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Hypertension is a key feature of the metabolic syndrome in subjects aging with HIV

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Abstract

With widespread and effective antiretroviral therapy, the life expectancy in the HIV population has dramatically improved over the last two decades. Consequently, as patients are aging with HIV, other age-related comorbidities, such as metabolic disturbances and cardiovascular disease (CVD), have emerged as important causes of morbidity and mortality. An overrepresentation of traditional cardiovascular risk factors (RF), toxicities associated with long exposure to antiretroviral therapy, together with residual chronic inflammation and immune activation associated with HIV infection are thought to predispose to these metabolic complications and to the excess risk of CVD observed in the HIV population.

The metabolic syndrome (MS) represents a clustering of RF for CVD that includes abdominal obesity, hypertension, dyslipidemia, and insulin resistance.

Hypertension is a prevalent feature of the MS in HIV, in particular in the aging population, and constitutes an important RF for CVD.

Physicians should screen their patients for metabolic and cardiovascular risk at the regular visits to reduce MS and the associated CVD risk among people aging with HIV, since many of RF are under-diagnosed and under-treated conditions.

Interventions to reduce these RF can include life-style changes and pharmacological interventions such as antihypertensive and lipid-lowering therapy, and treatment of glucose metabolism

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Statements

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Conflict of interest

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disturbances. Changes in antiretroviral therapy to more metabolic neutral antiretroviral drugs may also be considered.

Keywords

Metabolic syndrome; antiretroviral therapy; cardiovascular risk; HIV infection; hypertension

Introduction

With the wide availability of potent and well-tolerated highly active antiretroviral therapy (HAART) the HIV-infected population have experienced a dramatic improvement in life expectancy. Consequently, people aging with HIV are now facing age-related comorbidities and antiretroviral (ARV)-related complications such as metabolic disturbances, renal impairment, osteopenia/osteoporosis, neurocognitive impairment, atherosclerosis and cardiovascular disease (CVD).

The long-term exposure to ARV drugs, the chronic inflammation and immune activation associated with HIV infection, even if successfully treated, together with an overrepresentation of some traditional CVD risk factors (RF) in the HIV-infected individuals, predispose to different morphological and metabolic disturbances, including the features included in the metabolic syndrome (MS), which probably in part explains the increased risk of CVD described in the HIV-infected population.

The MS definition, developed for the general population, is used to describe a clustering of RF for CVD that includes abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia and insulin resistance (IR) and hypertension (HTA), and constitutes an important RF for the subsequent progression towards diabetes, atherosclerosis and CVD [1].

The MS shares some of these metabolic disturbances with the lipodystrophy syndrome (LDS) observed in some HIV-infected patients, which consists of a complex syndrome of fat redistribution with peripheral lipoatrophy and central lipohypertrophy, often together with metabolic and endocrine disorders as dyslipidaemia and IR.

Several definitions of MS have been developed (table 1), which makes comparison between studies difficult. The most widely used are the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF). The NCEP ATP-III requires the presence of 3 or more of 5 features of the definition. The definition was recently revised in 2005 to include lipid lowering and antihypertensive therapy as part of the criteria and reduced cut-off for serum glucose [2]. In the IDF definition abdominal obesity is an essential criterion for establishing the diagnosis and includes both gender and race specific cut-offs for waist circumference (WC)[3]. However, a recent consensus between the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and IDF have elaborated the AHA/NHLBI definition of the MS not including central obesity as a prerequisite [4].

Diagnosis, prevention and management of these modifiable RF are of pivotal importance in order to reduce progression of the atherosclerotic process and CVD risk in this population. In this article we review the recent literature on MS in the HIV-infected population and its clinical implications. We used for the purpose a systematic search in the literature using PubMed. The incorporating criteria were "*Metabolic syndrome*", "*HIV infection*", "*Hypertension*", "*Diabetes mellitus*" and "*Cardiovascular disease*".

Prevalence and predictors of the metabolic syndrome in HIV-infected populations

According to recent data from National Health and Nutrition Examination Survey (NHANES), the overall age-adjusted prevalence of MS in U.S. adults is increasing and between 2007–2010 was 34.3% [5]. However, lower prevalence rates are reported in European countries, ranging from 6–30% [6–9]. The real prevalence of MS among HIV-infected individuals is still of debate, with many observational studies reporting very wide-range estimates from 7–52% (table 2)[10–52]. These large differences are probably due to differences in study design, most being cross-sectional with small study groups, different population characteristics, and differences in the definition of MS applied, making it difficult to conclusively establish if the prevalence in individuals living with HIV-infection is comparable to that seen in the general population. However, two US studies observed similar MS prevalence rates in HIV-infected and HIV-uninfected individuals from the NHANES matched for age, sex, and race [14,25].

