

Position statement by the D:A:D steering committee

Regarding: *The Lancet* article "Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration" and CROI Abstract entitled "Do Thymidine Analogues, Abacavir, Didanosine and Lamivudine Contribute to the Risk of Myocardial Infarction (MI)? (vis a vis: Recent Use of Abacavir and Didanosine, but not of Thymidine Analogues, Is Associated with Risk of Myocardial Infarction): the D:A:D Study" presented at Conference on Retroviruses and Opportunistic Infections (CROI), Boston, 2008

This article published in *The Lancet* and abstract presented at CROI detail new findings suggesting that current use of the antiretroviral drugs, abacavir and didanosine (ddl), may be linked to an increased risk of heart attacks (myocardial infarctions). This was shown in patients who used either of the two drugs. Abacavir use was associated with a 90% increased risk of getting a heart attack. The risk of a heart attack with use of ddl was increased by 49%.

The data showed that the effect from abacavir and ddl on increased risk of a heart attack was observed only while patients were receiving the drug(s), but not in patients that previously had received them but had stopped them more than 6 months previously. This finding suggests that the drug effect is reversible upon cessation of the drug(s). There is no evidence to suggest that duration of exposure to either drug(s) increased the risk of a heart attack.

Conversely, no increased risk of heart attacks was noted with the use of d4T (stavudine), AZT (zidovudine) and 3TC (lamivudine), three other drugs in the same drug class of nucleoside reverse transcriptase inhibitors (NRTIs). There were insufficient amount of data to assess the role of two other drugs in this class - tenofovir and emtricitabine.

It is important to keep in mind that the associations described in this article and abstract are based on follow-up of a large number of patients over a long period of time. However, the findings are not based on a trial in which patients were randomized (assigned by chance) to receive one drug or another so it is impossible to definitively exclude the possibility that the findings are explained by bias. However, the authors extensively investigated this possibility and could not find any evidence for appreciable bias.

These findings are derived from the year seven analyses of the (D:A:D) study (Data collection of Adverse effects of anti-HIV Drugs Study)¹. This study was initiated in 1999, and includes 33,347 patients from around the world, of whom 517 developed a heart attack during 157,912 prospective observational person-years. Of the 517 patients with a heart attack, 192 were using abacavir and 124 were using ddl, as part of their anti-HIV drug regimen at the time when the heart attacks occurred.

The effect of abacavir and ddl was most pronounced in absolute terms in patients with a high underlying cardiovascular risk due to other factors². Therefore, the clinical implications of the results of this abstract must take into account an individual patient's underlying cardiovascular risk.

¹ Caroline Sabin, Signe Worm, Rainer Weber, Wafaa El-Sadr, Peter Reiss, Francois Dabis, Stephane DeWit, Matthew Law, Antonella D'Arminio Monforte, Simon Collins, Christian Pradier, Nina Friis-Møller, Ole Kirk, Ian Weller, Andrew N. Phillips, Jens D. Lundgren for the D:A:D study group (only 10 authors could be displayed on the abstract).

² The underlying cardiovascular risk in HIV-infected population as well as in the general population, is estimated based on the age, sex, smoking habits, cholesterol levels, blood pressure and presence of diabetes in the population. These factors are combined in a mathematical model – the Framingham equation – that allows determining an individual's underlying risk of coronary heart disease (CHD) (Anderson *et al*, *Circulation*, 1991). This equation has been validated in HIV populations and is available online: <http://www.cphiv.dk/tools.aspx>. The calculation predicts what percentage of a population with a specific risk factor profile and without CHD at present time will get this disease within the next 10 years. In the literature, CHD risk is traditionally broadly subclassified into low (<10), moderate (10-20) and high (>20) percent risk of developing CHD in 10 years. The D:A:D study findings suggest that the drug effect would increase an individual patients underlying risk by a specific factor (for abacavir, by 1.9 (i.e. 90%)). For example, a person with a 10-year underlying risk of contracting a heart attack of 10%, will increase this risk to 19% (10% \times 1.9) if this person e.g. is currently using abacavir.

To give an estimate of the magnitude of the increased risk of heart attacks associated with the use of these drugs, the 1.9-fold (90%) increased risk associated with use of abacavir compares with a 2-3 fold increased risk of heart attack associated with current cigarette smoking. Thus, a patient who is a smoker and is using abacavir is at substantial risk of a heart attack. However, in this situation it would appear that for such a patient, stopping smoking would do more to reduce the risk of having a heart attack and other serious diseases more than by stopping abacavir. It is important to keep in mind that smoking has other detrimental health effects in addition to risk of heart attacks.

