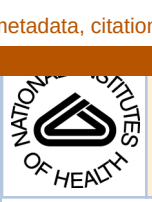

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Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-naïve HIV-infected individuals

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Abstract

Background—Metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease and diabetes, many of which are associated with HIV and antiretroviral therapy (ART). We examined prevalence and incidence of MetS, and risk factors for MetS in ART-naïve HIV-infected individuals starting ART.

Methods—MetS, defined by the Adult Treatment Panel III criteria, was assessed at and after ART initiation in HIV-infected individuals who enrolled in selected AIDS Clinical Trials Group (ACTG) trials and were followed long-term after these trials as part of the ACTG Longitudinal Linked Randomized Trials cohort. Cox proportional hazards models were used to examine risk factors of incident MetS. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) are reported.

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Results—At ART initiation, the prevalence of MetS was 20%. After ART initiation, the incidence of MetS was 8.5 per 100 person-years. After adjusting for demographics and body mass index, the risk of MetS was decreased for CD4+ T-cell counts>50 cells/mm^3 (aHR = 0.62, 95% CI=0.43 to 0.90 for CD4>500), and the risk was increased for HIV-1 RNA >400 copies/mL (aHR=1.55 (95% CI=1.25 to 1.92) and use of a protease-inhibitor (PI) based regimen (relative to no PI use, aHR=1.25 (95% CI=1.04 to 1.51) for any PI use).

Conclusion—In HIV-infected individuals on ART, virologic suppression and maintenance of high CD4+ T-cell counts may be potentially modifiable factors that can reduce the risk of MetS. The effect of MetS on the risk of cardiovascular disease and diabetes needs to be evaluated.

Keywords

metabolic syndrome; HIV; incidence; prevalence; ART-naïve; risk factors

Introduction

The continuing success of potent antiretroviral therapy (ART) has resulted in dramatic reductions in HIV-associated morbidity and mortality. HIV-infected individuals are now living longer. This longer life span has exposed them to the effects of aging, and other host and environmental factors known to increase the risk of obesity, diabetes and cardiovascular disease (CVD) in the general population (1). The HIV virus itself can cause lipid abnormalities including high triglycerides and low HDL cholesterol (22), and the side effects of antiretroviral medications have also been associated with metabolic and body shape changes (2).

Metabolic syndrome (MetS) is an aggregation of central obesity and metabolic abnormalities that confers an increased risk of CVD and type 2 diabetes (3). Since its introduction, the definition of MetS has been under scrutiny especially since it excludes known CVD risk factors such as smoking. The existence of MetS as a diagnostic entity is also controversial, and there is limited data in HIV-infected populations.

The age-adjusted prevalence of MetS in the adult U.S. population is 34.3% (4); in HIV-infected populations, the estimated prevalence ranges from 7–45% (5). Data on the incidence of MetS in HIV-infected individuals receiving potent ART is limited by the cross-sectional nature of most of the studies. A US-based HIV-infected cohort that included both treatment experienced and naïve individuals reported an incidence of 1.2 per 100 person-months (6), and an international study of HIV-infected adults initiating ART reported an incidence of 12 per 100 person-years (7). Most of the existing data on factors associated with MetS are from cross-sectional studies (5); few studies have examined factors associated with MetS among ARV-naïve individuals after starting potent ART.

We examined the prevalence of MetS and factors associated with MetS in a large US-based cohort of HIV-infected ART-naïve individuals at the time they started their ART regimens. Further we determined the incidence of newly-developed MetS in this ART-naïve population after they had started their ART regimens through randomized clinical trials. We also examined the association of demographics, clinical factors, and ART use on the prevalence and incidence of MetS.

Methods

Study population

The AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) is a prospective cohort of HIV-infected participants (age ≥13 years) randomized to receive ART regimens, immune-based therapies or treatment strategies in selected ACTG clinical trials (8). ACTG sites that enrolled participants to ALLRT received approval by their designated institutional review boards to conduct this study, and all ALLRT participants provided written informed consent.

The present analysis included 2,554 ART-naïve individuals who enrolled in ALLRT from 3 parent trials (A5095, A5142 and A5202; enrollment period 2001–2007) (9–11). The ART regimens used in these trials included either 1) three nucleoside reverse transcriptase inhibitors (NRTIs), 2) two/three NRTIs with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted- protease inhibitor (PI), or 3) an NNRTI with a boosted PI.

