Update on Antiretroviral Therapy: The 15th CROI

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By AIDS Reader

The 15th Conference on Retroviruses and Opportunistic Infections (15th CROI) was held in Boston from February 3 to 6, 2008. There were more than 1000 oral and poster presentations at this conference and, as is usually the case, some were quite important.

In this column, we summarize and discuss key studies, results of which you may want to consider and discuss with colleagues and patients.

**THERAPIES FOR INITIAL TREATMENT**

**What Are the Optimal First-Line NRTIs?**

Several presentations provided important new data regarding the optimal NRTI combination as part of an initial drug regimen. These studies were presented shortly after a new iteration of the Department of Health and Human Services (DHHS) guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents, which were posted online on January 29, 2008. A notable change was the demotion of the zidovudine/ lamivudine fixed-dose combination (FDC) to an “alternative” therapy and the promotion of abacavir/lamivudine (ABC/3TC) once-daily FDC to a “preferred” therapy, so clinicians still have 2 preferred choices of a fixed NRTI backbone when starting treatment. (The tenofovir/emtricitabine [TDF/FTC] FDC remains a preferred choice.)

However, the revised DHHS guidelines now specifically state that abacavir is only for patients who test negative for HLA-B*5701. The guidelines also note that such patients should be warned about and monitored for an abacavir-related hypersensitivity reaction.

• **HEAT trial.** Remarkably, just 1 week after release of these updates to the DHHS guidelines, the 48-week data from the HEAT study—a prospective, randomized study comparing the 2 preferred once-daily FDCs—were presented. In the HEAT study, 688 patients received either blinded ABC/3TC or TDF/FTC in combination with once-daily lopinavir/ritonavir (LPV/r) soft gel caps for 48 weeks. At baseline, the median CD4+ cell count was about 200/µL and the median HIV RNA level was 4.9 log_{10} copies/mL; approximately 40% of the participants had an HIV RNA level of 100,000 copies/mL or higher. Outcomes at 48 weeks are shown in Table 1.

![Table 1. HEAT Study: Efficacy Results for ABC/3TC Versus TDF/FTC at 48 Weeks](image)

In a previous trial, patients in whom emtricitabine failed had significantly lower rates of resistance than those given lamivudine. In the HEAT trial, among all patients in whom therapy failed, more patients in the TDF/ FTC arm than in the ABC/3TC arm had some evidence of emtricitabine or lamivudine resistance; however, because of the small number of treatment failures in this study, the difference was not statistically significant. Also, while no primary protease inhibitor (PI) mutations were found on virological failure, some secondary mutations occurred (10V/F, 16E, 36I, 71T) that have been included in LPV/r resistance scores.
The adverse-event profile of both regimens was similar except for abacavir hypersensitivity rates (4% with ABC/3TC FDC vs 1% with TDF/FTC FDC). However, HLA-B*5701 testing was not allowed. Two of the key safety analyses of the trial focused on differences in lipid profile and renal tolerability between the regimens, and only minor differences were found. There was a slight advantage with TDF/FTC: cholesterol and triglyceride levels were lower by 11 and 26 mg/dL, respectively, from baseline. There was no difference in renal function (using the Cockcroft-Gault equation (+7 for ABC/3TC vs +6 for TDF/FTC)); only a small difference using the Modification of Diet in Renal Disease calculation (+7 vs 0); and very few discontinuations because of renal problems (0% vs less than 1%). From a clinical perspective, the HEAT trial revealed little new information regarding meaningful differences between these 2 thymidine-sparing FDCs. Virological efficacy and immunological improvement were statistically similar, as were all adverse events except for abacavir hypersensitivity. The use of HLA-B*5701 testing, which was not allowed in this study, may decrease the risk of a hypersensitivity reaction. However, the tolerability and safety of both combinations was outstanding, and the risk of any renal problems with tenofovir was remarkably low. Based on the results of this study, either of these 2 combinations appears to be a reasonable choice. However, as always, the decision about which NRTI backbone to use should be based on the individual patient profile and choice.

