Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection

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Background: Metabolic syndrome (MS) identifies individuals at risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Little is known about MS and its consequences following initiation of antiretroviral therapy (ART).

Methods: HIV-infected adults (881) initiating ART were evaluated for prevalence and incidence of MS and subsequent diagnosis of CVD and T2DM over a 3-year period. MS was defined by criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (*Third Report*; ATP-III) or of the International Diabetes Federation (IDF).

Results: The prevalence of baseline MS was 8.5% and 7.8% (ATP-III and IDF, respectively). During follow-up, 234 (12/100 patient-years) (ATP-III) and 178 (8/100 patient-years) (IDF) progressed to MS. MS at baseline had a borderline association with increased risk of CVD [ATP-III: hazard ratio (HR), 2.56; 95% confidence interval (CI), 0.86–7.60; $P = 0.095$; IDF: HR, 2.89; 95% CI, 0.98–8.63; $P = 0.058$] and was significantly associated with an increased risk of T2DM (ATP-III: HR, 4.34; 95% CI, 1.83–10.25; $P = 0.001$; IDF: HR, 3.33; 95% CI, 1.35–8.17; $P = 0.009$). Incident MS was significantly associated with an increased risk of both CVD (ATP-III: HR, 2.73; 95% CI, 1.07–6.96; $P = 0.036$; IDF: HR, 3.05; 95% CI, 1.20–7.75; $P = 0.019$) and T2DM (ATP-III: HR, 4.89; 95% CI, 2.22–10.78; $P < 0.0001$; IDF: HR, 4.84; 95% CI, 2.20–10.64; $P < 0.0001$).

Conclusions: Substantial progression to MS occurs within 3 years following initiation of ART. Since baseline and incident MS identifies individuals at risk for subsequent CVD and T2DM, it warrants evaluation in patients commencing ART.

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Introduction

Metabolic syndrome (MS) is an aggregation of central obesity and metabolic abnormalities that confer an increased risk of cardiovascular disease (CVD) and type 2 diabetes (T2DM) [1]. Approximately 25% of the US general population has MS [2]. The clinical utility of MS for predicting cardiovascular risk beyond individual risk factors is subject to intense international discussion [3]. Findings from a recent British male cohort put the prevalence of MS at 26% and established the validity of MS as a simple clinical tool for identifying subjects predisposed to T2DM [4]. In most general populations studied to-date, the prevalence of MS increases with age

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and varies with ethnicity. There are several definitions of MS, the most widely promulgated being the definitions in the *Third Report* of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP-III) and the International Diabetes Federation (IDF) [5,6]. The ATP-III definition requires three of five simple clinical measures [waist circumference, triglycerides, high density lipoprotein (HDL) cholesterol, blood pressure and glucose]. The IDF definition uses a gender- and race-specific waist circumference threshold and places a greater emphasis on abdominal obesity, making it an essential requirement for diagnosis.

Combination antiretroviral therapy (ART) for HIV-1 infection is frequently complicated by lipodystrophy (peripheral fat loss and relative visceral obesity), dyslipidaemia and insulin resistance [7,8]. The clustering of these metabolic and morphological abnormalities has striking similarities with MS. HIV-infected adults receiving ART have an increased incidence of elevated blood pressure and cardiovascular morbidity [9–13] and might be at increased risk of developing MS and its complications. A better understanding of links between MS and subsequent morbidities in this patient population might allow for more effective clinical management of patients.

Data on the prevalence of MS in HIV-infected populations are limited and were acquired using different methodologies and applied to different populations. A Spanish study demonstrated MS prevalence at 17%, while a US study described a prevalence of 26% [14–16]. An international cohort, examined cross-sectionally, determined a prevalence of 14% and 18% by IDF and ATP-III criteria, respectively [17]. A recent report indicated 24% prevalence of MS in a US cohort. In this setting, the incidence of MS was determined as 1.2/100 patient-months [18].

No study has examined the predictive value of MS for CVD or T2DM in any population commencing ART. INITIO, an international, multicentre, randomized clinical trial, compared three treatment strategies for initial ART [19] and this allowed the examination of (a) the prevalence of MS, CVD and T2DM in treatment-naive HIV-infected participants, (b) the 3-year incidence of MS, CVD and T2DM; and (c) the predictive factors for the development of MS, CVD and T2DM.

