

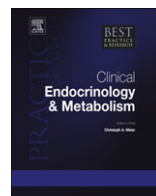


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The metabolic syndrome in HIV

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The metabolic syndrome (MS) is a term used to describe the clustering of risk factors for cardiovascular disease (CVD), including elevated triglyceride (TG), low high density lipoprotein cholesterol (HDL), hypertension, hyperglycemia/ insulin resistance and intra-abdominal obesity. This paper discusses why the prevalence of MS in the setting of HIV has been reported to range from 7–45% and how antiretroviral drugs might contribute to the development of MS. The MS has been reported to be a ‘CVD risk enhancer’, and much debate is ongoing on the independent risk of CVD associated with the MS. Based on a limited number of studies on MS in HIV with clinical end-points, there is no data to support that the MS is independently associated with an increased risk of CVD.

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Introduction

The metabolic syndrome (MS) specifies a cluster of interrelated risk factors for cardiovascular diseases, and was re-introduced by Reaven in 1988.¹ MS is a term used to describe this clustering of risk factors for cardiovascular disease (CVD), including elevated triglyceride (TG), low high density lipoprotein cholesterol (HDL), hypertension, hyperglycemia or insulin resistance/IR and intra-abdominal obesity.^{2–5} In studies, the prevalence of MS is highly dependent on individual's age, gender and ethnicity, and whether patients with diabetes mellitus (DM) have been included or not.⁶ Predictors for development of MS include excess body weight, physical inactivity, and aging.^{6,7} Since its introduction, the epidemiology and consequences of the syndrome have been studied intensively. However, these studies have been hampered by the lack of one widely accepted decision on how the MS should be defined. The four most commonly used definitions are released from The International Diabetes

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Federation (IDF),⁴ National Cholesterol Educational Guidelines (NCEP),² the World Health Organization (WHO),³ and the European Group for the Study of Insulin Resistance (EGIR)⁵; they are summarized in Table 1. In the IDF definition waist circumference is a key criterion while in the NCEP definition waist circumference is ranking alongside the other criteria. This is of potential relevance for establishing the prevalence of the MS in HIV-infected patients, since the fat redistribution and the reduced body mass index (BMI) characterizing this group will influence this estimate depending on which definition is used. Additionally there has been an increasing use of prophylactic interventions in HIV patients,^{8,9} such as use of lipid lowering drugs, which have a significant impact on the prevalence of dyslipidemia and thereby on the overall prevalence of MS.¹⁰ Finally, antiretroviral drugs may either directly (by affected the metabolism) or indirectly (by causing adipocyte injury) increase triglyceride levels, whereas increased triglyceride levels in the general population (in whom these definitions have been developed) obviously do not have such factors causing increased triglycerides and hence where increased triglyceride levels are particularly related to life style (abdominal obesity and alcohol consumption).

Prevalence of metabolic syndrome in HIV (untreated, treated)

The prevalence of the MS in HIV-infected individuals has been estimated to range from 7–45% depending on study design and available parameters,^{10–27} Table 2. The majority of studies have found elevated triglycerides and low HDL cholesterol to be the most predominant features of the MS, irrespective of which definition of MS was applied.^{10–16,18,19,21,23–26,28} This is in contrast with several studies in the general population in the resource-enriched part of the world, where the increasing fat epidemic causes increased waist circumference to be the most frequently seen component of the MS.^{29–32}

It is questionable to rely on single based measurements of the components in the MS. One study showed that the prevalence of MS was almost halved if two consecutive laboratory values were above (TG) or below (HDL) threshold, instead of only one measurement.¹⁰ Another concern, in particular in the setting of HIV where MS components may be affected by ART, is whether MS “reflects” the cumulative effect of the risk factors of blood pressure, HDL cholesterol and triglycerides acting over many years. As

Table 1
Definitions of the metabolic syndrome.

