raising questions about their applicability to other settings (including resource-rich settings such as the UK where the ethnicity of WLHIV, and access to healthcare are different). Furthermore, few studies have been conducted in populations over the age of 50, in whom CVD risk and prevalence would be expected to be greatest. Therefore, it is clear that research priorities in HIV in women include identifying appropriate CVD screening, understanding the sex-specific drivers of CVD risk in HIV, and the development of interventions that address and modify CVD risk in WLHIV. Potential future directions of research in WLHIV include the identification of biomarkers that predict CVD risk in WLHIV, investigation of the role of menopausal hormone therapy as primary prophylaxis for CVD, and the development of behavioural interventions to modify CVD risk in WLHIV. Furthermore we call for longitudinal studies of women ageing with HIV, and more data from non-US populations including sub-Saharan Africa.

Three of this review's authors (AW, CS, and ST) lead large UK multicentre studies exploring HIV and ageing that include women. The POPPY Study (Pharmacokinetic and Clinical Observations in People Over Fifty, https://clinicaltrials.gov/ct2/show/NCT01737047) has recruited 699 HIV-positive people aged ≥50 years (12.0% WLHIV), 374 HIV-positive people aged <50 years (19.3% WLHIV), and 304 lifestyle and demographically similar HIV-negative people aged ≥50 years (36.0% women). The study is the first large-scale study to assess the clinical outcomes and healthcare needs of both men and women living with HIV over the age of 50 in England and Ireland. The PRIME Study (Positive Transitions Through the Menopause) has recruited 970 WLHIV aged 45-60 years to explore the impact of the menopause transition on the health and well-being of WLHIV (www.ucl.ac.uk/prime-study). We hope that both studies will contribute to a greater understanding of HIV and ageing in women, including comorbid conditions such as CVD,

and to the development and implementation of evidence-based recommendations for the optimal management and clinical monitoring of WLHIV.

Clinicians working with WLHIV need to be aware that this patient group may be at elevated cardiovascular risk. European HIV guidelines advise two-yearly screening for CVD risk in PLWH aged >50 years.[53] Current British HIV Association (BHIVA) guidelines recommend annual measurement of lipids and HbA1c in patients who are over the age of 40 years, smokers, and/or have a body mass index >30. For those with established CVD or at increased risk of CVD (10 year CVD risk >10%), BHIVA advises annual screening for hypertension, diabetes, dyslipidaemia and chronic kidney disease, and annual review of BMI, smoking status and ART regimen.[54] Cardiovascular risk factors and disease in WLHIV should be appropriately and pro-actively managed, with close liaison between HIV physicians, cardiologists and primary care.

Contributors

ST and DS designed the literature search and drafted the first version of this article. Both ST and DS selected the final studies to be included in this review. All authors critically reviewed the first version of the article and approved the final draft for publication.

Conflicts of interest

ST has previously received a travel bursary funded by Janssen-Cilag through the British HIV Association, and speaker honoraria and funding for preparation of educational materials from Gilead Sciences. ST and CS are members of the steering group of SWIFT, a networking group for people involved in research in HIV and women, funded by Bristol Myers Squibb. CS has received funding for membership of Data Safety and Monitoring Boards, Advisory Boards, speaker panels and for preparation of educational materials from Gilead Sciences, ViiV Healthcare and Janssen-Cilag. PWGM has received funding for Advisory Boards, speaker panels, preparation of educational materials and/or research grants to his institution from Gilead Sciences, ViiV Healthcare, BMS, MSD, Abbvie and Janssen-Cilag.