Methods

Study aims and participants

Individuals (881) commencing randomly assigned regimens of initial ART in INITIO were evaluated for the prevalence, incidence of MS and subsequent CVD and T2DM. Demographic and clinical features were examined at baseline and during follow-up for associations with MS and subsequent diagnoses of CVD or T2DM. All analyses were posthoc.

INITIO participants were randomized in a 1 to 1 to 1 ratio to receive the nucleoside reverse transcriptase inhibitors didanosine and stavudine together with efavirenz (288), nelfinavir (305), or efavirenz plus nelfinavir (288). Episodes of study drug intolerance were managed by switches within drug class. This preserved the randomized treatment strategy and was well adhered to during study conduct [19]. Median follow-up was 192 weeks [interquartile range (IQR), 165–215]. All participants provided written, informed consent that was approved by participant institution review committees.

Assessments

All participants were assessed for the components of MS at baseline and every 12 weeks thereafter. At each visit, blood pressure was measured and blood collected for HDL cholesterol, triglyceride and glucose determination. In addition, body habitus parameters (weight, umbilical waist and maximum hip circumference) were measured and ART changes recorded. Height was recorded at baseline. Blood pressure and anthropometric assessments were not subject to external quality control. Procedures were standardized by protocol. Blood pressure was assessed in a seated subject who had rested for at least 5 min prior to recording. Waist and hip measurements were performed using a flexible tape applied loosely to defined landmarks in subjects without outer clothing. Weight was measured without shoes or other heavy garments.

Definitions

MS was defined using ATP-III and IDF criteria [5,6]. ATP-III MS comprises three or more of the following: (a) fasting glucose ≥ 6.1 mmol/l; (b) fasting triglycerides ≥ 1.7 mmol/l; (c) HDL cholesterol < 1.04 mmol/l; (d) systolic blood pressure > 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg; and (e) waist circumference > 102 cm for men and > 88 cm for women. IDF MS requires central obesity as defined by a waist circumference > 94 cm for men and > 80 cm for women. In addition, two of the following four factors are required: (a) fasting glucose ≥ 5.6 mmol/l; (b) fasting triglycerides ≥ 1.7 mmol/l; (c) HDL cholesterol < 1.29 mmol/l; and (d) systolic blood pressure > 130 mmHg or diastolic blood pressure ≥ 85 mmHg. When nonfasting blood was collected, triglyceride and glucose thresholds were 2.26 mmol/l (200 mg/dl) and 8 mmol/l, respectively [20,21].

All spontaneously reported cardiovascular events were reviewed, and the following events included in these analyses: arrhythmia, shock or heart failure,

congestive cardiac failure, pulmonary oedema, angina, ischemic heart disease, myocardial infarction, other/unspecified CVD. Symptomatic and asymptomatic cardiomyopathy and hypertension were not included. Patients with T2DM at baseline or a clinical history of CVD at baseline were not included in the analyses of cardiovascular events. Diagnosis of T2DM during INITIO was defined by a fasting glucose >7 mmol/l or a nonfasting glucose > 11.1 mmol/l in the absence of symptoms of diabetes [21]. CVD and T2DM diagnoses included for analysis were not subject to independent verification.

The formulation of the Framingham risk score used was that of Anderson [22]. The Framingham equation was used to estimate the risk of CVD (defined as myocardial infarction, fatal coronary heart disease plus angina and coronary insufficiency) over 10 years for each participant at baseline, which was then compared with the MS estimates of risk for CVD and T2DM.

Statistical analysis

Participants were assessed for MS according to both ATP-III and IDF criteria at each nominal study week using a time-window approach with available data. Time to incident MS was defined as the time from randomization to the study week of first MS. The last visit was defined as the week 156 data. Any patient with data missing at intermittent study weeks was recorded as not having MS at that study visit. Factors associated with MS at baseline were assessed using χ^2 tests and two-sample *t*-tests. Factors considered were sex, age, body mass index (BMI), smoking status, hip circumference, waist/hip ratio, CD4 cell count, $\log_{10}$ HIV RNA, HIV disease stage at baseline, and the components of MS (waist circumference, systolic and diastolic blood pressure, triglycerides, glucose and HDL) and total cholesterol.