**D:A:D study.** The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study sparked considerable controversy with the presentation of some potentially important data regarding the cardiovascular risk associated with abacavir and didanosine. The D:A:D study is a collaboration of 11 prospective cohorts, and it includes data on 33,347 patients. Thus far, based on data from 157,912 person-years, 517 myocardial infarctions have been reported. Poisson regression analysis was used to assess the effects of cumulative, recent (current or within past 6 months), and past (more than 6 months ago) use of thymidine nucleoside analogues, abacavir, didanosine, and lamivudine on myocardial infarction and stroke after adjustment for baseline demographics, known cardiovascular risk factors, study cohort, year of study enrollment, body mass index, and use of other antiretrovirals.

Not surprisingly, 98% of myocardial infarctions occurred among patients exposed to at least 1 NRTI. While neither cumulative nor recent use of the stavudine, zidovudine, or lamivudine was associated with risk of myocardial infarction, cumulative use of either abacavir or didanosine was associated with a slight increase in risk: relative risk/years of use of abacavir = 1.14 (95% confidence interval (CI), 1.08 to 1.21; P < .01); relative risk/years of use of didanosine = 1.06 (95% CI, 1.01 to 1.12; P = .03). This risk of cumulative exposure to these drugs is similar to that described for PIs in previous publications. Other risk models suggested that recent—but not past—use of abacavir and didanosine was associated with an elevated risk of myocardial infarction (abacavir relative risk = 1.90; 95% CI, 1.47 to 2.45; P < .01 and didanosine relative risk = 1.49; 95% CI, 1.14 to 1.95; P < .01). Risk of myocardial infarction appeared to decline after drug discontinuation. This suggested that the effect was independent of established cardiovascular risk factors. Absolute rates of myocardial infarction (per 1000 person-years) for patients with recent abacavir exposure compared with no recent abacavir exposure were 3.3 versus 1.2, 9.8 versus 7.1, and 31.3 versus 11.2 in those with low, moderate, and high predicted Framingham cardiovascular risk, respectively, indicating a similar increase in risk with abacavir use in all strata. The risk of myocardial infarction associated with recent abacavir and didanosine use remained after adjustment for age, current HIV RNA level, CD4+ cell count, presence of diabetes, and lipid levels. These data could represent a potentially important safety signal with abacavir and didanosine; however, clinicians should temper this idea with the fact that these data are from a single cohort study; potential biases, as yet unexplained, could have affected the findings. Still, the authors of the study took the unusual step of issuing a position paper urging all clinicians to discuss these findings with their patients. Only time—and more data—will tell if this is a real issue with abacavir and didanosine or the type of erroneous association that can result from cohort studies. In the meantime, each clinician and patient needs to decide what to do with these data on an individual basis.

**What Is the Preferred “Third Drug” for Initial Antiretroviral Therapy?**

The current DHHS guidelines list the NNRTI efavirenz and 3 ritonavir-boosted PIs—atazanavir/ritonavir (ATV/r) once daily, fosamprenavir/ritonavir (FPV/r) twice daily, and LPV/r twice daily—as the preferred choices for the third drug to combine with 2 NRTIs when starting antiretroviral therapy. Of course, which of the preferred regimens is actually best has been an area of some controversy and marketing. We are now getting close to having adequate data to draw some conclusions. Two presentations at this year’s CROI—the CASTLE study and updated data from
the AIDS Clinical Trials Group (ACTG) 5142 study—help us in doing so.

