



DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

NOTICE TO PHYSICIANS

DATE: March 10, 2003

TO: HIV/AIDS Health Care Providers

FROM: Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases,
National Institutes of Health

**SUBJECT: Important Interim Results from a Phase III, Randomized, Double-Blind
Comparison of Three Protease-Inhibitor-Sparing Regimens for the Initial
Treatment of HIV Infection (AACTG Protocol A5095)**

Dear HIV/AIDS Health Care Provider:

The purpose of this letter is to inform you of the interim results from the Adult AIDS Clinical Trials Group (ACTG) study known as A5095. A recent review of the study by the National Institute of Allergy and Infectious Diseases (NIAID) Data and Safety Monitoring Board (DSMB) found that in antiretroviral treatment-naïve patients, a combination preparation of three nucleoside analogues, Trizivir®, was inferior to two other efavirenz-containing treatment regimens being evaluated in the study. The data met pre-specified guidelines for stopping this one arm of the study based on virologic failure. There were no concerns about the toxicity of the study drugs.

Antiretroviral-naïve patients randomized to receive a combination of abacavir (ABC), lamivudine (3TC), and zidovudine (ZDV) (ABC/3TC/ZDV, Trizivir®) experienced virologic failure earlier and more frequently than patients who were randomized to receive either of the two other treatment regimens being evaluated in the study. The two other treatment regimens are: 1) a combination of 3TC and ZDV (Combivir®) plus efavirenz (EFV, Sustiva®), and 2) the combination ABC/3TC/ZDV plus EFV. Study drugs were given in a double-blind, placebo-matched manner.

A total of 1,147 antiretroviral-naïve patients were followed for changes in their viral load and CD4+ T cell counts. Virologic failure was defined as having an HIV RNA level in plasma above

200 copies/ml (measured by the Roche Amplicor® HIV-1 test) at least 4 months after starting study treatment.

After an average of 32 weeks on study, a total of 167 study volunteers experienced virologic failure: 21% in the group receiving ABC/3TC/ZDV versus 10% in the other two groups combined. Virologic failure occurred sooner and more often in those receiving ABC/3TC/ZDV alone, regardless of their initial viral load (whether above or below 100,000 copies/mL). Although data on CD4+ T cell counts were not available at the time of the interim analysis, the DSMB felt that they would not reverse the outcome.

As a result of these data, the DSMB recommended that the ABC/3TC/ZDV treatment arm be stopped. Therefore, the study volunteers receiving ABC/3TC/ZDV have been unblinded as to what treatment they were taking, and they have been asked to remain in the study for continued follow-up. These volunteers have been offered several alternatives to the use of ABC/3TC/ZDV alone. GlaxoSmithKline, one of the pharmaceutical companies involved with this study, is also working with DAIDS and the A5095 study team to provide ABC/3TC/ZDV outside the study for patients who choose this option.

Study volunteers originally given one of the other two drug treatments will continue on the study as planned and will not yet be unblinded. They will, however, be told that they are receiving a combination treatment that contains efavirenz. All study volunteers, will continue to be followed for approximately 2 years after the last subject is enrolled – until approximately September 2004. This follow-up period will allow a comparison of the 3TC/ZDV + EFV and ABC/3TC/ZDV + EFV groups. It also will allow more information to be collected from all three groups about how to use antiretroviral drugs.

Although we are confident of these findings, they have not been presented at a scientific meeting, peer reviewed, or published. These results will be submitted to the upcoming International AIDS Society meeting in Paris (July 2003), and further analyses (e.g., CD4+ T cell count and adherence data) will be forthcoming. A manuscript is in preparation.

It is important to consider this interim study finding in the context of published results, particularly those from prior studies that investigated either triple nucleoside regimens or EFV-based regimens. The risk of virologic failure is clearly an important factor in selecting an initial antiretroviral regimen. Other factors such as safety, toxicity, adherence, preservation of future treatment options, access, cost, and other issues also remain important in selecting the optimal first regimen for an individual patient.

Additional information about the study design and interim analysis are available on the National Library of Medicine Web site at http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html, and on NIAID's Division of AIDS Web site at <http://www.niaid.nih.gov/daids/default.htm>.

**Background on the NIAID Adult AIDS
Clinical Trials Group Study 5095 (A5095)**

Study Design

This study, known as A5095, is being conducted in the Adult AIDS Clinical Trials Group, supported by the National Institute of Allergy and Infectious Diseases (NIAID), to compare the ability of the three protease-inhibitor sparing antiretroviral regimens to suppress and maintain a low level of HIV RNA (< 200 copies/mL) in antiretroviral treatment-naïve patients.

A5095 is a Phase III, randomized, placebo-matched, multicenter study of three antiretroviral drug combinations as initial treatment of HIV infection.

Study Drug Treatments	Abbreviations	Trade Names
(1) lamivudine/zidovudine + efavirenz (5 active pills and 2 placebos)	3TC/ZDV* + EFV	Combivir® + Sustiva®
(2) abacavir/lamivudine/zidovudine (2 active pills and 5 placebos)	ABC/3TC/ZDV*	Trizivir®
(3) abacavir/lamivudine/zidovudine + efavirenz (5 active pills and 2 placebos)	ABC/3TC/ZDV* + EFV	Trizivir® + Sustiva®

*also known as AZT

To assure double-blinding of all study drugs, each subject took two pills each morning and five pills each evening.

Changing study drugs for treatment-limiting toxicity (in the opinion of the investigator) is allowed during the study (for example, stavudine [d4T, Zerit®] for ZDV, didanosine [ddI, Videx®] for ABC, and/or nevirapine [NVP, Viramune®] for EFV).