Despite these limitations, an increasing prevalence of MS with increasing age has uniformly been observed in different study populations [15,18,20,25,26,28–30,35–37,39,53,54]. In the Data-collection on Adverse effects of antiretroviral Drugs (D:A:D) study, prospectively following 33347 HIV-infected individuals at 212 clinics in Europe, Australia and the U.S., an increasing prevalence of MS was reported over time, from 19.4% in 2000–2001 to 41.6% in 2006–2007, partly due to aging of the cohort and growing awareness among physicians. Among those with MS, the majority had hypertriglyceridemia, low HDL-cholesterol and HTA (Table 3) [24]. MS prevalence also varies with gender and ethnicity. Few studies describe significantly higher rates of MS in women [30,36,43], whereas others report similar or higher prevalence in men [25,39]. In the latter, however, women developed MS at younger age, were more likely to be African American, less likely to be on ARV and had a higher BMI, central obesity and lower triglycerides (TG) compared to HIV-infected men with MS [25,39]. One US study including only women (1725 seropositive and 668 seronegative), found a significantly higher prevalence of MS in the HIV-infected group (33% vs. 22%, OR 1.79, 1.48–2.16)[20].

Regarding ethnic differences, data from NHANES showed that the prevalence of MS in the general adult population was lower among African American men than White or Mexican American men, and lower among White women than among African American or Mexican American women [55]. Mondy et al. reported similar findings, with HIV-infected women with MS more likely to be African American with high prevalence of obesity, whereas men with MS were more likely to be White [25]. In contrast, MS was less prevalent among

African American HIV-infected women than among White or Hispanic HIV-infected women in another recent study (31%, 42% and 34%, respectively, p 0.030) in which the MS diagnosis was mainly driven by high TG and low HDL-cholesterol levels [20]. However, most studies in HIV-infected individuals include mainly males and small proportion of minorities, making it difficult to draw clear conclusions on the impact of gender and ethnicity in the development of MS in this population.

The D:A:D study further explored the impact of applying the various definitions of MS, highlighting the difficulties assessing the MS in observational studies due to potential bias, missing data and measurement variability [24]. These difficulties were also revealed in another recent study reporting significantly higher prevalence rates of MS when applying the European Group for the Study of Insulin Resistance (EGIR) definition which requires insulin measuring and has lower thresholds for abdominal obesity, pointing at the central role of IR in the development of MS [45].

Abdominal obesity and sedentary lifestyle are key components in the development of the MS in the general population and also observed in HIV-infected populations, although there are notable differences in specific constituents of the MS [14,25,28,35,37,39,56–58]. HIV-infected individuals are more likely to have a lower BMI and a smaller waist circumference (WC) and waist-to-hip ratio than the HIV-uninfected individuals [25,27]. However, high prevalence of obesity is described among some groups of HIV-infected individuals, reflecting the epidemic rates of obesity also observed in the general population [25,51].

Changes in fat mass or adipocyte function are strongly associated with MS [14,18,22,54]. Lypodistrophy (LDS) is associated with HIV infection and ARV, especially thymidine analogues and older PI, and was more prevalent in earlier studies [59]. LDS is usually associated with IR, dyslipidemia and increased risk of CVD[43]. The body fat disturbances found in these patients might imply underdiagnosis of MS as they may have a low or normal BMI and low WC [43], not meeting the anthropometric MS criteria. Since individuals infected with HIV have increased visceral fat despite lower WC some has proposed different anthropometric cut-offs for HIV-infected persons [60]. One study showed that individuals with LDS meeting the MS criteria were at higher risk of CVD than those with LDS without MS [43]. ARV-induced mitochondrial toxicity, altered adipokine secretion and activity, hypoadiponectinemia and leptin deficiency, increased levels of inflammatory and prothrombotic makers such as CRP, TNF-alfa, IL6 and PAI-I, alterations in lipid metabolism with increased circulating free-fatty acids and reduced lipid storage ability resulting in IR, are some of the proposed underlying mechanisms [61–63].