**CASTLE study.** This trial compared once-daily boosted atazanavir and twice-daily boosted lopinavir, both given in combination with the TDF/FTC FDC, in 883 treatment-naïve patients. The baseline demographics were balanced. The median CD4+ cell count was approximately 200/µL, and the median HIV RNA level was 5.0 log_{10} copies/mL, with approximately half of the participants having HIV RNA levels greater than 100,000 copies/mL. After 48 weeks of treatment, there were no significant between-group differences in overall virological response or CD4+ cell increase. A confirmed virological response to less than 50 and 400 copies/mL occurred in 78% and 86%, respectively, with ATV/r and 76% and 82%, respectively, with LPV/r. The median CD4+ cell counts rose by 203/µL with ATV/r and 219/µL with LPV/r. Virological responses were also similar in the 2 arms in patients with HIV RNA levels of 100,000 copies/mL or higher; however, while ATV/r had similar virological efficacy across baseline CD4+ cell count strata (eg, for baseline CD4+ cell counts above 200/µL vs below 50/µL: 80% vs 78% achieved HIV RNA level below 50 copies/mL; P = .51), LPV/r efficacy significantly declined as the baseline CD4+ cell count declined (eg, 80% vs 63% achieving HIV RNA levels below 50 copies/mL for these same CD4 strata; P = .0085). There were no reported differences in drug resistance development between the 2 arms, and the rates of virological failure were similar in both arms.

Both regimens were also well tolerated. Adverse event–related discontinuations were 2% for ATV/r (fewer than 1% related to jaundice/hyperbilirubinemia) and 3% for LPV/r. There were similar rates of grade 2 - 4 adverse events in both groups (26% vs 30%), with a lower incidence of treatment-related diarrhea (2% vs 11%) and nausea (4% vs 8%) with ATV/r. As expected, there were significantly lower levels of total cholesterol, non–high-density lipoprotein cholesterol, and triglycerides in patients receiving ATV/r, and fewer participants in the ATV/r arm than in the LPV/r arm (2% vs 7%) began lipid-lowering therapy. Finally, this study also confirms the safety of TDF/FTC FDC with ritonavir-boosted PIs. There were only 2 discontinuations (0.2%), and these were related to renal events.

This study, along with the previously reported KLEAN trial—which found twice-daily FPV/r to be similar to twice-daily LPV/r in efficacy, tolerability (13% vs 11% for grade 2 - 4 diarrhea), and lipid profiles—demonstrates that the 3 preferred PIs are similar regarding both virological and immunological efficacy. However, there are some significant differences regarding tolerability and lipid profile.

**ARTEMIS study.** The data from the recently reported ARTEMIS study, in which once-daily ritonavir-boosted darunavir (DRV/r) performed as well as or better than LPV/r and had a better adverse-event profile, should also be considered by clinicians (although the 800/100 mg once-daily dose of DRV/r used in that trial is not yet available). Since well-tolerated, nontoxic, once-daily regimens are the preferred therapy, data need to be generated from a head-to-head clinical trial of ATV/r and DRV/r both given once daily to assist clinical management in patients given their first PI.

**ACTG 5142 trial.** A continuing stream of highly favorable data has made once-daily efavirenz a popular choice for initial therapy for many years, and it is now available in a coformulation with TDF/FTC to form the first highly active triple-drug antiretroviral regimen that can be taken as 1 tablet once a day. Multiple trials over the past 10 years have compared efavirenz with other “third” drugs, and efavirenz has always proved to be superior or equivalent in virological efficacy. In one of these trials, the ACTG 5142 study, a prospective, randomized trial of 753 treatment-naïve patients, participants were randomized to receive either efavirenz and 2 NRTIs, LPV/r and 2 NRTIs, or LPV/r (533/133 mg twice daily) and efavirenz. At 96 weeks, virological responses and lipid profiles favored the efavirenz and 2 NRTIs group, while the LPV/r and 2 NRTIs group experienced a statistically significant greater rise in CD4+ cell counts (the clinical significance of which was unclear) and had a lower risk of developing resistance if virological failure occurred and of protocol-defined lipoatrophy.

At the 15th CROI, ACTG 5142 investigators reported on their evaluation of the baseline predictors of the risk of virological failure, treatment discontinuation (called “regimen completion”), and toxicity-related discontinuation among various study regimens. Baseline factors evaluated in this analysis included sex, race, age, CD4+ cell count, and HIV RNA level. Cox proportional hazard models were used to analyze associations between these factors and outcome. A shorter time to virological failure was associated with younger age, female sex, lower CD4+ cell count (but not HIV RNA level), and black race. None of these parameters correlated with the likelihood of regimen completion. There were differences in regimen success by sex: Women in the LPV/r and efavirenz arm had a lower risk of virological failure and a longer time to treatment-limiting toxicity than women in the other treatment arms. Men were more likely to have metabolic toxicities,
especially those receiving a regimen with LPV/r. When patients with baseline CD4+ cell counts below 50/µL were evaluated based on time for counts to exceed 200/µL, there were no differences among the 3 regimens.