The “baseline” visit was the parent trial entry visit (prior to the start of ART). When individuals were enrolled in the parent trial, visits were scheduled according to the parent trial protocol. When the parent study ended, data collection continued according to the ALLRT protocol. Data were recorded by the study site staff using standard ACTG forms.

Definition of metabolic syndrome (MetS)

Since its introduction in 1998, various diagnostic criteria for MetS have been proposed (12); The more widely used definitions for MetS are from International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI). In HIV-infected patients, there was 85% agreement in patient classification based on these two definitions (33). More recently, the IDF and AHA/NHLBI agreed upon a common definition, which was used in our study (12).

Based on the Adult Treatment Panel III (ATPIII) criteria (12), MetS was defined as the presence of three or more of the following components: 1) waist circumference >88 cm in women or >102 cm in men; 2) blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic or use of antihypertensive medications; 3) triglycerides ≥150 mg/dL or use of lipid lowering medications (niacin, fenofibrate, and gemfibrozil); 4) fasting blood glucose ≥100 mg/dL, physician diagnosed diabetes or use of diabetic medications; 5) high density lipoprotein cholesterol (HDL) <50 mg/dL in women or <40 mg/dL in men.

According to the ALLRT protocol, blood pressure readings, fasting lipid panel and glucose were assessed every 16 weeks, and waist circumference was measured every 48 weeks. For 800 individuals, the first available waist circumference measurement was within 16 weeks after baseline due to the timing of their ALLRT entry visit; for these individuals, the waist circumference at week 16 was considered as baseline.

At baseline, there were 307 (12%) of 2,554 individuals with missing data on one or more of the MetS components, and who could not be classified as having or not having MetS; these 307 individuals were excluded from the study population. Among the remaining 2,247 individuals, 450 individuals with three or more components at baseline were defined as prevalent cases of MetS (even if they were missing data on other components). Those without MetS at baseline were categorized as one of the following: 1) those with two components and no missing data; 2) those with one component and missing data on ≤1 component, and; 3) those with no components and missing data on ≤2 components. Similarly, incident cases were assessed during follow-up among the 1,797 individuals without MetS at baseline.

Analysis

Prevalence of MetS at baseline (at ART initiation) was calculated as the number of cases at baseline divided by the total analyzed population. Binary regression (log-binomial) was used to evaluate associations between covariates and MetS at ART initiation. Baseline covariates examined included age (years), sex, race/ethnicity, years of education, history of cigarette smoking, body mass index (BMI, kg/m^2), history of intravenous (IV) drug use, family history of CVD, HIV-1 RNA viral load (copies/mL), and CD4+ T-cell count ($cells/mm^3$).

Incidence of MetS was evaluated among those who did not have MetS at baseline. Person-years at risk were calculated from baseline until first MetS diagnosis, death, end of follow-up or June 30, 2009 (whichever came first). The incidence rate (IR) of MetS was calculated as the number of incident cases divided by the total person-years at risk. Exact 95% confidence intervals (CI) were calculated under a Poisson distribution. Cox proportional hazards models and extended Cox models for time-dependent covariates were used to calculate unadjusted (HR) and adjusted (aHR) hazard ratios and 95% CI. Baseline covariates examined included all those stated above. Time-varying covariates (updated every 48 weeks) included CD4+ T-cell count, HIV-1 RNA viral load and ART use. Specifically, we examined time-updated class of ART use (for example PI-containing regimen versus regimen without PI) and time-updated use of specific antiretroviral medications.

Each subject's follow-up time from baseline was divided into 48-week intervals. We examined the association between ART use (any current ART use during the 48 week period versus none), CD4+ T-cell count and HIV-1 RNA viral load for a 48-week interval, and risk of MetS in the next interval. The "last value carried forward" method was used for missing CD4+ T-cell and HIV-1 RNA viral load values.

For both prevalence and incidence analyses, univariate models were used to examine the unadjusted associations between covariates and MetS. All covariates with a p-value ≤ 0.1 were added to the multivariable model. For the final multivariable model, age, sex, and race/ethnicity were included regardless of p-value. For all other variables, only those that were statistically significant ($p<0.05$) were retained in the final multivariable model.

We determined the frequency of each combination of metabolic abnormalities for all prevalent and incident cases of MetS. For the incident cases, we examined the status of all MetS components at baseline to see if the metabolic abnormality was already present at baseline or developed during follow-up.

All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Of the 3761 participants who enrolled in the three parent studies, 2554 had enrolled in ALLRT. As stated in the Methods section, 307 of the 2554 individuals were excluded because there was not enough information to classify their MetS status at baseline. There were no significant differences in most demographic and clinical characteristics between the final study population (N=2247) and the excluded individuals (N=307); the mean (SD) fasting triglyceride level was higher in the excluded group than the final study population (221 (226) versus 138 (117), p <.0001).

