Journal of Diabetes & Metabolic Disorders (2020) 19:1671–1683
https://doi.org/10.1007/s40200-020-00552-x

REVIEW ARTICLE

Prevalence of cardiometabolic syndrome in HIV-infected persons: a systematic review

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Received: 21 February 2020 / Accepted: 21 May 2020 / Published online: 9 June 2020

Abstract

Introduction HIV infected persons are twofold likely to experience a heart attack, stroke, and other forms of Cardiometabolic Syndrome (CMetS).

Methods Electronic searches of databases (MEDLINE and Google Scholar) were queried for articles written in English from 2000 to 2019.

Results In this review (16 publications), a total of 14,002 participants from 8 countries were included. Two continents contributed to 62.5% of the CMetS studies while 38.1% from Latin America and 24.4% from North America. The studies were conducted in 113 different centers, with an average study length of 2.8 years. The majority of the study designs were cross-sectional (62%) followed by a cohort study (25%) and clinical trials (12.5%). The mean age of the population enrolled was 41.9 years and 54.6% of the participants were males. The overall prevalence of CMetS using the National Cholesterol Education Adult Treatment Panel definition was 20.6%. Only 31.3% of the studies were reported using the International Diabetes Federation definition. Smoking and high blood pressure were reported as a risk factor in 62.5% of the studies, while diabetes (31.3%), family history of CMetS (25%), and cardiac vascular and cancer diseases were reported in 12.5% of the studies. The average duration of stay with HIV after confirmation was 5.23 ± 1.4 (years ± SD) and the median duration on HAART was 4.5 ± 2.3 (years ± SD).

Conclusions CMetS was a common problem among HIV infected persons. Several RFs can contribute to the development of CMetS with smoking and hypertension highly interrelated.

PROSPERO-number CRD42018107187.

Keywords Prevalence · Cardiometabolic Syndrome (CMetS) · Human Immunodeficiency Virus (HIV) · HIV comorbidities · Highly Active Antiretroviral Therapy (HAART)

Introduction

The Human Immunodeficiency Virus (HIV) associated morbidity and mortality have declined significantly since the introduction of Highly Active Antiretroviral Therapy (HAART) [1] and consequently, HAART extended the life expectancy of persons infected with HIV [2, 3]. As the life expectancy of HIV-infected patients increased, lifestyle-related co-morbidities such as Cardiovascular Diseases (CVDs), Diabetes Mellitus (DM) and hyperlipidemia began to emerge as a problematic issue and challenging the treatment of HIV [4]. People Living with HIV/ AIDS (PLWHA) exhibit multiple known Risk Factors (RFs) for Cardiometabolic Syndrome (CMetS) [2, 3]. The likelihood to experience heart attacks, strokes, and other forms of CVDs, is two-fold as compared to people who do not have the virus, even when HIV infection is well-controlled with HAART [5, 6].

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CMetS is a constellation of metabolic dysfunctions including insulin resistance, impaired glucose tolerance, atherogenic dyslipidemia (high serum Triglycerides (TGs), and low High-Density Lipoprotein (HDL) levels), hypertension, intra-abdominal adiposity, and high blood sugar [7]. Additionally, diseases involving the cardiac system such as myocarditis, dilated cardiomyopathy, pericardial effusion, endocarditis, malignant neoplasms, etc., can also be included after confirmed by measuring the cardiac biomarkers in the laboratory and using the imaging modalities (echo and ECG) [8–10]. Hence, the term metabolic syndrome (MetS) can be used interchangeably with CMetS considering the overlap of the problems [11, 12]. There are five widely used definition tools for CMetS/MetS. These are the International Diabetes Federation (the IDF-2005), the Modified National Cholesterol Education Programme Adult Treatment Panel III (NCEP_ATP III-2005), the European Group for the Study of Insulin Resistance (EGIR-1999), the World Health Organization (the WHO-1998) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/ NHLBI) definitions [13–15]. Each definition tool has a unique purpose. For example, there are no absolute requirements for measurement of NCEP-ATP III definition, whereas in case of the WHO definition measuring insulin-like growth factor (IGF)/ impaired glucose tolerance (IGT)/ presence of type two diabetes mellitus (T2DM) or evidence of insulin resistance (IR) is an absolute requirement. In the case of EGIR, hyperinsulinemia I must measure, and in case of the IDF, the waist grid measurement is an absolute requirement and also microalbuminuria included [13, 14]. In all of the definitions fulfilling three out of the five requirements (any of three out of the five in case of NCEP and two of any plus one absolute requirement for the WHO, the EGIR, and the IDF) defines the criteria of CMetS. The five requirements are hypertension, hyperglycemia, dyslipidemia type one (uses the measurement of TG) and dyslipidemia type two (use measurement of HDL), and central obesity [16–19].

