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Review of Cardiovascular Disease in HIV-Infected Women

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Abstract

Rates of coronary heart disease (CHD) are over twice as high in younger HIV-infected patients compared to uninfected patients, but most of these studies were conducted in men or in predominantly male cohorts. In the general population, the death rate from CHD has decreased among men, but continues to increase in women. It is unclear if the same increased rate of deaths due to CHD exist in HIV-infected women, and whether rates or risk of CHD differ between HIV-infected men and women, and between seropositive and seronegative women. We reviewed the literature on the rates of cardiovascular events and surrogate measures of atherosclerosis or CHD risk in HIV-infected women. We also reviewed rates of metabolic disease and other markers of inflammation and immune activation that could contribute to increased cardiovascular risk. We found that HIV-infected women have increased rates of acute myocardial infarctions and ischemic strokes compared to HIV-uninfected women and likely HIV-infected men despite women being projected to have lower CHD risk based on Framingham risk scores. Studies assessing CHD risk by measuring anatomical or physiological measures of subclinical atherosclerosis have reported mixed results, and there are no well-validated risk assessment tools or surrogate measures of subclinical CHD among HIV-infected patients to help identify high-risk women for targeting intensive preventive measures. Potential explanations for the increased rates of CHD and subclinical atherosclerosis may be partly explained by increased levels of inflammation and immune activation in HIV-infected women despite virological suppression on antiretroviral therapy. It appears unlikely that disproportionate representation of traditional CHD risk factors and metabolic indices among HIV-infected women can explain well the observed increased rates of CHD. Future studies that include large numbers of HIV-infected women with extended follow-up periods using surrogate measure of CVD and investigating pathogenic mechanisms underlying these observations are urgently needed.

Keywords: Cardiovascular disease and HIV and women; Subclinical cardiovascular disease and HIV and women; HIV and cardiovascular disease risk; Coronary heart disease and HIV and women; Acute myocardial infarction and HIV and women; Framingham risk and HIV and women; HIV and women; HIV/AIDS

Introduction

Individuals infected with Human Immunodeficiency Virus (HIV) are now living longer due to improved and expanded access to antiretroviral therapy (ART). However, all-cause mortality rates continue to be higher in HIV-infected patients than in the general population and there has been an increased percentage of non-AIDS-defining illnesses [1]. Coronary heart disease (CHD) represents the second cause of death among HIV-infected patients currently, and is expected to increase as the population ages [2].

Numerous studies report increased risk of CHD in HIV-infected people, but most of these studies were conducted in men or in predominantly male cohorts [3-5]. In the general population, men have been reported to have higher rates of CHD and at younger age than women [6,7]. The death rate from cardiovascular disease (CVD) has decreased among men, but continues to increase in women [8]. Recent statistics show that 42 percent of women who have heart attacks die within one year compared with 24 percent of men. As such, there has been increased attention in the scientific community as well as the general media surrounding missed opportunities to accurately diagnose CHD early and intervene in timely manner among women. It is unclear if the same increased rate of deaths due to CHD exist in HIV-infected women, and whether rates or risk of CHD differ between HIV-infected men and women, and between seropositive and seronegative women.

The purpose of our review was several-fold. We reviewed the literature on the rates of cardiovascular events and surrogate measures of atherosclerosis or CHD risk in HIV-infected women. We also reviewed rates of metabolic disease and other markers of inflammation and immune activation that could contribute to increased cardiovascular (CV) risk.

Methods

We searched PubMed and Embase for English-language articles published from January 1, 2005 – October 27th, 2015 using search terms "Cardiovascular disease, HIV, Women," "Coronary heart disease, HIV, Women," "Framingham risk and HIV and women," "Acute MI, women, and HIV," and "Acute myocardial infarction, HIV, and women. We also searched using terms "Carotid intimal thickness, HIV, women" and "Coronary atherosclerosis, HIV, women." A total of 323 references were found, but 213 references were not selected because they were abstracts, poster presentations, correspondences, letters, or other report types. 76 more studies were excluded after reading the abstracts because they did not have findings specific to HIV-infected women. Four studies were removed from the review because they did not contribute any additional information than those included. Four were reviewed in the manuscript text but not included in the tables because they reported sample sizes of less than 100 participants. 12 relevant studies were included from references of selected manuscripts.

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A total of 37 full-length articles were included in the final review (Figure 1). Of note, there were two studies included in our review that reported on more than one end point, and therefore they appear in more than one table. Selected studies were presented in the tables and the remainder were described in the section corresponding to the relevant endpoint or risk factor for CHD discussed.

Study designs included one randomized clinical trial, 13 prospective observational cohorts, one retrospective analyses, 18 cross-sectional studies, and four case-control studies. Endpoints assessed were: CHD incidence and mortality, risk scores to assess risk for developing CVD, anatomical and physiological surrogate markers of CVD including carotid intimal media thickness (CIMT), pulse wave velocity (PWV), computed tomography coronary angiography (CTA) and ankle-brachial index (ABI), biomarkers of CVD, and alterations of the metabolic profile. Adjusted odds ratio (OR), hazard ratio (HR), relative risk (RR), along with associated confidence intervals (CI) and p-values were extracted and reported from all studies whenever available.

Results

Clinical outcomes

The cardiovascular events reported in studies include acute myocardial infarction (AMI), unstable angina, ischemia heart failure, and ischemic stroke. Table 1 summarizes the six studies that reported clinical cardiovascular outcomes in HIV-infected women. In a study from the Partners HealthCare System of 3851 HIV-infected patients including 1172 women, there was RR of 2.98 (95% CI 2.33, 3.75; p<0.0001) of developing AMI for HIV-infected women compared to seronegative women whereas HIV-infected men had RR of 1.40 (95% CI 1.16, 1.67; p=0.0003) compared to seronegative men [9]. The Veterans Aging Cohort Study that included 2187 HIV-infected women demonstrated that incident CHD per 1000 person-years was significantly higher among HIV-infected women with incident rate (IR) 13.5 (95% CI 10.1, 18.1) compared to uninfected women with IR 5.3 (95% CI 3.9, 7.3; **p**<0.001). In addition, the median age to first CHD event was 49.3 years vs. 51.2 years for HIV-infected female veterans compared to HIV-uninfected female veterans (p=0.05) [10]. Similarly, a French study showed that the risk of MI was higher in both HIV-infected men and women, but the standardized morbidity ratio for HIV-infected women was 2.7 compared to 1.4 for HIV-infected men [11]. Chow et al. demonstrated that HIV-infected women have higher rates of ischemic stroke compared with HIV-infected men with HR 2.16 (95% CI 1.53, 3.04; p<0.001) for women vs. HR 1.18 (95% CI 0.95, 1.47; p=0.14) for men [12]. These studies confirm that HIV-infected women have increased rates of CHD compared to HIV-uninfected women, and in some instances may carry a greater risk of CHD than HIV-infected males.