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Table 1: Epidemiology of cardiovascular disease in women living with HIV

Reference	Aims	Sample	Design	Outcomes measured	Findings
[13]	To assess HIV as an independent risk factor for CVD in women by comparing CVD incidence in HIV-positive and HIV-negative women	USA HIV-negative and HIV-positive All female Mean age: HIV-positive 43.2, HIV-negative 44.0	Subgroup analysis of Veteran's Aging Cohort Study	CVD (Acute MI, unstable angina, ischemic stroke, or congestive heart failure)	• Higher incidence of CVD in HIV-positive women when compared to HIV-negative women. • Shorter time to cardiovascular event in HIV-positive women.
[14]	To predict CVD risk within HIV-positive cohort using D:A:D model	20 countries (Europe and Australia) All HIV-positive 28% female Median age: 39	Prospective cohort	CVD events (MI, stroke, invasive procedures)	• Male gender associated with increased CVD events.
[15]	To assess MI risk among an HIV-positive cohort	Italy HIV-positive (comparing with general population data) 29% female Mean age: 38.1	Retrospective cohort Review of notes within local health authority	CVD events (coronary artery disease including coronary bypass and angioplasty, MI, congestive heart failure, and cerebrovascular accident or stroke)	• HIV conferred higher risk of cardiovascular events in women.
[16]	To assess the effect of obesity on demographic differences in risk among HIV-positive patients	USA HIV-positive 33% female Median age: 44.3	Observational cross-sectional study nested in clinic cohort Disaggregate race and gender analyses	Measurement of demographic and physiological factors and clinical recording of dyslipidaemia, diabetes mellitus, hypertension, chronic kidney disease, cardiovascular disease	• Being white and male associated with increased incidence of MI.
[17]	To assess incidence of myocardial infarction in French HIV-positive population	France HIV-positive (comparing with general population data) 10% female	Nested case-control study French Hospital Database on HIV	MI	• HIV-positive serostatus associated with increased risk of MI • HIV confers higher risk of MI in women.
[18]	To assess the pattern of CVD mortality within an HIV-positive cohort over 14 years	USA HIV-positive 50% female	Epidemiologic study Population analysis using CDC Wide-Ranging Online Data for Epidemiologic Research (WONDER) database	"Diseases of the circulatory system" (International Classification of Diseases (ICD)10 codes I00 to I99) as underlying cause of death	• Increase in proportionate CVD mortality between 1999 and 2013 in both men and women, but greater in men ($\beta = 0.0022$ in men, compared to $\beta = 0.011$ in women).

Table 1: Epidemiology of cardiovascular disease in women living with HIV continued

Reference	Aims	Sample	Design	Outcomes measured	Findings
[19]	To determine MI rates and CVD risk in HIV-positive patients, in comparison to non-HIV-positive patients	USA HIV-negative and HIV-positive 30% female Median age 38	Observational cohort	Acute MI	• HIV conferred higher risk of acute MI in women.
[20]	To determine risk factors for CVD-related morbidity and mortality in HIV-positive cohort	Brazil All HIV-positive 35% female Median age 37	Longitudinal Retrospective analysis of hospital notes	Hospitalisation or death related to cardiovascular disease	• Male gender associated with increased CVD-related morbidity and mortality.

CVD, cardiovascular disease; MI, myocardial infarction.

Table 2: Pathogenesis of cardiovascular disease in women living with HIV

Reference	Aims	Sample	Design	Outcomes measured	Findings
[21]	To characterise traditional and novel risk factors for coronary artery disease in HIV-positive African Americans	USA All HIV-positive African American 37% female Mean age 46	Cross-sectional study	Coronary artery stenosis (measured using coronary CT angiography)	• Male gender associated with coronary artery stenosis.
[22]	To describe prevalence of markers for subclinical atherosclerosis in HIV-positive adults.	Uganda All HIV-positive 26% female Mean age 45 (male) 42 (female)	Cross sectional study	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• Higher c-IMT in HIV-positive men. • In HIV-positive women, predictors of higher c-IMT were age, systolic blood pressure, and diastolic blood pressure.
[23]	To assess the variation in coronary plaque between HIV-positive and negative women	USA HIV-negative and HIV-positive All female	Cohort study with CT angiography, measurement of metabolic, biochemical, immunologic and body composition parameters, flow cytometry	Coronary plaque (measured using coronary CT angiography), CD4+ and CD8+ T-cell counts, markers of immune activation	• HIV associated with increased non-calcified coronary plaque and immune activation.
[24]	To assess association between HIV/ HCV coinfection and c-IMT	USA HIV-negative and HIV-positive All female Mean age 48 (co-infected), 49 (HCV mono-infected), 39 (HIV mono-infected), 36 (uninfected)	Cohort study – sub-study of WIHS	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• No association between HCV infection and greater c-IMT, regardless of HIV status.
[25]	To investigate the association between subclinical atherosclerosis and HIV-related and traditional cardiovascular risk factors in HIV-positive people	South Africa All HIV-positive 69% female Mean age 40.7	Cross sectional study	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• Traditional CVD risk factors associated with increased c-IMT, rather than HIV-related factors.
[26]	To characterise risk factors for atherosclerosis in HIV-positive women	USA HIV-negative and HIV-positive All female Mean age 42	Cohort study – sub-study of WIHS	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• HIV not associated with c-IMT.