Results of other studies evaluating the influence of sex and race on treatment outcome have generally not shown an association once adjustment is made for other sociodemographic factors. While the results presented here appear in conflict with those data, notably absent in this evaluation is a measure of economic status. In the United States, women and minorities with HIV are generally poorer than non-minority men with HIV and, hence, have more barriers to care. The fact that the NRTI-sparing regimen performed best overall in the women in this study (but not in the men) underscores the importance of continuing to measure the impact of demographic factors on treatment outcome. One potential limitation of this finding is that only one-third of the study subjects received tenofovir as 1 of the NRTIs in the 2 backbone NRTI regimens, and thus two-thirds of the participants were receiving more toxic NRTIs (eg, stavudine or zidovudine) that are no longer listed as preferred in current treatment guidelines. Finally, it is reassuring that all 3 of these potent regimens were highly successful in bringing patients with severe immunosuppression above the clinically relevant CD4+ cell threshold of 200/µL.

THERAPIES FOR TREATMENT-EXPERIENCED PATIENTS

TITAN Study

The TITAN study, the results from which were presented and published last year, compared the activity of DRV/r and LPV/r in LPV/r-naive, treatment-experienced patients. This study enrolled 595 patients, most of whom were PI-experienced (36% had been exposed to only 1 PI, 32% had a history of exposure to 2 or more PIs). At week 48, there were twice as many virological failures in the lopinavir arm (65/297 patients; 21.9%) as in the darunavir arm (31/298 patients; 10.4%).

Important new data from this study that were presented at the 15th CROI included an analysis of the incidence of NRTI and PI resistance mutations at the time of failure, as well as a phenotypic analysis of the cross-resistance implications of the resistance patterns observed. New primary PI mutations developed in 6 and 20 patients in the darunavir and lopinavir treatment arms, respectively. Similar trends were observed for development of new NNRTI mutations, which occurred in 4 patients receiving the DRV/r regimen and in 15 receiving the LPV/r regimen. Phenotypic testing was done of the genotypic resistance mutations to analyze the loss of additional drug options. Three patients taking the DRV/r regimen lost susceptibility to darunavir; 13 others taking the LPV/r regimen lost susceptibility to lopinavir. Furthermore, there was significantly more cross-resistance to other PIs in patients in whom LPV/r therapy failed than in those in whom DRV/r therapy failed. Most PIs, including LPV/r, were considered to be active in all patients after treatment failure with the DRV/r arm. In those in whom LPV/r therapy failed, there was some degree of loss of susceptibility to several of the available PIs. Darunavir resistance developed in a small number of these patients.

These data demonstrate that there are multiple factors to consider when selecting a PI for treatment-experienced patients. While the response rates to both PIs were high, these data indicate that there would be fewer virological failures and fewer PI and NRTI resistance mutations with DRV/r therapy than with LPV/r therapy. Consequently, there are more options for subsequent therapy for such patients.

New Medications

The FDA has recently approved 3 new agents, including 2 in new classes:

- A “second-generation” NNRTI, etravirine.
- An integrase inhibitor, raltegravir.
- A CCR5 coreceptor inhibitor, maraviroc.

These drugs, which will most likely be given in combination with 1 of the new PIs—either boosted darunavir or boosted tipranavir—have the potential to revolutionize the treatment of antiretroviral-experienced patients, but only when used correctly. Several studies presented at the 15th CROI added reassurance regarding the power and safety of these drugs and should provide some guidance regarding their optimal use.