Prevalence of MetS at ART initiation

At baseline, 450 (20%) of the 2247 individuals had MetS. Table 1 shows the baseline characteristics of the study population by baseline MetS status. At baseline, 88% of those with MetS and 76% of those without MetS were greater than 30 years of age. Among those

with MetS, 47% were white, 27% were black and 24% were Hispanic; among those without MetS, 42% were white, 35% were black and 20% were Hispanic. In the multivariable model shown in Table 2, older age and high BMI were significantly associated with an increased prevalence of MetS, and black race was associated with a decreased prevalence of MetS at baseline. Baseline CD4+ T-cell count, HIV-1 RNA viral load and other factors listed in Table 1 were not associated with MetS at baseline, and were not included in the final model presented in Table 2.

Incident MetS during follow-up after ART initiation

There were 478 incident cases of MetS among the 1,797 individuals (5,617 person-years of follow-up) who were MetS-free at baseline. The estimated IR of MetS was 8.5 per 100 person-years (95% CI= 7.8 to 9.3). Table 3 presents the unadjusted IRs for covariates of interest.

The factors that were independently associated with the incidence of MetS are presented in a multivariable model in Table 4. Age at study entry, race/ethnicity, baseline BMI, time-updated CD4+ T-cell count, time-updated HIV-1 RNA viral load, and time-updated use of a PI-based regimen during follow-up were significantly associated with incident MetS. The adjusted HR increased with increasing age and also with increasing BMI. Relative to a CD4+ T-cell count of ≤50 cells/mm^3, the adjusted HR decreased from 0.68 (95% CI= 0.48 to 0.96) for a CD4+ T-cell count of 51–200 to 0.62 (95% CI= 0.43 to 0.90) for a CD4+ T-cell count of >500. The adjusted HR was 1.55 (95% CI= 1.25 to 1.92) for an HIV-1 RNA viral load ≤400 copies/ml compared to >400 copies/ml. Finally, use of a PI-based regimen was associated with an increased risk of MetS. We examined the prevalence of individual MetS components by PI use: 26% of the 48-week time intervals when individuals were on a PI-based regimen had elevated triglycerides, and 18% of the 48-week time intervals when individuals were on a non-PI based regimen had elevated triglycerides; none of the other MetS components had notable differences by PI-based regimen use. When we stratified by time period (enrollment before and after 2005), the HRs for PI use were similar, but no longer statistically significant. Education, family history of CVD and history of cigarette smoking were not associated with MetS in the multivariable model.

We also examined time-updated use of specific PIs. Among 5617 person-years of follow-up, 62% were from a non-PI based regimen, 20% were from a lopinavir/ritonavir-containing regimen, 16% were from an atazanavir/ritonavir-containing regimen, and the rest were from other PI-containing regimens. In a model that adjusted for age, race/ethnicity, baseline BMI, time-updated CD4 and time-updated HIV-1 RNA and excluded time on atazanavir/ritonavir regimens, the HR for a time-updated lopinavir/ritonavir-containing regimen was 1.28 (95% CI= 1.00 to 1.64, p-value=0.05) relative to a regimen without any PIs. The HR was 1.12 (95% CI= 1.00 to 1.25, p-value=0.04) for a time-updated atazanavir/ritonavir-containing regimen relative to a regimen without PI (model adjusted for same covariates as above and excluded time on lopinavir/ritonavir regimens). The use of an NRTI-based regimen (overall NRTI use, stavudine use, abacavir use, tenofovir use) or a NNRTI-based regimen was not significantly associated (p>0.05) with incident MetS.

Distribution of MetS components among prevalent and incident cases

The combination of high blood pressure, high triglycerides and low HDL was found among 40% of the prevalent and 49% of the incident cases. Figure 1 presents the distribution of factors defining MetS among the 478 incident cases at baseline and at MetS incidence. The figure shows that among the incident cases with low HDL as one of the components of incident MetS, 59% had low HDL at baseline. In contrast, among the incident cases with high triglycerides as one of the components of incident MetS, 58% developed

hypertriglyceridemia during follow-up. Fifty-seven percent of the cases with high blood pressure as one of the components of incident MetS had developed the high blood pressure during follow-up.