Time to MS in participants without MS at baseline was summarized using Kaplan–Meier survival plots. Survival plots were compared using the log-rank test. Risk factors for incident MS were assessed using Cox regression adjusted for age, sex and smoking status. Risk factors considered were as for baseline MS plus randomized ART arm. To assess the role of ART exposure, participants randomized to receive nelfinavir or nelfinavir plus efavirenz (on a common backbone of didanosine plus stavudine) were treated as one group and compared with the group randomized to receive efavirenz (plus backbone didanosine plus stavudine). Multivariate models considered all variables statistically significant ($P < 0.05$) in initial analyses and used forward stepwise methods.

The effects of MS and the other covariates on the risk of CVD events and T2DM during the study follow-up were evaluated by Cox regression analyses. In these analyses, participants with established CVD or T2DM at baseline were excluded, and MS was fitted as a time-dependent covariate. There was no adjustment of *P* values for multiple comparisons. All analyses were performed using Stata Statistical Software 8.2 (Stata Corporation, College Station, Texas, USA).

Results

A total of 881 randomized subjects commenced allocated regimens of ART (288 to efavirenz, 305 to nelfinavir and 288 to efavirenz plus nelfinavir) and formed the intention-to-treat population. After 3 years, a total of 741 (84%) subjects remained in follow-up (246 efavirenz, 258 nelfinavir and 237 efavirenz plus nelfinavir). At every scheduled assessment, 75–89% of patients provided required datasets for the stated analyses. The mean age of the 881 INITIO participants included in these analyses was 38.7 years (SD, 10). The mean BMI was 23.0 kg/m^2 (SD, 3.6) and 21% were female.

During follow-up, approximately 25% of patients at each visit provided fasted blood samples. As such, approximately 75% of the cut-offs for serum triglycerides and glucose were at the higher level described in the Methods.

Prevalence of metabolic syndrome at baseline

Prior to initiation of ART, 75 (8.5%) and 69 (7.8%) participants had MS using the ATP-III criteria and IDF definitions, respectively. Table 1 presents the baseline demographic and clinical characteristics of participants according to the two MS definitions. Participants with MS (ATP-III or IDF) at baseline were significantly older and had a higher BMI, hip circumference and waist/hip ratio. Each MS component was significantly associated with the presence of MS at baseline.

Incidence of metabolic syndrome

During follow-up, 234 (12/100 patient-years) and 178 (8/100 patient-years) developed MS according to ATP-III and IDF definitions, respectively. Among the 234 participants who developed ATP-III-defined MS, the most prevalent MS-defining presentation was high triglycerides in association with high blood pressure and elevated glucose (in 50%; data not shown). A further 30% had presentations comprising high blood pressure with high triglycerides and high waist circumference; high blood pressure with high triglycerides and high waist circumference; high triglycerides with high glucose and low HDL cholesterol; and high triglycerides with high glucose and low HDL cholesterol. The Kaplan–Meier survival curves of MS for both definitions are shown in Fig. 1. The overall incidence was slightly higher for ATP-III-defined MS than for that defined by IDF. There were no significant differences in MS incidence between randomly allocated regimens of ART based on the comparison of efavirenz recipients with the combined

Table 1. Baseline characteristics of 881 INITIO participants by metabolic syndrome criteria.