There are RFs believed to be contributed a lot for the development of CMetS in HIV infected persons, particularly with the advent of HAART [9, 20]. Proposed hypotheses include increased lipogenesis (independent of HAART) [21–24], increased monocytes [25], inflammation, abnormal blood clotting, tissue factors (TFs) [26], interleukin VI (IL-VI) & D-dimer [27, 28]. Of specific concern are the fact that the use of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and HIV protease inhibitors (PIs) has been reported to be associated with an increment in total cholesterol (TC) and TGs plasma levels irrespective of CD4 cell counts and HIV viral load (VL) [2, 29]. A report from the Multicenter AIDS Cohort Study (MACS) showed that HIV infection was associated with alteration in TC, HDL, and LDL [30]. Hence, our review study aimed to determine the prevalence of CMetS and associated RFs among PLWHA from articles published in English from 2000 to 2019 and fulfilling the criteria used for this purpose. The interaction of the different variables in the development and progression of CMetS has been illustrated in the following conceptual framework (Fig. 1).

Methods

All methods for this systematic review were outlined through a Prospectively Registered Protocol (PROSPERO), which is found online with URL (https://www.crd.york.ac.uk/PROSPERO/#myprospero) and ID (CRD42018107187) and using the Preferred Reporting Items for Systematic Review (PRISMA) guidelines. The detail of the PRISMA has been shown in the following figure (Fig. 2).

Eligibility criteria

Eligible studies were randomized controlled trials and non-randomized studies (observational, cohort, and case-control) and cross-sectional studies that have investigated CMetS in HIV-infected persons.

Search strategy

Electronic searches of databases (MEDLINE and Google Scholar) were queried for articles written in English from 2000 to 2019. The following key search terms were used: “Risk”[Mesh] AND “Metabolic Syndrome”[Mesh] AND “HIV Infections/complications”[Mesh] AND “HIV Infections/diet therapy”[Mesh] OR “HIV Infections/drug therapy”[Mesh].

Inclusion criteria

Participants 18 years old and above (adults), all English language articles, and all eligible articles published in the last 20 years. Only published articles with abstract and/or full text were reviewed and assessed for inclusion in the study. Those meeting the following inclusion criteria were used for review: having described data on the relevant cardiometabolic risks in comparable HIV-infected populations, or comparable to the class of HAART medications, and included adult (aged 18 years or over). Studies were assessed for eligibility and, when sufficient information was not available from the title and/or abstract, the full- text was used and where the full-text was not available online, the authors were contacted via email.

Exclusion criteria

Studies not meeting both eligibility criteria were not included in the final review. Case reports, and case series were excluded. Duplicate articles and the number of authors fewer than

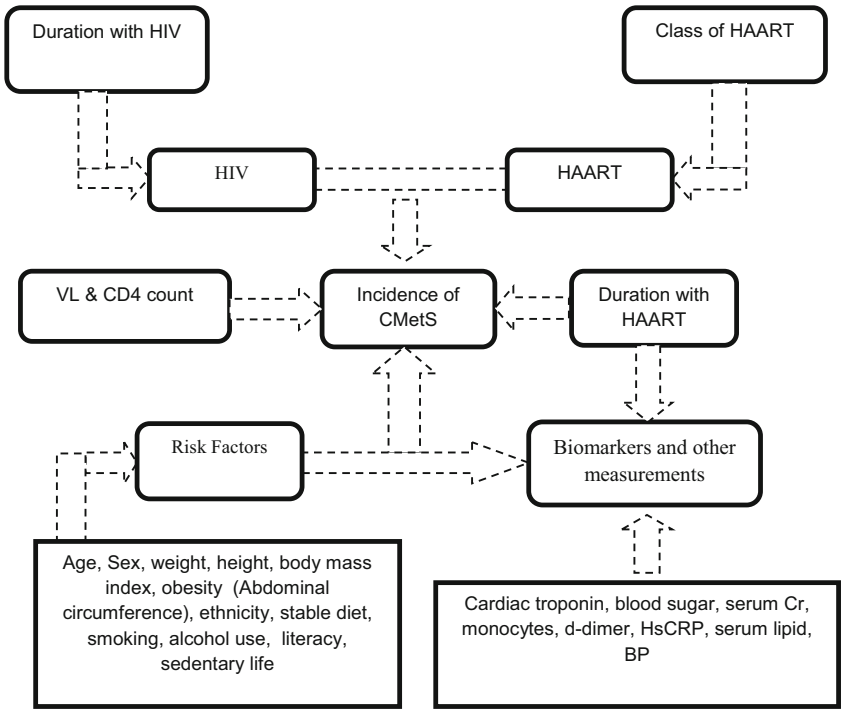

Fig. 1 Conceptual framework depicting the interaction of HIV, HAART medication and RFs to produce CMetS in HIV infected persons

