High prevalence of the metabolic syndrome in HIV-infected patients: impact of different definitions of the metabolic syndrome

Signe W. Worm[a], Nina Friis-Møller[a], Mathias Bruyand[d], Antonella D'Arminio Monforte[e], Martin Rickenbach[f], Peter Reiss[c], Wafaa El-Sadr[g], Andrew Phillips[b], Jens Lundgren[a], Caroline Sabin[b], for the D:A:D study group

Introduction: This study describes the characteristics of the metabolic syndrome in HIV-positive patients in the Data Collection on Adverse Events of Anti-HIV Drugs study and discusses the impact of different methodological approaches on estimates of the prevalence of metabolic syndrome over time.

Methods: We described the prevalence of the metabolic syndrome in patients under follow-up at the end of six calendar periods from 2000 to 2007. The definition that was used for the metabolic syndrome was modified to take account of the use of lipid-lowering and antihypertensive medication, measurement variability and missing values, and assessed the impact of these modifications on the estimated prevalence.

Results: For all definitions considered, there was an increasing prevalence of the metabolic syndrome over time, although the prevalence estimates themselves varied widely. Using our primary definition, we found an increase in prevalence from 19.4% in 2000/2001 to 41.6% in 2006/2007. Modification of the definition to incorporate antihypertensive and lipid-lowering medication had relatively little impact on the prevalence estimates, as did modification to allow for missing data. In contrast, modification to allow the metabolic syndrome to be reversible and to allow for measurement variability lowered prevalence estimates substantially.

Discussion: The prevalence of the metabolic syndrome in cohort studies is largely based on the use of nonstandardized measurements as they are captured in daily clinical care. As a result, bias is easily introduced, particularly when measurements are both highly variable and may be missing. We suggest that the prevalence of the metabolic syndrome in cohort studies should be based on two consecutive measurements of the laboratory components in the syndrome definition.

AIDS 2010, **24**:000–000

Keywords: epidemiology, HIV, metabolic syndrome, observational study

[a]Copenhagen HIV Programme (CHIP), University of Copenhagen, Copenhagen, Denmark, [b]Research Department of Infection and Population Health, University College London, London, UK, [c]HIV Monitoring Foundation, Academic Medical Center, Amsterdam, The Netherlands, [d]INSERM E0338 and U593, ISPED, Université Victor Segalen, Bordeaux, France, [e]Hospital San Paolo, University of Milan, Milan, Italy, [f]University Hospital, Lausanne, Switzerland, and [g]Columbia University/Harlem Hospital, New York, New York, USA.

Correspondence to Dr Signe W. Worm, MD, PhD, Copenhagen HIV Programme (CHIP), University of Copenhagen, Copenhagen, Denmark.

Tel: +45 3545 5757; e-mail: sww@cphiv.dk
Received: 20 August 2009; revised: 6 October 2009; accepted: 14 October 2009.

DOI:10.1097/QAD.0b013e328334344e

ISSN 0269-9370 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

Introduction

The metabolic syndrome is the term used to describe a clustering of risk factors for cardiovascular disease (CVD): high triglycerides, low high-density lipoprotein (HDL), hypertension, hyperglycemia/insulin resistance and abdominal obesity [1]. The underlying premise of the metabolic syndrome requires that individuals should have at least one measurement/assessment for each of the five components; individuals are then defined as having the metabolic syndrome if at least three of the five components are present. In the general population, the prevalence of the metabolic syndrome increases with older age. In HIV infection, dyslipidaemia and alterations in glucose homeostasis are often observed, both as a consequence of exposure to antiretroviral drugs and due to dietary and lifestyle factors [2–4]. Prior studies [5–8] have reported that the composition of the components making up the metabolic syndrome differs in HIV-infected individuals compared with the general population, with hypertriglyceridemia and low HDL cholesterol being predominant features in HIV metabolic syndrome. Furthermore, the metabolic syndrome has several features in common with the lipodystrophy syndrome observed in HIV-infected individuals, including insulin resistance, dyslipidaemia and fat redistribution [9].

The application of the metabolic syndrome to an observational research setting may be complicated by the presence of missing data and/or measurement variability. Several HIV studies [5,8,10,11–13] have explored the prevalence of the metabolic syndrome, very often without presenting information on how they dealt with these issues. However, both factors are likely to have an impact on the estimated prevalence of the metabolic syndrome. Therefore, the aim of this study is to explore differences in the reported prevalence of the metabolic syndrome when these factors are incorporated into statistical analyses.

Methods

Study population

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is a prospective, observational study formed by the collaboration of 11 cohorts following 33 347 HIV-infected individuals at 212 clinics in Europe, Australia and the United States. The primary objective of the study is to investigate the possible association between combination antiretroviral therapy (cART) and the risk of myocardial infarction (MI). The D:A:D study methodology has been described in detail elsewhere [14,15]. Secondary objectives include the assessment of other risk factors for CVD in this population, including the metabolic syndrome [16].

Data collection

Patients are followed prospectively during visits to outpatient clinics scheduled as a part of regular medical care. At enrolment and at least every 8 months thereafter, standardized data collection forms are completed at the sites providing information concerning family history of coronary heart disease, prior history of CVD and diabetes, cigarette smoking, blood pressure (BP), lipid-lowering and antihypertensive therapy, the presence of clinical signs of lipodystrophy and serum lipid levels (total cholesterol, HDL cholesterol, triglycerides and information on fasting conditions), as well as HIV-related information (antiviral therapy, CD4 cell counts, HIV viral loads and dates of diagnoses of all AIDS-defining diseases).