Baseline characteristic	ATP-III definition			IDF definition		
	Not present ($n=806$)	Present ($n=75$)	*P* value	Not present ($n=812$)	Present ($n=69$)	*P* value
Male [No. (%)]	634 (79)	60 (80)	0.82	640 (79)	54 (78)	0.88
Mean age [years (SD)]	38 (10)	44 (10)	< 0.0001	38 (10)	47 (10)	< 0.0001
Mean BMI [kg/m^2 (SD)]	23 (3)	26 (4)	< 0.0001	22 (3)	28 (3)	< 0.0001
Smoking status [No. (%)]						
Never	338 (42)	31 (42)	0.58	339 (42)	28 (41)	0.045
Past	133 (17)	16 (21)		130 (16)	19 (27)	
Current	326 (41)	28 (38)		332 (41)	22 (32)	
Mean hip circumference [cm (SD)]	92 (9)	100 (10)	< 0.0001	92 (9)	104 (9)	< 0.0001
Mean waist/hip ratio (SD)	0.89 (0.08)	0.93 (0.08)	< 0.0001	0.89 (0.08)	0.96 (0.08)	< 0.0001
Mean CD4 cell count [cells/μl (SD)]	220 (170)	227 (179)	0.72	217 (171)	258 (162)	0.058
Mean plasma HIV RNA [$\log_{10}$ copies/ml (SD)]	4.94 (0.72)	5.00 (0.77)	0.47	4.95 (0.72)	4.87 (0.69)	0.40
Total cholesterol [mmol/l (SD)]	4.27 (1.01)	4.52 (1.20)	0.05	4.27 (1.00)	4.49 (1.10)	0.12
HIV stage [No. (%)]						
Asymptomatic	473 (59)	77 (63)	0.72	471 (58)	59 (72)	0.10
Symptomatic non-AIDS	161 (20)	15 (20)		165 (20)	11 (16)	
AIDS	170 (21)	13 (17)		174 (22)	9 (13)	
Mean metabolic syndrome components (SD)						
Waist circumference (cm)	82 (10)	93 (11)	< 0.0001	82 (9)	99 (8)	< 0.0001
Systolic blood pressure (mmHg)	118 (14)	133 (13)	< 0.0001	118 (14)	132 (14)	< 0.0001
Diastolic blood pressure (mmHg)	75 (10)	83 (10)	< 0.0001	75 (10)	83 (10)	< 0.0001
Triglycerides (mmol/l)	1.48 (1.00)	2.72 (2.00)	< 0.0001	1.55 (1.00)	2.03 (1.00)	0.0009
Glucose (mmol/l)	4.84 (1.00)	5.72 (2.00)	< 0.0001	4.87 (1.00)	5.52 (1.00)	< 0.0001
HDL-cholesterol (mmol/l)	1.05 (0.40)	0.80 (0.20)	< 0.0001	1.05 (0.40)	0.83 (0.20)	< 0.0001

ATP-III, criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; IDF, International Diabetes Federation definition; BMI, body mass index; HDL, high density lipoprotein.

results for recipients of nelfinavir and nelfinavir plus efavirenz ($P=0.46$ and 0.39; respectively; Fig. 2).

Multivariate analyses of baseline covariates associated with the development of MS are summarized in Table 2. High baseline BMI, waist/hip ratio, diastolic blood pressure, or triglyceride and low baseline HDL cholesterol were all significantly associated with an increased risk of ATP-III-defined MS. In contrast, only high BMI, hip circumference, waist/hip ratio and triglyceride levels were significantly associated with IDF-defined MS.

Metabolic syndrome as a predictor of cardiovascular events

During follow-up, 21 CVD events were reported among 19 (2.2%) individuals. These events included 11 episodes