Interestingly, a recent cohort study found that 37% of HIV-positive naïve individuals with MS at baseline no longer met MS criteria after 96 weeks of ARV, experiencing improvement in their metabolic profiles, especially in HDL and WC after cART initiation [58]. These data suggest the possible impact of the virus itself in the pathogenesis of MS.

The features of MS in the HIV-infected individuals differ from those in the general population, with HTA, hypertriglyceridemia and low HDL-cholesterol constituting the most prevalent components (Table 3), whereas in the general population abdominal obesity is a

major driver [25,29,36]. These differences might be attributed to the pathogenic contribution of the HIV infection and the metabolic effects of ARV in the development of MS in the HIV-population.

Hypertension in HIV-related MS

Hypertension is common among HIV-infected people with prevalence ranging from 4–54% [21,25,64–67], and as high as 96% among HIV-infected persons with MS in some studies (Table 3) [24,27,38,40,58]. HTA is a key feature of MS in HIV-infected patients, and an important RF for CVD in this population [25].

Some studies have found a higher HTA prevalence in HIV patients compared to HIV-uninfected individuals [68–70], whereas other studies have reported comparable estimates [25,27,71,72]. Similar to findings in the general population, identified predisposing factors for HTA in HIV patients includes older age, male gender, African-American or African-Caribbean ethnicity, higher BMI, central obesity, previous CV events, chronic kidney disease, family story of HTA and CVD, diabetes, dyslipidemia, MS and LDS [29,73–79]. It is thought that both HIV infection and exposure to ARV, especially duration of the exposure, through metabolic disturbances and endothelial damage might have an additional role in development of HTA in HIV patients. In the Multicenter AIDS Cohort Study (MACS) higher prevalence of systolic HTA was found in individuals on HAART for more than 2 year than HIV-infected men on HAART for less than 2 years or HIV-uninfected men after adjusting for age, race, BMI, and smoking [64]. In a Norwegian study the lowest prevalence of HTA was observed in HIV patients on cART for less than 2 years, observing a continuous increase in the prevalence from 23% in those treated for less than 2 years to 44% in those treated with cART for more than 5 years [66]. Similarly, finding from the D:A:D revealed increases in blood pressure (BP) over the first 2.3 years following cART initiation, although no independent deleterious effect of any specific ARV class was observed [67].

Findings from a recent Italian cross-sectional study assessing 1182 unselected consecutive HIV patients from outpatient clinics found that duration of HIV infection, CD4 T-cell count < 200/μl and duration of ARV were independently associated with HTA [74]. Similar findings are reported from recent studies from Uganda and Tanzania finding that lower nadir CD4 T-cell count and ARV were associated with HTA [70,80].

In a recent systematic review with meta-analysis including 30 cross-sectional and 9 cohort studies, exposure to ARV was significantly associated with higher mean systolic and diastolic BP and with increased risk of HTA in ARV-treated compared to ARV-naïve HIV-infected subjects (14.5% vs 10.5%, OR 1.68, 1.35–2.10) [81]. However, other studies have not found association of ARV and HTA [35,71,82].

Hypertension is associated with an increased risk of CVD, including AMI and stroke in HIV-infected as in the general populations [83]. Findings from the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) prospectively following 27059 HIV-positive veterans who are matched by age, gender, ethnicity, clinical site and calendar year to HIV-uninfected veterans, found that HIV, prehypertension and HTA were associated with an increased risk

of AMI. AMI risk increased with increasing BP in both HIV-infected and –uninfected veterans. However, AMI rates were significantly higher among HIV-infected veterans with HTA compared to HIV-uninfected veterans with HTA (aHR 2.57, 1.76–3.76 vs 1.47, 1.02–2.11), as well as in those on antihypertensive medication (aHR 2.76, 1.90–4.02 vs 1.92, 1.35–2.72). A 10mmg Hg increase in pulse pressure was associated with a 12% increased risk of AMI (HR 1.12, 1.06–1.19)[84].

Similarly, in the Swiss HIV Cohort Study assessing 2595 patients with HTA found that a 10 mm Hg increases in systolic BP was associated with a HR of 1.18 (1.06–1.32) of CV events [65].

Pre-diabetes in HIV-related MS

The prevalence of glucose metabolism disorders is an increasing condition among HIV-infected individuals. Markers of IR and increased glucose levels fulfilling criteria for pre-diabetes are included in the MS definitions (Table 1). Reported rates of pre-diabetes in HIV infected persons are ranging from 6–59%, and highly dependent on the applied screening methods (Table 3).