Statistical methods

We described the prevalence of the metabolic syndrome among patients under follow-up in the cohort at the end of each calendar period (2000–2001, 2002, 2003, 2004, 2005 and 2006–2007) and changes in the relative contribution of each of the metabolic syndrome components over these six periods.

Among patients who were not known to have the metabolic syndrome at study enrolment, we then described the incidence of the metabolic syndrome over time using multivariable Poisson regression models (GENMOD procedure, SAS software, version 9.1; SAS Institute Inc., Cary, North Carolina, USA). Follow-up time was counted from the date of study entry to the date when the patient first met the criteria for the metabolic syndrome, death, 1 February 2007 or 6 months after the patient's last clinic visit, whichever occurred first. As the main analyses assumed that the metabolic syndrome was irreversible, only one period of follow-up was included for each patient in these analyses. As with other analyses from the D:A:D study, to fit these models, each person's follow-up was divided into a series of consecutive 1-month periods, and a patient's covariate data were updated at the start of each month.

Definition of the metabolic syndrome

For our main analyses (definition 1), we considered a modified National Cholesterol Education Program (NCEP) definition of the metabolic syndrome [1], which incorporates five criteria: triglycerides of at least 1.7 mmol/l, HDL of 1.0 mmol/l or less in men and of 1.3 mmol/l or less in women, hypertension (SBP >130 mmHg or DBP >85 mmHg), BMI of more than 30 kg/m^2 as a surrogate for waist circumference and a diagnosis of diabetes mellitus replacing fasting glucose. A patient was defined as having the metabolic syndrome on the first date when at least three of the five components were present. As these data were collected as a part of routine medical care, information on some components of the metabolic syndrome may have been missing at times; for the purposes of our main analyses, where information was missing for an individual on any

component of the definition, that component was assumed to be absent. Furthermore, for these main analyses, the various components of the metabolic syndrome were assumed to be irreversible; thus, once an individual had met one of the five criteria, it was assumed that the individual would always meet those criteria.

We then compared the results from the analysis using definition 1 with those obtained when the definition was modified to deal with missing data and/or measurement variability. In particular, we considered the following modifications to the definition. First, the use of lipid-lowering therapy (LLT) was treated as an equivalent criterion to triglycerides or HDL in the definition, with the restriction that each patient could meet a maximum of two lipid criteria (i.e. if a patient met the triglycerides, HDL and LLT criteria, then the patient would still only be considered as meeting two of the five metabolic syndrome criteria). Similarly, the use of antihypertensive medication was treated as an equivalent criterion to high SBP or DBP when assessing the criteria for hypertension (definition 2). Second, we explored the effect of missing data on our conclusions, by only including follow-up that occurred while a patient had complete information on at least three of the five metabolic syndrome components (definition 3). Third, our analyses of trends over time were repeated after assuming that the lipid and hypertension components of the metabolic syndrome could be reversible; thus, if a patient experienced a drop in triglycerides or BP below the threshold, or an increase in HDL above the threshold, irrespective of the cause, they no longer met those criteria (definition 4). Fourth, we modified the definition of the metabolic syndrome further to ensure that all measurements (triglycerides, HDL cholesterol or BP) had been done in the previous year; if a patient did not have a measurement within any 1-year period, this information was assumed to be missing until a new measurement became available (the requirement that patients had information on at least three of the five components was also applied here, definition 5). Fifth, as the laboratory components of the metabolic syndrome may be subject to considerable measurement variability, we re-ran our main analyses (irreversible metabolic syndrome, missing = absent) after requiring that at least two consecutive measurements were required to be above (or below) each threshold before that criterion was met (definition 6).

Results

The prevalence of the metabolic syndrome at entry in the Data Collection on Adverse Events of Anti-HIV Drugs study

The main characteristics of the 33 347 individuals included in the D:A:D study and the components of the metabolic syndrome that were present at study entry are shown in Table 1. At study entry, 15 759 (47.3%) individuals were known to have high triglycerides, 10 038 (30.1%) had low HDL cholesterol, 5291 (15.9%) had hypertension, 1705 (5.1%) had high BMI and 952 (2.9%) had a diagnosis of diabetes mellitus. Overall, 2439 (7.3%) individuals met the criteria for the metabolic syndrome at study entry. Of the 33 347 patients in the study, 523 (1.6%) had already experienced a cardiovascular event prior to study entry.

Table 1. Characteristics of individuals at entry in the Data Collection on Adverse Events of Anti-HIV Drugs study.

Total number of patients	33 347 (100.0)
Male sex; *n* (%)	24 692 (74.0)
Mode of infection; *n* (%)	
Homosexual/bisexual	14 376 (43.1)
IDU	5951 (17.9)
Heterosexual	10 047 (30.1)
Other/unknown	2973 (8.9)
Race; *n* (%)	
White	14 890 (44.7)
Black	3470 (10.4)
Other	978 (2.9)
Unknown	14 009 (42.0)
Median age, years (IQR)	38 (33-45)
Diagnosed with AIDS; *n* (%)	8214 (24.6)
Current smoker; *n* (%)	11 316 (33.9)
Ex-smoker; *n* (%)	5617 (16.8)
Any exposure to; *n* (%)	
PIs	19 332 (58.0)
NNRTIs	11 063 (33.2)
NRTIs	24 299 (72.9)
Previous CVD; *n* (%)	523 (1.6)
Components of the MS; *n* (%)[a]	
Triglycerides	15 759 (47.3)
HDL	10 038 (30.1)
BMI	1705 (5.1)
Hypertension	5291 (15.9)
DM	952 (2.9)
Met definition of the MS; *n* (%)	2439 (7.3)

CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IQR, interquartile range; MS, metabolic syndrome; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Where data were missing, it was assumed that the component was absent; thus, the denominator for all percentages was 33 347.