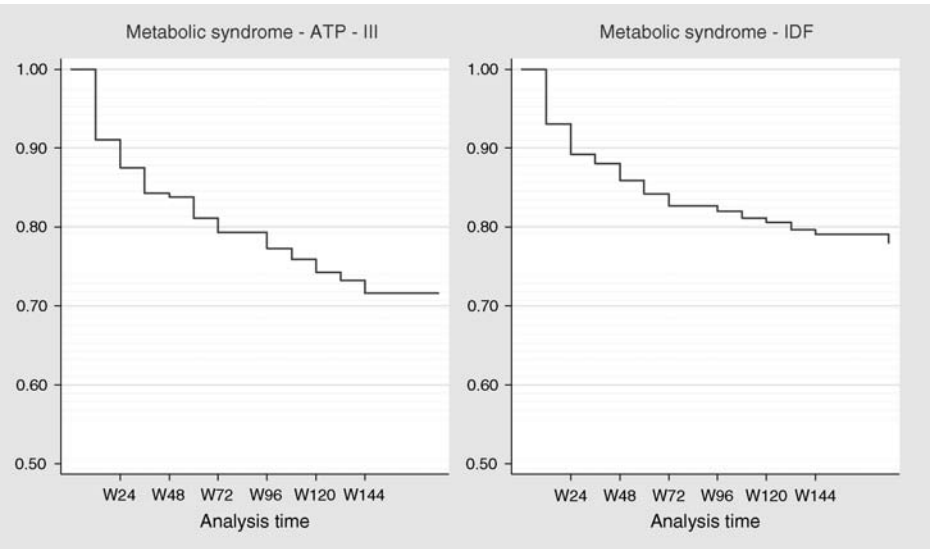

Fig. 1. Survival curves for progression to metabolic syndrome during study follow up as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) or the International Diabetes Federation (IDF).

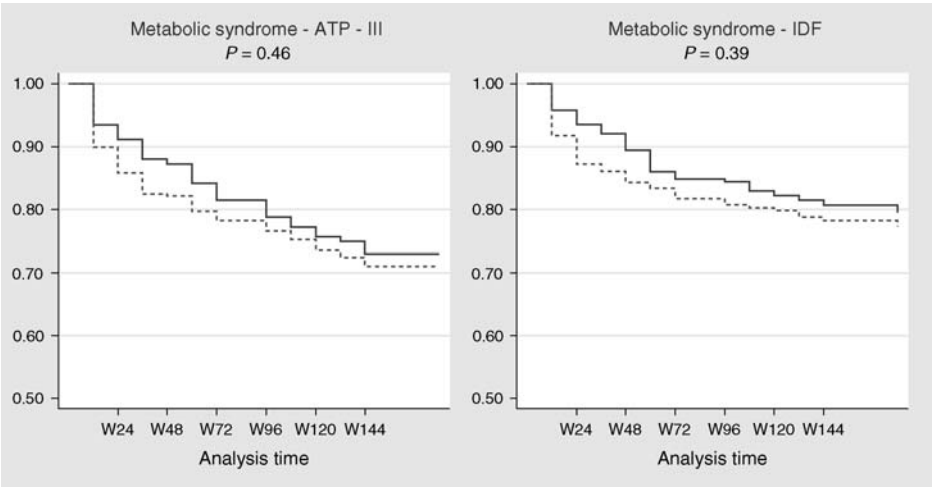

Fig. 2. Survival curves for progression to metabolic syndrome as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) or the International Diabetes Federation (IDF) during study follow up, by baseline treatment groups: didanosine/stavudine/efavirenz (—); didanosine/stavudine/nelfinavir or didanosine/stavudine/nelfinavir/efavirenz (- - -). *P* values obtained by log rank test.

of shock/heart failure, 6 episodes of angina/ischaemic heart disease, 2 episodes of arrhythmia and 1 episode for each of myocardial infarction and unspecified CVD. Factors associated with developing a CVD event are summarized in Table 3. IDF-defined MS at baseline showed a borderline, nonsignificant association with an increased risk of CVD [hazard ratio (HR), 2.89; 95% confidence interval (CI), 0.98–8.63; $P = 0.058$], whereas ATP-III-defined MS at baseline did not show a significant association (HR, 2.56; 95% CI, 0.86–7.60; $P = 0.095$). Progression to MS during follow-up by ATP-III and IDF definitions was significantly associated with an increased risk of developing cardiovascular events during follow-up (ATP-III: HR, 2.73; 95% CI, 1.07–6.96; $P = 0.036$; IDF: HR, 3.05; 95% CI, 1.20–7.275; $P = 0.019$). Of MS components, only waist circumference and systolic blood pressure were significantly associated with cardiovascular events during follow-up. Higher baseline Framingham score was not significantly associated with an increased risk of CVD (HR, 1.29 95% CI, 0.35–4.82; $P = 0.7$).

Metabolic syndrome as a predictor of type 2 diabetes

The incidence of T2DM during 3 years of follow-up was 5% (per 100 patient-years) derived from a total of 41 diagnoses. In total, 13 of these patients had more than one episode of casual plasma glucose > 11.1 mmol/l. Participants with ATP-III- or IDF-defined MS at baseline showed a significantly increased risk of developing T2DM during follow-up (ATP-III: HR, 4.34; 95% CI, 1.83–10.25; $P = 0.001$; IDF: HR, 3.33; 95% CI, 1.35–8.17; $P = 0.009$). Several individual components of MS (waist circumference, systolic blood pressure, triglycerides and glucose) were significant predictors of incident T2DM (Table 3). Progression to MS during follow-up according to both ATP-III and IDF definitions

Table 2. Multivariate risk factors for progression to metabolic syndrome.