Table 2: Pathogenesis of cardiovascular disease in women living with HIV continued

Reference	Aims	Sample	Design	Outcomes measured	Findings
[27]	To assess the association between HIV infection and markers of subclinical atherosclerosis	US HIV-negative and HIV-positive Combined sub-study of 55% female Mean age 40 (women) 49 (men)	Seven-year cross-sectional analysis of two cohort studies	c-IMT (measured using high-resolution B-mode carotid artery ultrasound) New plaque formation (defined as an area with localized IMT >1.5mm)	• HIV associated with increased risk of plaque formation in both women and men.
[28]	To measure associations between serum lipids and sub-clinical markers of atherosclerosis in HIV-positive and negative women	USA HIV-negative and HIV-positive All female Mean age 38.0 (HIV-negative) 40.4 (HIV-positive, untreated) 42.2 (HIV-positive, treated)	Cohort study – sub-study of WIHS	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• Among HIV-positive women, hyperlipidaemia has the strongest association with subclinical atherosclerosis in those on ART, especially earlier in the disease course.
[29]	To compare microvascular relaxation and endothelial damage between HIV-positive and negative pre-menopausal African-American women	USA HIV-negative and HIV-positive All female Mean age 39 (HIV-negative) 41 (HIV-positive)	Cohort study – sub-study of Metropolitan Washington Women's HIV Study Group (WHIS)	Small vessel contraction and relaxation – measured using small-vessel myography of samples from gluteal biopsy	• HIV was associated with increased endothelial damage and microvascular contraction.
[30]	To investigate CVD risk indices in HIV- positive women	USA HIV-negative and HIV-positive All female Mean age 41 (HIV-positive), 40 (HIV negative)	Cohort study	C-reactive protein (CRP), IL-6, adiponectin, LDL (low-density lipoprotein), HDL (high-density lipoprotein), total cholesterol and glucose	• HIV associated with elevated CRP, IL-6, triglyceride, 2-hour glucose, fasting insulin, and 2-hour insulin concentrations.
[31]	To assess the association between HIV infection and markers of subclinical atherosclerosis in women	USA HIV-negative and HIV-positive All female Median age 37	Cross-sectional study – sub-study of WIHS	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• Inflammatory markers higher in pre-HAART women when compared to HIV-negative women. • Greater c-IMT associated with higher levels of IL-2, IL-6, D-dimer and MCP-1 after ART initiation, but other inflammatory markers normalise with treatment.

Table 2: Pathogenesis of cardiovascular disease in women living with HIV continued

Reference	Aims	Sample	Design	Outcomes measured	Findings
[32]	To compare serum gonadotropin and sex steroid levels between HIV-positive and negative women	USA HIV-negative and HIV-positive All female Mean age (HIV-positive) 38, (HIV negative) 39 Premenopausal women	Cohort study – sub-study of WIHS	c-IMT (measured using high-resolution B-mode carotid artery ultrasound) and arterial distensibility (calculated using distensibility index with IMT as primary variable)	• Lower E2, T, and DHEAS levels and higher SHBG levels among the HIV-positive women. • Higher T level associated with greater arterial distensibility. • Higher E2 level associated with greater distensibility among immunocompromised women.
[33]	To investigate the correlation between subclinical coronary atherosclerotic plaque and degree of ovarian reserve and menopause status	USA HIV-negative and HIV-positive All female Mean age: 40 (premenopausal), 47 (premenopausal, reduced ovarian reserve), 52 (postmenopausal)	Cohort study	Subclinical atherosclerosis (measured using contrast-enhanced coronary computed tomography angiography)	• HIV not associated with AMH, E2, and FSH levels. • Decreased AMH associated with increased immune markers and subclinical coronary atherosclerotic plaque regardless of HIV status.