Surrogate measures of cardiovascular disease

There are several risk assessment tools and non-invasive anatomical and physiological surrogate measures of CVD developed to assess the risk of developing CHD in the general population [13]. There were 28 studies reporting on risk scores to assess CVD or at least one surrogate

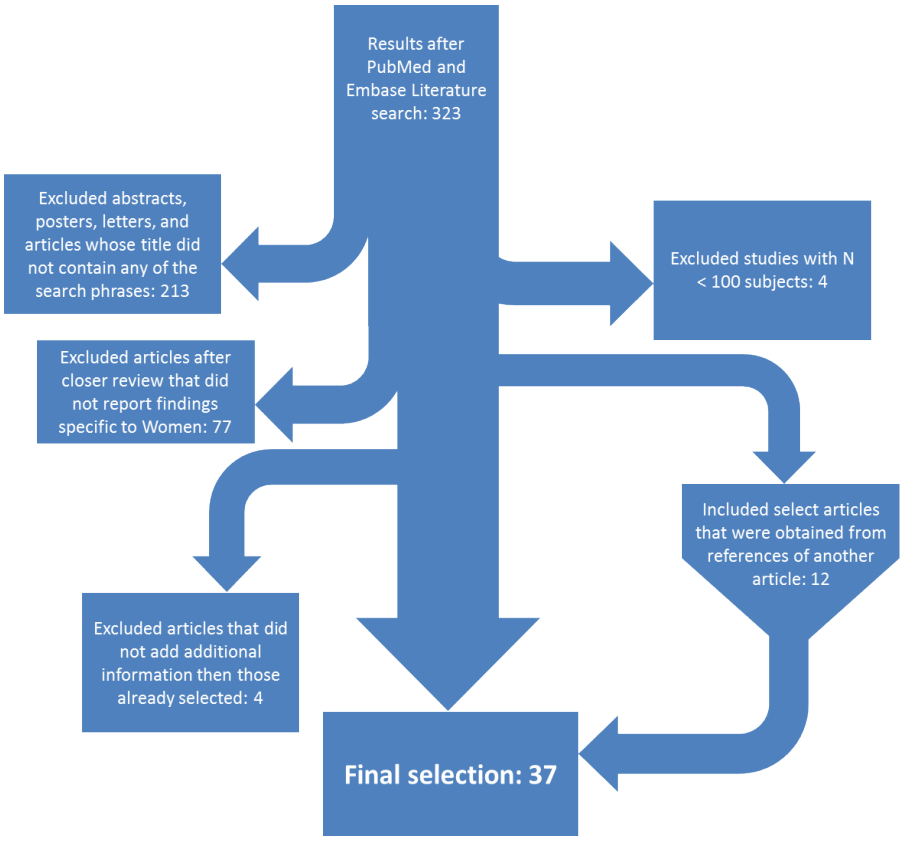

Figure 1: Article selection process of literature review.

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Triant et al. [9].	Prospective, observational cohort	3851 HIV-infected and HIV-uninfected 1,044,589 Urban, hospital-based, multicenter, Mass	AMI rates among HIV-infected patients compared to HIV-uninfected patients	HIV Cohort with 16,983 PY (5,430 PYs were women), non-HIV cohort with 3,747,329 PY (2,217,127 women PY) in 92 months follow up	-AMI occurred in 189 HIV patients and in 26,142 HIV-uninfected patients -Rates of AMI were 11.13 per 1000 PY (95% CI 9.6, 12.7) in HIV vs 6.98 per 1000 PY in HIV-uninfected -Unadjusted rates of AMI were 12.71 per 1000 PY in HIV-infected women vs. 4.88 per 1000 PY for HIV-uninfected women -No difference in rates of AMI was found in HIV-infected vs HIV-uninfected men
Womack et al. [10].	Prospective, longitudinal, observational cohort	710 HIV-infected women, 1477 HIV-uninfected women Urban, hospital-based, multicenter, Yale, Pittsburgh, and Connecticut	Rates of AMI, unstable angina, ischemic stroke, and congestive heart failure in HIV-infected compared to HIV-uninfected women	72 months	-Total of 86 incident CVD events. 53% of CVD events occurred in HIV-infected women -Incident CVD per 1000 PY was significantly higher among HIV-infected: IR 13.5 (95% CI 10.1, 18.1) vs IR 5.3 (95% CI 3.9, 7.3; p<0.001) HIV-uninfected -HIV-infected women had an increased risk of CVD compared to HIV-uninfected women, HR 2.8 (95% CI 1.7, 4.6; p<0.001)
Lang et al. [11].	Nested case control study	74,958 HIV-infected persons Hospital-based in three regions of France	Incidence of MI in the HIV-infected population compared to the general population	HIV cohort with 298,156 PY follow up (207,300 PYs were men and 90,856 PYs were women) in 72 months	-360 cases of MI (325 men, 35 women) among the HIV-infected patients. IR of 1.24 per 1000 PYs -Risk of MI was higher in both HIV-infected men and women than in the general population, with SMRs of 1.4 (95% CI 1.3, 1.6) for men and 2.7 (95% CI 1.8, 3.9) for women
Chow et al. [12].	Prospective observational cohort	2958 HIV-infected men and 1350 HIV-infected women Urban, hospital-based, multicenter, Mass	Incidence of ischemic stroke among HIV-infected patients compared to HIV-uninfected patients	HIV cohort with 233,700 PYs follow up in 69 months and non-HIV with 206,600 PYs follow up in 76 months	-Ischemic strokes in 914 patients, 132 HIV and 782 non-HIV -The IR of ischemic stroke was 5.27 per 1000 PY in HIV-infected patients vs 3.75 per 1000 PY in HIV-uninfected patients - HIV-infection was significantly associated with ischemic strokes for women with HR 2.16 (95% CI 1.53, 3.04; p<0.001), but not in men with HR 1.18 (95% CI 0.95, 1.47; p=0.14)
Hessamfar-Bonarek et al. [57].	Prospective study	766 HIV-infected males and 247 HIV-infected women Hospital-based, multicenter, France	Changes in patterns of gender-specific causes of death between 2000 and 2005.	60 months	-1013 HIV-infected adults who died in 2005; 247 (24%) were women -In 2005, AIDS-defining causes of death was higher in women than in men (43 vs 34%; p=0.01), whereas it had been the same in 2000 (47% in women and men) -In 2005, women died less frequently than men from cardiovascular disease (9% of all causes of death in women compared with 16% in men; p=0.004)
French et al. [2].	Prospective, longitudinal cohort	710 HIV-infected women died Urban, multicenter, USA	Temporal trends, causes and predictors of mortality	120 months	-712 HIV-infected patients died -Death rate was 8.0 per 100 PY in 1996, but decreased to mean rate of 2.6 per 100 PY in 2001 through 2004 -Cardiovascular mortality was the second leading cause of non-AIDS deaths

Mass: Massachusetts; AMI: Acute Myocardial Infarction; PY: Person-Years; CI: Confidence Interval; CVD: Cardiovascular Disease; IR: Incidence rate; HR: Hazard ratio SMR: Standardized Morbidity Ratios

Table 1: Studies assessing cardiovascular disease clinical outcomes.

measure of CVD in HIV-infected women. Table 2 lists selected studies that used these risk assessment tools and surrogate measures of subclinical CVD in the HIV population.

Risk scores to assess CVD risk: There were 11 studies included that reported on the Framingham risk scores (FRS) in HIV-infected women. The Framingham risk score has been the most common risk assessment tool used to evaluate the risk of developing CHD in HIV-infected men and women. Studies demonstrate that HIV-infected women have low Framingham risk scores [10,14,15], but there are no studies validating the FRS in this population. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) equation was derived to assess the potential increased risk of CHD in HIV-infected people using combination ART. Law et al. estimated the 3-year risk of myocardial infarction (MI) using the DAD equation in HIV-infected men and HIV-infected women and found that it was higher in men than in women, 0.92% (0.47 ± 1.42%) vs. 0.07% (0.05 ± 0.19%) [16]. Given the increased rates of CHD reported among HIV-infected women compared to HIV-infected men and to seronegative patients as described above, there is significant concern that the FRS and DAD equation may not be an accurate risk assessment tool for this patient population.