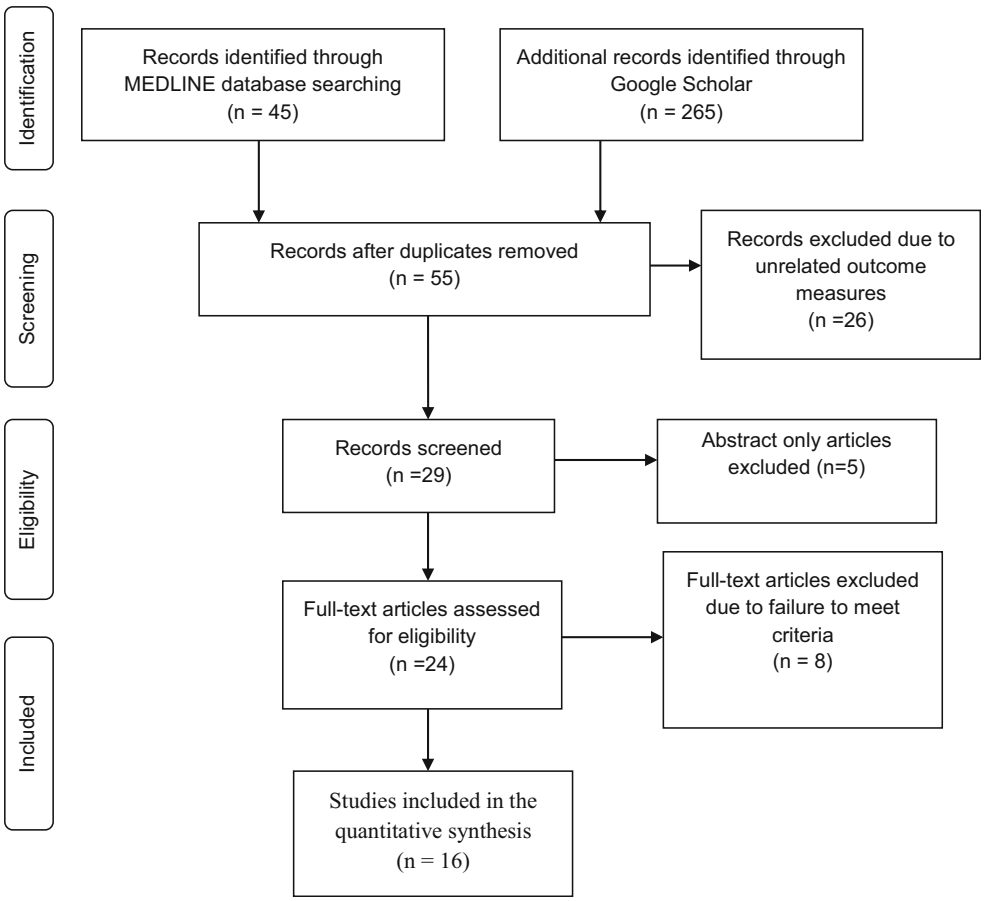

Fig. 2 Flow diagram of the study selection

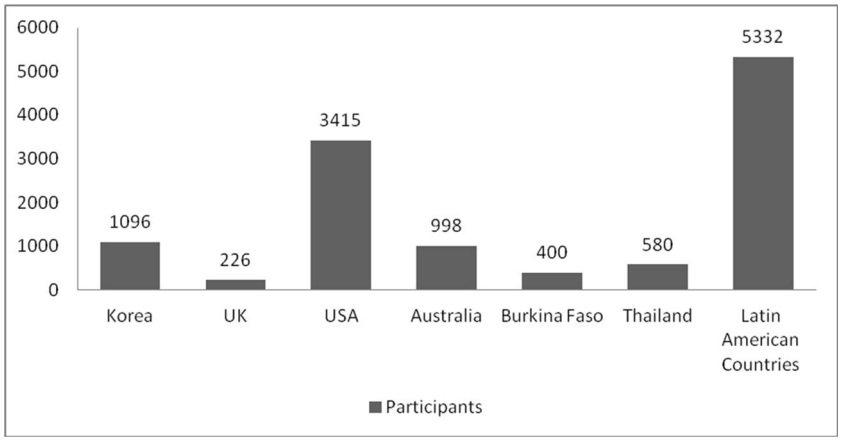

Fig. 3 Sample size of the study participants from a different geographic location

three, as well as the volume of the article less than 5, were automatically excluded (Fig. 3).

Review questions

How prevalent is CMetS among HIV- infected persons?

What were the risk factors contributing to the development of CMetS among HIV-infected persons?

Outcome

- Prevalence of CMetS in HIV infected persons
- Risk factors contributing to CMetS in HIV infected persons

Risk of bias (quality) assessment

The risk of bias was assessed using the Cochrane risk of bias tool. The principal researcher's background was tracked against the study area and the minimum number of researchers involved. The minimum number of researchers expected to be involved in the study would be three. The quality of the work of the researchers was checked against the volume of the publication (volume 5 or more) and published in international journals indexed to the PubMed database and also using a review of the article by our research team in case of any discrepancies.

Strategy for data synthesis

Only aggregate data were summarized and used for data analysis and interpretation of results. Quantitative and descriptive analysis was used to present the result. SPSS 21 was used to manage the quantitative data, to present results, and to do a descriptive analysis of the results. Our research team was composed of 2 professors and 1 assistant professor.

Search results

The search results have been illustrated in Fig. 1.

Analysis of subgroups or subsets

Subgroup analysis was not done due to the use of articles with different study designs.

Definition of terms

Cardiovascular diseases Pathological conditions involving the cardiovascular system including heart; blood vessels; or pericardium [31].

HIV infections Includes the spectrum of human immunodeficiency virus infections that range from asymptomatic seropositivity, thru AIDS-related complex (ARC), to acquired Immunodeficiency Syndrome (AIDS) [32].