Discussion

In this large cohort of HIV-infected ART-naïve individuals followed for a median of 2.8 years after ART initiation (maximum follow-up was 8.3 years), the incidence of MetS was 8.5 per 100 person-years. The most common set of MetS components during follow-up included high triglycerides, low HDL and high blood pressure. In addition to age, race/ethnicity, and high BMI, low CD4+ T-cell counts, lack of virologic suppression, and use of a PI-based antiretroviral regimen were independently associated with a higher risk of developing MetS. To our knowledge this is one of the few studies to prospectively examine factors associated with incident MetS in ART-naïve HIV-infected individuals after ART initiation.

At ART initiation, 20% of the individuals had MetS; at the end of follow-up, the prevalence of MetS in those who were MetS-free at ART initiation was 27%. A small study of 60 ARV-naïve subjects (83% male) in Spain found that the prevalence of MetS increased from 17% to 25% after 48 weeks of ART (13). In a larger international study of 881 ARV-naïve subjects (79% male), the prevalence before ART initiation was 8.5% and incidence during follow-up after ART initiation was 12 per 100 person-years (7). Other studies reporting on MetS in HIV-infected populations have been predominantly cross-sectional or have included subjects already taking antiretroviral medications (5, 6, 14, 15). Using our large cohort of ART-naïve individuals, we were able to assess the prevalence of MetS before ART initiation as well as the progression to MetS during follow-up after ART initiation. Although some studies suggest an association between MetS and the risk of CVD and diabetes in the HIV-infected population, the role of MetS as an independent predictor of risk for CVD is unclear (7, 16). Whether the incidence of MetS in our cohort contributes to a subsequent increased risk of CVD and diabetes in this population of ART-naïve individuals after ART initiation needs to be examined. Majority of subjects in our study qualified for MetS based on hypertension, hypertriglyceridemia and low HDL, compared to NHANES in which the majority qualified due to hypertension, hyperglycemia and abdominal obesity (28). A possible explanation for this difference is that hypertriglyceridemia and low HDL are associated with HIV disease and ART, while in the general population these conditions are probably the result of obesity and other lifestyle factors (exercise and alcohol consumption). Data comparing HIV-infected and HIV-infected populations are needed to examine if MetS confers similar CVD risk in both populations.

Previous reports on the association between CD4+ T-cell count and the risk of MetS are conflicting. While some have found no association (15, 16), two cross-sectional studies found that a higher CD4+ T-cell count is associated with a higher risk of MetS (14, 17). In contrast, in a cross-sectional study of 293 subjects, a CD4+ T-cell count less than 100 cells/mm^3 was associated with a higher risk of MetS (18). Using prospective data from our study, we were able to examine time-updated CD4+ T-cell levels in ART-naïve subjects after ART initiation using a multivariable model that included demographic and other HIV-associated factors. Relative to CD4+ T-cell counts of ≤50 cells/mm^3, the risk of MetS was decreased for each increasing level of CD4. The association of CD4+ T-cell count with MetS may be explained by higher levels of inflammation and immune activation among those with more advanced HIV disease. Data from the ALLRT cohort on inflammation and risk of diabetes show that those who developed diabetes had lower CD4+ T- cell counts (19). Residual immune activation/inflammation similar to that observed by Brown et al, may also explain the association with time-updated CD4+ T-cell count even though there was a lack of

association with baseline CD4 count. It is also possible that a higher CD4+ T-cell count is reflective of better adherence to medications and a healthier lifestyle consisting of a good diet and physical activity; and this then further reduces the risk of MetS. However, we did not have data on diet and exercise to evaluate this hypothesis.

Consistent with previous reports (14, 18, 6, 20), HIV-1 RNA >400 copies/mL was associated with a higher risk of incident MetS in our cohort. A possible explanation for this finding is that HIV can cause lipid abnormalities including elevated triglycerides due to a combination of hepatic very low-density lipoprotein overproduction and reduced triglyceride clearance, and low HDL due to poor nutritional state and weight loss (21–23). Indeed, we also found that high triglycerides and low HDL were the most common MetS components; similar observations have been reported in other studies (5).