Carotid intimal media thickness (CIMT): There were 11 studies included evaluating CIMT in HIV-infected women. Carotid Intimal Medial Thickness can be a useful marker of atherosclerosis and has been shown to correlate with CV risk factors and predict stroke and myocardial infarction in the general population [17]. Results of CIMT in HIV-infected women have been mixed with a few studies finding no significant difference between HIV-infected females and HIV-uninfected females [15,18]. Increased CIMT has been associated with several CV risk factors, however. One study of 97 HIV-infected women noted that participants receiving protease inhibitors (PI) had increased CIMT compared to those not receiving PIs [18]. Another study found that in untreated HIV-infected women, there were no significant associations between lipid levels and CIMT, but in treated women higher levels of low-density lipoprotein cholesterol (LDL-c) and non-high density lipoprotein cholesterol (non-HDL-c) were associated with higher CIMT values [19]. Mangili et al. found that significantly more HIV-infected women than men had metabolic syndrome, and the mean common CIMT measurement was significantly higher among participants with metabolic syndrome than among those without metabolic syndrome (0.66 mm vs. 0.59 mm; p=0.005) [20]. The association between HIV infection, CV risk factors and CVD remains unclear based on the available studies in HIV-infected women.

Pulse wave velocity (PWV): Pulse wave velocity is a surrogate marker of arterial stiffness that has been associated with CVD and

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Fuchs et al. [58].	Cross-sectional study	2086 HIV-infected men and 1743 HIV-infected women Urban, community-based facilities, multicenter, three regions in Brazil	10-year risk of coronary heart disease using the FRS in HIV-infected patients	NA	-Prevalence of FRS ≥10 was 4.5% in the South, 4.2% in the Midwest, and 3.9% in the Northeast of Brazil. -RR for CHD 3.0 (95% CI 2.1, 4.2; *p*<0.001) for HIV-infected women compared to men
Lake et al. [59].	Cross-sectional study	408 HIV-infected men and 178 HIV-infected women Urban, community-based, USA, multiple cities	Association between regional adipose tissue distribution and FRS	NA	-Levels of CVD risk by FRS were higher in HIV-infected men vs control men (median 4.7% vs. 3.7%; *p*=0.0002) -Levels of CVD risk by FRS were similar in HIV-infected and control women (1.1% vs. 1.2%; *p*=0.91) -Prevalence of 10-year CVD risk >10% was low in HIV-infected and control women (3% vs. 1%; *p*=0.25). -None of the women had 10-year CVD risk >20%, regardless of HIV status -VAT showed a strong positive association with FRS in both HIV-infected men and women (r=0.34, *p*<0.0001)
Kaplan et al. [60].	Prospective, observational cohort	2386 HIV-infected and 1675 HIV-uninfected Urban, community-based, USA, multiple cities	Prevalence of major CVD risk factors and FRS among HIV-infected women and men	23 months	-HIV-infected men: 81% had low predicted risk, 2% had moderate, and 17% had high predicted risk based on FRS -HIV-infected women: 86% had low predicted CHD risk, 2% had moderate12% had high risk based on FRS -HIV-uninfected women: 87% had low predicted CHD risk 1% had moderate and 12% had high risk based on FRS
Aboud et al. [61].	Cross-sectional study	756 HIV-infected men and 265 HIV-infected women Urban, hospital-based, international, England	10-year CVD risk as determined by FRS in a large HIV cohort	15 months	-Median FRS for CVD was 4%, (0-56%/decade) in men and 1.4% (0-37%/decade) in women -CVD risk was >20% in 6% of men and 1% of women -CVD risk was >10% in 12% of men and 4% of women
Law et al. [16].	Prospective observational cohort	13,328 HIV-infected men and 4272 HIV-infected women Community-based facilities, international, 20 different countries in Europe, North America and Australia	3 year risk of MI	36 months	-3-year risk of MI was higher in men than in women, 0.92% (0.47 ± 1.42%) vs. 0.07% (0.05 ± 0.19%) -Majority of MIs projected to occur in men: 123 (63 ± 189) among 13,328 men vs. 3 (2 ± 8) among the 4272 women
Mangili et al. [20].	Cross-sectional study	234 HIV-infected men and 80 HIV-infected women Urban, community-based, USA, Mass	Associations between carotid and coronary atherosclerosis and metabolic syndrome	NA	-Significantly more women than men had metabolic syndrome (*p*=0.018) -Mean common CIMT higher among those with metabolic syndrome than among those without (0.66 mm vs. 0.59 mm; *p*=0.005) -Detectable CAC score was more common in those with metabolic syndrome than without (80.3% vs. 46.7%; *p*<0.0001)
Mangili et al. [28].	Cross-sectional study	242 HIV-infected men and 85 HIV-infected women Urban, community-based, USA, Mass	Associations between CIMT and CAC measurements and cardiovascular risk factors	NA	-Mean common CIMT (± SD) was 0.62 ± 0.2 mm in men and 0.59 ± 0.2 mm in women (*p*=0.173) -Mean internal CIMT (± SD) was 0.76 ± 0.5 mm in men and 0.66 ± 0.4 mm in women (*p*=0.109) -Women: age (*p*=<0.001) and BMI (*p*=0.004) correlated with common CIMT; age (*p*=<0.001) correlated with internal CIMT; age (*p*=0.004) and glucose (*p*=0.009) correlated with CAC score
Seaberg et al. [62].	Cross-sectional study	924 HIV-infected men from MACS study and 924 HIV-infected women from WIHS Study Urban, community and hospital-based, USA, multiple cities	Associations between HIV infection and HAART use and arterial stiffness using measurements of CIMT	NA	-Median carotid distensibility was similar in MACS vs. WIHS -CD4 <200 did not differ significantly between MACS (PD -6.9) and WIHS (PD -9.2, *p*=0.46) -HIV infection was associated with lower distensibility (PD -4.3, 95% CI -7.40, -1.10), with the effect greater in MACS (PD -5.5) compared to WIHS (PD -1.9) -Distensibility was significantly lower among those taking HAART in the MACS (PD -4.2, 95% CI -7.00, -1.40), but not in the WIHS
Karim et al. [63].	Nested Case-control study	414 HIV-infected women and 170 HIV-uninfected women (sex and hormone data). 771 HIV-infected and 323 HIV-uninfected women (androgen analyses) Urban, Community-based, USA, multiple cities	Associations between sex hormones, gonadotropin, a marker of ovarian reserve (inhibin-B), and SHBG and CIMT	NA	-CIMT was similar between HIV- and HIV+ women 0.722 (± 0.100) vs 0.715 (± 0.106) *p*=0.52 (sex hormone data cohort) and 0.714 (± 0.099) vs 0.718 (± 0.109) *p*=0.59 (androgen cohort) -Serum E2, T, and DHEAS concentrations were significantly lower, whereas SHBG was higher in HIV-infected vs HIV-uninfected women) and >350 (0.056, *p*=0.001)
Parrinello et al. [64].	Cross-sectional	601 HIV-infected women and 90 HIV-uninfected women Urban, community-based, USA, multiple cities	Association between CMV IgG titers and subclinical vascular disease (carotid ultrasound)	NA	-HIV-infected women had higher serum CMV IgG levels compared with uninfected women: mean, 25.4 IU/mL; SD, 9.9 vs. 19.4 IU/mL SD 9.2 *p*<0.01 -In HIV-infected women, CMV IgG was not associated with either CIMT (r=0.01; *p*=0.86) or carotid artery lesions prevalence RL 1.12 (95% CI 0.87, 1.49; *p*=0.38) -In HIV-infected women CMV IgG levels were associated with carotid artery distensibility and increased Young's elastic modulus (both *p*<0.01)