	NCEP 2001	NCEP modified 2004	EGIR 1999	WHO 1999	IDF 2005
No. of abnormalities or requirements	≥3	≥3	≥3	≥ 2 Glucose intolerance, insulin resistance or DM*	≥ 3 High risk, incl BMI ≥ 25**
Obesity	Men:WC ≥ 102 cm Women: WC ≥ 88 cm	Men: WC ≥ 102 cm Women: WC ≥ 88 cm	Men:WC ≥ 94 cm Women: ≥ 80 cm	Men:W/H ratio >0.9 Women: W/H ratio >0.85 and/or BMI ≥ 30	** see above
Triglycerides	≥1.7 mmol/L	≥ 1.7 mmol/L	≥ 2.00 mmol/L	≥ 1.7 mmol/L	≥ 1.7 mmol/L
HDL	Men:≤1.00 mmol/L Women: ≤1.3 mmol/L	Men:≤1.00 mmol/L Women:≤1.3 mmol/L	All: <1.00 mmol/L	Men: <0.9 mmol/L Women: <1.0 mmol/L	Men:≤1.00 mmol/L Women:≤1.3 mmol/L
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg	≥140/90 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg
Fasting glucose	≥6.1 mmol/L	≥ 5.6 mmol/L	≥ 6.1 mmol/L	*see above	≥5.6 mmol/L
Microalbuminuria	–	–	–	Urinary albumin excretion rate ≥ 20 µg/min	–

Table 2

Prevalence of the metabolic syndrome in HIV positive persons.

	MS prevalence	Definition used	% Males	Age	N	Design	Comments
Gazzarusso 2002	45.5%	NCEP	66	37	553	? Letter, cohort study	HIV patients exposed to ART
Bruno 2002	39.6	EGIR	80	39	201	Observational, prospective	Heavily pre-treated with ART
Estrada 2006	15.8	NCEP	66	41	146	Cross-sectional	Use of ART not assessed. MS higher in patients with LDS
Bergersen 2006	15	NCEP	80	42	357	Cross-sectional	Higher proportion of MS and IR in ART treated compared to naive
Palacios 2007	16.6	NCEP modified	83	41	60	RCT, prospective	No risk associated with use of ART
Bonfanti 2007	20.8	NCEP	50	43	1263	Case-control	No risk associated with use of ART
Samaras 2007	22.1	IDF	72	41	114	Cross-sectional	Risk of MS associated with use of PI's
Jerico 2005	14%	NCEP	84	41	139	Cross-sectional	Risk of MS associated with past use of PI's
Mondy 2006	18%	NCEP	80	42	710	Cross-sectional	Risk of elevated TG's associated with use of PI's
Baum 2006	17	NCEP	66	43	471	Cross-sectional	HIV drug users
	25.5	NCEP	74	42	118	Cross-sectional	Risk of elevated TG's associated with use of PI's
Hansen 2009	15.1	NCEP	80	44	566	Cross-sectional	Risk of elevated TG's associated with use of PI's and NRTI's
Wand 2007	27	NCEP	80	38	881	RCT, prospective	No risk associated with use of ART
Falasca 2007	8.5	IDF	41	74	54	Cross-sectional	Patients with LDS
Sobie.. 2008	42	NCEP	0	42	36	Cross-sectional	Risk of MS associated with ART
Jacobson 2006	33	NCEP	75	40–49	477	Prospective cohort	No risk associated with use of ART
Mangili 2007	24	NCEP	64	45	314	Cross-sectional	Use of LPV/r and ddi associated with MS
Adeyemi 2008	22.9	NCEP	79	54	121	Cross-sectional	MS in patients < 50 years: 31.2%
Worm 2009	34	NCEP	74	38	24,349	Observational, prospective	Cohort of HIV-infected patients, predominantly ethnic minorities >50 years old
Jevtovic 2009	19.4	NCEP modified	69	44	399	Cross-sectional	Use of ART not assessed. Impact of different definitions of MS explored
Bonfanti 2010	29.1	NCEP	75	37	357	Cross-sectional	Use of PIs associated with MS
	12.3	NCEP				Cross-sectional	Advanced HIV disease associated with MS

MS = Metabolic syndrome, NCEP = National Cholesterol Educational Guidelines Programme, EGIR = European Group for the Study of Insulin Resistance, IDF = The International Diabetes Federation, LDS = Lipodystrophy syndrome, TD = elevated triglycerides, ART = Antiretroviral therapy PI = Protease inhibitors, NRTI = Nucleoside reverse transcriptase inhibitor, IR = Insulin resistance, LPV/r = ritonavir-boosted Lopinavir, ddi = Didanosine.

such, baseline measures of the components might not be appropriate or give a clinically relevant index of metabolic syndrome prevalence. The relative change of components might be of greater relevance, however no data exist in this regard, particularly in people with treated HIV-infection.