The prevalence of the metabolic syndrome by calendar year

Between 23 853 and 28 661 individuals were under follow-up in the D:A:D study in the six calendar periods. Among all patients under follow-up, the proportion of individuals with each component of the metabolic syndrome increased over time (Table 2). As a result, the proportion of patients with the metabolic syndrome (definition 1) also increased from 19.4% of those under follow-up in 2000/2001 to 41.6% of those under follow-up in 2006/2007. Among those with the metabolic syndrome, the majority of patients met the triglycerides, HDL and hypertension criteria; the relative importance of these components of the metabolic syndrome remained similar over time, although the proportion of patients meeting the hypertension and triglycerides

Table 2. Individuals under follow-up in the Data Collection on Adverse Events of Anti-HIV Drugs study, the proportion of individuals meeting each of the metabolic syndrome criteria (definition 1) and the proportion with the metabolic syndrome at the end of each calendar period.

	Calendar period[a]					
Up to end of	2000/2001	2002	2003	2004	2005	2006/2007
Number of patients under follow-up	24 349	26 615	28 449	28 661	26 265	23 853
% of patients under follow-up with						
DM	1008 (4.1)	1140 (4.3)	1303 (4.6)	1344 (4.7)	1275 (4.9)	1245 (5.2)
BMI	1469 (6.0)	1796 (6.8)	2094 (7.4)	2323 (8.1)	2343 (8.9)	2288 (9.6)
Triglycerides	16 325 (67.1)	18 283 (68.7)	19 728 (69.4)	20 842 (72.7)	19 894 (75.7)	18 826 (78.9)
HDL	11 660 (47.9)	13 671 (51.4)	15 531 (54.6)	16 896 (59.0)	16 099 (61.3)	15 583 (65.3)
Hypertension	7243 (29.8)	9069 (34.1)	10 670 (37.5)	12 429 (43.4)	12 634 (48.1)	12 998 (54.5)
n (%) with MS	4712 (19.4)	6328 (23.8)	7647 (26.9)	9121 (31.8)	9418 (35.9)	9913 (41.6)
% of patients with the MS with						
DM	706 (15.0)	850 (13.4)	1034 (13.5)	1120 (12.3)	1073 (11.4)	1098 (11.1)
BMI	790 (16.8)	1013 (16.0)	1223 (16.0)	1408 (16.1)	1564 (16.6)	1652 (16.7)
Triglycerides	4639 (94.4)	6238 (98.6)	7538 (98.6)	9007 (98.8)	9314 (98.9)	9810 (99.0)
HDL	4447 (94.4)	60 221 (95.2)	7294 (95.4)	8736 (95.8)	9021 (95.8)	9502 (95.9)
Hypertension	4300 (91.3)	5891 (93.1)	7167 (93.7)	8643 (94.8)	8973 (95.3)	9526 (96.1)

DM, diabetes mellitus; HDL, high-density lipoprotein; MS, metabolic syndrome.
[a]Model assuming that MS is irreversible, and where information on components of the MS is missing, then these components are absent.

criteria increased slightly from 91.3 to 96.1% and from 94.4 to 99.0%, respectively, over the study period, whereas the proportion meeting the diabetes mellitus criteria dropped from 15.0 to 11.1%.

The overall trends in the prevalence of the metabolic syndrome in the six calendar periods, according to the different definitions, are shown in Table 3. For all definitions, there was an increasing prevalence of the metabolic syndrome over time, although the prevalence estimates themselves varied widely. For example, when the definition of the metabolic syndrome was modified to include the use of LLT and antihypertensive medication (definition 2), the proportion of patients who met the criteria for the metabolic syndrome each year increased slightly (e.g. from 19.4 to 21.2% in 2000/2001 and from 41.6 to 44.1% in 2006/2007), but the trends remained similar. In contrast, when allowing the criteria of the metabolic syndrome to be reversible (definition 4), the proportion of individuals who were identified as meeting the criteria of the metabolic syndrome was substantially lower than in other analyses, although the increasing trend over time remained apparent. Finally, when we required each individual to have two consecutive values above (or below) each threshold to meet the laboratory criteria (definition 6), the proportion with the metabolic syndrome increased from 9.8% in 2000/2001 to 21.1% in 2006/2007. The trends over time were weakest in definitions that allowed the components of the metabolic syndrome to be reversible, presumably reflecting the

Table 3. Proportion of individuals meeting each definition of the metabolic syndrome in each of the six calendar periods, according to the analytical approach used.

		Calendar period					
	Study entry	2000/2001	2002	2003	2004	2005	2006/2007
Definition 1: Main analyses							
Number of patients included in analysis	33 347	24 349	26 615	28 449	28 661	26 265	23 853
% meeting the definition	7.3	19.4	23.8	26.9	31.8	35.9	41.6
Definition 2: Inclusion of LLT and antihypertensive medications							
Number of patients included in analysis	33 347	24 349	26 615	28 449	28 661	26 265	23 853
% meeting the definition	8.7	21.2	25.7	29.0	34.1	38.2	44.1
Definition 3: Information required on ≥3 of 5 components							
Number of patients included in analysis	27 853	22 504	24 662	26 399	27 158	25 036	22 942
% meeting the definition	8.8	20.9	25.7	29.0	33.6	37.6	43.2
Definition 4: Components reversible, missing = absent							
Number of patients included in analysis	33 347	24 349	26 615	28 449	28 661	26 265	23 853
% meeting the definition	5.5	9.6	10.8	11.2	12.7	13.7	15.3
Definition 5: Components reversible, laboratory measurements in the previous 12 months							
Number of patients included in analysis	27 310	20 282	23 552	25 598	26 651	24 758	22 721
% meeting the definition	6.2	9.2	10.1	10.2	11.2	11.8	11.7
Definition 6: Two consecutive laboratory values above (below) threshold							
Number of patients included in analysis	33 347	24 349	26 615	28 449	28 661	26 265	23 853
% meeting the definition	4.0	9.8	12.0	13.8	16.4	18.6	21.1