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Parrinello et al. [19].	Nested Case-control study	1305 HIV-infected women and 522 HIV-uninfected women - Urban, community-based, USA, multiple cities	Association between serum lipids and CIMT	NA	-In HIV-uninfected women, higher TC (2.17; CI 0.07, 4.27; *p*=0.04), LDL-c (3.46; 95% CI 1.02, 5.90; *p*=0.01), and non-HDL-c (2.40; 95% CI 0.36, 4.44; *p*=0.02) were associated with increased CIMT -In HIV-infected women on ART, LDL-c (2.27; 95% CI 0.19, 4.35, *p*=0.03) and non-HDL-c (1.66; 95% CI 0.03, 3.36; *p*=0.05) were associated with increased CIMT -In HIV-infected women not on ART, no associations were seen between lipids and CIMT
Lazar et al. [23].	Prospective observational cohort	276 HIV-infected women and 67 HIV-uninfected women Community-based, international, Rwanda	Comparison of arterial stiffness in HIV-infected vs. HIV-uninfected women	6 months	-Mean C-AI was significantly lower in HIV-infected vs HIV-uninfected women (20.3 ± 12.0 vs. 25.5 ± 12.1; *p*=0.002) -P-AI (74.6 ± 18.8 vs. 83.7 ± 20.0; *p*<0.001) was lower in the HIV-infected group -C-PP was similar between the groups (28.1 ± 8.0 vs. 27.4 ± 9.0; *p*=0.54) -In HIV-infected women, CD4 count was not correlated with C-AI (Rho=−0.01, *p*=0.84), central PP (Rho=0.09, *p*=0.16), or peripheral AI (Rho=−0.01, *p*=0.83)
Sharma et al. [29].	Cross-sectional study	238 HIV-infected women and 97 HIV-uninfected women Urban, community-based, USA, multiple cities	Prevalence of and risk factors for PAD using ABI	NA	-Overall prevalence of low ABI (<0.9) was 0.9% and high ABI (>1.40) was 6.9% [95% CI 4.4, 10.2%; n=23] -The prevalence rates of high ABI among HIV+ vs HIV - subjects were similar (7.2% vs. 6.3%; *p*=0.84) -The prevalence of low ABI was too low to allow analyses

Studies with N>100 subjects were included. FRS: Framingham Risk Score; NA: Not applicable; RR: Relative Risk; CI: Confidence Interval; CHD: Coronary Heart Disease; MI: Myocardial Infarction; HAART: Highly Active Antiretroviral Therapy; CIMT: Carotid Intimal Medial Thickness; MACS: Multicenter AIDS Cohort Study; WIHS: Women's Interagency HIV Cohort Study; CD: Cluster of differentiation; PD: Percent Difference; E2: estradiol; T: testosterone; DHEAS: Dehydroepiandrosterone Sulphate; SHBG: Sex Hormone Binding Globulin; C-AI: Central Augmentation Index; P-AI: Peripheral Augmentation Index; C-PP: Central Pulse Pressure; PAD: Peripheral Arterial Disease; ABI: Ankle-Brachial Index; Mass: Massachusetts; CAC: Coronary Artery Calcium; SD: Standard Deviation; CVD: Cardiovascular Disease; VAT: Visceral Adipose Tissue

Table 2: Studies assessing surrogate measures of cardiovascular disease.

mortality in the general population [21]. There is limited data on PWV in HIV- infected women, and only two studies reported on gender in their results. Eira et al. noted that there was a significant trend towards higher values of aortic PWV in HIV-infected women with diabetes or on ART among 18 HIV-infected women [22]. A Rwandan study of 276 HIV-infected women found no significant differences in measures of radial arterial wave reflection between HIV-infected and HIV-uninfected women after adjustment for potential confounders and age [23]. More studies with larger numbers need to be conducted in order to obtain more conclusive results on the association between HIV infection and PWV in women.

Computed tomography coronary angiography (CTA): There were three studies that evaluated CTA in HIV-infected women. Computed tomography coronary angiography has been used to evaluate coronary atherosclerosis in the general population, and its use has been promoted by recent studies [24,25]. There is a growing body of literature using the computed tomography coronary angiography (CTA) to assess subclinical CVD in HIV-infected individuals. Fitch et al. evaluated atherosclerotic plaque morphology among HIV-infected and HIV-uninfected women. The presence of coronary plaques was similar in both groups, but HIV-infected females had a significantly higher prevalence of non-calcified coronary artery plaques (35% vs 12% in female control subjects; p=0.04) which remained significant even after adjustment for CV risk factors such as age, race, FRS, smoking status, levels of triglycerides (TGs), HDL-c and LDL-c, and BMI. The percentage of coronary segments with non-calcified plaques was significantly higher in HIV-infected women (median 75% IQR 63%–100%) compared to HIV-infected men (median 50% IQR 3%–100%; p<0.05,) [26] which is important because non-calcified plaques are considered vulnerable and more susceptible to rupture leading to acute coronary syndromes [27]. Coronary artery calcium scores (CAC) have been found to be higher in HIV-infected patients with metabolic syndrome compared to those without metabolic syndrome [20]. The same study showed that HIV-infected women had higher rates of metabolic syndrome compared with HIV-infected men. Conversely, another study found that HIV-uninfected women had statistically significant higher percentage of CAC >100 (p=0.02) compared to HIV-infected women [26]. Other studies did not demonstrate gender differences in CAC [20,28]. From the limited studies of CTA in HIV-infected women, there is a suggestion that certain plaque morphologies may be greater in HIV-infected women compared to controls, but larger studies need to be performed to establish firmer conclusions.

Ankle-brachial index (ABI): There is limited data on ABI in HIV-infected women, and only one study reported on gender in their results. Sharma et al evaluated ABI in 238 HIV-infected women and 97 HIV-uninfected women. The presence of low ABI was too few for analysis (n=3, 0.9%), but it was noted that the presence of high ABI was more frequent than expected (n=23, 6.9) with an unclear clinical significance [29]. More studies with larger numbers need to be conducted to further evaluate the association between ABI and HIV infection in women and to develop meaningful clinically significant cut-off values.

Risk factors and metabolic indices

Several studies have evaluated traditional CHD risk factors, metabolic indices, and markers of inflammation in HIV infected women. Table 3 lists selected studies that reported on traditional CHD risk factors, markers of inflammation, and HAART. Table 4 lists selected studies that reported on metabolic indices that contribute to CHD risk.

