Presence of the metabolic syndrome (MS) is not a better predictor of cardiovascular disease (CVD) than the sum of its components; Data from the D:A:D Study

BACKGROUND
Metabolic syndrome (MS) is a cluster of CVD risk factors associated with a 2-fold increased risk of CVD in the general population:
- MS is usually defined as the presence of 3 or more risk factors: elevated triglycerides, low HDL cholesterol, increased fasting glucose and hypertension.
- In HIV-infected persons, metabolic changes are often induced by medicine rather than by diet and lifestyle.
- It is debated whether the MS, as an entity, confers additional prognostic information about CVD over and above that provided by the individual risk factors alone.

OBJECTIVE
We investigated whether the presence of MS in an HIV-infected individual constitutes an additional risk for CVD, over and above that, which would be expected in the individual given his/her known risk factors for CVD. In particular, we:
- studied whether any pair-wise combinations of the risk factors included in the definition of MS were associated with an increased risk of CVD;
- investigated whether the presence of specific pairs of risk factors was associated with a higher risk of CVD than would be expected from adding the individual risk factors and comparing to the MS;
- investigated whether MS as an entity was predictive for CVD after adjusting for the individual risk factors making up the MS.

METHODS
D:A:D is a prospective multi-center cohort study of 33,598 HIV-infected subjects, from 88 clinics in Europe, the US and Australia.

- The CVD risk factors encompassed in the definition of MS (modified NCEP criteria (1)) are listed below.
- The abbreviations indicate the presence of the risk factor at levels above (and for HDL below) the threshold (see Box 1 for conversion of units):
  - Elevated triglycerides (≥1.69 mmol/L);
  - Low HDL cholesterol (<1.04 mmol/L, in women <1.3 mmol/L); in women (HDL);
  - Hypertension: Systolic blood pressure (BP) ≥139 or diastolic BP ≥89 mmHg (BP);
  - Body mass index (BMI) ≥25 kg/m² (BMI);
  - Diagnosis of diabetes mellitus (DM)
- The incidence of a composite CVD endpoint (myocardial infarction (MI), stroke, invasive CV procedures (CPV), or death from other CV cause) was calculated by doubling the number of such events by the total person-years of follow-up (PYFU) in the cohort. Patient follow-up was counted from the time of enrolment in D:A:D until the date of first CVD event, or death, or 5 years after the patient’s last clinic visit.
- For each pair of factors considered, patients were grouped into four strata depending on their risk factor status at entry to D:A:D (whether risk factor present, one (or other) risk factor present, both risk factors present) and incidence rates were calculated for each strata.
- Multivariable analyses further explored these relationships through Poisson regression models; these models allowed us to formally test whether the risk factors acted synergistically on the composite endpoint, by the incorporation of each pair of risk factors along with the interaction between them - any statistically significant interaction (p<0.05) with a rate ratio (RR) value >1.00 would suggest a positive synergistic effect between the MS components.
- Finally, we examined whether the presence of MS, as an entity, was significantly associated with the risk of CVD, both before and after controlling for each of the 5 individual risk factors and other possible confounders (age, sex, body mass index, calendar year, cohort and exposure to combination antiretroviral therapy (cART)).

RESULTS
Overall 19.7% had MS at enrolment in D:A:D (20% of training set and 19% of validation set).
- The risk of CVD increased by 70% (RR 1.70 [1.50-1.93]; p=0.0001) for each additional risk factor that was present (Figure 2).
- There is a strong positive correlation between an increasing number of the components of the MS in individual patients and CVD risk.
- In particular, patients with the MS had a 6 fold higher risk of CVD compared to patients without the MS.

CONCLUSIONS
- There is a strong positive correlation between an increasing number of the components of the MS in individual patients and CVD risk. In particular, patients with the MS had a 6 fold higher risk of CVD compared to patients without the MS.
- However, this finding did not remain after controlling for each of the individual risk factors considered.
- Furthermore, whilst the underlying concept of the MS as a specific entity would suggest, that the risk factors making up the MS act synergistically on an individual’s risk of CVD, we found no significant positive interactions between any of the risk factors considered.
- Thus, the presence of the MS in HIV appears not to increase the CVD risk over and above that conferred by the components of the syndrome separately.