LLT, lipid-lowering therapy.

natural variability of some of these measurements (lipids were often measured in nonfasting conditions) and the impact of the increasing use of LLT and antihypertensive medication and potentially the switching of antiretrovirals. Overall, the relative importance of each component of the metabolic syndrome remained similar for all definitions (data not shown), although the nonlaboratory components of the metabolic syndrome (i.e. diabetes mellitus and BMI) were relatively more frequent when using definitions that allowed the laboratory components of the metabolic syndrome to be reversible.

Discussion

Reports of the metabolic syndrome amongst HIV-infected individuals have been relatively small and of cross-sectional design [6,7,10,12]. Large differences in prevalence of the metabolic syndrome in HIV-infected individuals have been published. Our findings are similar to other European estimates in patients of similar age [8,11,12]. Until now, studies have compared the different established definitions of the metabolic syndrome, often focusing on the definitions proposed by the NCEP and the International Diabetes Federation (IDF). These studies have reported that more patients were identified with the metabolic syndrome when the NCEP definition was used [6,17]. However, it is well known that observational datasets may often be affected by missing data and several components of the metabolic syndrome are based on laboratory measurements that are known to exhibit variability. It is likely that currently published studies differ in the way in which the definitions of the metabolic syndrome are applied in the presence of missing and/or variable data, but to our knowledge, the impact of these factors on the reported prevalence of the metabolic syndrome has not been described. Finally, there is no consensus about the way in which lipid-lowering and/or antihypertensive medications should be incorporated into definitions of the metabolic syndrome.

The D:A:D study has the strength of including more than 33 000 patients and is the largest study to date which has prospectively collected information on CVD risk factors in HIV-infected individuals. However, in common with all observational studies, the collection of data may be limited by missing data. Furthermore, as lipid and BP measurements are collected as a part of routine clinical care, there may be many sources of variation in these markers. By using different analytical approaches in this study, we identified several methodological challenges in our attempt to evaluate the change in prevalence of the metabolic syndrome over time.

Although our main analysis showed a considerable rate of progression of metabolic syndrome over the 6 years from 19.4 to 41.6%, this increase could represent a combination of aging of the cohort: an increased awareness, in general (and in this cohort, in particular), towards increased monitoring of dyslipidaemia and of hypertension, that is, persons are now better screened for the components of the metabolic syndrome. However, other factors also need to be taken into account.

Although our main analyses have applied the definition of the metabolic syndrome that is in current use, in clinical practice, it is unlikely that a diagnosis of the metabolic syndrome would be based on a single abnormal laboratory measurement only (an abnormal measurement would most often be followed by a confirmatory measurement), and likewise, a diagnosis of diabetes mellitus would also be based on repeated measurements of fasting glucose. By requiring this more 'strict' definition of the metabolic syndrome – and thereby allowing for some of the known biological variation within lipids – we required (using definition 6) that the metabolic syndrome definition could only be fulfilled if an individual had two consecutive laboratory values above or below each threshold. In doing this, we increased the likelihood that each laboratory measurement was really abnormal and reduced the chance that a patient had met a particular metabolic syndrome criterion simply following an on–off high (or low) measurement for that value. As a result, the apparent prevalence of the metabolic syndrome was half of that reported in our main analysis. A similar effect was noticed when we allowed the components of the metabolic syndrome to be reversible (definition 4). With this approach, there was almost no increase in prevalence throughout the study period. This probably reflects the fact that many high-risk patients started LLT, and as a result, their lipids were reduced to a level such that they no longer met the criteria for the metabolic syndrome.

Because of the increasing use of LLT and antihypertensive drugs amongst HIV-infected individuals [12,18], and a recent update of the NCEP III guidelines from the American Heart Association [19], we also repeated the analyses after modifying our definition of the metabolic syndrome to allow for the use of these drugs (definition 2). In particular, following recommendations by Gotto *et al.* [20], the use of LLT was treated as an equivalent criterion to triglycerides or HDL, and the use of antihypertensive medication was treated as an equivalent criterion to high SBP or DBP when assessing the criteria for hypertension. As suspected, this approach led to an increase in metabolic syndrome prevalence throughout the study period, that is, an increase of around 2.5% in each year compared with the main analysis, resulting in our highest estimates of the prevalence. One study from the background population has included LLT in a similar manner: among patients with established CVD, an additional 7% were identified with the metabolic syndrome when including LLT use in the definition [21–23].

Limitations

By using diabetes mellitus diagnosed under prospective follow-up instead of fasting glucose values, we get a rather conservative estimate of the prevalence and might underestimate the prevalence of the metabolic syndrome as well as the contribution of diabetes mellitus to the risk of the metabolic syndrome. Others have shown a much higher prevalence of impaired fasting glucose of above 20% [12]. As the D:A:D study does not collect waist circumference, we used increased BMI in place of this component of the metabolic syndrome, as in other studies [24]. The use of BMI may have resulted in lower estimated effects compared with waist circumference because BMI includes total fat mass. Furthermore, the lipodystrophic changes with central fat accumulation and loss of peripheral subcutaneous fat may underestimate the prevalence of the metabolic syndrome, as these patients might have a normal BMI and might not be sufficiently captured by our modified NCEP definition. Our information on the fasting conditions for the measurements of lipids were available in only around 60% of patients, and as a result, we may have overestimated the contribution of these components.