The prevalence of overt diabetes in HIV-infected subjects have been reported in some studies to be two-four fold increased than in healthy subjects[85–87], however, this excess risk has not been confirm in other studies [88–90]. A recent large study from the South Carolina Medicaid system, reported lower diabetes incidence in the HIV-group compared to HIV-uninfected controls in the latest period from 2004–2011 [88]. Similarly, the Danish HIV Cohort Study found no increased risk of diabetes compared to population-based matched controls in the latest period 1999–2010 [89]. The availability of newer ARV drugs with better metabolic profile could partly explain this difference, which is likely also related to genetic, demographic, dietary and other differences between study populations.

In addition to traditional RF for the development of diabetes including male gender, older age, BMI, African or Asian ethnicity, other HIV-related factors such as ARV (particularly exposure to older PI and thymidine analogues) and LDS are predictors of diabetes [41,90–92]. The D:A:D Study Group found that higher TG levels and low HDL were independently predictive of the development of diabetes[92].

The cardiovascular risk associated with MS

Occurrence of MS in the general population is associated with two-fold increased risk of CVD and in those without diabetes with a five-fold increase risk for development of diabetes [93].

Most studies of CVD risk in HIV-infected adults with MS have utilized surrogate measures of subclinical atherosclerosis through arterial imaging, which are independent predictors of CVD. A cross-sectional study investigated carotid intima-media thickness (c-IMT) and coronary artery calcium (CAC) scores, in 314 HIV-infected patients, 22.9% fitting the criteria for having MS. Persons with MS were more likely to have an abnormal common c-IMT measurement (OR 2.9, $p= 0.020$) and detectable CAC scores (OR 4.9, $p< 0.0001$)[30].

Another recent study found presence of CAC more common among HIV-infected patients with MS compared to HIV-uninfected controls [94]. Maloberti et al. explored arterial stiffness measured by aorto-femoral pulse wave velocity (PWV) and found that PWV was significantly greater in individuals with MS on HAART compared to HIV-infected individuals without MS on HAART or with HIV-uninfected controls both with and without MS [44]. Of note, treatment with metformin has been shown to prevent progression of CAC and calcified plaque volume in HIV patients with MS [95].

Nonetheless, although few studies have explored the predictive value of MS on CVD outcome, an increased risk of cardiovascular events has been observed among patients with MS. In the D:A:D study, a strong positive correlation between increasing number of the components of the MS and CVD risk in HIV individuals was observed. The risk of CVD among patients with MS at study entry was almost 3-fold higher (RR 2.89, 2.34–3.59) compared to those without MS, with a median follow-up of 5.1 person-years (3.2–6.5) and adjusting for age, sex, family history of CVD, smoking, calendar year and ARV exposure. The rate of CVD increased by 46% for each additional component (RR 1.46, 1.34–1.58) after adjustment for potential confounders. Diabetes was the strongest predictor of CVD (RR 2.31; 95% CI 1.83–2.92), while the presence of HTA was associated with a 26% increased risk of CVD (RR 1.26, 0.98–1.62). However, the correlation between MS and risk of CVD disappeared after adjusting for each of the individual components of the MS, with no evidence of synergistic effect between individual RF. These findings might suggest that the presence of MS as such in HIV-infection does not confer an extra CVD risk beyond its individual components [23].

The INITIO trial followed 881 HIV infected adults initiating HAART with thymidine analogues and efavirenz or/and nelfinavir for 3 years, and found that the presence of MS at baseline was associated with CVD without reaching statistical significance. However, incident MS during the study period was significantly associated with the development of CVD (HR 2.73, 95%CI 1.07–6.96). MS predicted CVD even more strongly than the Framingham Risk Score [15].

A recent study explored the impact of MS on all-cause mortality in 567 HIV-infected individuals and found that MS and high TG were both significantly associated with an increased risk of death after 36 months of follow-up (aHR 2.31 and 3.97, respectively) [96].

The role of antiretroviral therapy in the metabolic syndrome

In addition to genetic predisposition and lifestyle factors, ARV-related metabolic side effects and the HIV infection itself might play an important role in the pathogenesis of MS in HIV-infected patients.