Specific ART regimens show associations with individual components of MetS. Proposed mechanisms for PIs can induce insulin resistance by inhibiting the glucose transporter 4 and by reducing peroxisomal proliferator-activated receptor activity, and NRTIs can cause mitochondrial toxicity that leads to fat cell apoptosis, elevated free fatty acids and finally insulin resistance and hypertriglyceridemia (24, 25). Evidence also suggests a link between MetS and PIs, and specifically an increased risk for lopinavir/ritonavir (6, 26). For NRTIs, studies suggest an increased risk of MetS for those on stavudine (15, 26), or didanosine (6). In our study, we found an association between the use of a PI-based regimen and the risk of MetS; however there was no association between NRTI use, NNRTI use and MetS risk. The high prevalence of elevated triglycerides when subjects were on a PI-based regimen relative to when they were not on a PI-based regimen suggests that the association between PI use and MetS is probably mediated by high triglycerides. When we examined the use of specific antiretroviral medications, none were significantly associated with MetS in the multivariate model that included demographics, CD4+ T-cell count and HIV-1 RNA viral load. Since enrollment in the parent studies began in 2001, some of the older regimens examined may no longer be in use. A next step to understanding the role of ART in the development of MetS would be to evaluate if newer ART drugs and regimens are associated with MetS.

Current treatment options for MetS include switching antiretroviral agents (24). Evidence suggests that switching a PI to certain NRTIs or NNRTIs in virally suppressed patients does not affect antiviral efficacy and may partly reverse metabolic changes (27). Whether such switching of regimens decreases the incidence of MetS needs to be evaluated.

Similar to findings from other HIV-infected populations, the risk of MetS increased with increasing age (17, 20, 26). The prevalence of MetS also varies by race/ethnicity, with lower prevalence in non-Hispanic black men than non-Hispanic white men possibly due to lower triglycerides, higher HDL, and lower waist circumferences in non-Hispanic black men (28, 29). In our study that was largely male (80% male), compared to those of white race, non-Hispanic blacks had a lower risk of MetS. Obesity was independently associated with a higher risk of developing MetS in our cohort; relative to those with a normal BMI at baseline, the risk of MetS was almost four times higher in those who were obese. Prior studies in the general population and in the HIV-infected population have also reported a similar association between obesity and MetS (30). At entry, 31% and 8% of our cohort were overweight and obese, respectively; similar prevalences were noted in the US military cohort (31) that concluded that HIV-infected patients are increasingly overweight or obese at HIV diagnosis and during the course of HIV infection.

Our study has some limitations. We had to exclude 307 individuals at baseline because of missing data on MetS components; however, a comparison of demographics and clinical characteristics showed that the excluded group was similar to the study population. We did

not have data on alcohol use, exercise, or nutrition/caloric intake, all of which have been shown to be associated with MetS in other studies (15, 17). Also, we did not have data on use of supplements such as fish oil that can be used to lower triglycerides (32). And finally, the regimens used in our study population only included a limited number of PIs; the majority of PI-based regimens in our study consisted of either lopinavir/ritonavir or atazanavir/ritonavir.

A primary strength of our study is the unique cohort of HIV-infected individuals who were treatment naïve at entry, randomized to treatment regimens in clinical trials, and rigorously monitored and followed long-term after completion of the original clinical trial. This prospectively followed cohort had scheduled visits during their parent trial and during follow-up in ALLRT which ensured that all components of MetS were collected using standardized methods at regular intervals. This standardized data collection also made it possible for us to examine a large array of demographic and clinical risk factors for MetS.

In conclusion, in our large cohort of HIV-infected ART-naïve persons, we found that apart from the traditional factors such as age and BMI, HIV-associated factors such as low CD4+ T-cell count and lack of virologic suppression are associated with an increased risk of developing MetS. In addition, use of a PI-based regimen was associated with an increased risk of developing MetS. Our findings support the importance of achieving both virologic suppression and immune restoration to avoid MetS. If indeed MetS increases the risk of diabetes and CVD, reducing MetS in HIV-infected populations may be an important step in reducing the burden of CVD and diabetes in this population.