• Etravirine. This new NNRTI was evaluated in the DUET studies, a pair of randomized, placebo-controlled studies that included 1208 triple-class–experienced patients with documented NNRTI resistance and 3 or more PI mutations. These studies demonstrated that etravirine was significantly better than placebo when given with darunavir and a regimen of an optimized background therapy of NRTIs and enfuvirtide, as selected by the investigator. At the 15th CROI, the durability of response as well as the longer-term adverse-effect profile of etravirine at 48 weeks in the DUET studies was reported.
At week 48, 61% of those taking etravirine achieved an HIV RNA level below 50 copies/mL (using an intention-to-treat, time-to-loss-of-virological-response analysis) compared with 40% of those in the placebo arm \( (P < .0001) \). The proportion of patients maintaining virological suppression at week 24 was essentially identical to that observed at week 48. The CD4\(^+\) cell response paralleled the outcomes in virological suppression: there was a mean CD4\(^+\) cell increase of 98/µL with etravirine versus a 73/µL increase with placebo \( (P = .0006) \).

Several subsets of interest from the 48-week data were also presented. Of patients given etravirine or placebo who used enfuvirtide for the first time on study, 71% and 59%, respectively, achieved an HIV RNA level below 50 copies/mL \( (P = .01) \). Those who did not use enfuvirtide or who recycled it had response rates of 57% and 33%, respectively \( (P < .001) \).

Another analysis explored the impact of the baseline phenotypic fold change of darunavir combined with the overall number of active drugs in the regimen. In patients with a darunavir phenotypic fold change below 10, for each additional active drug in the optimized background therapy, there was an approximate 15% increase in the proportion of patients achieving virological suppression, with an HIV RNA level of less than 50 copies/mL, with etravirine: from 46% for a phenotypic susceptibility score (PSS) of 0, to 78% for a PSS of 2 or higher. Interestingly, in the patients with a darunavir phenotypic fold change below 40, the results were similar: 33% for a PSS of 0, and 82% for PSS of 2 or higher. These data support the combination of etravirine and darunavir across a broad susceptibility range.

Although there remained a higher incidence of rash and nausea in patients taking etravirine than in those taking placebo, there were no new safety concerns noted at week 48. Only 2% discontinued etravirine because of rash, and no case of grade 4 rash was observed in the etravirine group. One case of Stevens-Johnson syndrome occurred in the placebo group. No consistent laboratory abnormalities were observed other than about a 3% higher rate of elevated total cholesterol and triglyceride levels; however, elevations in low-density lipoprotein cholesterol levels were the same as those seen with placebo.

These data support etravirine as an active NNRTI in many patients despite a history of NNRTI use and some resistance to the “first-generation” NNRTIs (efavirenz, nevirapine, and delavirdine). This conclusion is supported by another study presented at the 15th CROI that found that of the approximately 90,000 patients in the Virco database with NNRTI resistance, 93% had 2 or fewer etravirine-related mutations.\(^19\) As such, these patients should experience significant benefit from etravirine use.\(^20\)

Perhaps the clearest illustration of the activity of etravirine is in patients currently being treated with a highly compromised background regimen. Of those in the etravirine arm who received no other active drugs and who experienced a greater than 40-fold change resistance to darunavir at study entry, 33% achieved and maintained an HIV RNA level below 50 copies/mL at week 48. Of course, adding more active antiretroviral drugs will improve outcomes: 82% had virological suppression if they received 2 or more active drugs in addition to etravirine. However, the fact that one-third of patients can achieve and maintain an undetectable viral load at week 48 with etravirine without any other active antiretroviral drugs should increase confidence in its use.