Traditional risk factors

Studies report differing impact of traditional CV risk factors on CHD risk. There were six studies that evaluated traditional risk factors in HIV-infected women. Triant et al. noted increased rates of hypertension, diabetes, and dyslipidemia stratified by gender in HIV-infected patients compared to HIV-uninfected patients [9]. Womack et al. observed an increased prevalence of dyslipidemia and smoking

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Kroll et al. [65].	Cross-sectional study	208 HIV-infected men and 146 HIV-infected women Community-based, international, Brazil	Prevalence of obesity and cardiovascular risk in HIV/AIDS outpatients according to sex, antiretroviral therapy and other variables	NA	-Women were more frequently obese compared to men (14.1% vs. 4.4%) -Women had a higher odds of CVR than men (OR=6.97; CI 95%, 4.16<OR<11.76) -Very high CVR was more prevalent in women than men (51.4% vs. 9.4%; p<0.001) -No statistically significant differences noted in associations between nutritional status, CD4 counts, and VL and ART type (p value not provided) between men and women
Mateen et al. [66].	Prospective, observational cohort	1841 HIV-infected men and 3722 HIV-infected women Urban, community-based, secondary care center, international, Uganda	Hypertension and risk of CVD	NA	-Men were more likely to carry a diagnosis of HTN prior to the age of 40 (p<0.0001) -83% women were in the very low risk FRS category -20% of men were in≥10% or FRS category
Kaplan et al. [37].	Prospective, observational cohort	127 HIV-infected women and 127 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between levels of markers of inflammation pre and post HAART and subclinical atherosclerosis (CIMT)	29 months	-Both pre- and post-HAART: higher HIV RNA was associated with higher levels of TNF-alpha (p<0.01), IL-2 receptor (p<0.0001), IL-10 (p<0.00), MCP-1 (p<0.001) and D-dimer (p<0.04) -Prior to HAART initiation, biomarker levels were not associated with CIMT -After HAART: -TNF and IL-2 remained elevated compared to HIV-uninfected women (p<0.0001 and p<0.01 respectively). -CIMT was associated with higher levels of soluble IL-2 (p=0.02), IL-6 (p=0.05), and D-Dimer (p=0.03) in HIV+ women
Shaked et al. [36].	Cross-sectional study	264 women participants Urban, community-based, USA, multiple cities	Association between plasma markers of macrophage inflammation and activation and subclinical atherosclerosis (carotid ultrasound)	NA	-4 groups: 66 HIV-/HCV-, 66 HIV+/HCV-, 66 HIV-/ HCV+, 66 HIV+/ HCV+ -HIV+/HCV+ had the highest mean levels of sCD163 and sCD14 (11.25 ng/mL and 1,649 ng/mL, respectively) -HIV-/HCV- had the lowest mean (10.07 ng/mL and 1,179 ng/mL, respectively) -Gal-3BP was higher in HCV+ women than in HCV− women (mean 12.4 µg/mL vs. 8.6 µg/mL; p<0.01), but did not differ based on HIV status (mean 10.3 µg/mL vs. 10.7 µg/mL; p=0.34) -Levels of gal-3BP (OR=1.48; p=0.04), sCD163 (OR=1.85; p=0.005), and sCD14 (OR=1.4; p=0.03) were associated with an increased odds of having a carotid artery lesion. -Levels of Gal3BP (1.44; p<0.001) and sCD14 (-1.11; p=0.03) were associated with distensibility
Kaplan et al. [67].	Nested Case-control study	115 HIV-infected women and 43 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between HIV infection and plasma markers of inflammation, immune activation, and immunosenescence and vascular disease (carotid ultrasound)	30 month	-HIV-infected women had higher levels of CD4+ and CD8+ T cell activation (both p<0.01) than uninfected women. -Percentage of CD28− CD57+ was increased among the HIV-infected women (p<0.01) compared to uninfected women -HIV-infected women with carotid lesions had a higher percentage of both CD4+ and CD8+ CD38+ HLA-DR+ than HIV-infected women without carotid lesions (p=0.02) -CIMT was not associated with T cell activation or senescence markers in HIV-infected women
Shikuma et al. [47].	Retrospective study	145 HIV-infected men and 51 HIV-infected women Urban, multicenter, USA	Effect of virologically suppressive EFV-based ART on hsCRP levels with particular attention to the effect of gender and ABC use	22 months	-At week 0, hsCRP did not differ by gender between men and women [median (Q1, Q3): men 1.4 mg/liter (0.7, 3.9) versus women 2.3 mg/liter (0.9, 5.3); p= 0.13 -At week 96, women had higher levels of hsCRP (median 6 mg/liter; Q1, Q3, 1.8, 13.8) compared to men (median 1.6 mg/liter; Q1, Q3, 0.9, 4.2; p< 0.001) -There was no difference in hsCRP levels when comparing ABC based vs. EFV-based use at week 0 (p= 0.95) or at week 96 (p= 0.38) -Changes in hsCRP did not correlate with changes in insulin resistance or with changes in fasting lipids (all p>0.3)
Tien et al. [46].	Cross-sectional study	716 HIV-infected women and 361 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between HIV and HAART use and LDL-p and HDL-p in HIV-infected women compared to uninfected women	NA	-75th, 90th, and 95th percentiles of small LDL-p in women on HAART were higher than in HIV-infected and HAART Naïve (CI or p values not provided) women -After further adjustment for TG and HDL-C, the association between HAART and small LDL-p was no longer significant -HIV-uninfected women had higher total and small HDL-p than HIV-infected women at each of the percentiles. This remained significant after adjustment for TG and HDL-C
Estrada et al. [44].	Cross-sectional study	922 HIV-infected women Urban, multicenter, international, pain	Lipid profile in a large cohort of HIV-infected women on ART	NA	-Significantly higher HDL values were observed in NNRTI-treated patients - NRTI vs NNRTI (p=0.001) and PI vs NNRTI (p<0.001) -Patients on PI treatment had higher TC/HDL ratio than those on NNRTI (p<0.001). -In a multivariate analysis, the following factors were independently associated with TC/HDL ratio: age (p=0.045), TG levels (p=0.001), and HCV co-infection (p=0.002)

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Shaffer et al. [45].	Two parallel, randomized, open-label trials	741 women randomized Multicenter, international; 7 countries in sub-Saharan Africa	CVD risk factors following initiation of NNRTI vs. PI-based ART	33.1 months	-Prior to ART, both NVP and LPV/r groups had similar mean lipid levels (TC, HDL, non-HDL, LDL, and TG) -The following are the changes at 144 weeks -TC (adjusted p=0.090), LDL (adjusted p=0.118), and non-HDL was higher in NVP group compared to LPV/r group -HDL increase was less and TG decreased (adjusted p=0.001) in NVP group (adjusted p=0.002)

Studies of N>100 subjects were included. HAART: Highly Active Antiretroviral Therapy; CIMT: Carotid Intimal Medial Thickness; TNF-α: Tumor Necrosis Factor Alpha; IL: Interleukin; MCP - 1: Monocyte Chemoattractant Protein – 1; CVD: Cardiovascular Disease; FRS: Framingham Risk Score; CHD: Coronary Heart Disease; NA: Not Applicable; HCV: Hepatitis C Virus; CD: Cluster of differentiation; Gal-3BP: Galectin-3 binding protein; CVR: Cardiovascular Risk; OR: Odds Ratio; CI: Confidence Interval; VL: Viral Load; ART: Antiretroviral Therapy; LDL-p: Low-Density Lipoprotein Cholesterol Particle; HDL-p: High-Density Lipoprotein Particle; TG: Triglycerides; HDL – C: High Density Lipoprotein Cholesterol; EFV: Efavirenz; hsCRP: High Sensitivity C-Reactive Protein; ABC: Abacavir; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitors; PI: Protease Inhibitor; TC: Total Cholesterol; NVP: Nevirapine; LPV/r: Lopinavir/Ritonavir; HTN: Hypertension; HLA: Human Leukocyte Antigen; RL: Ratio Lesions; CMV: Cytomegalovirus; SHBG: Sex Hormone Binding Globulin; T: Testosterone ; E2: Total Estradiol

Table 3: Studies assessing Traditional Cardiovascular Risk Factors, Markers of Inflammation, HAART.