	ATP-III definition		IDF definition	
Baseline characteristic[a]	HR[b] (95% CI)	*P* value	HR[b] (95% CI)	*P* value
BMI (kg/m^2)	1.14 (1.09–1.20)	< 0.0001	1.10 (1.02–1.19)	0.012
Hip circumference (cm)	–	–	1.03 (1.00–1.06)	< 0.0001
Waist/hip ratio (> 0.90)	1.45 (1.04–2.02)	0.028	2.55 (1.59–4.09)	< 0.0001
Metabolic syndrome components				
Diastolic blood pressure (10 mmHg)	1.03 (1.01–1.04)	< 0.0001	–	–
Triglycerides (mmol/l)	1.32 (1.18–1.49)	< 0.0001	1.29 (1.16–1.43)	< 0.0001
HDL cholesterol (mmol/l)	0.32 (0.17–0.60)	< 0.0001	–	–

ATP-III, criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; IDF, International Diabetes Federation definition; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein.
[a]All factors are adjusted for age, gender and smoking status.
[b]Hazard ratios are per unit change for each covariate as indicated; a dash indicates a nonsignificant HR and omission of the characteristic from the multivariate model.

Table 3. Risk factors for cardiovascular disease and type 2 diabetes mellitus.

Baseline characteristic[a]	CVD[b]		T2DM[c]	
	HR[d] (95% CI)	*P* value	HR[d] (95% CI)	*P* value
Baseline metabolic syndrome				
ATP-III definition	2.56 (0.86–7.60)	0.095	4.34 (1.83–10.25)	0.001
IDF definition	2.89 (0.98–8.63)	0.058	3.33 (1.35–8.17)	0.009
On-study metabolic syndrome				
ATP-III definition	2.73 (1.07–6.96)	0.036	4.89 (2.22–10.78)	<0.0001
IDF definition	3.05 (1.20–7.75)	0.019	4.84 (2.20–10.64)	<0.0001
ART class				
NNRTI	1.00		1.00	
PI	0.83 (0.30–2.31)	0.73	0.84 (0.33–2.13)	0.72
NNRTI + PI	0.49 (0.15–1.64)	0.25	1.00 (0.41–2.47)	0.99
BMI (kg/m^2)	1.03 (0.92–1.15)	0.59	1.13 (1.04–1.22)	0.003
Hip circumference (cm)	1.01 (0.97–1.06)	0.64	1.05 (1.02–1.09)	0.003
Waist/hip ratio[e] (>0.90 male, >0.80 female)	4.92 (1.48–16.40)	0.009	1.54 (0.61–3.90)	0.36
CD4 cell count (per 100 cells/ml higher)	1.00 (0.99–1.003)	0.28	1.00 (0.99–1.002)	0.82
Plasma HIV RNA (per $\log_{10}$ copies/μl higher)	1.25 (0.64–2.45)	0.52	0.97 (0.61–1.54)	0.90
Total cholesterol (mmol/l)	1.28 (0.84–1.93)	0.25	1.37 (1.01–1.84)	0.04
HIV disease stage				
Asymptomatic	1.00		1.00	
Symptomatic, non-AIDS	1.57 (0.58–4.26)	0.38	0.33 (0.10–1.10)	0.071
AIDS	0.99 (0.31–3.10)	0.98	0.97 (0.45–2.07)	0.93
Metabolic syndrome components				
Waist circumference (cm)	1.03 (1.00–1.07)	0.072	1.05 (1.02–1.08)	<0.0001
Systolic blood pressure (10 mmHg)	1.02 (0.99–1.04)	0.13	1.03 (1.01–1.05)	0.001
Diastolic blood pressure (10 mmHg)	1.02 (0.99–1.06)	0.17	0.99 (0.96–1.02)	0.71
Triglycerides (mmol/l)	1.04 (0.71–1.52)	0.84	1.30 (1.04–1.61)	0.019
Glucose (mmol/l)	1.21 (0.87–1.69)	0.26	1.84 (1.49–2.28)	<0.0001
HDL-cholesterol (mmol/l)	2.58 (0.87–7.56)	0.10	0.44 (0.13–1.48)	0.19
Framingham risk score[f] ($>3\%$)	1.29 (0.35–4.82)	0.70	1.10 (0.42–2.67)	0.90

CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; ATP-III, criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; IDF, International Diabetes Federation definition; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high density lipoprotein; ART, antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]All characteristics are per unit change for each covariate as indicated.
[b]CVD as described in Methods.
[c]T2DM as described in Methods.
[d]All Hazard ratios are adjusted for age, gender and smoking status.
[e]Included in the model as a time-varying covariate.
[f]Calculated using available data from approximately 500 patients.

was associated with a significantly increased risk of developing T2DM (ATP-III: HR, 4.89; 95% CI, 2.22–10.78; $P<0.0001$; IDF: HR, 4.84; 95% CI, 2.20–10.64; $P<0.0001$). These relative risk values were higher than those for the individual risk factors. The baseline median glucose levels for patients who later developed T2DM were 5.4 mmol/l (IQR, 5.0–6.2) and 5.2 mmol/l (IQR, 5.0–6.1) for those with metabolic syndrome defined by ATP-III and IDF criteria, respectively. Higher baseline Framingham score did not predict risk of T2DM (HR, 1.10 95% CI, 0.42–2.67; $P=0.9$).

Discussion

In this study of 881 HIV-infected adults commencing combination ART and followed for 3 years, the baseline prevalence of MS was 8.5% assessed by ATP-III criteria and 7.8% assessed by IDF criteria. The presence of MS at baseline was associated with at least a 2.5-fold increase in risk for development of CVD ($P=0.095$) and at least a 3.3-fold increase in risk of T2DM ($P=0.009$). Incident MS was significantly associated with the development of CVD and T2DM. This findings, based on relatively few incident cases of CVD (21) or T2DM (41), is striking.

Our analyses showed that baseline and incident MS had greater predictive value than a baseline dichotomized Framingham Risk Score for subsequent CVD and T2DM. These results provide an evidential basis for the use of MS in risk determination. Previous investigations have indicated that the Framingham Risk Score underestimates myocardial infarction in HIV-infected patients treated with ART but overestimates myocardial infarction in HIV-infected patients who are not treated with ART [23]. In both patient groups, the Framingham Risk Score was sensitive. In the present study, we employed a more extensive list of CVD events than myocardial infarction alone. These differences in endpoint definition might have contributed to the lack of prediction for CVD events provided by the Framingham

Risk Score at baseline. It is also possible that the Framingham Risk Score lacks precision when assessed in a treatment-naive, HIV-infected subject (there are physiological features not included in the Framingham equation that are important and independent determinants of CVD risk). This would argue for assessment of CVD risk to include MS as well as the Framingham Risk Score. An additional benefit from this approach would be the assessment of risk for T2DM.

The prevalence of MS in the US general population exceeds 23% and is approximately 26% in British men [2,4]. The prevalence of MS in this HIV-infected cohort was substantially less than these HIV-negative populations. It was also lower than that reported elsewhere for HIV-positive populations, where prevalence ranged between 14 and 24% [14–18]. INITIO participants were young (mean age 38.7 years), recruited in diverse clinical settings (119 sites in 21 countries), and 21% were female. The relatively low baseline prevalence of MS may reflect the differing demographic characteristics of study participants. The influence of age and race on MS has been well described; the potential contribution of underlying HIV wasting in the absence at baseline of ART should also be considered. Uncontrolled HIV replication also affects serum lipid concentrations (reducing HDL and low density lipoprotein cholesterol but increasing triglycerides) [24–26]. These derangements in lipid metabolism would be expected to increase the prevalence of MS in the INITIO population at baseline, and particularly for the ATP-III definition. Although higher MS prevalence has been described in HIV-positive cohorts, these studies were cross-sectional and predominantly included individuals already taking ART [14–17,27,28]. The INITIO trial provided a unique opportunity to examine MS progression in HIV-infected, treatment-naive individuals. Importantly, the lower rates of MS in this population suggests that HIV infection *per se* probably does not contribute to MS or may perhaps confer protection from components of the syndrome. Whether ART-naive patients are at reduced risk of subsequent CVD or T2DM is unclear, particularly in light of emerging data from randomized trials and cohorts indicating rates of CVD are higher in people with HIV who are not treated with ART [29,30].

