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# The Metabolic Syndrome in the D:A:D study

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## BACKGROUND

The Metabolic Syndrome (MS) is a cluster of metabolic disorders that lead to a 2 fold higher risk of cardiovascular diseases (CVD) in the general population (1). Components of the metabolic syndromes includes elevated TG, low HDL, hypertension, hyperglycemia and abdominal obesity. In HIV, the relative contribution of the risk factors defining MS is thought to differ from the general population, in part due to fact that the medicine induces some of the metabolic changes in the syndrome. MS is closely related with insulin resistance and has several features in common with lipodystrophy. The aim of this study is to investigate the baseline prevalence of the syndrome and factors associated with MS in HIV-infected individuals.

## OBJECTIVES

To investigate the baseline prevalence and predictors of the MS by using the American NCEP ATPIII guidelines (National Cholesterol Education Panel, Adult Treatment Panel III (2)) among patients at entry in to the D:A:D Study.

## METHODS

D:A:D is a prospective, observational cohort study following > 33,000 HIV-1 infected patients from Europe, Australia and USA. 10,111 patients with complete baseline measurements on the risk factors in the MS definition were included in a cross sectional analysis of the prevalence of the MS and components. The MS was defined by using modified NCEP ATPIII criteria, ie. the presence of three or more of the following:

- Plasma HDL cholesterol (HDL) <1,0 mmol/l (men), < 1,3 mmol/L (women)
- Plasma Triglycerides (TG) ≥ 1,7 mmol/L
- Hypertension (HYP) blood pressure >130/85 mm Hg (or anti-hypertension treatment)
- Diabetes mellitus (DM) (or anti DM treatment)
- Body-mass index (BMI) >25 kg/m2

(regardless of fasting status; replacing impaired glucose tolerance; replacing increased waist circumference)

The prevalence of the MS was assessed for the study population overall, and separately for men and women

Factors independently associated with the presence of MS at baseline were assessed from a logistic regression model, that included baseline values of: gender, age, cumulative exposure to protease inhibitors (PIs), cumulative exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs),smoking status, CD4+ lymphocyte count, HIV RNA, physician defined lipodystrophy, and cohort.

## RESULTS

### Metabolic syndrome

In the study population (N=10,111) 20% fulfilled the NCEP definition for MS.

The patients with MS were significantly older than patients without MS.

Cigarette smoking (current) was higher in the patients without MS (53 versus 43% (p= 0.0001). Lipodystrophy was more common among patients with MS, 38% versus 21% in those without MS (p=0.0001). There were differences in the two groups in exposure to antiretroviral therapy, with more PI experience in the MS group compared to the no-MS group (table 1).

### Gender and age

Men had a higher prevalence of the syndrome than women, with a prevalence of 22% compared to 12% in women. The prevalence of each of the components of the MS as well as the overall prevalence of MS in men and women, are illustrated in Figure 1.

### Factors independently associated with MS at baseline

After adjustment, the strongest relationships were seen with lipodystrophy (Odds Ratio OR 1,91 (95% Confidence interval 1,70-2.15)) male gender (1,76 (1,53-2.01), and age (OR 1,22 (1,18-1,25) per 5 years increment) (Table 2).

Other independent predictors were exposure to PI (OR 1,07 ( 1,03-1,10)) and CD4 lymphocyte count per 100 cells/uL increment (OR 1,02 (1,01-1,03)) and HIV RNA per log10 higher OR 1.04 (1.00-1.09). There was a borderline significant association with NNRTI in the adjusted model (OR 0,93(0,87-1,00) p= 0.04). Smoking was associated with a decreased risk of MS (OR 0,73 (0,66-0,81).

## DISCUSSION

- The prevalence of MS among 10,111 HIV positive was 20 % at baseline in the D:A:D study. - 22 % in men and 12% in women. This is similar to what is found in non-HIV populations at similar ages. The size of this prevalence is also comparable to previous findings in HIV positive populations.
- The relative contribution of components of the MS differs from what has been described in the general population, with dyslipidemia (high triglycerides and low HDL) and hypertension being the most prevalent components in HIV+ rather than abdominal obesity and impaired glucose tolerance.
- Host factors such as age and male gender were associated with MS to a similar extent as in the general population. Smoking was associated with a lower prevalence of MS, possibly as a result of smoking known to be associated with lower BMI
- Treatment related predictive factors in this study included PI exposure and lipodystrophy. Lipodystrophy might be phenotypically linked to MS, with central fat accumulation, and associated changes in fat and glucose metabolism. The association between PI as an independent risk factor for the metabolic syndrome is not surprising, since PIs are known to cause dyslipedemia and changes in glucose homeostasis.