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Mangili et al. [20].	Cross-sectional study	234 HIV-infected men and 80 HIV-infected women Urban, community-based, USA, Mass	Associations between carotid and coronary atherosclerosis and MS	NA	-Significantly more women than men had MS (p=0.018) -Mean common CIMT higher among those with MS than among those without (0.66 mm vs. 0.59 mm; p=0.005) -Detectable CAC score was more common in both HIV-infected men and women with MS than without (80.3% vs. 46.7%; p<0.0001)
Janiszewski et al. [14].	Cross-sectional study	1481 HIV-infected men and 841 HIV-infected women Urban, community-based, Italy	Associations between WC and TG levels and severity of lipodystrophy and CVR	NA	-In the women, VAT was highest among the high WC groups (p<0.05), but not different between the low TG/high WC and high TG/high WC groups (139.2 ± 146.7 cm^2 and 150.0 ± 97.9 cm^2, respectively) -CVR was greatest among men in the high TG/high WC group (p<0.05) -Prevalence of MS was significantly higher in the high TG/high WC women than in any other group (55.7% vs. range of 2.1 to 25.8%; p<0.05 for all comparisons)
Pullinger et al. [67].	Cross-sectional study	217 HIV-infected men and 79 HIV-infected women Urban, community-based, USA, San Francisco	Parameters that contribute to MS and estimating the 10-year risk of CHD	NA	- The prevalence of MS was similar in HIV-infected women and men (35.3% vs. 28.1%; p=0.0266) -High WC was associated with MS more in women than in men (p<0.001) -Elevated TG was associated with MS more in men than in women (p<0.01) -10-year FRS were higher in men (7.6 ± 5.4%) compared to women (4.6 ± 5.4%; p<0.001). - FRS for those with MS was 10.5 ± 7.6 (74 SD) vs. 5.6 ± 41 (183 SD) in those without MS; p<0.001
Baum et al. [32].	Cross-sectional study	87 HIV-infected men and 31 HIV-infected women, all drug users Urban, community-based, USA, Miami	10-year CHD risk and the prevalence of MS with further stratification of those who are on HAART with or without PIs	NA	-10-year CHD risk was significantly higher in men (5.9 ± 6.1; p<0.001) than in women (1.7 ± 2.4) -The rate of MS was significantly higher in women (29% vs 10.3%; p=0.013) compared to men -The factors associated with higher prevalence of MS among women: higher rate of abdominal obesity (54.8% in women vs. 8.1% in men; p<0.001) and lower HDL (61.3% in women vs. 40% in men; p=0.042) -HAART with or without PI was not associated with an increased risk of CVD (data not provided)
Sobieszczyk et al. [31].	Prospective, observational cohort	1725 HIV-infected women and 668 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between prevalence of MS and HIV infection, antiretroviral therapies, and sociodemographic factors	48 months	-Prevalence of MS was significantly higher in HIV-infected women than uninfected women (33% vs 22%; p<0.0001) -HIV status was associated with MS in multivariate analyses (OR=1.79; p<0.0001) -Factors associated with higher prevalence of MS in HIV-infected women included: white race (OR=1.91; p<0.001), older age (OR=1.38 per 5 year increase; p<0.0001), higher BMI (OR=2.05 for BMI 26–30 and OR=5.72 for BMI .30 kg/m2 vs BMI 21–25; p<0.0001), current smoking (OR=1.31; p<0.014), HIV-1 RNA 50,000 (OR=1.36; p<0.019, and use of d4T (OR=1.28; p<0.009)
Mulligan et al. [30].	Cross-sectional study	173 HIV-infected female adolescents and 65 HIV-uninfected female adolescents Urban, community and hospital based, multiple sites	Associations between prevalence of abnormalities in glucose metabolism, lipids, and body composition and different classes of ART regimens.	NA	-Average BMI, height, and weight did not differ among groups (p=0.96) -TGs were higher in all HIV(+) groups compared with HIV(-) (p=0.008) and significantly higher in NNRTI than ART-naïve (p<0.0001) -TC was higher in NNRTI and PI groups compared to both HIV(-) and ART-naïve (p=0.002) -Fasting and 2-h glucose, insulin, pro-insulin, C-peptide, and HOMA-IR decreased with BMI (all p- values <0.01)
Freitas et al. [69].	Cross-sectional study	239 HIV-infected men and 106 HIV-infected women Community-based, Portugal	Prevalence of MS and its components and determination of whether patients with or without CL have a different prevalence of MA	NA	-There was no significant association with presence of CL and MS in either HIV-infected women or men by ATPIII criteria: Women- prevalence of MS in women with CL vs. w/o CL was 25 (46.3%) vs. 25 (46.3%); p=0.854; Men- prevalence of MS in men with CL vs. w/o CL was 84 (54.5%) vs. 46 (54.5%.); p=0.949 -No significant differences in HIV risk factors or in ART regimens were found between patients with or without CL using ATPIII criteria - In women, CL was significantly associated with higher odds of having MS as defined by IDF with OR=5.290 (95% CI 1.502, 18.635)

Study	Design	N Study Population	Outcome	Follow up (months)	Results
Womack et al. [70].	Prospective, observational study	885 HIV-infected and 408 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between progestin-only and combined HC and parameters of glucose and lipid metabolism	60 months	-Progestin-only HC was associated with lower HDL in HIV-infected as compared with uninfected women (-3 mg/dl (95% CI -5, -1; *p*=0.02) and -6 mg/dl (95% CI -9, -1; *p* <0.0001) respectively -Progestin-only HC was associated with higher HOMA-IR in HIV-infected and HIV-uninfected women 0.86 (95% CI 0.51, 1.22; *p*<0.0001) and 0.56 (95% CI 0.12, 1.01; *p*=0.01) respectively -Combined HC was associated with higher HDL in HIV-infected and uninfected women 5 mg/dl (95% CI 2, 7; *p*=0.001) and 5 mg/dl (95% CI 3, 7; *p*<0.0001) respectively
Parrinello et al. [19].	Nested Case-control study	1305 HIV-infected women and 522 HIV-uninfected women - Urban, community-based, USA, multiple cities	Associations between serum lipids and CIMT	NA	-In HIV-uninfected women, higher TC (2.17 mg/d; CI 0.07, 4.27; *p*=0.04), LDL-c (3.46 mg/d; 95% CI 1.02, 5.90; *p*=0.01), and non-HDL-c (2.40mg/d; 95% CI 0.36, 4.44; *p*=0.02) were associated with increased CIMT -In HIV-infected women on ART, LDL-c (2.27mg/d; 95% CI 0.19, 4.35; *p*=0.03) and non-HDL-c (1.66 mg/d; 95% CI 0.03, 3.36; *p*=0.05) were associated with increased CIMT -In HIV-infected women not on ART, no associations were seen between lipids and CIMT
Adeyemi et al. [71].	Cross-sectional Study	95 HIV-infected men and 26 HIV-infected women Urban, community-based, USA, Chicago	Prevalence and predictors of MS and association between 10-year FRS and MS	NA	-Rates of MS did not differ by gender (males 34% and females 36%) -FRS was higher in men than women (11.8 (± 7.1) vs. 3.1 (± 2.8); *p*=0.001) -For components of MS, women had a higher prevalence of glucose intolerance and increased WC (*p*<0.001) compared to men
Tien et al. [72].	Observational, prospective study	1614 HIV-infected and 604 HIV-uninfected women Urban, community-based, USA, multiple cities	Associations between type of ART, duration of ART exposure, and non–HIV-related factors and IR using HOMA		-Median FG levels were similar in HIV-infected and HIV-uninfected women (83 mg/dL; *p*=0.69) -HIV-infected women had higher median insulin levels (11 versus 9 μIU/mL; *p*<0.001) -HIV-infected women had higher median HOMA (2.19 versus 1.83; *p*<0.001) -NRTI exposure was associated with a higher median HOMA compared to no NRTI exposure in the adjusted analysis 1.13 (1.02 to 1.25) -HIV-infected women regardless of ART had higher HOMA compared to HIV-uninfected after adjustment for cofounders (1.91 vs. 2.07-2.30 in various ART groups)