A possible biological mechanism underlying the increased risk of a heart attack in association with use of abacavir and didanosine was not identified in the study and remains unknown, although the analyses did not suggest that known metabolic abnormalities were the culprits.

The authors of the study¹ recommend that patients receiving abacavir or ddl should consult their doctor, and discuss whether a modification of their anti-HIV drug regimen is appropriate. Patients should NOT stop any drug without prior discussion with their doctor.

Frequently asked questions:

1. What are the main findings from this study?

This analysis from the D:A:D study found that two anti-HIV drugs, were associated with an increased risk of a heart attack. Abacavir was associated with a 90% increased risk and ddl was associated with a 49% increased risk. These excess risks were most pronounced in absolute terms in patients with high underlying cardiovascular risk due to other factors (for example, older age, smoking, diabetes, high cholesterol levels) and appears reversible upon cessation of the drugs. Other drugs in the same class – AZT, d4T and 3TC - were not found to have this effect.

2. What does e.g. a 90% increased risk mean?

A 90% increased risk means that the risk of having a myocardial infarction increased by 90% compared to an individual's underlying risk (ie the risk they already had; see QA # 6 below). This means that the risk almost doubled with use of abacavir compared to not being on abacavir. There are formulas to calculate the underlying risk (see footnote # 2 above).

3. What is the context of these results?

The “Data collection of Adverse effects of anti-HIV Drugs” (D:A:D) study was initiated in 1999, with the aim of assessing associations between use of anti-HIV drugs and risk of a heart attack. The study prospectively follows 33,347 HIV-infected persons that each – on average – have been followed for 5 years in the study; some longer than others. More than 90% of the patients have received anti-HIV drugs, and most were on such treatment when they entered the D:A:D study. After enrolling in D:A:D, 517 persons developed a heart attack.

This study was conducted in adults many of whom had risk factors for cardiovascular risk which most children do not have. Also there are not as many medicine options for children. However, more long term safety information on all HIV medications in children is very much needed.

4. Why was this line of research initiated?

This line of research was pursued because of previous findings from the D:A:D study suggesting that drugs within the NRTI drug class may contribute to risk of a heart attack³. It was hypothesized that d4T and AZT were most likely to be the culprits, as both drugs had effects on lipid and glucose metabolism, changes that were likely to be involved in causing heart attacks. This hypothesis was subsequently was not substantiated by the findings reported in this abstract. As such, the identification of an elevated risk associated with use of abacavir and ddl were both surprising and unexpected findings.

³ D:A:D study group. Class of antiretroviral drugs and the risk of myocardial infarction. New England Journal of Medicine. 2007 356(17):1723-35.

5. *Was the D:A:D study designed to demonstrate whether these two drugs (abacavir and ddI) were definitely linked to risk of a heart attack?*

Only a randomised clinical trial can demonstrate a definitive link between use of a specific drug and risk of a specific side effect e.g. a heart attack. However, because heart attacks are not common events, such a study has not been done and none are ongoing. A study of this nature would have to enroll a very large number of patients and would probably not be feasible. The D:A:D study is a prospective observational study, but not a randomized controlled trial. The results from observational studies can report an observed association. This is followed by different analyses of the data to see whether other factors could explain the results. However, it cannot definitively prove a causal link.

6. *Do the study findings suggest that abacavir and ddI may also affect the risk of stroke or other manifestations of cardiovascular disease?*

The available data suggest that abacavir and ddI do not affect the risk of developing a stroke. However, there are insufficient data to fully define the extent to which the occurrence of other types of cardiovascular diseases are affected by these drugs.

7. *Other than the use of abacavir and ddI, what other risk factors affect the risk of a heart attack in HIV-infected people?*

The same risk factors for heart disease in the general population, also apply to HIV-infected people. These include age (the risk increases as one gets older), sex (men are at higher risk than women), smoking status (current or recent smokers are at higher risk), higher cholesterol levels, diabetes, and elevated blood pressure. Other research suggests that use of protease inhibitors (another class of anti-HIV drugs) also increases the risk of heart attacks (see further comments in QA below). However, recent research also suggests that HIV treatment in general has a positive effect on reducing the risk of heart disease and that stopping or interrupting antiretroviral therapy may increase this risk. Thus, it appears that the choice of anti-HIV drugs may influence risk of heart attacks.

8. *The D:A:D study previously reported an association between use of protease inhibitors and risk of a heart attack: how does that report and the findings in this abstract interlink?*

In April 2007, the D:A:D study group reported that use of drugs from the protease inhibitors drug class increased the risk of a heart attack, in a paper published in the New England Journal of Medicine³. The findings from this abstract suggest that the use of abacavir, ddI also increase the risk of a heart attack.

Additional questions – non-technical Q&A for HIV-positive readers.