Despite low baseline prevalence, we observed substantial rates of progression to MS (12/100 patient-years by ATP-III and 8/100 patient-years by IDF) over the 3 years following initiation of ART. These estimates are substantially higher than those recently reported in the prospective follow up of a US cohort [18]. It seems probable the difference arises because we assessed incidence in a truly treatment-naive cohort while only 25% (135) of the recently reported population were ART naive at baseline and it is not clear how many of these actually commenced ART during follow-up.

The most prevalent progression to MS was elevated triglycerides in association with increased blood pressure and glucose. In HIV-negative populations, the most common features associated with MS are obesity and hypertension. Elevated blood pressure and triglycerides were also reported as common components in the prospective follow up of a US HIV-positive cohort and the most frequent abnormalities that led to MS diagnosis in a cross-sectional HIV-infected cohort [18,31]. Prevention and management of MS in HIV-positive patients might need to be tailored accordingly.

This study found the risk of T2DM increased at least 3.3-fold in those with MS at baseline (ATP-III: HR, 4.34; 95% CI, 1.83–10.25; IDF: HR, 3.33; 95% CI, 1.35–8.17). In addition, incident MS was significantly associated both with a diagnosis of T2DM and with the development of CVD. These findings are consistent with observations made in the general populations studied to date [30]. The adjusted HR values for MS were higher than those for the individual MS components. This finding is important, indicating a higher predictive value from MS than the predictive value of its individual components. The validity of MS has been under substantial international debate and this study is one of the first to use prospective data to support the multiplicative effects of the combined risk factors over the assessment of individual risk factors [3].

We did not observe any significant differences in rates of progression to MS between the randomized treatment groups in INITIO. This is despite the well-described impact of ART class or drugs on the components of MS [7,9–14,18,31–33]. There was departure from the protocol-defined initial regimens of therapy in INITIO [19]. It is possible this dilution tended to mask any real differences arising from the different regimens in this study. Similarly, all patients received a common nucleoside reverse transcriptase inhibitor component in their ART regimen, didanosine and stavudine. This too, may have masked any contributions of either nelfinavir or efavirenz on progression to MS in this cohort.

There are some important caveats to this work. First, all of the analyses were post hoc and there was no adjustment for multiple analyses. There is a possibility of type I errors. Second, our CVD endpoints were assessed from spontaneous study site reports that were not subjected to any type of validation. It is also true that our analyses included only a limited number of defined clinical events (21 CVD and 41 T2DM), resulting in very limited overall power. Third, it should be noted that the INITIO regimens would no longer be recommended for initial therapy [34]. Currently recommended initial ART would be expected to induce less dyslipidaemia and lipodystrophy. Fourth, we do not have reliable data on race or ethnicity and cannot comment on any racial differences within our cohort. Finally, we were not able to

confirm that assessment of serum triglycerides or glucose was performed on blood drawn from fasted subjects for all but a minority of scheduled visits. We selected an applicable definition of T2DM and selected a CVD diagnosis that we felt to be clinically related to atherosclerosis and vascular disease. Collectively, we urge caution against overinterpretation of these findings.

Debate continues on the validity of MS for clinical management. We did not observe substantial differences between the ATP-III and IDF assessment of MS in this cohort. Because the IDF system now adjusts for race, we would propose that it is likely to be more applicable. Our data indicate that MS is less prevalent in HIV-infected individuals who are ART naive compared with that in the general population. We observed an incident rate of progression to MS in HIV-infected patients treated with combination ART somewhat higher than previously reported. The finding that MS possibly identifies those at increased risk of CVD and T2DM may be of value for selecting patients for risk assessment and possibly preventive strategies. This is particularly true given the need for lifelong ART in people with HIV-1 infection. The impact of preventive strategies would need evaluation.

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