As mentioned above, HAART initiation might contribute to an improvement in the metabolic profile in naïve HIV-infected patients [58] and the results from SMART study demonstrated its benefits in overall mortality and CVD[97,98].

However, some ARV drugs, and in particular PIs, can induce diverse metabolic disturbances like proatherogenic dyslipidaemia, lipodystrophic body changes (especially thymidine

analogues and older PI), impaired insulin sensitivity, adipocyte injury with altered adipocytokines secretion, vascular inflammation and endothelial dysfunction. Some retrospective studies have found a higher prevalence of MS associated with exposure to HAART [13,18,31,39] and in particular with older PIs [14,18,19,31,34,36,38,39,42,51,99] and thymidine analogues [14,19,33,42], however this has not been confirmed in other studies [12,15,16,20,25,27,29].

Specific PIs like lopinavir/ritonavir and indinavir have been associated with MS [14,19,34,100,101]. It is not clear if this association is also applicable for newer PI as darunavir and atazanavir with a more favourable metabolic profile [33,52]. Recent results from the Swiss HIV Cohort Study revealed that individuals exposed to atazanavir were less likely to develop MS [33]. Similarly, in the D:A:D analysis, atazanavir was not associated with acute myocardial infarction (AMI) or stroke. Data on darunavir are not yet available [102].

There are concerns about abacavir exposure and increased risk of AMI, although a causal relationship has not been confirmed [103]. The metabolic profile of abacavir is not unfavourable and the AMI risk associated with abacavir has been observed relatively soon after drug exposure. Proposed underlying mechanisms include platelet dysfunction and altered endothelial function. However, studies examining markers of endothelial function, coagulation and inflammation have not provided clear results.

Hypertriglyceridemia is generally less prevalent with NNRTI-regimens compared to PI-based regimens. Although efavirenz exposure was associated with MS in one recent cross-sectional study, nevirapine has been associated with safer lipid profile with increases in HDL-cholesterol [104,105] and lower prevalence of MS [29].

The role of HIV infection in the metabolic syndrome

HIV infection is associated with chronic inflammation and immune dysfunction even in virologically suppressed patients. Contributing factors to this residual inflammation includes microbial translocation, immune reactivation and immune senescence [106]. This may lead to changes in lipid metabolism, altered thrombosis and endothelial dysfunction.

The role of inflammation and hypercoagulation in the pathogenesis of MS, DM and atherosclerosis is well established in the general population and in the HIV-infected population [61,93,107]. In a number of studies, inflammatory markers such as hsCRP and IL-6 were increased in HIV-infected patients with MS compared to those without MS, and these markers have been identified as independent predictors of atherosclerosis and CVD also in the HIV population [18,34,108].

Uncontrolled HIV replication is a significant independent predictor of dyslipidemia with low levels of total cholesterol, low-density lipoprotein (LDL)- and HDL-cholesterol and increased levels of TG [109–111]. This is consistent with the findings from the SMART study, where in the ARV-interruption arm was observed an increased in TC/HDL ratio, decreases in HDL and increases in IL-6 levels observed in relation to increase in HIV-RNA [104]. HIV infection and chronic inflammation is associated with hypoalphalipoproteinemia,

altered HDL metabolism redirecting cholesterol to apo-B containing lipoproteins resulting in predominance of very-low-density lipoprotein (VLDL)-cholesterol and LDL-cholesterol, which is associated with an increased risk of CVD [112].

HIV-related chronic inflammation is thought to predispose to development of DM. Brown et al. observed a decline in most inflammatory markers after ARV initiation; however, markers of TNF-α activation remained associated with DM, suggesting that residual inflammation despite suppressive antiretroviral therapy could play a role [113]. Lower values of nadir CD4 T-cell count and longer duration of HIV infection have been reported to be associated with development of DM [85].

Clinical implications

Physicians should assess individuals for metabolic complications and CV risk at the routine clinic to reduce MS and the associated CVD risk among people aging with HIV, since many of components of MS are under-diagnosed and under-treated conditions.

Although the presence of MS is associated with an increased risk of CVD, important established CVD RF such as age, smoking, total cholesterol and physical inactivity are not included in the MS definition [24]. Thus, risk assessment for the individuals' absolute CVD risk is recommended and can be performed using a conventional risk prediction models such as Framingham, SCORE or other national prediction models, or by using newer models tailored to HIV-infected persons [114]. The estimated absolute CVD risk can guide the need for interventions.