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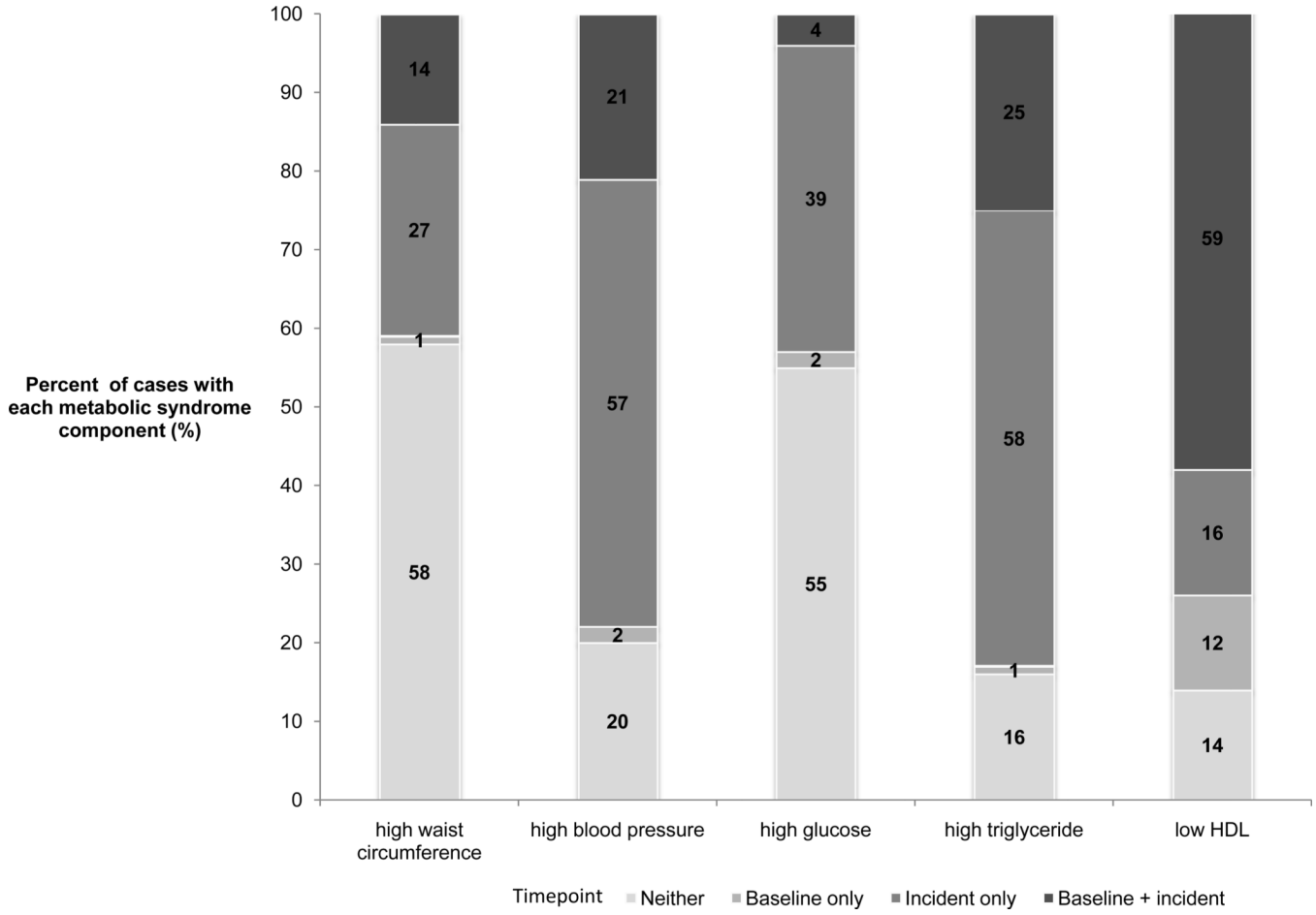

Figure 1.
Presence of MS components among incident cases at baseline and/or at MS incidence

Table 1

Baseline characteristics by MetS status for ART-naïve HIV-infected individuals at ART initiation (N=2247).

		MetS at baseline N=450 (20)	No MetS at baseline N=1797 (80)
Age (years)	≤30	57 (12)	437 (24)
	31–40	144 (33)	717 (40)
	41–50	166 (36)	484 (27)
	>50	83 (19)	159 (9)
Sex	male	330 (73)	1511 (84)
Race	white non-Hispanic	212 (47)	753 (42)
	black non-Hispanic	120 (27)	628 (35)
	Hispanic	108 (24)	357 (20)
	other	10 (2)	55 (3)
Education (years)	<12	87 (19)	294 (16)
	12	106 (23)	392 (22)
	13–15	159 (35)	644 (36)
	≥16	98 (22)	467 (26)
Family History of CVD	yes	109 (24)	310 (17)
Smoking status	ever smoker	265 (59)	1053 (59)
Body mass index (kg/m^2)	<25	92 (21)	1103 (61)
	25–29	163 (36)	551 (31)
	≥30	194 (43)	137 (8)
IV drug use (current or previous)	ever	40 (9)	168 (9)
CD4+ T-cell count (cells/mm^3)	≤50	78 (17)	354 (20)
	51–200	112 (25)	464 (26)
	201–350	147 (33)	603 (33)
	351–500	74 (16)	251 (14)
	>500	39 (9)	123 (7)
HIV-1 RNA (copies/mL)	<10,000	55 (12)	199 (11)
	10–100,000	259 (58)	1050 (58)
	>100,000	136 (29)	548 (31)
Randomized ART regimen *	2NRTI+1NNRTI	192 (43)	725 (40)
	PI+1NNRTI	29 (7)	141 (8)
	PI+2NRTI	150 (34)	574 (32)
	3NRTI	47 (11)	183 (10)
	3NRTI+1NNRTI	31 (7)	172 (11)
Waist circumference (cm) **	mean (SD)	101 (14)	86 (10)
Blood pressure diastolic (mmHg)	mean (SD)	82 (10)	74 (9)
Blood pressure systolic (mmHg)	mean (SD)	129 (15)	117 (13)
Fasting blood glucose (mg/dl)	mean (SD)	99 (34)	83 (13)
Fasting triglycerides (mg/dl)	mean (SD)	218 (195)	119 (75)
Fasting HDL cholesterol (mg/dl)	mean (SD)	33 (16)	38 (13)