Conclusion

Our main analysis, assuming that the metabolic syndrome is irreversible, suggested an increasing prevalence of the metabolic syndrome in the D:A:D study from 19.4% in 2000 to 41.6% in 2006/7. However, other suggested definitions did not confirm the dramatic increase in prevalence over time. We believe that some of this increase is most likely an artifact representing a combination of aging of the cohort and an increased awareness towards screening for the components of the metabolic syndrome. Additionally, it is questionable whether the underlying assumption of the metabolic syndrome on the basis of one single measurement being irreversible is correct [25]. For the assessment of the metabolic syndrome in observational cohort studies, we would recommend that the definition of the metabolic syndrome requires that at least two consecutive measurements of each of the laboratory components are abnormal before the individual is allowed to meet that criterion.

Acknowledgements

This study was designed by S.W.W., N.F.M., J.D.L. and C.S. C.S. did the statistical analysis. Analysis and interpretation of the data was done by S.W.W., N.F.M., J.D.L. and C.S. Drafting of the manuscript was done by S.W.W., N.F.M., C.S., M.B. A.P., J.D.L., M.R., P.R. and W.E.S. Data were collected by M.R., P.R., W.E.S. and M.B. and coordinated by S.W.W., N.F.M., J.D.L. and C.S.

D:A:D principal investigators: Ole Kirk, Stephane De Wit, Matthew, Law, Antonella D'Arminio Monforte, Peter Reiss, Rainer Weber, Wafaa El-Sadr, Francois Dabis, Christian Pradier and Jens D. Lundgren (chair). Additional members: S. Collins, S. Storpher, D. Pizzutti, I. Weller; D:A:D central coordination: S.W. Worm, N. Friis-Møller, C.A. Sabin, A Sjøl (verification of primary endpoint), J.D. Lundgren; D:A:D data managers: A. Sawitz (coordinator), M. Rickenbach, P. Pezzotti, E. Krum, L. Gras, E. Balestre, A. Sundström, M. Delforge, E. Fontas, F. Torres, K. Petoumenos, J. Kjær.

AIDS Therapy Evaluation Project Netherlands (ATHENA): Central coordination: F. de Wolf, S. Zaheri, L. Gras; Participating physicians (city): W. Bronsveld, M.E. Hillebrand-Haverkort (Alkmaar), J.M. Prins, J.C. Bos, J.K.M. Eeftinck Schattenkerk, S.E. Geerlings, M.H. Godfried, J.M.A. Lange, F.C. van Leth, S.H. Lowe, J.T.M. van der Meer, F.J.B. Nellen, K. Pogány, T. van der Poll, P. Reiss*, Th.A. Ruys, Sankatsing, R. Steingrover, G. van Twillert, M. van der Valk, M.G.A. van Vonderen, S.M.E Vrouenraets, M. van Vugt, F.W.M.N. Wit, A. van Eeden, J.H. ten Veen, P.S. van Dam, J.C. Roos, K. Brinkman, P.H.J. Frissen, H.M. Weigel, J.W. Mulder, E.C.M. van Gorp, P.L. Meenhorst, A.T.A. Mairuhu, J. Veenstra, S.A. Danner, M.A. Van Agtmael, F.A.P. Claessen, R.M. Perenboom, A. Rijkeboer, M. van Vonderen (Amsterdam); C. Richter, J. van der Berg, R. van Leusen (Arnhem); R. Vriesendorp, F.J.F. Jeurissen, R.H. Kauffmann, E.L.W. Koger, HAGA (Den Haag); B. Bravenboer (Eindhoven); C.H.H. ten Napel, G.J. Kootstra (Enschede); H.G. Sprenger, W.M.A.J. Miesen, R. Doedens, E.H. Scholvinck (Groningen); R.W. ten Kate (Haarlem); D.P.F. van Houte, M. Polee (Leeuwarden); F.P. Kroon, van den Broek, J.T. van Dissel, E.F. Schippers (Leiden); G. Schreij, S. van de Geest, A. Verbon (Maastricht); P.P. Koopmans, M. Keuter, F. Post, A.J.A.M. van der Ven (Nijmegen); M.E. van der Ende, I.C. Gyssens, M. van der Feltz, J.G. den Hollander, S. de Marie, J.L Nouwen, B.J.A. Rijnders, T.E.M.S. de Vries (Rotterdam); J.R. Juttmann, C. van de Heul, M.E.E. van Kasteren, St. Elisabeth (Tilburg); M.M.E. Schneider, M.J.M. Bonten, J.C.C. Borleffs, P.M. Ellerbroek, I.M. Hoepelman, C.A.J.J. Jaspers, I. Schouten, C.A.M. Schurink (Utrecht); W.L. Blok, A.A. Tanis (Vlissingen); P.H.P. Groeneveld (Zwolle).