Current HIV recommendations encourage the use of standard lifestyle interventions to prevent CVD including weight reduction, exercise, smoking cessation and eventually pharmacological interventions with anti-hypertensive and lipid-lowering therapy, and treatment of glucose metabolism alterations. In addition, other specific HIV-related recommendations have to be implemented in this population. Recent results of the START study proved the benefits of early ARV-initiation with reduced risk of AIDS and non-AIDS events [115]. In patients with high risk of CVD and diabetes, choice of ARV drugs with a more neutral metabolic and lipid profile as well as minimal drug-drug interactions with co-medications should be considered.

The ACC/AHA guidelines for the management of dyslipidaemia were recently updated, adapting lower thresholds for recommending statins, compared to the European guidelines [116,117].

Regarding glucose metabolism abnormalities, if glucose control is not achieved by lifestyle interventions alone, pharmacological therapy should be initiated, with metformin as the first choice of therapy. However, the current ADA and European Association for the Study of Diabetes guidelines emphasize a patient-centred approach, individualizing the choice of therapy with regards to patient preference, tolerability and drug-drug interactions [118].

Regarding clinical management of HTA, age, ethnicity and the presence of comorbidities such as renal impairment, diabetes, heart failure and ischemic heart disease together with

potential drug-drug interactions should guide the selection of the antihypertensive therapy [119].

Conclusions and future directions

Multiple studies have demonstrated an increased risk of CVD in patients living with HIV. Numerous factors are thought to explain this excess in risk such as ARV and its metabolic toxicities, chronic inflammation and immune activation associated with HIV infection and an overrepresentation of traditional RFs.

MS is a multifactorial and heterogeneous disorder constituting a cluster of modifiable RF for CVD, which varies in prevalence and features within and across populations. The clinical validity of MS in detecting individuals at high-risk of CVD is still controversial, based on the heterogeneity of the syndrome; however it encompasses several important CVD risk factors. Among these, the prevalence of HTA is notably high in HIV-related MS.

A number of novel strategies are currently being investigated as adjuvant therapy in HIV infected persons in order to further reduce inflammation (statins, hydroxychloroquine, leflunomide), and platelet activation (aspirin, clopidogrel), to alter gut microbiota (probiotics) and to treat other persistent viral co-infections like CMV or HSV [120].

While eagerly expecting the results of these studies, and their potential benefit in clinical use, there is still room to improve the appliance of conventional preventive measures. Smoking cessation and targeted interventions with anti-hypertensives and lipid-lowering therapy have reduced CVD rates, in the settings where these have been rigorously implemented (ref: Petoumenos, HIV Med. 2011 Aug;12(7):412-21., Klein, Clin Infect Dis. 2015 Apr 15;60(8):1278-80.).

However, the prevalence of HTA, metabolic disturbances and MS will continue to increase, as the HIV population grows older. It is important that physicians remain vigilant and identify individuals at high-risk of CVD in order to implement preventive and therapeutic interventions to halt disease progression.

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Table 1

Main work definitions for the metabolic syndrome

Definition	AHA/NHLBI 2009[4]	NCEP-ATPIII 2004[2]	IDF 2005[3]
Mandatory criteria			
	None	None	WC[a] with ethnicity specific values For Europeans: ≥ 94 cm (men) ≥ 80 cm (women)
Additional criteria	At least 3 of the following features	At least 3 of the following features	At least 2 of the following features
Central Obesity	Increased WC[a,b]	WC ≥ 102 cm (men) WC ≥ 88 cm (women)	
Triglycerides (TG)	≥ 150 mg/dL (1.7 mmol/L) or specific drug treatment for elevated TG	≥ 150 mg/dL (1.7 mmol/L) or specific drug treatment for elevated TG	≥ 150 mg/dL (1.7 mmol/L) or specific drug treatment for elevated TG
HDL-cholesterol	< 40 mg/dL (1.0 mmol/L) (men) < 50 mg/dL (1.3 mmol/L)(women) or specific drug treatment for dyslipidaemia	< 40 mg/dL (1.0 mmol/L) (men) < 50 mg/dL (1.3 mmol/L)(women) or specific drug treatment for dyslipidaemia	< 40 mg/dL (1.0 mmol/L) (men) < 50 mg/dL (1.3 mmol/L) (women) or specific drug treatment for dyslipidaemia
Blood Pressure	SBP ≥ 130 or DBP ≥ 85 mmHG or specific treatment for hypertension	SBP ≥ 130 or DBP ≥ 85 mmHG or specific treatment for hypertension	SBP ≥ 130 or DBP ≥ 85 mmHG or specific treatment for hypertension
Fasting glucose	≥ 100 mg/dL (5.5 mmol/L) or specific treatment for hyperglycaemia	≥ 100 mg/dL (5.5 mmol/L) or specific treatment for hyperglycaemia	≥ 100 mg/dL (5.5 mmol/L) or previously diagnosed type 2 diabetes