Cardiometabolic Syndrome (CMetS) Since its introduction in 1998, various diagnostic criteria for CMetS have been proposed [19]; the more widely used definitions for CMetS are from International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/ NHLBI) [33]. In HIV-infected patients, there was an 85% agreement inpatient classification based on these two definitions [34]. More recently, the IDF and AHA/NHLBI agreed upon a common definition, which was used in our study [19, 35]. The other definition is using the National Cholesterol Education Program (NECP) Adult Treatment Panel III (ATP III) criteria [36], based on this CMetS was defined as the presence of three or more of the following components: i) waist circumference > 88 cm in women or > 102 cm in men; ii) blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or use of antihypertensive medications; iii) triglycerides ≥150 mg/dL or use of lipid-lowering medications (niacin, fenofibrate, and gemfibrozil);

iv) fasting blood glucose ≥100 mg/dL, physician-diagnosed diabetes or use of diabetic medications; v) high-density lipoprotein cholesterol (HDL) <50 mg/dL in women or < 40 mg/dL in men. The use of a lipid-lowering agent such as the use of a statin, fibrate, or niacin and antihypertensive medications can be used to define the criteria in the absence of laboratory evidence [37, 38].

Obesity defined as a body mass index (BMI; calculated as the weight in kilograms divided by the square of height in meters) ≥30. HAART was defined as the use of 2 nucleosides (NRTIs) and a non-nucleoside reverse-transcriptase inhibitor (NNRTI), 2 NRTIs and a PI, or an NNRTI and a PI.

Risk factors The probability that an event will occur. It encompasses a variety of measures of the probability of a generally unfavorable outcome. A group of six commonly accepted cardiometabolic risks were selected a priori for inclusion in this analysis: These are:- (i). Central Obesity: BMI > 30 kg/M2; (Waist girth >94CM for males and > 88 cm for females; or Waist/Hip ratio > 0.9; (ii). Hypertension: SBP > 140 and DBP > 90 [DM/CKD/HF BP > 130/85]; (iii). Impaired glucose handling: IR = FPG 100–125 mg/dL; DM = FPG >126 mg/dL or Random BSL >200 mg/dL; (iv). Dislipidemia: TG > 150 mg/dl (1.7 mmol/L); HDL-C 35 mg/dL (0.9 mmol/L); (v). Microalbuninuria: Urinary albumin excretion of 30–300 mg/day; (vi). Framingham risk >10% or cardiac/prothrombotic: Cardiac troponin T (cTnT) > 4.0 ng/ml; Positive echocardiography or d-dimer >500 ng/mL. Additional RFs used were older age, active cigarette smoking, family history, sedentary life, duration with HIV, type of HAART medication and substance use [39–41].

Definition of terms

Cardiovascular diseases: Pathological conditions involving the cardiovascular system including the heart; the blood vessels; or the pericardium.

HIV Infections: Includes the spectrum of human immunodeficiency virus infections that range from asymptomatic seropositivity, thru AIDS-related complex (ARC), to acquired Immunodeficiency Syndrome (AIDS). The year introduced 1990.

Cardiometabolic Syndrome (CMetS): Since its introduction in 1998, various diagnostic criteria for CMetS have been proposed (12); the more widely used definitions for CMetS are from International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/ NHLBI). In HIV-infected patients, there was 85% agreement inpatient classification based on these two definitions (33). More recently, the IDF and AHA/NHLBI agreed upon a common definition, which was used in our study (12). CMetS is a constellation of metabolic dysfunction including insulin resistance, impaired glucose tolerance, atherogenic dyslipidemia [high Serum Triglycerides and low High-Density Lipoprotein levels], hypertension, intra-abdominal adiposity, high blood sugar, plus diseases involving the cardiac system like myocarditis, dilated cardiomyopathy, pericardial effusion, endocarditis, malignant neoplasms, etc. Based on the Adult Treatment Panel III (ATP III) criteria [42], CMetS was defined as the presence of three or more of the following components: 1) waist circumference > 88 cm in women or > 102 cm in men; 2) blood pressure ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or use of antihypertensive medications; 3) triglycerides ≥150 mg/dL or use of lipid-lowering medications (niacin, fenofibrate, and gemfibrozil); 4) fasting blood glucose ≥100 mg/dL, the physician diagnosed diabetes or use of diabetic medications; 5) high-density lipoprotein cholesterol (HDL) <50 mg/dL in women or < 40 mg/dL in men. The use of a lipid-lowering agent such as the use of a statin, fibrate, or niacin and antihypertensive medications can be used to define the criteria in the absence of laboratory evidence. Obesity was defined as a body mass index (BMI; calculated as the weight in kilograms divided by the square of height in meters) ≥30. HAART was defined as the use of 2 nucleosides (NRTIs) and a non-nucleoside reverse-transcriptase inhibitor (NNRTI), 2 NRTIs and a PI, or an NNRTI and a PI

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Results

Demographic data

In this review (16 publications), a total of 14,002 participants from 8 countries were included. Two continents contributed to 62.5% of the CMetS studies in HIV- infected persons: Latin