CVD, cardiovascular disease; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; c-IMT, coronary intimal media thickness; IL-6, interleukin-6; HCV, Hepatitis C virus; WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study; ART, antiretroviral therapy; E2, oestradiol; T, testosterone; DHEAS, dehydroepiandrotestosterone; SHBG, sex hormone binding globulin; AMH, anti-Müllerian hormone

Table 3: Traditional risk factors for cardiovascular disease in women living with HIV

Reference	Aims	Sample	Design	Outcomes measured	Findings
[16]	To assess the effect of obesity on demographic differences in risk among HIV-positive patients	USA All HIV-positive 33% female Median age 44.3	Observational cross-sectional study nested in a clinic cohort study	Measurement of demographic and physiological factors and clinical recording of dyslipidaemia, diabetes mellitus, hypertension, chronic kidney disease, cardiovascular disease	• Highest prevalence of dyslipidaemia in white men. • Highest prevalence of hypertension and diabetes in Black women.
[30]	To investigate CVD risk indices in HIV-positive women	USA HIV-negative and HIV-positive All female Mean age 41 (HIV-positive), 40 (HIV negative)	Cohort study	C-reactive protein (CRP), IL-6, adiponectin, LDL (low-density lipoprotein), HDL (high-density lipoprotein), total cholesterol and glucose	• HIV associated with elevated C-reactive protein (CRP), interleukin-6, triglyceride, glucose and insulin concentrations. • HIV associated with lower total body fat, extremity fat, subcutaneous abdominal fat area, and hip circumference. • HIV associated with higher abdominal visceral fat area.
[34]	To investigate the relationship between abuse, nocturnal cortisol/norepinephrine and CVD risk in HIV-positive women	USA All HIV-positive All female Mean age 48	Cross-sectional analysis – sub-study of WIHS	CVD risk (using FRS), and urinary NE and cortisol	• Higher CVD risk associated with history of abuse. • Higher CVD risk associated with lower cortisol and higher NE/cortisol ratio.
[35]	To assess the impact of treatment and Western lifestyle on incidence of metabolic syndrome in HIV-positive patients	France/Cote D'Ivoire All HIV-positive 61.4% female (CI), 50.7% female (France) Mean age 35.7 (CI) 36 (France)	Cohort study	Incidence of metabolic syndrome, insulin resistance, and lipodystrophy (via measurement of demographic and physiological factors including blood pressure, weight, height, and anthropometric measurements, protein electrophoresis, amylase, lactate and fasting glucose)	• Female gender highly predictive of metabolic syndrome regardless of country of residence.
[36]	To investigate CVD risk among HIV-positive cohort	Brazil All HIV-positive 39.9% female Mean age 39.0	Ten-year cross-sectional analysis of three cohort studies	CVD risk (using FRS)	• Female sex predicts intermediate or high FRS.

Table 3: Traditional risk factors for cardiovascular disease in women living with HIV continued