The majority of studies in HIV have consisted of predominantly males (Table 2), reflecting the HIV epidemic in gender distribution in the resource-enriched part of the world. Only one study has explored the prevalence amongst HIV positive females and compared this to that in HIV negative female and reports a prevalence of MS of 33% vs 22%, respectively.¹⁸ No firm conclusions on the impact of gender can be drawn as only a few studies have sufficient power to make such stratified analyses,

however, one study found that women with MS are younger than their male counterparts, are less likely to be on ART and are more obese,²⁶ whereas the opposite is reported in older HIV females.²¹

Impact of treatment on MS, and incidence of MS

It is well documented that ART can induce dyslipidemia,³³ insulin resistance/DM^{34–36} and morphological changes with loss of peripheral subcutaneous fat and/or central fat accumulation, the lipodystrophy syndrome (LDS).³⁷ Conversely, the relationship between hypertension and ART is controversial.^{38,39} In particular elevated TG is a frequent side-effect of antiretroviral therapy.^{40–42,33} Specific antiretroviral therapies are known to affect individual components of the metabolic syndrome adversely, such as increasing triglycerides (ritonavir lopinavir/ritonavir, more so than other ritonavir-boosted protease inhibitors),^{33,41,43} but also efavirenz.^{42,44} Increasing fasting glucose has been associated with use of indinavir and lopinavir/ritonavir.^{45,46} Other therapies have been associated with improvements in metabolic profiles, such as increases in HDL cholesterol (nevirapine and efavirenz⁴⁷ 48). HIV-infected individuals are less likely to be obese^{49,26} and have a smaller waist circumference and smaller waist-to-hip ratio than HIV-uninfected controls.^{26,50} One paper studying body composition and obesity using several different anthropometrics did however not find any differences in BMI, but found an accumulation of abdominal subcutaneous fat in particular amongst HIV-infected women, compared to HIV-uninfected women.⁵¹

The exact contribution from ART to the prevalence of MS remains unclear. This is explained by the fact that the majority of HIV patients in studies on MS are already on ART, and only a few of studies have studied use of ART, or individual drugs. There is a trend (albeit not always statistical significant) of a higher prevalence of MS in “ART exposed” compared to ART naïve populations^{20,15,26} (Table 2). A small study in ART naïve HIV positive persons commencing ART (n = 60) found an increase in MS prevalence from 16.6% before to 25% after 48 weeks of ART (P = 0.0001). During follow-up, 7/50 patients developed MS – i.e. an incidence of 14/100 patient-year.⁵² Another study, also in treatment-naïve young HIV positive persons (n = 881) also reported an increase in MS after treatment initiation. During 3 years of follow-up, 234 (12/100 patient-years) and 178 (8/100 patient-years) developed MS according to NCEP and IDF definitions, respectively.¹² A much lower incidence rate was reported in treatment experienced patients; 88 new cases of metabolic syndrome over a total of 7026 person-months of follow-up for an incidence rate of 1.2 per 100 person-months. In this study the risk of developing MS was not associated with duration of treatment.¹⁶

There are not sufficient data from these predominantly cross-sectional studies to fully understand if there is relationship with duration of therapy, or if the higher percentages of MS in ART exposed is caused by the fact that these patients are older than the naïves. However, based on data from prospective studies it seems like use of ART has an impact of the incidence of the MS.

Impact of HIV-infection per se

HIV in itself is well-known to cause lipid perturbations – in particular the combination of increased TG and reduced HDL.^{53,54} Based on findings from the SMART study⁵⁵ and others, attention and research agenda's have focused in recent years on the impact of inflammation on CVD risk factors. Recently it has been suggested that a higher risk of MS is associated with advanced HIV disease. A viral HIV RNA load exceeding 100,000 RNA copies/ml and a low CD4 count of less than 100 cells/mm³ were found strongly associated with the development of MS in a cross-sectional study of 293 patients.⁵⁶ Others have also reported high viral load, or a previous AIDS defining condition as risk factors for MS^{16,18} or elevated CRP to be involved in the development of MS in HIV positive persons.^{11,52} The largest study of cardiovascular disease risk factors, the prospective D:A:D study of more than 33,000 patients, did not find neither HIV nor CD4 count associated with a risk of MS.⁵⁷

Metabolic syndrome and cardiometabolic outcomes

It remains unclear whether the MS, as an entity, contributes independent additional prognostic information on CVD risk over and above the well-established CVD risk factors it is based on. If so, we

would expect to see synergism or interactions between the 5 components. So far, few studies from the non-HIV population exploring the predictive value of MS on a CVD outcome have specifically addressed this question by adjusting for all the components of the syndrome. These found lower hazard ratios for the MS compared to the individual risk factors or that MS by itself does not contribute with any additional information.^{58,59,60} Or they find the risk of MI associated with MS in similar range to that risk DM confers. In a large-scale multi ethnic study of more than 26,000 persons from 52 countries, the risk of MI associated with MS was 2.69 (95%CI 2.45–2.95), DM conferred a risk of 2.72 (95%CI 2.53–2.92) and hypertension 2.30 (95%CI 2.46–2.76).³² From this, there does not seem to be any multiplicative effects or interactions between the 5 risk factors in the syndrome definition, thereby questioning if the MS provides any information additional CVD risk information.