Table 1 Demographic data

No	Country of study	Study design	Sample size	Number of sites	Study length in a year	Mean age	Percentage of male	References
1	Korea	CSS	1096	19	7	46	93	[4]
2	UK	Cohort	226	1	1	47	54	[43]
3	Brazil	CSS	87	1	1	37	76	[44]
4	USA	Cohort	567	1	4	43	47	[45]
5	Brazil	CSS	319	7	2	41	61	[46]
6	USA	RCT	2247	3	6	46	79	[47]
7	Brazil	CSS	819	1	1	41	55	[48]
8	Australia	CSS	788	32	3	45	18	[49]
9	Burkina Faso	CSS	400	1	1	41	38	[50]
10	Thailand	CSS	580	1	1	38	46	[51]
11	Brazil	Cohort	539	1	10	40	45	[52]
12	Latin America*	Cohort	4010	61	1	42	74	[53]
13	Brazil	CSS	273	1	2	48	55	[54]
14	USA	CSS	601	1	1	39	52	[55]
15	Brazil	CSS	1240	1	2	37	32	[56]
16	Australia	RCT	210	1	2	39	48	[57]
Average			875	8.3	2.8	41.9	54.6	

Latin America* Countries (Argentina, Brazil, Venezuela, Colombia, Peru, Ecuador, and Chile); CSS = Cross-sectional study; RCT = Randomized Clinical Trial

America mainly Argentina, Brazil, Venezuela, Colombia, Peru, Ecuador, and Chile had enrolled 38.1% of the population, while from North America, USA enrolled 24.4% participants (Table 1 & Fig. 3). The studies were done in around 113 different centers with an average study length of 2.8 years. The majority of the study design was cross-sectional (62%) followed by Cohort study (25%) and RCTs (12.5%). There was a shortage of articles reports from both Europe and Africa (Figs. 3 and 4).

The mean age of the population was 41.9 years and 54.6% of the participants were males. The study area, study design, and sample size distribution are shown in Table 1.

Clinical outcome

The overall prevalence of CMetS using the NCEP ATP III criteria was 20.6%. The average time after the first diagnosis with HIV among the participants was 5.23 + 1.4 (years + SD)

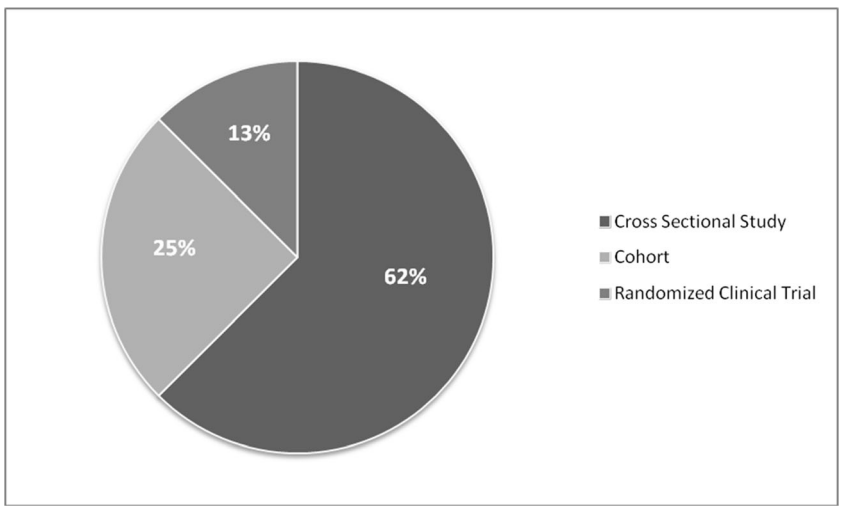

Fig. 4 Type of study designs used by the reviewed articles

Table 2 Clinical data prevalence in association with CMetS

Description	Mean	Median	Std. Deviation
CMetS using the NCEP ATP III, percent	20.6	19.0	10.5
CMetS using the IDF, percent	13.5	13.5	2.9
Average time since HIV was diagnosed, Year	5.23	5.00	1.373
Duration on HAART, Year	4.46	3.80	2.302
HAART use, percent	72.19	70.00	9.425
PI use, percent	34.64	31.15	11.833
NNRTIs use, percent	61.88	63.70	11.733
INSTI use, percent	2.50	2.50	1.211
NRTIs use, percent	18.31	18.00	5.095
2NRTIs + NNRT, percent	46.313	45.500	5.3006
2NRTI + PI, percent	33.625	34.000	3.9306
median CD4 cell count at the baseline, cells/mm^3	328.063	344.000	116.5467
2NRTIs + NRT, percent	22.188	22.000	9.8130
2NRTIs + INSTI, percent	1.072	0.900	0.5348
3NNRTIs, percent	0.325	0.200	0.2910
BMI > 25 kg/m2 (overweight), percent	21.500	21.000	2.4495
BMI > 30 kg/m2 (obesity), percent	12.688	12.500	2.7741

National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III); IDF = National diabetes federation; PI = protease inhibitors; NNRTIs = Non-nucleoside reverse transcriptase inhibitors; NRTIs = nucleotide reverse transcriptase inhibitors; INSTI = integrase inhibitors

and the median duration on HAART was 4.5 + 2.3 years. Around 72.2% of the study participants were on HAART medications and there were 20.6 HAART naïve participants in the studies at baseline. The NNRTIs were the most prevalent (61.9%) while only 2.5% were receiving INSTI (Table 2). 2NRTIs + NNRT regimen was the predominant combination (46.3%) followed by 2NRTI + PI (33.6%). The median CD4 cell count at the baseline was 328 cells/mm3 (Table 2).