## PERSPECTIVES

Studies within the D:A:D will explore the incidence of MS over 7 years of follow-up and is investigating whether the concept of the MS results in a better prediction of CVD than inclusion of the individual risk factors in a standard multiplicative model. These analyses will seek to identify specific interactions between the individual risk factors.

(1) Dekker JM et al. Circulation 2005 Aug 2;112(5):666-73.

(2)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(19):2486-97

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Table 1

### Baseline characteristics in the D:A:D study patients with and without MS

| | | MS | Non- MS | p value |
|---|---|---|---|---|
| N | | 1987 | 8124 | |
| Male | | 1678 (85%) | 5846 (72%) | 0.0001 |
| Age years | | 42 (36-51) | 38 (33-44) | 0.0001 |
| HIV mode: | Homo/bi % | 45.50 | 41.30 | <0.001 |
| | IV % | 18.10 | 24.80 | |
| | Blood % | 29.70 | 29.40 | |
| | Hetero % | 6.60 | 4.50 | |
| CD4 x 106cells/L (med, IQR) | | 439 (286-651) | 429 (276-620) | 0.007 |
| HIV RNA log 10 range (med, range) | | 1.9 (1.7-3.6) | 2.1 (1.7-3.9) | 0.0001 |
| Current a smoker % | | 43 | 52 | 0.0001 |
| Lipodystrophy % | | 38 | 20 | 0.0001 |
| PI years (med, IQR) | | 3.32(1.98-4.88) | 2.83 (1.17-4.36 ) | 0.0001 |
| NNRTI years (med, IQR) | | 0 (0.0-0.6) | 0.0 (0.0-0.4) | 0.004 |

Figure 1

### Prevalence of the Metabolic Syndrome and its components overall and after stratification on gender at entry in D:A:D among patients with MS

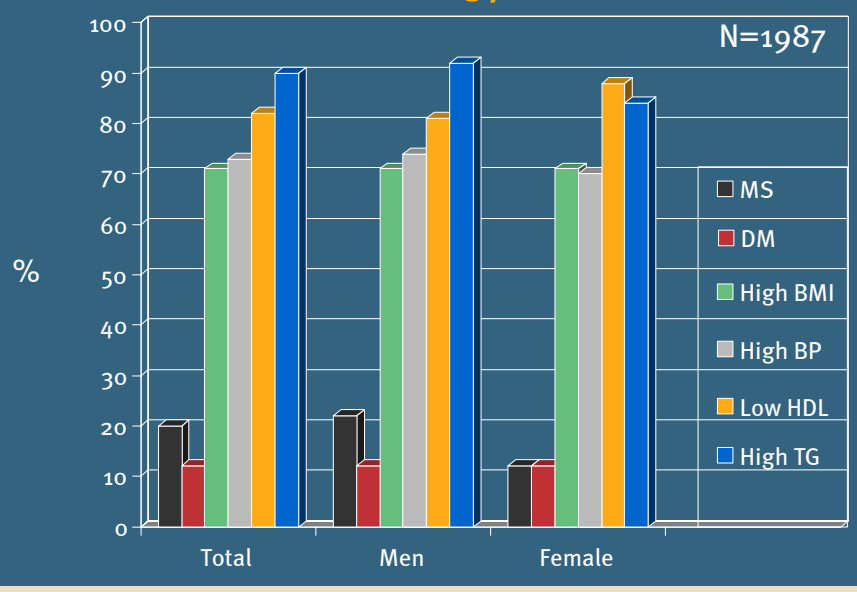


Table 2

### Predictors of the Metabolic Syndrome at Baseline in the D:A:D study

| | | Adjusted* | | |
|---|---|---|---|---|
| | | Odds ratio | 95% CI | p-value |
| Age/5 year increment | | 1.22 | 1.18-1.25 | 0.0001 |
| Male gender | | 1.69 | 1.70-2.15 | 0.0001 |
| CD4/100 cells increment | | 1.05 | 1.01-1.03 | 0.0001 |
| HIV RNA/log10 higher | | 1.04 | 1.00-1.09 | 0.09 |
| Smoking status | Never | 1 | - | - |
| | Current | 0.73 | 0.66-0.81 | 0.003 |
| Lipodystrophy | No | 1 | - | - |
| | Yes | 1.91 | 1.70-2.15 | 0.0001 |
| Exposure to PIs/ additional year | | 1.07 | 1.03-1.10 | 0.0004 |
| Exposure to NNRTIs/ additional year | | 0.93 | 0.87-1.00 | 0.04 |

*Also adjusted for cohort

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