NA: Not Applicable; Mass: Massachusetts; MS: Metabolic Syndrome; CIMT: Carotid Intimal Medial Thickness; VAT: Visceral Adipose Tissue; WC: Waist Circumference; CVR: Cardiovascular Risk; SD: Standard Deviation; TG: Triglycerides; FRS: Framingham Risk Score; CHD: Coronary Heart Disease; HDL: High Density Lipoprotein; HAART: Highly Active Antiretroviral Therapy; PI: Protease Inhibitor; CVD: Cardiovascular Disease; OR: Odds Ratio; BMI: Body Mass Index; d4T: Stavudine; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitors; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TC: Total Cholesterol; ART: Antiretroviral Therapy; CL: Clinical Lipodystrophy; ATPIII: Adult Treatment Panel III; IDF: International Diabetes Federation; HC: Hormonal Contraception; MA: Metabolic Abnormalities; FG: Fasting Glucose; NRTI: Nucleoside Reverse Transcriptase Inhibitor

Table 4: Studies assessing Metabolic Indices Contributing to Cardiovascular Risk.

but a lower prevalence of hypertension and obesity in HIV-infected women compared to HIV-uninfected women (p<0.05) [10]. Mulligan et al. found that 40% of both HIV-infected and HIV-uninfected young women were overweight or obese (BMI>25), but there was no difference between groups. On the other hand, fasting TGs and total cholesterol (TC) levels were significantly worse among HIV-infected participants than HIV-negative participants. The authors concluded that obesity and dyslipidemia were prominent among HIV-infected adolescent women, and when coupled with other CV risk factors may accelerate the lifetime risk of CHD and other adverse events [30].

Metabolic indices

There were 15 studies included that evaluated metabolic indices in HIV-infected women. Metabolic syndrome was noted to be particularly prevalent in HIV-infected women. There are several definitions for metabolic syndrome but they all include insulin resistance, obesity, atherogenic dyslipidemia (elevations in TGs or low HDL) and hypertension. Sobieszczyk et al. found that HIV infection was independently associated with metabolic syndrome with a rate of 33% vs 22% (p<0.0001) in HIV-positive women compared with HIV-negative women [31]. Janiszewski et al. investigated the association between waist circumference (WC) and TG levels and CV risk and observed that HIV-infected women with high TG and WC had higher rates of metabolic syndrome than any other group (p<0.05) [14]. Another study in intravenous drug users observed that the prevalence of metabolic syndrome was significantly higher among HIV seropositive females than among seropositive males (29% vs 10.3%, p=0.013) [32]. Mangili et al. showed that HIV-infected women had higher rates of metabolic syndrome compared to HIV-infected men, and mean common CIMT measurements were higher among those with metabolic syndrome than those without metabolic syndrome (0.66 mm vs. 0.59 mm; p=0.005) [20]. However, other studies did not consistently demonstrate increased rates of metabolic syndrome in seropositive women compared to men, nor that increased rates of metabolic syndrome was consistently associated with increased CHD risk (Table 4).

Markers of inflammation and immune activation

There were eight studies that investigated markers of inflammation and immune activation in HIV-infected women. Conceivably, HIV-infected patients may have higher rates and increased risk of CHD because of increased levels of inflammation and immune activation than seronegative patients. This increased immune activation persists even in patients on ART who have achieved virological suppression and immune reconstitution with CD4 cell count >200 mm^3 [33]. Soluble CD163 (sCD163) is a monocyte-macrophage specific scavenger receptor cleaved from activated monocytes and macrophages during inflammation, and elevated levels have been associated with coronary artery disease in the general population and HIV-infected men suggesting this inflammatory and immune pathway may be involved in the pathogenesis of atherosclerosis [34,35]. Fitch et al. reported that sCD163 levels were significantly higher in HIV-infected females than HIV-infected and non-infected males [26]. 98% of the women were on

ART with a median duration of eight years and 84% had undetectable viral loads. Shaked et al. demonstrated elevated levels of sCD163 in HIV-infected and HIV/hepatitis C co-infected women, though 46% of total study cohort (29% of HIV+/HCV- cohort and 17% of HIV+/HCV+ cohort) were not on ART and the median viral load was 885 copies/mL [36].

Kaplan et al. compared changes in several inflammatory markers in 127 HIV-infected women and matched control women before and after Highly Active Antiretroviral Therapy (HAART) initiation in the Women's Interagency HIV Study (WIHS). They found that HIV-infected women had statistically significant higher levels of tumor necrosis factor (TNF)-alpha, soluble interleukin (IL)-2 receptor, IL-10, monocyte chemoattractant protein (MCP)-1 and D-dimer prior to ART initiation, and though the levels of TNF-alpha and soluble IL-2 receptor decreased among HIV-infected women after ART these levels remained higher than in HIV-uninfected women. These studies demonstrating higher levels of plasma markers of inflammation and immune activation in HIV-infected women provide a potential mechanism by which these women could have increased rates of subclinical atherosclerosis and CHD [37].

Highly active antiretroviral therapy (HAART)

There were 12 studies that evaluated the association of HAART and CHD in HIV-infected women, and selected ones were listed in Table 3. Studies in predominantly male cohorts suggest that ART, particularly protease inhibitors, is an independent risk factor for increased CHD [38,39]. Abacavir (ABC) has also been implicated in increased risk of and rates of cardiovascular events though results have been mixed among studies, [5,40-43]. These studies, however, again included predominantly male populations. In a study of 2187 women of whom 710 were HIV infected, Womack et al. found no association between ART and CVD outcomes [10]. Conversely, Chow et al. observed that longer duration of any ART regimen was associated with significantly decreased risk of strokes (HR 0.80; 95% CI 0.73, 0.88, p=<0.001) [12]. Therefore, it not clear whether ART exposure or specific antiretroviral medications (ARVs) truly increase rates of CVD in HIV-infected women.