In 69% of the reported studies, CMetS was defined using the NCEP ATP III criteria. Only 31.3% were reported using the IDF criteria. A family history of cardiac and metabolic diseases was reported by 25%, while smoking was identified as a risk factor in 62.5% of the reports. The prevalence of DM, high BP, cardiac diseases, and cancer were associated with CMetS in 31.3%, 62.5%, 12.5%, and 12.5% of the studies respectively. Lipodystrophy was reported in 18.8% and concerning dyslipidemia low HDL-c and high TG was reported in 87.5% and 81.3% of the studies (Table 3).

Discussion

This review aimed to assess the prevalence of CMetS, its risk factors, and co-morbidities in HIV infected persons using a systematically designed review study. Our finding revealed that the prevalence of CMetS in HIV infected persons was 20.6% by the NCEP-ATP III and 13.5% by IDF criteria. This was in agreement with the investigation done by Samaras & colleagues, where the prevalence was 18% by the ATP III and 14% by the IDF criteria. However, a bit higher figure was reported by Obirikorang & colleagues, where prevalence was 48.3% by ATP III and 42.3% by IDF criteria in HIV infected persons [58].

The European AIDS Clinical Society (EACS) guidelines on "the prevention and management of metabolic diseases in HIV" have strongly addressed that the risk of contracting CMetS is age-related [59]. In our aggregated data male participant was the predominant figure with 54.6% and the mean age was 42 year. This was a slightly higher figure than a survey done by Barbaro & colleagues in Italy, where the median age was 35 years (range, 22–50 years), [60]. Similarly, Mashinya and colleagues from South Africa reported that males were 2.94 times ($p < 0.05$) more likely to have metabolic disorders than females [61]. In another study conducted by Philip & colleagues from the U.S.A, 96.5% of patients who developed CMetS were male [9]. However, the issue of CMetS with gender has been reported differently among researchers. For example, Berhane and colleagues from Jimma (South West-Ethiopia) reported that female sex was independently associated with the prevalence of CMetS among PLWHA on HAART [62]. While Max and colleagues from Brazil reported that there was no significant association of CMetS by age and sex among the research participants [63].

Sedentary behavior has been defined as any activity with an energy expenditure of 1.0–1.5 metabolic equivalent units (METs). One MET is equivalent to the amount of oxygen

Table 3 Clinical report prevalence in association with CMetS

Descriptions	Count (Percent)
Report on CMetS using the NCEP ATP III definition	11(68.8)
Report of CMetS using the IDF definition	5(31.3)
Report of Framingham cardiac risk score (10–19%)	5(31.3)
Report of Framingham cardiac risk score (>20%)	2(12.5)
FH of CMetS	4(25.0)
High BP	10(62.5)
DM	5(31.3)
Current smoking	10(62.5)
Cardiac disease	2(12.5)
Cancer	2(12.5)
Alcohol consumption	4(25.0)
Baseline CD4 count report	10(62.5)
Baseline VL report	4(25.0)
LD report	3(18.8)
Sedentary life	3(18.8)
High TC	7(43.8)
High LDL-c	7(43.8)
Low HDL-c	14 (87.5)
High TG	13 (81.3)
High blood glucose	4(25.0)
BMI > 25 kg/m2 (overweight & obesity) report	10(62.5)

National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III); LD = Lipodystrophy; FH=Family History; CMetS = cardiometabolic Syndrome; DM = Diabetes Mellitus; BP = Blood Pressure; HAART = Highly Active Antiretroviral treatment; VL = viral load; High BP = BP ≥ 130/85 mmHg; Sedentary Life = <30 min active hours per day; High TC = Total cholesterol ≥ 200 mg/dL; High LDL = Low density lipoprotein ≥ 160 mg/dL; Low HDL = High density lipoprotein ≤ 40 mg/dL, High TG = Triglycerides ≥ 150 mg/dL; High blood glucose = Fasting blood glucose > 100 mg/dL; Body Mass Index (BMI)

consumed while sitting at rest and is equal to 3.5 ml O_2 per kg body weight x min [64]. A sedentary lifestyle such as watching television, playing video games, surfing the internet/using a computer, doing homework/revisions, attending extra classes (not within regular school hours), reading, and sitting while playing for more than 4 h per day can contribute to the incidence of CMetS [65–67]. In this review, only 18.8% of the studies reported that sedentary life was associated with CMetS. However, measuring a person's level of physical activity and measuring sedentary behaviors was a difficult task [68]. Guimarães and colleagues reported that a sedentary lifestyle was observed in 81% of HIV infected individuals. That was 4 times higher than our report [69]. Després JP reported that a sedentary lifestyle had contributed to the emergence of new drivers of CVD risks such as obesity and type 2 diabetes mellitus [70].