[a] Waist circumference

[b] It is recommended that the IDF cutoffs are used for non-Europeans and either the IDF or NCEP-ATPIII cut points used for people of European origin until more data are available.

Table 2

Prevalence studies of the metabolic syndrome in the HIV population

Study	Period	MS prevalence	MS definition	Age	% males	Study group	Design	Area
Bruno 2002[10]	–	39.6	EGIR	39.5	69	201	Cross-sectional	Italy
Gazzaruso 2002[11]	–	45.4	NCEP	37.1	58	553	Cross-sectional	Italy
Bernal 2007[12]	2003	15.2 11.4	NCEP IDF	42	83.3	210	Cross-sectional	Spain
Bergersen 2006[13]	2001	13.3	NCEP	43	80	357	Cross-sectional	Norway
Jacobson 2006[14]	2000–2003	24 Incidence 15/100py	NCEP	42	75	477	Prospective Cohort	US
Wand 2007[15]	2001–2004	8.5 7.8 Incidence 12/100py after 3 y follow-up	NCEP IDF	38	79	881	RCT, prospective	International
Palacios 2007[16]	2002–2004	16.6 baseline 25 after 48w of cART Incidence 14/100 py	NCEP, modified	40.9	83.6	60	Observational, prospective	Spain
Saint Martin 2008[17]	2003	7.1	NCEP	41	72	140	Cross-sectional	France
Samaras 2006[18]	–	17.6 14.4	NCEP IDF	41	84.1	788	Cross-sectional	International
Jerico 2005[19]	2003	17	NCEP	41.9	72	710	Cross-sectional	Spain
Sobieszczyk 2008[20]	2000–2004	33	NCEP	40	0	1725	Cross-sectional	US
Hansen 2009[21]	2004–2006	27	NCEP	44.1	81.4	566	Cross-sectional	Denmark
Estrada 2006[22]	–	15.8	NCEP	40.6	65.7	146	Cross-sectional	Spain
Worm 2009[23] **2010**[24]	2000–2007	19.4 (2000-2001) 41.6 (2006-2007)	NCEP, modified	38	74	24349	Observational, prospective	International (D:A:D)
Mondy 2007[25]	2005	25.5	NCEP	43	65	471	Cross-sectional	US
Adeyemi 2008[26]	2005–2006	34	NCEP	54	79	121	Cross-sectional	US
Bonfanti 2007[27]	2005	20.8 22.1	NCEP IDF	43	50	1263	Cross-sectional	Italy
Bonfanti 2010[28]	2007	12.3%	NCEP	37	75	292	Cross-sectional	Italy
Elgalib 2010[29]	2005–2006	14 10	NCEP IDF	39.5	74	678	Cross-sectional	UK
Mangili 2007[30]	2002–2004	22.9	NCEP	45	64	314	Cross-sectional	US