9. *What is the D:A:D study?*

In the D:A:D study, researchers were looking for risk factors for heart attacks in a large group of patients. Over 33,000 patients, followed on average for 5 years, make this the largest study of its kind. This is necessary in order to be able to evaluate rare events that would only be seen in small numbers in studies that include fewer participants.

10. *What did this study find?*

The study found that over 7 years, 517 patients were reported as having a heart attack. This is still a relatively rare event. However, patients using either abacavir or ddI had a higher chance of having a heart attack than patients not using either of these drugs.

11. *What is the real risk compared to the relative risk?*

The 'real risk' (often called the 'absolute risk') of having a heart attack in this group of patients as a whole, was low. The total number of patients followed in the study, divided by the number of heart attacks (33,400 divided by 517), shows a risk of 1 in 64 (approximately 1.6%) over 5 years.

The 'relative risk' indicates how one factor increases or decreases the chance of having a heart attack compared to a person who does not have this factor. In this study for example, abacavir was one of the factors examined. The study found that being on abacavir increased the risk of having a heart attack by 90% compared to someone not using abacavir.

12. Is this the first time that this link between abacavir and ddI and heart attacks has been reported?

Yes. As far as the researchers are aware, this is the first time such a link has been found.

13. Why did it take so long for this risk to be found?

The D:A:D study needed a large number of patients who needed to be followed for seven years to be able to look for the effects of abacavir and other anti-HIV drugs on heart attacks. This is because the risk of heart attacks is low, and because so many drugs are used in different combinations.

14. Could other factors explain the link of heart attacks with abacavir and ddI?

An observational study such as D:A:D that follows patients cannot definitely prove that one thing causes another. Statisticians can however try to figure out if other factors could have influenced the findings. For example, all the standard known risk factors for heart attacks, such as age, sex, smoking, cholesterol levels, blood pressure, family history) were evaluated. Even when taking into account all these factors, abacavir and didanosine were still associated with having heart attacks. Another way of saying this, is that the researchers tried, and were unable, to find any other explanation for these results.

15. Does this mean I have an increased chance of a heart attack if I am taking abacavir or ddI?

The results show that using abacavir or ddI does increase the chance of having a heart attack.

This was especially evident for those who already had a high chance of having a heart attack because of other risk factors. For example, in people who start abacavir or ddI with a low risk based on other factors (for example if they are young, do not smoke, have no diabetes or high blood pressure and have normal cholesterol), increasing this low risk by 90%, still results in a low absolute risk of having a heart attack. However, in someone who starts off with a high risk of a heart attack based on other factors, increasing this existing high risk by 90% means that the additional effect from abacavir or ddI will be more important.

A current smoker who is taking abacavir would reduce their risk of a heart attack slightly more by stopping smoking than by switching abacavir to an alternative drug,

To decide what to do if a patient is taking abacavir or ddI requires a discussion between the patient and doctor to decide where a patient stands in terms of their risks for heart attacks. Also the history of treatment with anti-HIV drugs needs to be taken into account in order to judge whether equally effective alternative anti-HIV drugs are available for a patient.

16. Does this mean I need to change from using abacavir or ddI?

The authors of the study¹ recommend that patients receiving abacavir or ddI should consult their doctor, and discuss whether a modification of their anti-HIV drug regimen is appropriate. Patients should NOT stop any drug without prior discussion with their doctor. The decision regarding what to do if you are using abacavir or ddI needs to be based on a discussion with your doctor. Whether you stop or continue with these drugs will depend on your other risk factors for heart attacks and other treatment options that are available for you.

17. Will having taken abacavir and ddI make me at risk of a heart attack in the future even after I stop these drugs?

The study found that the risk of heart attacks with use of abacavir and ddI disappeared once people were switched to other drugs. This should mean that people who switch to other drugs, should not have their future risk of heart attacks affected by their earlier use of abacavir or ddI.

Other risk factors (age, sex, smoking status, family history, diabetes and high blood pressure etc) will continue to contribute to the risk of a heart attack.

18. Do other anti-HIV drugs from the same class as abacavir and ddI increase risk of heart disease?

The study found no increased risk of heart attacks with use of stavudine (d4T), zidovudine (AZT) or lamivudine (3TC). Not enough information is available to study the risk of heart attacks with use of tenofovir or emtricitabine (FTC).

It is important to keep in mind that earlier results from the D:A:D study showed that protease inhibitors as a class of drugs are associated with an increased risk of heart attacks. This earlier study found no link with NNRTIs (nevirapine or efavirenz) with heart attacks.

However, both these findings looked at drug classes and not individual drugs within the classes .

Further information on the D:A:D Study, including the article and this position statement and related FAQs:

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