Reference	Aims	Sample	Design	Outcomes measured	Findings
[37]	To investigate the prevalence of CVD risk in HIV-positive population	Brazil All HIV-positive 43% female Mean age: 43.05 (NNRTI), 42.22 (PI), 38.66 (untreated)	Cross-sectional study	BMI, waist circumference, CVD risk measured using waist circumference, as per WHO guidelines	• Female gender associated with obesity (BMI >30). • 77.5% of women had increased CVD risk (33% of men). • 51.4% of women had very high CVD risk (9.4% of men).
[38]	To investigate the effect of pregnancy on CVD in HIV-positive women	Italy HIV-negative and HIV-positive All female Median age: 32.5 (HIV-positive), 33 (HIV negative)	Longitudinal cohort study	Brachial artery diameter and flow-mediated vasodilation	• Pregnancy did not affect flow-mediated vasodilation or brachial artery diameter in women, regardless of HIV status.
[39]	To investigate the distribution of CVD within HIV-positive population	Uganda All HIV-positive 68% female Median age: 36	Cross-sectional study	CVD risk (using FRS)	• Metabolic syndrome associated with female gender. • Obesity more prevalent in women than men (16.6% vs 2.4%). • CVD risk > 5% more prevalent in men than women (26% vs 13%).
[40]	To investigate the relationship between CVD, depression and HIV	US HIV-negative and HIV-positive All female Mean age: HIV-positive 35.8, HIV-negative 34.6	Cross-sectional analysis – sub-study of WIHS	CVD risk (using FRS)	• Chronic depressive symptoms associated with higher FRS, regardless of HIV status.
[41]	To assess prevalence of CVD risk factors within HIV-positive population	Kenya All HIV-positive 65% female Mean age 43 (men) 40 (women)	Cross-sectional study	Record of traditional CVD risk factors (diastolic blood pressure>90 mmHg, systolic blood pressure>140 mmHg, BMI)	• Women more likely to have raised BMI but less likely to be hypertensive.

Table 3: Traditional risk factors for cardiovascular disease in women living with HIV continued

Reference	Aims	Sample	Design	Outcomes measured	Findings
[42]	To determine CVD risk within HIV-positive population and assess role of HAART	UK All HIV-positive 34% female Mean age 41 years	Cross sectional Measurement of anthropometric, physiological and biochemical parameters	CVD risk (using FRS)	• CVD risk > 20% in 1% of women and 6% of men. • CVD risk > 10% in 4% of women and 12% of men.
[43]	To model 3-year myocardial infarction risk within HIV-positive population	International All HIV-positive 25% female Mean age 39	Subgroup analysis of the D:A:D cohort	MI risk (using risk equations based on FRS)	• MI risk greater for men than women (0.92% vs. 0.07%).
[44]	To evaluate changes in risk factors for CVD in HIV-positive individuals between December 1999 and February 2006	International All HIV-positive 25% female Median age 36 – 43 (six distinct calendar periods)	Large observational study combining 11 cohorts of HIV-positive patients across Europe, US and Australia	CVD risk factors (based on the American National Cholesterol Education Program guidelines)	• Increase in CVD risk factors over time in both men and women. • Increase more pronounced in men (40.1% to 47.8% in men; 20.4% to 22.9% in women).
[45]	To investigate CVD risk among HIV-positive cohort	US HIV-negative and HIV-positive 50% female Mean age: HIV-positive women 42, HIV-negative women 37.8	Cross-sectional analysis of two cohort studies	CVD risk (using FRS)	• Proportion with medium and high risk for CVD similar in women and men (2% and 12% for women; 2% and 17% for men). • CVD risk factor profile similar in women and men.
[46]	To assess CVD risk in female African-American HIV-positive population	USA All HIV-positive All female Average age 42	Cross-sectional study Notes review	CVD risk (using FRS)	• Average 10 year CVD risk = 7.6 (comparable to previously published scores for HIV-negative African-American women).
[47]	To compare CVD risk in HIV-positive and negative postmenopausal minority women	US HIV-negative and HIV-positive All female Mean age 56 (HIV-positive) 60 (HIV negative)	Cross-sectional analysis of cohort study	CVD risk (using FRS)	• HIV status did not affect FRS score. • 10% of HIV-positive women and 8% of HIV-negative women with an established history of CVD had FRS of <10%.

CVD, cardiovascular disease; FRS, Framingham Risk Score; BMI, body mass index; NE, norepinephrine; MS, metabolic syndrome; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study

