

DHHS Adults and Adolescents Antiretroviral Treatment Guidelines Panel's Communication Regarding Abacavir – April 4, 2008

Data from studies addressing the safety of abacavir (ABC) and efficacy of abacavir/lamivudine (ABC/3TC) as part of a combination antiretroviral regimen recently became available.

At the 15th Conference on Retroviruses and Opportunistic Infections (CROI), the D:A:D study group reported their analysis of association of NRTI use and risk of myocardial infarction (MI) in a large multi-national observational cohort.¹ Among the 33,347 patients enrolled, with 157,912 person-years follow-up, 517 subjects were diagnosed with an MI; 192 and 124 of these subjects reported use of ABC and didanosine (ddI), respectively, within the previous 6 months of the occurrence of the MI. In this analysis, recent (within 6 months) but not cumulative or past use (last use >6 months) of either ABC or ddI predicted risk of MI (relative risk of 1.94 [95% CI: 1.48-2.55] for ABC and 1.53 [95% CI: 1.10-2.13] for ddI). The heightened risk of MI with recent ABC exposure was accentuated in subjects with pre-existing cardiac risk factors (as defined by 10-year predicted coronary heart disease risk >20%). Use of tenofovir (TDF) or emtricitabine (FTC) was not analyzed in this study.

A separate analysis conducted by GlaxoSmithKline using their internal database containing data from 54 clinical trials and post-marketing reports identified 9,369 patients who received ABC for 7,845 person-years and 5,044 patients who did not receive ABC with 4,653 person-years follow-up. Eleven ABC-treated and seven subjects not on ABC were reported to have an MI during the follow-up period.² GlaxoSmithKline did not find any evidence of an increase in cardiovascular disease in their clinical trials among patients who received ABC. It should be noted that these studies were not designed to evaluate cardiovascular events as secondary endpoints, and the follow-up periods in these trials were 24-48 weeks.

On February 28, 2008, the National Institute of Allergy and Infectious Diseases released an announcement regarding a modification of the AIDS Clinical Trial Group (ACTG) 5202 study, a randomized controlled trial of antiretroviral-naïve participants evaluating the efficacy and safety of ABC/3TC vs. TDF/FTC when used in combination with either efavirenz (EFV) or ritonavir (RTV)-boosted atazanavir (ATV).³ Treatment randomization was stratified based on screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. Over 1,800 participants enrolled in this study. At a planned interim meeting of the independent Data Safety Monitoring Board (DSMB), the board noted that the majority of patients in all treatment arms had good virologic responses. The DSMB noted that among the participants with screening HIV RNA ≥100,000 copies/mL, those who were randomized to ABC/3TC had a significantly shorter time to study-defined virologic failure than those randomized to the TDF/FTC arm, regardless of whether they were using EFV or RTV-boosted ATV in combination. The DSMB also noted that within the stratum of subjects with a screening HIV RNA level ≥100,000 copies/mL, the ABC/3TC group had a shorter time to development of certain grade 3 or 4 side effects, including body aches and laboratory abnormalities such as lipid elevations. Based primarily on the difference in virologic efficacy, the DSMB recommended unblinding of the subjects who had screening HIV RNA ≥100,000 copies/mL, and counseling subjects on ABC/3TC about the findings, giving them the option to switch to other regimens. Subjects with HIV RNA <100,000 copies/mL at study screening are to remain blinded to their NRTI assignment.

The results of the HEAT study, a head-to-head trial of 688 subjects comparing ABC/3TC to TDF/FTC, (both in combination with once-daily lopinavir/ritonavir) were presented at the 15th CROI.⁴ A subgroup analysis according to baseline HIV RNA < or ≥100,000 copies/mL (43% and 57% of subjects, respectively) yielded similar percentages of subjects with HIV RNA <50 copies/mL at 48 weeks for the two regimens: 71% (ABC/3TC) vs. 69% (TDF/FTC) for those with baseline HIV RNA <100,000 copies/mL and 63% vs. 65% for those with HIV RNA ≥100,000 copies/mL.

At this point, the Panel concludes that the preliminary information available from these studies does not warrant a change in its current recommendations regarding the use of antiretroviral drugs in adults and adolescents. The Panel will continue to review additional data as they become available and will make further recommendations if needed. Meanwhile, the Panel recommends clinicians consider all available information so that the optimal therapeutic choice for each patient is based on individual patient characteristics and the potential risks and benefits of each treatment component.

Reference:

1. D:A:D Study Group. 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. *Lancet* 2008; DOI:10.1016/S0140-6736(08)60423-7. Available at <http://www.thelancet.com>. (Accessed April 2, 2008)
2. Cutrell A, Brothers C, Yeo J, Hernandez J, Lapierre D. Abacavir and the potential risk of myocardial infarction. *Lancet* 2008; DOI:10.1016/S0140-6736(08)60492-4. Available at <http://www.thelancet.com>. (Accessed April 2, 2008)
3. NIAID Bulletin: NIAID modifies HIV antiretroviral treatment study: Combination therapy that includes ABC/3TC found less effective in subgroup of antiretroviral-naïve individuals. February 28, 2008. <http://www3.niaid.nih.gov/news/newsreleases/2008/actg5202bulletin.htm>.
4. Smith K, Fine D, Patel P, et al. Efficacy and safety of abacavir/lamivudine compared to tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir through 48 weeks in the HEAT Study. Program and Abstract: 15th Conference on Retroviruses and Opportunistic Infections. Boston, MA, February 3-6, 2008. Abstract 774.