Aquitaine (France): Scientific committee: R. Salamon (chair), J. Beylot, M. Dupon, M. Le Bras, J.L. Pellegrin, J.M. Ragnaud; Central coordination: F. Dabis, G. Chêne, H. Jacqmin-Gadda, R. Thiébaut, S. Lawson-Ayayi, V. Lavignolle, E. Balestre, M.J. Blaizeau, M. Decoin, A.M. Formaggio, S. Delveaux, S. Labarerre, B. Uwamaliya, E. Vimard, L. Merchadou, G. Palmer, D. Touchard, D. Dutoit, F. Pereira, B. Boulant; Participating physicians (city): J. Beylot, P. Morlat, N. Bernard, M. Bonarek, F. Bonnet, B. Coadou, P. Gelie, D.

Jaubert, C. Nouts, D. Lacoste, M. Dupon, H. Dutronc, G. Cipriano, S. Lafarie, I. Chossat, J.Y. Lacut, B. Leng, J.L. Pellegrin, P. Mercié, J.F. Viallard, I. Faure, P. Rispal, C. Cipriano, S. Tchamgoué, M. Le Bras, F. Djossou, D. Malvy, J.P. Pivetaud, J.M. Ragnaud, D. Chambon, C. De La Taille, T. Galperine, S. Lafarie, D. Neau, A. Ochoa, C. Beylot, M.S. Doutre, J.H. Bezian, J.F. Moreau, J.L. Taupin, C. Conri, J. Constans, P. Couzigou, L. Castera, H. Fleury, M.E. Lafon, B. Masquelier, I. Pellegrin, P. Trimoulet, F. Moreau, C. Mestre, C. Series, A. Taytard (Bordeaux).

Australian HIV Observational Database (AHOD, Australia): Central coordination: M. Law, K. Petoumenos (Sydney, New South Wales); Participating physicians (city, state): J. Anderson, P. Cortossis, J. Hoy, K. Watson, N. Roth, J. Nicholson (Melbourne, Victoria); M. Bloch, T. Franic, D. Baker, R. McFarlane, A. Carr, D. Cooper (Sydney, New South Wales); J. Chuah, W. Fankhauser (Gold Coast, Queensland), S. Mallal, C. Forsdyke (Perth, Western Australia).

BASS (Spain): Central coordination: G. Calvo, F. Torres, S. Mateu (Barcelona); Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J. Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona).

The Brussels St Pierre Cohort (Belgium): N. Clumeck, S. De Wit, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, M.C. Payen, B. Poll, Y. Van Laethem.

Community Programs for Clinical Research on AIDS (CPCRA) (USA): Central coordination: J. Neaton, G. Bartsch, W.M. El-Sadr, E. Krum, G. Thompson, D. Wentworth; Participating physicians (city, state): R. Luskin-Hawk (Chicago, Illinois); E. Telzak (Bronx, New York); W.M. El-Sadr (Harlem, New York); D.I. Abrams (San Francisco, California); D. Cohn (Denver, Colorado); N. Markowitz (Detroit, Michigan); R. Arduino (Houston, Texas); D. Mushatt (New Orleans, Louisiana); G. Friedland (New Haven, Connecticut); G. Perez (Newark, New Jersey); E. Tedaldi (Philadelphia, Pennsylvania); E. Fisher (Richmond, Virginia); F. Gordin (Washington, District of Columbia); L.R. Crane (Detroit, Michigan); J. Sampson (Portland, Oregon); J. Baxter (Camden, New Jersey).

EuroSIDA (multinational): Central coordination: O. Kirk*, A. Mocroft, M. Ellefson, A.N. Phillips*, J.D. Lundgren*#; Participating countries and physicians: Argentina: (M. Losso), C. Elias; Austria: (N. Vetter), (R. Zangerle). Belarus: (I. Karpov), A. Vassilenko, V.M. Mitsura, O. Suetnov; Belgium: (N. Clumeck) S. De Wit, B. Poll, R. Colebunders; (L. Vandekerckhove); Bosnia: (V. Hadziosmanovic); Bulgaria: (K. Kostov); Croatia: (I. Begovac); Czech Republic: (L. Machala) H. Rozsypal, D. Sedlacek; Denmark: (J. Nielsen) G. Kronborg, T. Benfield, M. Larsen, J. Gerstoft, T. Katzenstein, A-B E. Hansen, P. Skinhøj, C. Pedersen, L. Oestergaard; Estonia: (K. Zilmer), Jelena Smidt; Finland: (M. Ristola); France: (C. Katlama), J-P Viard, P-M Girard, J.M. Livrozet, P. Vanhems, C. Pradier, F. Dabis, D. Neau; Germany: (J. Rockstroh), R. Schmidt, J. van Lunzen, O. Degen, H.J. Stellbrink, S. Staszewski, J. Bogner, G. Fätkenheuer; Greece: (J. Kosmidis) P. Gargalianos, G. Xylomenos, J. Perdios, G. Panos, A. Filandras, E. Karabatsaki, H. Sambatakou; Hungary: (D. Banhegyi); Ireland: (F. Mulcahy); Israel: (I. Yust) D. Turner, M. Burke, S. Pollack, G. Hassoun, S. Maayan; Italy: (A. Chiesi), R. Esposito, I. Mazeu, C. Mussini, C. Arici, Ospedale Riuniti, Bergamo, R. Pristera, F. Mazzotta, A. Gabbuti, V. Vullo, M. Lichtner, A. Chirianni, E. Montesarchio, M. Gargiulo, G. Antonucci, F. Iacomi, P. Narciso, C. Vlassi, M. Zaccarelli, A. Lazzarin, R. Finazzi, M. Galli, A. Ridolfo, A. d'Arminio Monforte; Latvia: (B. Rozentale) P. Aldins; Lithuania: (S. Chaplinskas); Luxembourg: (R. Hemmer), T. Staub; Netherlands: (P. Reiss); Norway: (J. Bruun) A. Maeland, V. Ormaasen; Poland: (B. Knysz) J. Gasiorowski, A. Horban, E. Bakowska, D. Prokopowicz, R. Flisiak, A. Boron-Kaczmarska, M. Pynka, M. Beniowski, E. Mularska; Chorzow: H. Trocha, (E. Jablonowska) E. Malolepsza, K. Wojcik; Portugal: (F. Antunes) E. Valadas, Mansinho, F. Maltez; Romania: (D. Duiculescu); Russia: (A. Rakhmanova), E. Vinogradova, S. Buzunova; Serbia: (D. Jevtovic); Slovakia: (M. Mokráš) D Staneková; Slovenia: (J. Tomazic); Spain: (J. González-Lahoz) V. Soriano, L. Martin-Carbonero, P. Labarga, (S. Moreno), B. Clotet, A. Jou, R. Paredes, C. Tural, J. Puig, I. Bravo, J.M. Gatell, J.M. Miró, P. Domingo, M. Gutierrez, G. Mateo, M.A. Sambeat; Sweden: (A. Karlsson), P.O. Persson, L. Flamholc; Switzerland: (B. Ledergerber) R. Weber, Francioli, M. Cavassini, B. Hirschel, E. Boffi, H. Furrer, M. Battegay, L. Elzi; Ukraine: (E. Kravchenko) N. Chentsova, (G. Kutsyna), (S. Servitskiy), (S. Antoniak), (M. Krasnov); UK: (S. Barton), A.M. Johnson, D. Mercey, A. Phillips, M.A. Johnson, A. Mocroft, M. Murphy, J. Weber, G. Scullard, M. Fisher, C. Leen.