Table 4: HIV-related factors and cardiovascular risk in women living with HIV

Reference	Aims	Sample	Design	Outcomes measured	Findings
[27]	To assess the association between HIV infection and markers of subclinical atherosclerosis	US HIV-negative and HIV-positive 55% female Mean age 40 (women) 49 (men)	Seven-year cross-sectional analysis of two cohort studies	c-IMT (measured using high-resolution B-mode carotid artery ultrasound) New plaque formation during the study period (defined as an area with localized IMT >1.5mm)	• Baseline CD4<200 associated with higher risk of new focal plaque formation.
[41]	To assess prevalence of CVD risk factors within an HIV-positive population	Kenya All HIV-positive 64.8% female Mean age 43 (men) 40 (women)	Cross-sectional study	Record of traditional CVD risk factors (diastolic blood pressure>90 mmHg, systolic blood pressure>140 mmHg, BMI)	• CD4>200 associated with increased CVD risk in both women and men.
[47]	To compare CVD risk in HIV-positive and HIV-negative postmenopausal minority women	US HIV-negative and HIV-positive All female Mean age 56.2 (HIV-positive) 60.0 (HIV negative)	Cross-sectional study	CVD risk (using FRS)	• Older age at HIV diagnosis and higher CD4 count associated with increased CVD risk.
[48]	To assess relationship between CD4 count/viral load and atherosclerosis risk	US HIV-negative and HIV-positive 67% female No median/mean age available	Cross-sectional analysis of two cohort studies	c-IMT (measured using high-resolution B-mode carotid artery ultrasound)	• CD4<200 associated with increased prevalence of carotid lesions in women and men. • No association between duration of PI use and carotid lesions in women.
[49]	To assess CVD risk in HIV-positive cohort after initiation of antiretroviral therapy	7 African countries All HIV-positive All female Mean age 33.5	Cohort study nested within open-label ART trial	TC, HDL-C, LDL-C, TG, systolic and diastolic blood pressures and BMI	• Nevirapine-based ART associated with increase in HDL and TG. • Lopinavir/ritonavir-based ART associated with increase in diastolic blood pressure.

CVD, cardiovascular disease; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; c-IMT, coronary intimal media thickness; TC, total cholesterol; WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 5: Management of cardiovascular disease in women living with HIV

Reference	Aims	Sample	Design	Outcomes measured	Findings
[44]	To evaluate changes in risk factors for CVD in HIV-positive individuals between December 1999 and February 2006	International All HIV-positive 25% female Median age 36 – 43 (six distinct calendar periods)	Large observational study combining 11 cohorts of HIV-positive patients across Europe, US and Australia	CVD risk factors (based on the American National Cholesterol Education Program guidelines)	• Male sex associated with more rapid initiation of lipid-lowering therapy.
[47]	To compare CVD risk in HIV-positive and HIV-negative postmenopausal minority women	US HIV-negative and HIV-positive All female Mean age 56 (HIV-positive) 60 (HIV negative)	Cross-sectional study	CVD risk (using FRS)	• Low prescription rate for statin therapy in both HIV-positive and HIV- negative women who met diagnostic criteria (statins prescribed in 52% of HIV-positive women with dyslipidaemia vs. 67% of HIV-negative women with dyslipidaemia).
[50]	To assess knowledge of CVD risk factors and risk perception within HIV-positive population	US All HIV-positive 38% female Average age 48 years (type of average not specified)	Cross-sectional study	Estimated risk of CVD (using FRS), CVD risk perception, CVD risk factor knowledge	• No significant difference in perceived risk or risk factor knowledge by gender.
[51]	To evaluate non-lipid CVD risk factor management and relationship to ART adherence in HIV-positive women	US HIV-negative and HIV-positive All female Median age 49	Cross-sectional analysis – sub-study of WIHS	Hypertensive sub-group: hypertensive treatment (use of antihypertension medications within the past 6months), and hypertension control (SBP <140mmHg or DBP <90mmHg) Diabetic sub-group: diabetes treatment (use of antidiabetic medications with the past 6 months) and diabetes control (fasting glucose level <130mg/dL)	• Antihypertensive treatment higher in HIV-positive women (77% vs 67%). • Fasting glucose better in HIV-positive women (73% vs 64% within recommended range). • No difference in smoking cessation rate by HIV serostatus.

CVD, cardiovascular disease; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglycerides; c-IMT, coronary intimal media thickness; TC, total cholesterol; WIHS, Women's Interagency HIV Study; MACS, Multicenter AIDS Cohort Study; SBP, systolic blood pressure; DBP, diastolic blood pressure