Data are number (%) unless otherwise indicated. MetS, metabolic syndrome; ART, antiretroviral therapy; CVD, cardiovascular disease; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

*PI use at baseline was either lopinavir/ritonavir (37%) or atazanavir/ritonavir (63%) of total PI use. NNRTI used was Efavirenz. Among those who started a regimen with NRTI, 74% were on lamivudine (3TC) and 26% on emtricitabine (FTC); additional NRTIs used included tenofivir (32%), abacavir (27%), abacavir+zidovudine (21%), zidovudine (16%) and stavudine (4%).

**All values measured at entry except waist circumference; waist circumference was measured either at entry or within 16 weeks based on the protocol design.

Table 2

Factors associated with MetS at ART initiation in ART-naïve HIV-infected individuals. (N=2247)

	Unadjusted		Adjusted*	
	RR (95% CI)	**p-value**	**RR (95% CI)**	**p-value**
Age at baseline (years)				
≤30	ref	-	ref	-
31–40	1.45 (1.09, 1.93)	0.001	1.19 (0.92, 1.56)	0.2
41–50	2.21 (1.68, 2.92)	<.0001	1.65 (1.29, 2.12)	<.0001
>50	2.97 (2.20, 4.01)	<.0001	1.99 (1.54, 2.56)	<.0001
Sex				
male	ref	-	ref	-
female	1.65 (1.38, 1.97)	<.0001	1.09 (0.97, 1.23)	0.2
Race				
white non-Hispanic	ref	-	ref	-
black non-Hispanic	0.73 (0.59, 0.89)	0.002	0.69 (0.58, 0.81)	<.0001
Hispanic and other	1.06 (0.86, 1.29)	0.59	1.00 (0.87, 1.16)	0.9
Baseline BMI (kg/m^2)				
<25	ref	-	ref	-
25–29	2.95 (2.33, 3.74)	<.0001	2.82 (2.22, 3.57)	<.0001
≥30	7.57 (6.11, 9.39)	<.0001	6.91 (5.55, 8.60)	<.0001

MetS, metabolic syndrome; ART, antiretroviral therapy; RR, relative risk; CI, confidence interval; BMI, body mass index.

*Model includes all covariates listed in the table. Baseline CD4+ T-cell count, baseline HIV-1 RNA viral load, years of education, IV drug use and smoking status were not significant at 0.05 level.

Table 3

Incidence rates of MetS by selected characteristics among ART-naïve HIV-infected individuals after ART initiation.

	Number of cases	Person-years	IR per 100 person-years (95% CI)
Baseline characteristics			
Age (years)			
≤30	76	1357	6.4 (4.4 to 7.0)
31–40	195	2264	8.6 (7.4 to 9.9)
41–50	150	1510	9.9 (8.4 to 11.7)
>50	57	486	11.7 (8.8 to 15.2)
Sex			
male	394	4664	8.5 (7.6 to 9.3)
female	84	954	8.8 (7.0 to 10.9)
Race			
White non-Hispanic	236	2304	10.2 (8.9 to 11.6)
black non-Hispanic	131	2074	6.3 (5.3 to 7.5)
Hispanic	104	1048	10.0 (8.1 to 12.0)
other	7	178	3.9 (1.6 to 8.1)
Education (years)			
<12	75	939	7.9 (6.3 to 10.0)
12	104	1193	8.7 (7.1 to 10.6)
13–15	172	2010	8.5 (7.3 to 9.9)
≥16	127	1475	8.6 (7.2 to 10.2)
Family History of CVD			
no	382	4666	8.1 (7.4 to 9.0)
yes	96	951	10.1 (8.2 to 12.3)
Body mass index (kg/m^2)			
<25	215	3605	5.9 (5.2 to 6.8)
25–29	194	1666	11.6 (10.0 to 13.4)
≥30	68	334	20.3 (15.8 to 25.8)
Smoking status			
never smoker	203	2416	8.3 (7.2 to 9.5)
ever smoker	275	3199	8.7 (7.7 to 9.7)
Time updated characteristics			
CD4+ T-cell count (cells/mm^3)			
≤50	56	363	15.4 (11.6 to 20.0)
51–200	81	810	10.0 (7.9 to 12.4)
201–350	131	1478	8.8 (7.4 to 10.5)
351–500	82	1286	6.4 (5.1 to 7.9)
>500	128	1732	6.5 (6.1 to 8.8)
HIV-1 RNA (copies/mL)			
≤400	231	3547	6.5 (5.7 to 7.4)