Study	Period	MS prevalence	MS definition	Age	% males	Study group	Design	Area
Falasca 2007[31]	–	42	NCEP	74	41	54	Cross-sectional	Italy
Baum 2006[32]	2002–2003	15.1	NCEP	41.7	74	118	Cross-sectional	US
Young 2009[33]	2000–2006	20	IDF	37 non-MS 39 MS	68	1218	Observational prospective	Switzerland
Biron 2012[34]	–	18.2	AHA/NHLBI	43	66.9	269	Cross-sectional	France
Bonfanti 2012[35]	2007–2010	7,5% develop MS in the 3 y follow-up Incidence: 2.6/100 py (at baseline 11.7% had MS)	NCEP	38	75.5	188	Observational, prospective	Italy
Alvarez 2010[36]	2006–2007	20.2	NCEP	41.9	74	4010	Cross-sectional	Latin America
Signorini 2012[37]	2005	20.6	NCEP	41	54.6	819	Cross-sectional	Brazil
Krishnan 2012[38]	2001–2007	Incidence 8.5/100 py (baseline 20%)	AHA/NHLBI	≤30 22% 30–40 38% 41–50 29% >50 11%	81.9	2247	Observational, prospective	US (ACTG-ALLRT)
Alencastro 2011 + 2012[39,40]	2006–2008	24.7 17.2 22.1	AHA/NHLBI NCEP IDF	38.6	50.1	1240	Cross-sectional	Brazil
Calza 2011[41]	2009	9.1	NCEP	36 non-MS 47 MS	66	755	Cross-sectional	Italy
Wu 2012[42]	2008–2009	26.2	NCEP	36.8 non-MS 44.5 MS	94.9	877	Cross-sectional	Taiwan
Freitas 2011 [43]	–	52.2 43.2	NCEP IDF	45	69	345	Cross-sectional (58.7% with LDS)	Brazil
Maloberti 2013[44]	–	19.4 cART 13.8 naïve (4.5 control)	NCEP	46.5 40.7 44.9	83 80.5 74.5	72 cART 36 naive	Cross-sectional	Italy
Cubero 2011[45]	–	10.1 15.1 28.3	NCEP IDF EGIR	39	75.5	159	Cross-sectional	Spain
Sawadogo 2014[46]	2011	12.3 10	NCEP IDF	41.4	29	400	Cross-sectional	Burkina Faso
Jantarapakde 2014[47]	2009–2011	22.2	AHA/NHLBI	37	46.2	584	Cross-sectional	Thailand
Guira 2015[48]	2011	18	IDF	44.8	31	300	Cross-sectional	Burkina Faso
Oguoma 2015[49]	2002–2013	31.7 27.9 28.1	WHO NCEP IDF	-	–	32 studies (10854)	Systematic review	Nigeria

Study	Period	MS prevalence	MS definition	Age	% males	Study group	Design	Area
Tesfaye 2014[50]	2012–2013	18.1 ARV 15.6 Naïve 25 ARV 22.5 Naive	NCEP IDF	32	32	374	Cross-sectional	Ethiopia
Tiozzo 2015[51]	2013	33	NCEP	48	46	89	Cross-sectional	US
Lombo 2015[52]	–	26 27	NCEP IDF	49.6	41	259	Cross-sectional	US

NCEP: National Cholesterol Education Program Adult Treatment Panel III

IDF: International Diabetes Federation

EGIR: European Group for the Study of Insulin Resistance

Table 3

Distribution of metabolic syndrome components among HIV-infected patients with metabolic syndrome.

Study	Worm 2010 (D:A:D)[24][a]	Krishnan 2012[38][b]		Krishnan 2015[58][c]				Bonfanti 2007[27][e]	Alencastro 2012[40][f]	
Total number of patients	23853	2247 Baseline	1797 During follow-up	2247		2247		1263	1240	
MS, n (%)	9913 (41.6)	450 (20)	478 (26.6)	139[d] (6.2) MS only at baseline		239[4] (10.6) MS both at baseline and after 96 weeks follow-up		263 (20.8)	213 (17.2) NCEP	274 (22.1) IDF 306 (24.7) AHA/NHLBI
				Baseline	After 96 w	Baseline	After 96 w			
High blood glucose (%)	11.1	6	43	45	22	42	59	12.7	15.1	
Increased BMI/WC (%)	16.7 (BMI)	15 (WC)	41	45	21	70	69	14.2 (WC)	20.9 (WC)	46.4 (WC)
High triglycerides (%)	99.0	26	83	66	29	69	87	50.4	35.9	
Low HDL (%)	95.1	71	75	96	26	93	72	44.9	38.8	
Hypertension (%)	96.1	23	78	63	33	76	74	35.9	28.3	

[a] Data form the Data Collection on Adverse Events of Anti-HIV Drugs study (D:A:D). The data in the table corresponds to the period 2006–2007

[b] Data from the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort from the enrolment period 2001–2007. The study examined prevalence, incidence and risk factors of MS in ARV-naïve HIV-infected patients initiating ARV

[c] Data from the ALLRT cohort study. They examined the progression of MS in ARV-naïve HIV-infected patients initiating ARV

[d] Individuals with evaluable data

[e] HIV-infected individuals from the SiMOne study

[f] Data from a cross-sectional study of HIV-infected patients from a public health Center for AIDS Care and Treatment in Porto Alegre, southern Brazil