The Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (4th IAS Conference) was held in Sydney, Australia, from July 22 to 25, 2007. This year provided some significant new insights into HIV therapeutics, especially in reducing the risk of abacavir hypersensitivity reactions, the use of novel agents in treatment-naive patients, and the use of darunavir and etravirine (a new NNRTI) in treatment-experienced patients. [See our September issue for a report from Dr William Valenti, University of Rochester School of Medicine and Dentistry, on the important findings related to the metabolic syndrome presented at the 4th IAS Conference.—Ed]

**USING HLA-B*5701 SCREENING TO PREVENT ABACAVIR HYPERSENSITIVITY REACTIONS**

Before the data were presented at the 4th IAS Conference, the association between clinically diagnosed abacavir hypersensitivity reactions (HSRs) and the presence of a positive HLA-B*5701 test was thought to be in the region of 40% to 50% in whites—with the percentage lower in blacks, who express this allele more rarely and have fewer reactions. Two studies presented at the 4th IAS Conference suggest that this screening test may be more accurate than previous studies have indicated, and consequently, these additional findings may lead to this test being the first pharmacogenetic screen to be used in HIV clinical practice to customize therapy.

The Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) is a retrospective case-control study that looked at 130 white and 69 black patients who had received a clinical diagnosis of abacavir HSR. To confirm the abacavir HSR diagnosis, all were tested with a skin patch test that contained abacavir. A total of 32% (42/130) of whites and 7% (5/69) of blacks tested positive and were considered to have immunologically confirmed cases of abacavir HSR. All of the immunologically confirmed cases were HLA-B*5701–positive, while only 44% and 14% in the white and black groups, respectively, with clinically diagnosed but immunologically unconfirmed abacavir HSR tested positive.

PREDICT-1 is a prospective study that enrolled almost 2000 abacavir-naive patients from 314 centers in Europe and Australia and randomized them to abacavir standard of care, where any patients with clinically suspected HSRs were retrospectively screened for HLA-B*5701, or to a prospectively screened arm in which patients who tested positive for HLA-B*5701 were not allowed to take abacavir. Abacavir HSR was clinically diagnosed in 7.8% and 3.4% in the standard of care and screened arms, respectively. As in SHAPE, the patients with clinically diagnosed abacavir HSR were given a skin patch test, and while 2.7% were confirmed positive in the standard of care arm, none were positive in the screened arm. The negative predicted value of HLA-B*5701 screening for immunologically confirmed HSR was 100%. There were quite a few HLA-B*5701–positive patients in the standard of care arm who were not positive for the skin patch test, so the positive predictive value was only 48%.

If found to be applicable to all populations, these studies indicate that if testing for HLA-B*5701 is widely used, such testing could virtually eliminate the risk of abacavir HSRs while denying abacavir to only a few persons who test positive for HLA-B*5701. Clinical judgment still must be used in assessing patients taking abacavir who present with symptoms suggestive of abacavir HSR, and appropriate warnings must still be given to patients before starting abacavir therapy. However, these data suggest that the incidence of abacavir HSR may be significantly reduced by the use of HLA-B*5701 testing.

**TREATMENT OF ANTIRETROVIRAL-NAIVE PATIENTS**

There are 3 classes of agents recommended by the IAS-USA and US Department of Health and
Human Services guidelines for use in initial antiretroviral regimens, an NRTI backbone and either a ritonavir-boosted protease inhibitor (PI) or an NNRTI. While these regimens are generally well tolerated and effective, there may be tolerability and toxicity problems with these options. The addition of a new target that would be potent and well tolerated could serve to increase the options for patients starting antiretroviral therapy.

Two studies, MERIT and Merck 004, evaluated the use of 2 new antiretrovirals, maraviroc and raltegravir, in antiretroviral-naive patients. In both of these studies, the comparator arm was, as it is in most trials, an efavirenz-containing regimen. One of the drugs, raltegravir, proved to be quite comparable to efavirenz in efficacy and to have some advantages regarding tolerability and adverse events. Maraviroc was well tolerated but not as potent as efavirenz as indicated by some key criteria.

The MERIT Study: Maraviroc in Antiretroviral-Naive Patients
In the ongoing phase 2b/3, double-blind MERIT study, maraviroc 300 mg twice daily is compared with efavirenz, both in combination with a coformulated zidovudine/lamivudine backbone, in 721 treatment-naive, R5-only, HIV-1–infected patients. A maraviroc 300-mg once-daily arm was previously discontinued at week 16 because of underperformance during a planned analysis.