	Number of cases	Person-years	IR per 100 person-years (95% CI)
>400	247	2124	7.3 (10.2 to 13.1)
NRTI use			
no	43	505	8.5 (6.2 to 11.5)
yes	435	5166	8.4 (7.6 to 9.2)
NNRTI use			
no	207	2391	8.6 (7.5 to 9.9)
yes	271	3280	8.3 (7.3 to 9.3)
PI use			
no	273	3531	7.7 (6.8 to 8.7)
yes	205	2140	9.6 (8.3 to 10.9)
Lopinavir/ritonavir use			
no	393	4763	8.2 (7.4 to 9.1)
yes	85	908	9.4 (7.5 to 11.6)
Atazanavir/ritonavir use			
no	365	4497	8.1 (7.3, 8.9)
yes	113	1174	9.6 (7.9, 11.5)
Stavudine use			
no	444	5338	8.3 (7.6 to 9.1)
yes	34	333	10.2 (7.1 to 14.3)

MetS, metabolic syndrome; ART, antiretroviral therapy; IR, incidence rate; CI, confidence interval; CVD, cardiovascular disease; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 4

Hazard ratios (HR) for incident MetS among ART-naïve HIV-infected individuals during follow-up after ART initiation.

	Unadjusted HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
Age (years)				
≤30	ref	-	ref	-
31–40	1.54 (1.18, 2.01)	0.001	1.33 (1.02, 1.74)	0.04
41–50	1.76 (1.34, 2.32)	<.0001	1.47 (1.11, 1.94)	0.01
>50	2.03 (1.44, 2.87)	<.0001	1.91 (1.35, 2.69)	0.0003
Sex				
male	ref	-	ref	-
female	1.06 (0.84, 1.34)	0.6	1.00 (0.78, 1.28)	0.9
Race				
white non-Hispanic	ref	-	ref	-
black non-Hispanic	0.62 (0.50, 0.77)	<.0001	0.53 (0.43, 0.67)	<.0001
Hispanic	0.96 (0.76, 1.21)	0.4	0.89 (0.70, 1.13)	0.3
other	0.39 (0.19, 0.83)	0.02	0.43 (0.20, 0.92)	0.03
BMI (kg/m^2)				
<25	Ref	-	ref	-
25–29	1.92 (1.58, 2.33)	<0.0001	2.00 (1.64, 2.43)	<.0001
≥30	3.19 (2.43, 4.19)	<0.0001	3.63 (2.71, 4.83)	<.0001
Time-updated CD4 ($cells/mm^3$)				
≤50	ref	-	ref	
51–200	0.65 (0.46, 0.92)	0.01	0.68 (0.48, 0.96)	0.03
201–350	0.58 (0.42, 0.79)	0.001	0.64 (0.46, 0.90)	0.01
351–500	0.42 (0.30, 0.58)	<.0001	0.50 (0.34, 0.72)	0.0002
>500	0.48 (0.35, 0.66)	<.0001	0.62 (0.43, 0.90)	0.01
Time-updated HIV-1 RNA (copies/mL)				
≤400	ref	-	ref	-
>400	1.79 (1.49, 2.14)	<.0001	1.55 (1.25, 1.92)	<.0001
Time-updated PI use				
no	ref		ref	-
yes	1.24 (1.03, 1.48)	0.02	1.25 (1.04, 1.51)	0.01

*model includes all covariates listed in the table.

Note: MetS, metabolic syndrome; ART, antiretroviral therapy; HR, hazard ratio; CI, confidence interval; BMI, body mass index; PI, protease inhibitor.