HivBivus (Sweden): Central coordination: L. Morfeldt, G. Thulin, A. Sundström; Participating physicians (city): B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Håkangård (Malmö).

The Italian Cohort of Antiretroviral-Naïve Patients (ICONA) Foundation (Italy): Governing body: M. Moroni (Chair), G. Carosi, R. Cauda, F. Chiodo, A. d'Arminio Monforte, G. Di Perri, M. Galli, R. Iardino, G. Ippolito, A. Lazzarin, F. Mazzotta, R. Panebianco, G. Pastore, C.F. Perno; Scientific secretary: d'Arminio Monforte; Steering committee: A. Ammassari, A. Antinori, C. Balotta, P. Bonfanti, M.R. Capobianchi,

A. Castagna, F. Ceccherini-Silberstein, A. Cozzi-Lepri, A. d'Arminio Monforte, A. De Luca, C. Gervasoni, E. Girardi, S. Lo Caputo, F Maggiolo, R. Murri, C. Mussini, M. Puoti, C. Torti; Statistical and monitoring team: A. Cozzi-Lepri, I. Fanti, T. Formenti, M. Prosperi; Participating physicians and centres:

Italy: M. Montroni, A. Giacometti, A Costantini, A. Riva (Ancona); U. Tirelli, F. Martellotta (Aviano-PN); G. Pastore, N. Ladisa, (Bari); F. Suter, F. Maggiolo (Bergamo); F. Chiodo, G. Verucchi, C. Fiorini, (Bologna); G. Carosi, G. Cristini, C. Torti, C. Minardi, D. Bertelli (Brescia); T. Quirino, C Abeli (Busto Arsizio); P.E. Manconi, P. Piano (Cagliari); J Vecchiet, M. Farenga (Chieti); G Carnevale, S Lorenzotti (Cremona); F. Ghinelli, L. Sighinolfi (Ferrara); F. Leoncini, F. Mazzotta, M. Pozzi, S. Lo Caputo (Firenze); G. Pagano, G. Cassola, G. Viscoli, A. Alessandrini, R. Piscopo (Genova); F. Soscia, L. Tacconi (Latina); A. Orani, R. Rossotto (Lecco); D. Tommasi, P. Congedo (Lecce); A. Chiodera, P. Castelli (Macerata); M. Galli, A. Lazzarin, G. Rizzardini, I. Schlacht, A. d'Arminio Monforte, A.L. Ridolfo, A. Foschi, A. Castagna, S. Salpietro, S. Merli, S. Melzi, M.C. Moioli, P. Cicconi, T. Formenti (Milano); R. Esposito, C. Mussini (Modena); A. Gori (Monza), N. Abrescia, A. Chirianni, C.M. Izzo, M. De Marco, R. Viglietti, E. Manzillo (Napoli); C. Ferrari, P. Pizzaferri (Parma); F. Baldelli, G. Camanni (Perugia); G. Magnani, M.A. Ursitti (Reggio Emilia); M. Arlotti, P. Ortolani (Rimini); R. Cauda, M Andreoni, A. Antinori, G. Antonucci, P. Narciso, V. Tozzi, V. Vullo, A. De Luca, M. Zaccarelli, R. Acinapura, P. De Longis, M.P. Trotta, M. Lichtner, F. Carletti, (Roma); M.S. Mura, G Madeddu (Sassari); P. Caramello, G. Di Perri, G.C. Orofino, (Torino); E. Raise, F. Ebo (Venezia); G. Pellizzer, D. Buonfrate (Vicenza).

Nice HIV Cohort (France): Central coordination: C. Pradier, E. Fontas, C. Caissotti; Participating physicians: P. Dellamonica, L. Bentz, E. Bernard, E. Cua, F. De Salvador-Guillouet, J. Durant, R. Farhad, S. Ferrando, V. Mondain-Miton, I. Perbost, B. Prouvost-Keller, P. Pugliese, V. Rahelinirina, P.M. Roger, M. Vassallo. Clinical research assistant: E. Baëz.