At baseline, the arms were similar, with median CD4+ cell counts ranging from 241 to 254/µL and a mean HIV RNA level of 4.9 log_{10} copies/mL. The key efficacy data at week 48, using an as-treated analysis, are summarized in Table 1.

| Table 1. MERIT Study: Key Efficacy Data at Week 48 (As-Treated Analysis) |
|---------------------------------|-----------------|-----------------|
| HIV RNA level < 400 copies/mL (%) | Maraviroc | Efavirenz |
| HIV RNA level < 50 copies/mL (%) | 65.3 | 69.3 |
| Mean change in CD4+ cell count (µL) | 170 | 143 |

Using a noninferiority margin of -10%, maraviroc proved to be noninferior to efavirenz in the less than 400 copies/mL analysis (one-sided; lower bound; 97.5% confidence interval [CI], -9.5%); however, it underperformed efavirenz in the less than 50 copies/mL analysis (one-sided; lower bound; 97.5% CI, -10.9%). In addition, using another indicator of potency, efficacy in patients with baseline HIV RNA levels higher than 100,000 copies/mL, maraviroc also underperformed relative to efavirenz (59.6% vs 66.6%). Taken as a whole, these data suggest, but do not establish, that efavirenz is more potent than maraviroc. Interestingly, maraviroc did just as well as efavirenz in achieving an HIV RNA level of less than 50 copies/mL in patients in the Northern Hemisphere (68% vs 67.8%) but significantly underperformed in the Southern Hemisphere (62.1% vs 71%). Until now, the basis for these differences are unexplained.

Another important factor to consider is the reason for discontinuation of either the maraviroc or efavirenz regimen. The percentage of subjects discontinuing from the study before week 48 was similar in the maraviroc (26.9%) and the efavirenz (25.2%) arms; however, the rate of discontinuation because of virological failure was higher with maraviroc (11.9% vs 4.2%), while the rate of discontinuation because of adverse events was higher with efavirenz (13.6% vs 4.1%). Thus, persons discontinuing efavirenz are likely to have little resistance and preserved antiretroviral choices, and those discontinuing maraviroc are likely to have resistance and a loss of antiretroviral options.

Overall, there is no question of the value of maraviroc in the treatment-experienced population. However, given the results of this treatment-naive patient trial and the current twice-daily dosing schedule, it is difficult to justify the use of this regimen in antiretroviral-naive patients, at least until more information is available to clarify why these differences in response were observed.

Merck 004 Study: Raltegravir in Antiretroviral-Naive Patients
The Merck 004 study compared raltegravir, an integrase inhibitor, with efavirenz in 198
antiretroviral-naïve patients. There were 4 doses of raltegravir tested, 100, 200, 400, and 600 mg twice daily, and these were compared with efavirenz, with all patients receiving a tenofovir/emtricitabine fixed-dose combination as the NRTI backbone. In the arms, the mean HIV RNA level ranged from 4.6 to 4.8 log_{10} copies/mL and the mean CD4^{+} cell count ranged from 271 to 338/µL at 48 weeks.

The results shown in Table 2 demonstrate similar virological efficacy between all raltegravir arms and the efavirenz arm, with no significant differences between the 5 arms of the study.

Similar CD4 count improvements were also seen in both arms. The only difference noted between the arms was the rapidity of response in achieving viral suppression in the raltegravir arms. This was discussed in another presentation, and the clinical significance is not clear.

Both compounds were well tolerated with fewer CNS adverse effects experienced in the raltegravir arms (13% vs 29%); no serious adverse events were reported in any of the groups. There was a significant difference in cholesterol level elevation in favor of raltegravir (-2.3 vs +20.7), and the remaining lipid profile was entirely neutral for raltegravir.

Thus, in this study, raltegravir had similar efficacy and somewhat better tolerability than efavirenz. This is an impressive achievement because few agents can match the efficacy or tolerability of an efavirenz-based regimen. The twice-daily administration of raltegravir may limit its widespread use in initial therapy, but this trial indicates that raltegravir may, with further study, become a solid alternative for initial antiretroviral therapy.

TREATMENT OF ANTIRETROVIRAL-EXPERIENCED PATIENTS

Important trials discussed at this conference increased our knowledge of how to use drugs in the PI class and established that a second-generation NNRTI etravirine (TMC125) is quite effective in treating antiretroviral-experienced patients. The TITAN trial indicates that darunavir, which is commonly used in heavily treatment-experienced patients, may be a reasonable option in earlier lines of therapy. The DUET trial demonstrated the efficacy of etravirine in heavily treatment-experienced patients and further defined our knowledge of when and how to use this new NNRTI. Finally, additional data from 3 presentations refined our knowledge regarding the use of maraviroc in treatment-experienced patients and raised concerns regarding the potential for cross-resistance in the integrase inhibitor class.

