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Position statement

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

Results from the D:A:D Study

Copenhagen, 20th November 2003

Today, The New England Journal of Medicine published data from the D:A:D study (Data collection on Adverse events of anti-HIV Drugs) on the association between myocardial infarction and exposure to combination antiretroviral therapy.

While the benefits of combination antiretroviral therapy have revolutionised the care of HIV-1 infected patients, frequent and sometimes severe treatment-associated metabolic side effects have been observed; many of these are known to be risk factors for cardiovascular disease, including dyslipidaemia, insulin resistance and sometimes overt diabetes mellitus.

D:A:D is an ongoing prospective observational study of 23,468 patients from 11 cohorts on three continents (USA, Europe and Australia), started in 1999. All patients followed in the cohorts – irrespective of whether they had started combination antiretroviral therapy or not – were included in D:A:D. When the study was started, some patients had already received combination antiretroviral therapy for several years.

The study was designed to allow for the detection of a two-fold increase in the rate of myocardial infarction with exposure to combination antiretroviral therapy. The study had to reach a given size (at least 30,000 person-years of follow-up) before this primary objective could be examined. At the current stage in the progress of the study, this milestone has been achieved.

Over 36,199 person years of follow-up in the 23,468 patients, 126 developed a myocardial infarction. The overall rate of myocardial infarction was 3.5 events per 1,000 person-years; 29% of the events were fatal. A total of 6.4% of all deaths were caused by myocardial infarction.

The rate of myocardial infarction gradually increased with more extended exposure to combination antiretroviral therapy. For example, in patients exposed to treatment for less than 1 year the rate was 2.2 events per 1,000 person-years, but the rate was 5.5 for patients exposed for more than 4 years. Few patients were exposed for more than 6 years, and hence the study does not – at present – allow for an evaluation of the effect of exposure to combination antiretroviral therapy beyond 5-6 years.

After adjustment for age, gender and other factors including smoking status, the relative rate of myocardial infarction per additional year of exposure to combination antiretroviral therapy was 1.26 (95% confidence interval: 1.12-1.41, $p<0.0001$)), i.e. a 26% relative increase in the rate of myocardial infarction per year of exposure.

The rate of myocardial infarction was also associated with older age, male gender, smoking status, presence of diabetes, higher cholesterol and triglyceride levels, and whether patients had previously experienced a cardiovascular disease. Immunological and virological factors known to influence the prognosis of HIV-infected persons were not associated with the rate of myocardial infarction.

The methodology applied in the D:A:D study has several advantages to that applied in prior studies, which already have presented results on this topic – some with conflicting results to ours. However, at the same time, the D:A:D study is a cohort study and findings from such a study cannot prove the existence of a causal relationship between exposure to combination antiretroviral therapy and myocardial infarction but merely demonstrate an association between the two. Only randomised trials can prove causality. There are also other important limitations of the D:A:D study which should be considered. When designing the study, it was not possible to identify an appropriate cohort of HIV negative persons with a comparable background risk of myocardial infarction. Hence, the study was limited to a comparison of the rate of myocardial infarction in those exposed and unexposed to combination antiretroviral therapy, and in those exposed for different periods of time. As the follow-up in D:A:D is less than 2 years, the study compares patients who started combination antiretroviral therapy in different calendar years. The statistical analysis, however, suggests that this has not influenced the results. At the present time, the study has insufficient power to examine the role of individual drugs and drug classes.

D:A:D will continue to collect information at least until January 2005. This will improve the ability of the study to address the limitations outlined above.

Combination antiretroviral therapy has substantially improved the prognosis of HIV since 1996. The rate of death among HIV-infected persons has been reduced by more than 8-fold and this benefit continues to be observed. It is important to bear this in mind when considering the implications of studies of potential side effects to treatment, such as those reported in this study.

The question as to whether antiretroviral therapy-associated metabolic disorders contribute to premature cardiovascular disease is of major importance for the way HIV infection is clinically managed. Although it should be noted that the absolute risk of myocardial infarction remains low, and does not outweigh the marked effectiveness of combination antiretroviral therapy in preventing HIV-related complications. The current results should not lead to withholding combination antiretroviral treatment when appropriately indicated.

Patients – especially those with an already high risk of cardiovascular disease - should be monitored carefully for cardiovascular risk factors when starting or changing combination antiretroviral therapy, and should be encouraged to make lifestyle changes to reduce modifiable risk factors for cardiovascular disease (particularly smoking, unhealthy diet, lack of exercise).

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20th November 2003

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ATHENA (AIDS Therapy Evaluation Project Netherlands); Aquitaine (France); AHOD (Australian HIV Observational Database, Australia); BASS (Spain); The Brussels St Pierre Cohort (Belgium); CPCRA (USA); EuroSIDA Study Group (Multinational); HivBivus (Sweden); ICONA (Italy); Nice Cohort (France); SHCS (The Swiss HIV Cohort Study, Switzerland).

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