Swiss HIV Cohort Study (SHCS, Switzerland): M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS), H.J. Furrer, M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, U. Lauper, B. Ledergerber, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach, C. Rudin P. Schmid, J. Schüpbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.

References

1. Expert panel on detection EaToHBCiA. **Executive summary of the third report of the national cholesterol educational program (NCEP) expert panel on detection, evaluation and treatment of high cholesterol in adults (Adult treatment III).** *JAMA* 2005; **285**:2486–2497.
2. Fontas E, van LF, Sabin CA, Friis-Moller N, Rickenbach M, d'Arminio MA, *et al*. **Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles?** *J Infect Dis* 2004; **189**:1056–1074.
3. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, *et al*. **Impact of HIV infection and HAART on serum lipids in men.** *JAMA* 2003; **289**:2978–2982.
4. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, *et al*. **Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study.** *Antivir Ther* 2005; **10**:585–591.
5. Jacobson DL, Tang AM, Spiegelman D, Thomas AM, Skinner S, Gorbach SL, *et al*. **Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey).** *J Acquir Immune Defic Syndr* 2006; **43**:458–466.
6. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. **Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia.** *Diabetes Care* 2007; **30**:113–119.
7. Bergersen BM, Schumacher A, Sandvik L, Bruun JN, Birkeland K. **Important differences in components of the metabolic syndrome between HIV-patients with and without highly active antiretroviral therapy and healthy controls.** *Scand J Infect Dis* 2006; **38**:682–689.
8. Sobieszczyk ME, Hoover DR, Anastos K, Mulligan K, Tan T, Shi Q, *et al*. **Prevalence and predictors of metabolic syndrome among HIV-infected and HIV-uninfected women in the Women's Interagency HIV Study.** *J Acquir Immune Defic Syndr* 2008; **48**:272–280.
9. Grinspoon SK. **Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus.** *Am J Med* 2005; **118 (Suppl 2)**:23S–28S.
10. Jerico C, Knobel H, Montero M, Ordonez-Llanos J, Guelar A, Gimeno JL, *et al*. **Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors.** *Diabetes Care* 2005; **28**:132–137.
11. Bonfanti P, Giannattasio C, Ricci E, Facchetti R, Rosella E, Franzetti M, *et al*. **HIV and metabolic syndrome: a comparison with the general population.** *J Acquir Immune Defic Syndr* 2007; **45**:426–431.
12. Mondy K, Overton ET, Grubb J, Tong S, Seyfried W, Powderly W, *et al*. **Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population.** *Clin Infect Dis* 2007; **44**:726–734.
13. Adeyemi O, Rezai K, Bahk M, Badri S, Thomas-Gossain N. **Metabolic syndrome in older HIV-infected patients: data from the CORE50 cohort.** *AIDS Patient Care STDS* 2008; **22**:941–945.
14. Friis-Moller N, Sabin CA, Weber R, d'Arminio MA, El-Sadr WM, Reiss P, *et al*. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 2003; **349**:1993–2003.
15. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio MA, *et al*. **Cardiovascular disease risk factors in HIV patients: association with antiretroviral therapy. Results from the DAD study.** *AIDS* 2003; **17**:1179–1193.
16. Worm SW, Sabin CA, Reiss P, El-Sadr W, Monforte AD, Pradier C, *et al*. **Presence of the metabolic syndrome (MS) is not a better predictor of cardiovascular disease (CVD) than the sum of its components in HIV-infected individuals. Data Collection on Adverse Events of Anti-HIV Drugs (The D:A:D study).** *Diabetes Care* 2009; **32**:474–480.

17. Wand H, Calmy A, Carey DL, Samaras K, Carr A, Law MG, *et al*. **Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection.** *AIDS* 2007; **21**:2445–2453.
18. Sabin CA, Weber R, Fontas E, Dabis F, Wit SD, Worm SW, *et al*.; On behalf of the D:A:D Study Group. **Underutilisation of recommended interventions for the prevention of coronary heart disease (CHD) in HIV-infected patients with established cardiovascular disease or diabetes mellitus: results from a multicohort study.** *14th Conference on Retroviruses and Opportunistic Infections (CROI)*, Los Angeles, USA, 2007.
19. Grundy SM. **Metabolic syndrome scientific statement by the American Heart Association and the National Heart, Lung, and Blood Institute.** *Arterioscler Thromb Vasc Biol* 2005; **25**:2243–2244.
20. Gotto AM Jr, Blackburn GL, Dailey GE III, Garber AJ, Grundy SM, Sobel BE, *et al*. **The metabolic syndrome: a call to action.** *Coron Artery Dis* 2006; **17**:77–80.
21. Olijhoek JK, van der GY, Haffner SM, Visseren FL. **Defining the metabolic syndrome: resolving unresolved issues?** *Eur J Intern Med* 2007; **18**:309–313.
22. Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, *et al*. **Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group.** *Clin Infect Dis* 2003; **37**:613–627.
23. Lundgren JD, Battegay M, Behrens G, De WS, Guaraldi G, Katlama C, *et al*. **European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV.** *HIV Med* 2008; **9**:72–81.
24. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, *et al*. **Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies.** *Lancet* 2008; **371**:1927–1935.
25. Kahn R, Buse J, Ferrannini E, Stern M. **The metabolic syndrome: time for a critical appraisal – joint statement from the American Diabetes Association and the European Association for the Study of Diabetes.** *Diabetes Care* 2005; **28**:2289–2304.