Cigarette smoking was the most important modifiable CV risk factor among HIV-infected patients (report from 62.5% of the studies). HIV-infected patients may have a higher prevalence of traditional CVD risk if they are smoking cigarettes than the general population [71]. Grinspoon and colleagues reported that smoking conferred a greater than twofold risk of Myocardial Infarction (MI). Hence, cessation of smoking is more likely to reduce CV risk than either the choice of antiretroviral therapy or the use of any lipid-lowering therapy [66].

Lipodystrophy (LD) was reported in 18.8% of our studies, whereas dyslipidemia such as low HDL-c and high TG was reported in 87.5% and 81.3% of the studies. Almost 63% of our studies reported that the combined overweight and obesity were responsible for greater than 33% of the metabolic alterations. This was in agreement with the study done by Max and colleagues, where the most frequent lipid abnormality in their research was Low HDL (53.5%), followed by high TG (36.1%). Ngatchou & colleague from Cameroon reported that fasting TGs and the atherogenic dyslipidemia ratio were significantly higher in HIV-infected persons than in controls [24]. According to Grinspoon and colleagues, such abnormalities in body composition had been responsible for 40 to 50% of ambulatory HIV-infected persons [66]. Similarly, Barbaro and colleagues reported that LD and metabolic alterations were associated with obesity in 62% of participants [60]. Dillon & colleagues further showed that HIV infection was associated with higher BMI [72] and many patients treated for HIV infection exhibit body composition changes, including peripheral fat atrophy and visceral lipodystrophy [73]. This is because people with HIV have an increased risk of developing a high waist circumference in both women and men [74].

In our review, the moderate to high risk of 10-year CVD risk using the Framingham equation was 31.3 and 12.5%, respectively. Mashinya and colleagues reported similarly that, a moderate to high 5-year CVD risk versus 10 year CVD risk was 31.1% and 6.7% respectively using the Framingham equation [61]. Barbaro & colleague reported that the annual incidence of Myocardial Infarction (MI) was 5.1/1000 ($P < 0.001$) (25). Philip & colleagues reported, 29 (4%) of the enrolled HIV infected participants developed acute MI in their investigation [9].

Our review revealed that 62% of the participants encountered high BP. Dillon & colleagues showed that HIV infection was associated with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP), [72]. Manner and colleagues reported that low CD4 cell count <50 cells/μL was associated with sustained hypertension as a complication of CVD [75]. The prevalence of DM was found to be 31.3% in our investigation. Ngatchou & colleague reported that the prevalence of impaired fasting glucose and diabetes was higher in HIV-infected persons than in controls (47% versus 27%, and 26% versus 1%, respectively; both $P < 0.01$) [24].

The median CD4 cell count at the baseline of our study was 328 cells/mm^3 as obtained from 62.5% of the studies.

However, the evidence for an association between viral replication, CD4 cells count and CVD events in large epidemiologic studies appeared even more robust than the link with immunosuppression [76]. One report by Kaplan and colleagues in the USA measured the impact of HIV infection on carotid artery stiffness (cardiovascular complication) and among HIV-infected women, adjusted for age, HIV medications, and vascular risk factors, and higher CD4 was significantly associated with decreased carotid artery dispensability [77]. Carter and colleagues reported that CMetS was associated with lower CD4 cell counts and higher HIV viral load [78]. Gutierrez and Balasubramanyam also reported that low CD4 count (<200 cells/μl) by itself was a risk factor for developing LD and dysglycemia [79]. Jotwani and colleagues found HIV-related factors such as high VL and low CD4 count increased the risk of end-stage renal disease as it was found to be increased by diabetes, hypertension, CVD, and hepatitis C co-infection [80].

Duration with HAART had also been a key determinant of CVD risk [81]. In our investigation, the mean duration with HAART medication was 4.5 ± 2.3 STD. Manner and colleagues found that duration with HAART was associated with sustained hypertension as a complication of CVD, and the highest proportion of hypertensive patients were observed in those who had prolonged HAART duration [75]. Mashinya and colleagues revealed that people on ART for less than 60 months were less likely to have a high TC/HDL-C ratio than people on ART for more than 60 months [61].

The use of HAART has significantly modified the course of HIV disease, lengthened survival, and improved the quality of life of HIV- infected persons. In contrast to this, recent data have raised concerns that HAART, HIV/AIDS itself, opportunistic infections (OIs), neoplasias, drugs used for OIs, and a combination of traditional vascular risk factors might have increased the risk for CMetS among PLWHA [60, 82, 83]. The common traditional vascular risk factors include aging, metabolic changes, smoking, high cholesterol, markers of innate immune activation, endothelial cell dysfunction, dilated cardiomyopathy, hyperinsulinemia, and thrombosis [83–85]. The emergence of such chronic disease complications in controlled HIV disease has then challenged the landscape of HIV clinical care [28, 86]. Some reports revealed HIV by itself can increase the relative risk of CVD by 61%, and the risk will be doubled for those taking HAART medications [87, 88]. HAART untreated patients had more likely to have low HDL and treated patients had high TGs level (39). Grinspoon and Deeks reported that compared with people without HIV infection, patients with the infection who are treated with HAART have an increased risk for several CMet complications [66, 89].