**Update on raltegravir.** At last year’s CROI, presentations of the 2 phase 3 raltegravir studies in heavily treatment-experienced patients ushered in the integrase inhibitor class.\(^21,22\) At this year’s meeting, the investigators updated the results by providing 48-week data.\(^23,24\)

In the BENCHMRK-1 and -2 trials, nearly 700 heavily treatment-experienced patients were randomized to receive optimized background therapy and either raltegravir (400 mg twice daily) or placebo. All had documented resistance to the 3 major drug classes (NRTI, NNRTI, and PI) at entry, and more than half had a genotypic sensitivity score (GSS) of 0 or 1. Background treatment was selected on the basis of results of resistance testing and treatment history and could include enfuvirtide as well as the newer PIs, eg, boosted tipranavir and, if available, boosted darunavir. The 48-week results are shown in Table 2.
A combined analysis of the 2 studies demonstrated strikingly different results with raltegravir and placebo when the GSS or PSS was 0 (ie, there were no predicted active drugs). An HIV RNA level below 50 copies/mL at week 48 was achieved in 45% and 3% of raltegravir-treated and placebo patients, respectively, with a GSS of 0 and in 51% and 2%, respectively, with a PSS of 0. Inclusion of additional active agents—most notably darunavir, enfuvirtide, or both—augmented responses to raltegravir. While enfuvirtide was slightly, but not significantly, more effective than darunavir when combined with raltegravir (80% vs 69%), the criteria for assessing darunavir susceptibility had not been established at the time of these studies. In most cases, another ritonavir-boosted PI was included in the regimen with enfuvirtide. There were few adverse events that lead to drug discontinuation, and there was no increased risk of malignancy with raltegravir in these studies; the same was true, when additional data from phase 2 studies were included. When virological failure with raltegravir occurred, it often was accompanied by resistance using 1 of 2 primary residues, Q148 or N155, in combination with at least 1 other mutation. Overall, these results are encouraging for clinicians and patients alike, because they suggest that initial virological responses to raltegravir will be sustained—especially if the drug is combined with other active agents. The low rate of drug discontinuation because of adverse events, which was comparable to or lower than that of placebo, is also good news, as is the absence of an increased incidence of malignancies. As more patients are treated with this agent from the newest drug class, further follow-up will be critical in assessing the long-term safety and efficacy of the drug.

MOTIVATE Studies

The MOTIVATE 1 and 2 studies were the main registrational studies used for maraviroc approval in the heavily treatment-experienced population. These studies evaluated R5-only virus in triple-class–experienced patients. Participants were randomized to receive placebo, once-daily maraviroc, or twice-daily maraviroc in combination with an optimized background therapy consisting of 3 to 6 antiretrovirals. The results of both studies have been presented independently. The results of a week-48 primary analysis in each study showed that maraviroc had immunological efficacy and a safety profile similar to that of placebo.25,26 At the 15th CROI, results of a planned analysis of pooled data, at week 48, from the 2 MOTIVATE studies were presented.27 The combined data set included 1049 patients who received at least 1 dose of once-daily maraviroc (n = 414), twice-daily maraviroc (n = 426), or placebo (n = 209). The results demonstrated that both maraviroc dosages were effective at week 48 with 45.5%, 43.2%, and 16.7%, respectively, achieving an HIV RNA level of less than 50 copies/mL. The benefits of maraviroc were also demonstrated in subgroups of patients with high baseline viral loads or low baseline CD4+ cell counts. In addition, maraviroc demonstrated a safety profile similar to that of placebo.

SUMMARY

The studies presented before and at the 15th CROI provide clear take-away messages:

- ABC/3TC and TDF/FTC combinations are similar in efficacy and safety, but the D:A:D study data add a new, and somewhat unexpected twist (for example, the potential for abacavir being associated with increased cardiovascular risk).
- In antiretroviral-naive patients, the ritonavir-boosted PIs have relatively similar efficacy, but FPV/r and LPV/r are associated with higher rates of adverse events—most notably, diarrhea and lipid disturbances.
- In antiretroviral-experienced patients, even those with relatively limited past PI use, DRV/r appears to offer some advantages over LPV/r (for example, lower rates of virological failure and lower risk of
resistance subsequently developing in patients who do experience viral breakthrough).
• Three new drugs—etravirine, raltegravir, and maraviroc—have the potential to breathe new life into antiretroviral regimens for heavily experienced patients. All of these drugs work best when combined with one of the newer boosted PIs (boosted darunavir or tipranavir) and other active agents.

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