A large cohort study of more than 33,000 explored the relationship between the metabolic syndrome and 617 clinical CVD end-points in HIV-infected individuals. A strong positive correlation was reported between the number of components of the metabolic syndrome that were present and CVD risk. Individuals with the MS at study enrolment (≥ 3 of the factors) were almost three times as likely (relative rate = 2.89; (95% CI 2.34, 3.59) to develop CVD as those without the MS at study enrolment but this did not remain significant (adjusted relative rate = 0.85 (95% CI 0.61, 1.17), $p = 0.32$) after controlling for each of the individual risk factors themselves, suggesting that it is these factors, rather than any particular combination of them, that determines CVD risk.⁵⁷ This study could not identify any synergistic effects between the 5 components in the syndrome. Data from the treatment-naïve sub-study of the INITIO trial, presented a *post hoc* analysis (based on 21 CVD events) suggested that incident MS was associated with CVD, but this did not reach statistical significance.¹² It remains unclear whether the metabolic syndrome, as an entity, in the setting of HIV contributes additional prognostic information on CVD risk.

The debate about the existence of the MS as an entity and its prognostic value is ongoing.^{61,62,63,64} Some of the critique has focused on the independent predictive ability of the MS for CVD, the arbitrary use of binary cut-offs and why some risk factors should be encompassed in the syndrome definition whereas other obvious CVD risk factors as smoking, total cholesterol (TC) and inflammatory markers should not.⁶¹ The MS provides no information on absolute underlying risk, which in many CVD risk equations includes smoking and TC as well. Another discussion point, in particular relevant for HIV positive persons, is that the MS ‘reflects’ the cumulative effect of risk factors, e.g. blood pressure, HDL cholesterol, and triglycerides, acting over many years. Measurements of such at baseline may not accurately represent lifetime exposure to these risk factors.⁵⁷ The metabolic syndrome was not devised as a predictive tool for cardiovascular disease but rather for the purpose of identifying persons with insulin resistance. However, current guidelines for the prevention of CVD encourage identification of the metabolic syndrome in clinical settings.² A recent WHO expert consultation states “the MS is a pre-morbid condition rather than a clinical diagnosis”.⁶⁴

The MS should not be used for identification of patient’s absolute underlying risk for CVD.

Summary

The 5 components in the MS, elevated triglyceride TG, low HDL, hypertension, hyperglycemia/insulin resistance and intra-abdominal obesity, are all well-established risk factors for DM and CVD. All components in the MS are (theoretically at least) modifiable risk factors. With the aging of the HIV-infected population, brought about by an increased life expectancy after the use of combination antiretroviral therapy, the prevalence of metabolic risk factors is likely to increase thereby leading to more DM and CVD.⁶⁵ The role of ART in the development of MS is not clear, but several studies has shown ART to have an impact of some of the individual components of the MS, such as high TG and low HDL, which are both frequently seen in HIV positive persons. Despite the fact that there is no data to support that MS as an entity to be an independent predictor of CVD in HIV positive persons, there seems to a strong association between an increasing number of the components of the metabolic syndrome and CVD risk. Identification and management of all CVD factors in this population, including those not included in the metabolic syndrome definition e.g., smoking and total cholesterol, continues to be of great importance. As the MS does not provide any information on the absolute underlying risk

of CVD, we recommend to assess this by using either conventional tools and⁶⁶ or the newly developed CHD risk calculator for HIV positive persons.⁶⁷

Practice point

- The prevalence of MS in HIV ranges from 7–45%
- The prevalence is highly dependent of which MS definition used
- Male gender, older age are risk factors for MS
- More risk factors are associated with an increased rate of CVD.
- There is no data to support that MS predicts the risk for CVD in HIV positive persons.

Research agenda

- Future studies should confirm and evaluate if the MS in HIV positive persons is an independent predictor of CVD.
- The contribution of ART to the development of MS is not fully understood.
- The MS does not provide any information on absolute underlying CVD risk, other prediction models are required for this assessment, therefore
- Future studies should focus on the prevention of individual risk factors of the MS.

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