Currently, there are more than 25 HAART medications from six therapeutic classes for the management of HIV infection [89]. The most frequently prescribed antiretroviral regimen may vary from areas to area based on the guiding protocols, patients' condition, and availability of HAART medication. In our review, around 72.2% of the participants were on HAART medications and there were 20.6 HAART naïve participants at the baseline. The NNRTIs were the most prevalent (61.9%) while only 2.5% were receiving INSTI (Table 2). 2NRTIs + NNRT regimen was the predominant combination (46.3%) followed by 2NRTI + PI (33.6%). In a study done by Max and colleague the most frequently prescribed HAART medication was the combination of two NRTI with one NNRTI in 50.4% of the research participants, followed by the combination of two NRTI with one PI in 42.5%. The use of three distinct classes of antiretroviral drugs (NRTI, NNRTI, and PI) was recorded for 4.4% of patients while the majority of patients (64.6%) were on three drugs; 25.7% were on four drugs and 8.0% on five or more drugs. The most commonly prescribed drugs were lamivudine (92.9%), zidovudine (66.4%), and efavirenz (49.6%), [63]. However, only some HAART medications have been reported to have a significant association with the incidence of CMetS in PLWHA. A systematic review done by P. Wilson showed that PLWHA on HAART is approximately as twice as likely to develop CMetS compared to non-HIV infected persons [88]. The risk differed between classes of ART and specific anti-HIV drugs [87, 88]. According to the study done by Sterne and colleague, CV risks were increased in a majority of patients initiated with HAART [90] and patients on a PI regimen had a 5.2-fold higher risk of dyslipidemia, even after adjusting for sex, age, and duration of HIV infection [63]. Barbaro & colleague reported that the annual incidence of MI was high in PI-positive wing than PI negative wing ($P < 0.001$). Additionally, PI-positive wing was more prone to develop lipodystrophy and metabolic alterations (62% of patients) compared to PI negative wing (4% of patients), [60]. Carter and colleagues reported that the PI exposed group had a significantly lower CD4 cell count and higher HIV viral load than the unexposed group [78]. Multiple reports from diverse longitudinally studied patient groups indicate links between PI uses in class or specific PI drug and increased risk for MI. Among the specific PI's which have been identified to be associated with increased risks of MI were ritonavir, indinavir, and the fixed-dose combination of lopinavir/ritonavir [30]. However, our review study did not allow as seeing the impact of each class and individual drugs on the prevalence of the CMetS because of the difference in design and targeted outcome of the studies.

Dillon & colleagues reported the use of HAART medications can increase LDL and HDL and decrease HbA1 [72]. The use of non-nucleoside reverse transcriptase inhibitors (NNRTI), particularly efavirenz, has been demonstrated to give rise to pro-atherogenic serum lipid profiles. Early treatment (level of CD4 count up on initiating HAART) might reduce the negative effect of HIV on overall CV risk but

may produce increased drug-related complications [30]. According to the study done by Barbaro & colleague patients were categorized based on the HAART regimen they received as 2 NRTIs + PIs (PI-positive wing) or 1 NNRTIs +2 NRTIs (PI negative wing) and underwent laboratory testing every 4 months. The cumulative annual incidence of Coronary Artery Disease (CAD)-related events was 9.8/1000 in PI-positive wing and 0.8/1000 in PI negative wing ($P < 0.001$) [60]. This was because PIs may induce lipoatrophy by inhibiting sterol regulatory enhancer-binding protein 1 (SREBP1)–mediated activation of the heterodimer consisting of adipocyte retinoid X receptor and peroxisome proliferator-activated receptor (PPAR) or related transcription factors such as PPARγ coactivator [66].

Conclusions

CMetS is a common problem among HIV infected persons. Different risk factors can contribute to the development of CMetS in HIV infected persons. The result of many of the published articles revealed that age, sex, weight, sedentary lifestyle, waist circumference, smoking, HIV itself, HAART medications, other co-morbidities like diabetes, hypertension, etc. could contribute to the incidence, pathogenesis, and progression of CMetS in HIV infected persons. From these, smoking and hypertension were highly interrelated with CMetS progression. Hence, identifying these RFs and monitoring their incidence could bring better HAART outcomes in HIV infected individuals. The findings of this review will be vital for researchers working in HIV and CMetS theme and also for quality service delivery and good treatment outcomes in clinical setups.

Limitations of the study

Research outputs inaccessible freely from database systems were not included in this study. This study is not a fully specific design study. Hence, comparing all outcomes among the different study designs was not possible.

Acknowledgements We would like to thank Muhimbili University Health and Allied Sciences (MUHAS), Addis Ababa University (AAU), and the German Academic Exchanges Services (DAAD).

Authors' contributions MA, OM, and EE made substantial contributions to the conception and design of the study, analyzed and interpreted the data, drafted the manuscript, revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Funding information The fund for conducting the review was sponsored by DAAD.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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