Studies also evaluated the contribution of ART and specific ARVs to changes in traditional CHD risk factors and markers of inflammation. Estrada et al. demonstrated that HIV-infected women receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens had better lipid profiles than HIV-infected women on PI-based regimens [44]. Shaffer et al. evaluated CHD risk factors following initiation of NNRTI vs. PI-based ART in women from 7 countries in sub-Saharan Africa over 144 weeks. ART with either nevirapine or lopinavir/ritonavir had similar lipid values with only TC increasing at 144 weeks (p=0.090) [45]. However, Tien et al. found no significant associations between ART and lipid values [46]. As such, the contribution of ARVs to lipid profiles remain uncertain.

Shikuma et al. looked at high sensitivity C-reactive protein (hsCRP) and its association with efavirenz (EFV) versus ABC over a 96 week period in HIV-infected women and men. Levels of hsCRP did not differ by gender at baseline, but by week 96 women had higher levels of hsCRP than men (median 6 mg/liter vs. median 1.6 mg/liter, p< 0.001), but no difference was noted between the EFV and ABC groups (p=0.38) [47]. Another study investigated the effects of ART on plasma markers of inflammation in HIV-infected and uninfected women and demonstrated that markers of inflammation decreased among HIV-infected women after ARV initiation, but levels of TNF-alpha and IL-2 remained elevated among HIV-infected women compared to uninfected women over time despite ART (p<0.0001 and p<0.01 respectively) [37]. It remains indeterminate to what degree plasma markers of inflammation and immune activation change with ART use and specific ARVs and whether these changes differ by gender.

Discussion

HIV-infected patients have increased rates of CHD compared to the general population, and these increased rates have been more frequently reported in HIV-infected men than in women. Freiberg et al looked at the veteran population and found an increase rate of cardiovascular events in HIV-infected male veterans compared with HIV-uninfected male veterans HR 1.48 (95% CI, 1.27-1.72) [3]. Similarly, Silverberg et al demonstrated a 44% increased risk of MIs among a predominately male HIV-infected population compared with a predominately male HIV-uninfected population [48]. Studies that included both male and female participants have mostly demonstrated that either gender was not a risk factor for development of CHD or that male rather than female gender was a risk factor for CHD in HIV-infected patients [9,11-12,32,49,50]. Differences in gender as a risk factor for CHD among studies in HIV-infected patients may be due to differences in study population as well as the vast majority of studies in which women were underrepresented. What this review highlights though is that HIV-infected women do have increased rates of AMI and ischemic stroke compared to HIV-uninfected women, and may also be increased compared to HIV-infected men as observed in some studies despite women being projected to have lower CHD risk based on FRS.

Studies assessing CHD risk by measuring anatomical or physiological measures of subclinical atherosclerosis have reported mixed results. Of these, studies using CTA have consistently demonstrated increased coronary atherosclerosis particularly non-calcified plaques in asymptomatic HIV-infected women without known CV risk compared to uninfected women highlighting the presence of subclinical atherosclerosis in these women. Similarly, CTA has demonstrated high risk morphology plaque types in asymptomatic HIV-infected males [51].

Potential explanations for the increased rates of CVD and subclinical atherosclerosis may be partly explained by increased levels of inflammation and immune activation in HIV-infected women despite virological suppression on ART. While studies have suggested that ART, particularly PIs, increase the risk of cardiovascular disease in HIV-infected men, the contribution of ART to clinical or subclinical CHD in seropositive women remains uncertain due to conflicting results among the number of limited studies available. It appears unlikely, however, that disproportionate representation of traditional CHD risk factors and metabolic indices among HIV-infected women can explain well the observed increased rates of CHD given the inconsistent findings of the prevalence of CV risk factors reported among studies.

Potential reasons for conflicting results among studies of surrogate measures of subclinical atherosclerosis could be heterogeneous study designs and study populations with varying periods of follow-up. Additionally, different outcomes were measured making it hard to compare studies directly. Many studies were of short duration, which makes it difficult to detect associations with chronic disease processes with cumulative risk such as CVD. Finally, the median age in most studies of HIV-infected women was young posing a challenge in detecting subclinical CVD, which is generally considered a co-morbidity of aging. Nonetheless, it is important to identify and validate surrogate measures of subclinical CVD as these test results

may be useful in further risk stratifying HIV-infected patients to maximize preventive measures to prevent clinical CHD events. The most promising surrogate measure of subclinical CHD currently may be the CTA, and larger studies to investigate this imaging modality in HIV-infected women seems warranted based on the suboptimal performance of other available surrogate measures. How to best assess the risk of CHD in HIV-infected women remains uncertain.

There are significant concerns that FRS does not accurately estimate CHD risk in HIV women. The D:A:D score has been suggested to be more accurate in HIV-infected patients because it accounts for history of exposure to ART [52]. However, it too has limitations because the original data used to develop the D:A:D score was obtained between 1999 and 2002 in a predominately male population and there have been dramatic changes in ART regimens since then. Thus it is not clear whether the D:A:D score will remain accurate, and no studies have evaluated it in the era of newer ARVs and specifically in women. When compared with the FRS, the Reynolds score was shown to be more accurate when assessing 10-year CV risk for women [53]. There are no studies using Reynolds score to assess CV risk in HIV-infected women, however. These limitations of our current risk assessment tools reinforce the need to identify and validate risk assessment tools and surrogate measures of clinical and subclinical atherosclerosis in HIV-infected women.

Elucidating the mechanisms for increased rates of CHD and increased risk of CHD in HIV-infected women remains a challenge due to the heterogeneity of study designs, study populations, sample sizes, and outcomes measured. There is a suggestion that metabolic syndrome characterized by insulin resistance may be more prevalent in HIV-infected women, and dyslipidemia appears to be more prominent though inconsistently so compared to HIV-uninfected women and HIV-infected men. Also, some markers of inflammation and immune activation appear to be elevated in HIV-infected women compared to HIV-uninfected women even after virological suppression has been achieved. sCD163 is of particular interest as it has been associated with coronary artery disease in the general population [54]. Another important potential factor contributing to premature, increased CHD risk that has not been extensively evaluated in the literature is the effects of menopause since HIV-infected women have been reported to undergo premature menopause secondary to loss of ovarian function at an earlier age [55,56].

There were several strengths of our review. It presented a comprehensive review of the current literature on the associations of HIV infection and CHD outcomes- namely, both clinical and subclinical surrogate measures of atherosclerosis- in women. We reviewed the prevalence of traditional CHD risk factors among HIV-infected women and compared them to HIV-uninfected women and HIV-infected men, and focused on other important potential mechanisms that may explain the reported associations with CHD, surrogate measures of CVD, and metabolic diseases that increase risk of CHD. Finally, the studies included ranged from urban hospital-based to rural community-based populations in the United States, Europe, Australia, sub-Saharan Africa, and Brazil thereby making the findings generalizable. One limitation of our review was that the review period was restricted to the past 10 years, though most data relevant to the current ART era were well-represented in that time period. Also, we did not perform a systematic meta-analysis but it would have been difficult to perform such an analysis given the scope of our review reporting on a wide range of endpoints such as clinical outcomes, surrogate measures of atherosclerosis, and risk factors.

In summary, HIV-infected women have increased rates of CHD compared to HIV-uninfected women and likely even HIV-infected men. However, there are no well-validated risk assessment tools or surrogate measures of subclinical CHD among HIV-infected to help identify high-risk women for targeting more intensive preventive measures. Additionally, our understanding of the biological and other reasons for the observed disparate CHD rates remains limited. Future studies that include large numbers of HIV-infected women with extended follow-up periods using surrogate measure of CVD and investigating pathogenic mechanisms underlying these observations are urgently needed.

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