TITAN Study: Darunavir/Ritonavir Versus Lopinavir/Ritonavir in Antiretroviral-Experienced Patients

The TITAN study is a phase 3 study that compared 2 boosted PI regimens—darunavir/ritonavir (DRV/r) and lopinavir/ritonavir (LPV/r)—in patients with an HIV RNA level of less than 1000 copies/mL on a stable, yet failing antiretroviral drug regimen for at least 12 weeks. The study enrolled 604 subjects who were randomized to open-label LPV/r 400/100 mg twice daily—initially using the soft gel capsule, but later, switches to the tablet were allowed when it became available—or to DRV/r 600/100 mg twice daily, together with an optimized background, selected on the basis of a resistance test, that included at least 2 drugs among the NRTI and NNRTI classes. Enfuvirtide and experimental drugs were not allowed.
Of the enrolled subjects, the median HIV RNA level was 4.35 log_{10} copies/mL and the CD4^+ cell count was 235/µL. Previous treatment was an NRTI plus an NNRTI in 29% of the subjects and an NRTI plus a PI in 22%, with 46% having 3-class treatment experience. In the PI class experience, 32% of subjects had received no PI, 36% had received 1, and 32% had received 2 or more; previous experience with LPV/r was an exclusionary criterion. The median number of primary PI mutations at baseline was 0 and the geometric mean fold-change of virus to darunavir in the darunavir group was 0.6 (range, 0 to 37), with 2% having a fold-change to darunavir greater than 10; while the fold-change of virus to LPV in the LPV group was 0.8 (range, 0 to 74), with 10% of subjects having a fold-change greater than 10.

Data from the 48-week primary end point of this 96-week study were presented, using per protocol, intent-to-treat analysis, and are summarized in Table 3. These findings demonstrate superiority of DRV/r over LPV/r in achieving an HIV RNA level of less than 400 copies/mL and that significantly more patients in the DRV/r arm achieved an HIV RNA level of less than 50 copies/mL. In addition, fewer patients in the DRV/r arm had virological failure (10% vs 22%) and had additional primary PI mutations (21% vs 36%) or lost active antiretroviral drugs. Furthermore, subgroup analyses were performed comparing outcomes by baseline CD4 count, baseline HIV RNA level, number of sensitive drugs in the background combination, number of baseline primary PI mutations, and baseline lopinavir and darunavir fold-change. In each comparison, DRV/r was either noninferior or superior to LPV/r. However, there is one cautionary note in interpreting these virological findings, and it relates to the baseline susceptibility of virus to each drug. Among the subjects with a baseline LPV/r fold-change of greater than 10, only 28% achieved an HIV RNA level less than 50 copies/mL, and therefore a significant proportion of the poorer virological outcomes in the LPV/r group may have been driven by the poor response to LPV/r in subjects with baseline phenotypic resistance.

Both PIs were well tolerated in the study, with only 7% of the subjects discontinuing because of toxicity. Rash was observed more commonly in the DRV/r group (16% vs 7%), while diarrhea was more common in the LPV/r group (42% vs 32%). All other adverse events were similar between the two groups, including elevations in lipid levels.

These results confirm the potency and safety of DRV/r and indicate that in this population, in which 68% of patients had 1 or more PIs fail, that DRV/r may lead to higher rates of viral suppression to less than 400 and less than 50 copies/mL, less virological failure, and less resistance than LPV/r. While, as noted, there are some flaws in these data, they certainly demonstrate that DRV/r may be a reasonable choice for patients with early PI failure.

**DUET Studies: Etravirine Activity Against NNRTI-Resistant Virus**

In a phase 2 study previously reported, etravirine demonstrated potent activity in patients with documented NNRTI resistance with 1 or 2 NNRTI-associated mutations. At this meeting, the DUET-1 and DUET-2 studies, 2 large phase 3 studies testing etravirine versus placebos...
In these trials, a total of 1203 subjects—all with documented NNRTI resistance—were randomized to receive etravirine 200 mg twice daily or a placebo with DRV/r and at least 2 investigator-selected antiretroviral agents from the NRTI class or enfuvirtide.

Notable baseline characteristics of the subjects are shown in Table 4. It should be noted that the majority of subjects had 2 or more NNRTI-resistant mutations and the median fold-change of virus demonstrated clear phenotypic resistance to efavirenz and nevirapine.

The 24-week results of the study were reported and are summarized in Table 5. Overall, the addition of etravirine to the optimized background therapy significantly increased the proportion of subjects achieving HIV RNA level reductions less than 400 and less than 50 copies/mL. When the phenotypic resistance to darunavir was 10-fold or higher, etravirine increased the proportion of subjects achieving an undetectable HIV RNA level by 30% or more. In both studies, etravirine significantly enhanced outcomes even when subjects had 3 or more NNRTI-associated mutations.

There were similar rates of adverse events in the etravirine and placebo groups. Rash was the most common adverse event with etravirine (20% vs 10%); however, discontinuation because of rash occurred in only 2% of the etravirine group. The incidences of CNS and psychiatric adverse events were similar, as were laboratory abnormalities.