The primary objectives of the study are: (1) to compare the ability of the drug combinations to decrease viral load (HIV-1 RNA level) to less than 200 copies per milliliter (c/mL); and (2) to describe the safety and tolerability of the drug combinations.

The study enrolled HIV-positive subjects who were antiretroviral therapy-naïve with HIV RNA \geq 400 c/mL and any CD4 + T cell count. Study subjects were randomized 1:1:1 to one of the three antiretroviral drug combinations listed above.

As defined by the study, virologic treatment failure occurs when HIV RNA is confirmed \geq 200 c/mL at least 16 weeks after starting the study treatment.

Subjects who stopped study medications early continue to be followed on the study. The length of the study is planned for about 2 years after the last subject entered the study (until September 2004).

Recommendations of the Data and Safety Monitoring Board

The NIAID Therapeutic Data and Safety Monitoring Board (DSMB) periodically reviews interim study data on the observed adverse events and viral load changes. Pre-specified guidelines to stop all or part of the study early were identified as part of the initial study design based on how well each study drug combination decreased viral load and maintained the decrease.

On February 6, 2003, the DSMB conducted its second annual review of this study. After reviewing pair-wise comparisons of the virologic failure data on each of the regimens, the DSMB concluded that some of the pre-specified guidelines to stop the study early had been met. Based on their review of this (and other) information, the DSMB made several recommendations that may be summarized as follows:

1. There are no toxicity (i.e., side effect) concerns regarding the study.
2. **The triple nucleoside regimen (ABC/3TC/ZDV) is demonstrably inferior to the other two regimens, based on rates and time to virologic failure and meeting the stopping criteria specified in the protocol.** Data on CD4+ T counts were not available, but the DSMB felt that those data could not reverse this outcome.

The DSMB recommended that the ABC/3TC/ZDV arm be discontinued, the study volunteers enrolled in this arm be unblinded, and the data be released with this arm compared to the pooled data from the other two arms.

3. The other two EFV-containing drug combinations should continue unchanged.

Because the other two EFV-containing treatments being studied in A5095 will continue unchanged, study results for these two treatment groups cannot be described separately at this time. Instead, the results from these two groups are being pooled together as the "EFV-containing arms," and are being compared to the results with the ABC/3TC/ZDV drug combination.

Interim Study Results

A total of 1,147 HIV+ individuals who had never taken antiretroviral therapy enrolled in A5095. The study population is diverse with 81% men and 19% women, 60% people of color, and 11% with a history of injection drug use participating in the study.

At baseline, the median CD4+ T cell count was 238/mm³, and the median viral load was 78,825 c/mL, with 57% of subjects having HIV-1 RNA <100,000 c/mL and 43% ≥100,000 c/mL. Study volunteers had completed 16 weeks on study and were followed for a median of 32 weeks when the results were given to the DSMB.

At the time of analysis, 1,064 (93%) study volunteers were still in active study follow-up, and 940 (82%) remained on the initial study regimens (allowing for substitutions). A total of 34 (9%) of those receiving ABC/ZDV/3TC and 57 (8%) of those receiving one of the other EFV-containing treatments permanently discontinued all study medications, for a variety of reasons. Regarding substitutions for treatment-related toxicities, 94 of 1,147 (8%) substituted d4T for ZDV, 40 of 765 (5%) substituted ddi for ABC, and 46 of 765 (6%) substituted NVP for EFV.

Grade 3 and 4 signs and symptoms were observed in 37 (10%) and 9 (2%) of those receiving ABC/ZDV/3TC and in 95 (13%) and 17 (2%) of those in one of the other treatment groups, respectively. Grade 3 and 4 laboratory toxicities were observed in 70 (19%) and 32 (8%) of those receiving ABC/ZDV/3TC and in 132 (17%) and 78 (10%) of those in either of the other two treatment groups, respectively. Typical signs, symptoms, and laboratory abnormalities previously described with these drug regimens were observed.

Overall, a total of 167 study volunteers reached virologic treatment failure (had confirmed HIV RNA ≥200 c/mL at or after week 16): 82 of 382 (21%) were in the ABC/3TC/ZDV group and a total of 85 of 765 (10%) were in the combined EFV-containing groups. Virologic failure occurred significantly earlier, on average, in the ABC/3TC/ZDV group compared to the combined EFV-containing groups (p<0.001). This held true for those study volunteers with baseline HIV RNA <100,000 or ≥100,000 c/mL (p≤0.001 for both groups). The percentage of those with HIV RNA ≤200 c/mL at 48 weeks on the study was 74% in the ABC/3TC/ZDV group (N=88) and 89% in the combined EFV groups (N=217) (intent-to-treat analysis).

Post-Review Analysis

In a post-hoc analysis of the group of study volunteers that decreased their HIV RNA to ≤200 c/mL at least once on the study, virologic failure occurred earlier in the ABC/3TC/ZDV group compared to the combined EFV-containing groups (p<0.001). The estimated risk of virologic failure (confirmed HIV RNA >200 c/mL) in those receiving ABC/3TC/ZDV with HIV RNA ≤200 c/mL is about 7% over 3 months, compared to 3.5% for subjects on the combined EFV-containing arms.

Study Team Recommendations

The A5095 study team notified the participating clinical trials sites of these results, and the unblinding results for study volunteers randomized to ABC/3TC/ZDV were made available. The team summarized their results in a letter to the sites, a letter to the study participants, and a confidential executive summary (for ACTG study investigators). The

study team recommended that all study volunteers on ABC/3TC/ZDV continue in the study and change therapy. Those with HIV RNA >200 c/mL are being advised to change their therapy based on current protocol guidelines. Those with HIV RNA <200 c/mL are being asked to remain in the study and will be offered an intensified treatment with EFV or tenofovir once the study is modified.