The high rate of successful outcomes in this trial was because the use of etravirine led to the majority of subjects receiving 2 or more active agents, an essential strategy for the selection of an antiretroviral combination for patients with resistant virus. Clearly, etravirine fills an important gap in our therapeutic armamentarium—the ability to use an NNRTI when another agent within the class...
has previously failed in the patient.

**MOTIVATE Studies: Maraviroc in Antiretroviral-Experienced Patients**

At the 2007 Conference on Retroviruses and Opportunistic Infections earlier this year, the initial 24-week data from the MOTIVATE 1 and 2 studies were presented. In these studies, the efficacy and safety of maraviroc were assessed in heavily treatment-experienced patients with R5-only HIV-1. At each of the 2 maraviroc dosages tested (150 mg once daily and 150 mg twice daily), maraviroc combined with an optimized background therapy was very active, with an average decline in the HIV RNA level of approximately 1.9 \( \log_{10} \) copies/mL from baseline to week 24 in both treatment arms.\(^{15,16}\)

Two subanalyses of the combined pooled data from these studies were presented at this conference and demonstrated that (a) increased drug activity in the optimized background therapy arm improves the chance that a patient treated with maraviroc will achieve an undetectable viral load,\(^{17}\) and that (b) while maraviroc once- and twice-daily dosing are equally safe, higher rates of virological suppression occurred in the twice-daily arm including patients with no active drugs in optimized background therapy arm, low baseline CD4 count, or high baseline HIV-1 RNA level.\(^{18}\) Thus, it appears that in treatment-experienced patients, maraviroc should be combined with as many active drugs as possible and preferentially used twice daily.

**Cross-Resistance of the Integrase Inhibitors Raltegravir and Elvitegravir**

One of the important strengths of the integrase inhibitor class of antiretroviral agents is that it is not cross-resistant with other antiretroviral classes. As a result, studies involving the 2 drugs in this class that are in advanced clinical trials, raltegravir and elvitegravir, have demonstrated that they maintain full potency in patients with significant previous antiretroviral treatment and resistance to other classes of antiretrovirals.

One of the potential downsfalls of the integrase inhibitor class, however, is that resistance appears to develop relatively rapidly after virological rebound and is associated with loss of activity of both elvitegravir and raltegravir. A small pilot study proposed to evaluate the clinical responses from patients with virological rebound on elvitegravir/ritonavir (EVG/r) who were then treated sequentially with raltegravir.\(^{19}\) In the study, patients with virological failure taking EVG/r (under the guidance of the ongoing GS-USA-183-0105 study) were given the option to monosubstitute EVG/r with raltegravir 400 mg twice daily for 1 week without any change to the background regimen. As of day 8, the background regimen was optimized in any manner on the basis of patient history and previous resistance testing. Baseline safety data, CD4 count, HIV-1 RNA level, PR/RT phenotype and genotype, replication capacity, and samples for integrase inhibitor genotyping were obtained at weeks 1, 2, 4, and monthly thereafter until week 24.

The HIV RNA level declines after 1 week of raltegravir monosubstitution were 0.16 to 0.29 \( \log_{10} \) copies/mL in the first 2 patients enrolled. These results suggest a lack of raltegravir efficacy, likely mediated by cross-resistance with elvitegravir. The initial mutation patterns that were observed in these patients did not follow the primary mutation patterns originally described in the elvitegravir in vitro data (principal mutations E92Q or T66I), but they are consistent with in vivo data collected from the GS-US-183-0105 study, in which about one third of patients with virological rebound did not follow 1 of these 2 main mutation pathways. In addition, one patient developed the integrase inhibitor mutation N155H at virological rebound while taking EVG/r, which has also been observed in patients in whom raltegravir has failed. Another interesting finding is that after a switch to raltegravir, one of the patients had persistence of the Q148R mutation while taking EVG/r, which has also been observed in patients in whom raltegravir has failed.

When the initial results for these 2 patients were known, the study was halted. While further research may be needed, based on these data it appears that failure of one integrase inhibitor will result in a significant fold reduction in response to the other integrase inhibitor and lead to rapid viral evolution to further decrease susceptibility to the integrase inhibitor being used.

**CONCLUSION**

The data presented at the 4th IAS Conference provide preliminary support for a number of new concepts in HIV therapeutics that clinicians should consider:

- Use of HLA-B*5701 testing to significantly reduce the incidence of abacavir HSR.
- Raltegravir as an initial therapy.
• Darunavir use earlier in therapy in patients in whom LPV/r would previously have been used.
• Etravirine use in heavily treated patients.

Thus, while some disappointments do occur, overall progress continues to be made and treatment options for patients continue to expand.

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