Presented by
The Johns Hopkins University School of Medicine

From the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy / 46th Infectious Disease Society of America Annual Meeting
Washington DC
October 25-28 2008

John Bartlett, MD (JB): Welcome to this review of the scientific papers addressing HIV/AIDS presented at the 2008 joint ICAAC/IDSA annual meeting. Discussing the most important papers will be Dr. Edwin DeJesus, Director of the Orlando Immunology Center, and Drs. Paul Sax and Cal Cohen from Harvard Medical School.

JB: Paul, what did you find at this meeting that was important regarding treatment-naïve patients?

Paul Sax, MD (PS): Well, there was a very important study presented on the question of when to start. The NA-ACCORD group, which stands for North American AIDS Cohort Collaboration on Research and Design, looked at the question of is it better to start therapy with a CD4 count >350 cells/mm³, or is it okay to wait? (Kitahata M, et al. Abst. H-896b) Some of the strengths of this study are the use of all cause mortality as the endpoint and a large number of participants that were well balanced for viral load, age and risk: 2000 started ARV therapy when their CD4 count was >350 cells/mm³ and nearly 6000 who waited. The study demonstrated that there was about a 42% reduction in the risk of death for people who started ARV therapy before their CD4 count fell to <350 cells/mm³. And, very sophisticated statistical analyses were performed to account for potential differences in the groups, and the results remained robust despite that. This study has generated a lot of controversy, but I think that it does help inform the decision about when to start therapy, and indicates that starting when the CD4 count is >350 cells/mm³ may be best.

The issue of which drugs are best to use in ARV-naïve patients was also covered quite extensively. There was a very important phase 3 trial presented called “STARTMRK”, which compared efavirenz (EFV), which is the gold standard third-drug in treatment-naïve patients, with raltegravir (RAL), the only approved integrase inhibitor, with all patients also receiving tenofovir and emtricitabine (TDF/FTC). (Lennox J, et al. Abst. H-896a) The previously presented phase 2 data comparing these two drugs showed them to be pretty much interchangeable, but this phase 3 study was done to definitively answer the question. And, it was a large, double-blind, well powered study, with about 600 people enrolled. The virologic results showed that RAL was clearly non-inferior to EFV for initial therapy (Figure 1). In some other measures, it was better. For example, the CD4 count increase was significantly greater with RAL than EFV (+189 vs. +163 cells/mm³, p<0.05) and RAL was better tolerated.
So this gives us the first third-drug option for treatment-naïve patients that is not either an NNRTI or a boosted PI, and already, I gather from our own clinical experience and from that of others, there is some use of RAL in this patient population.

The other clinical trials in treatment-naïve patients were extensions of studies that have previously been either published or presented. These include two studies that compared lopinavir/ritonavir (LPV/r) to either darunavir/ritonavir (DRV/r) 800/100 mg once-daily (QD) in the ARTEMIS study or atazanavir/ritonavir (ATV/r) 300/100 mg QD in the CASTLE study. (Mills A, et al. Abst. H-1250c; Molina J, et al. Abst. H-1250d) While the 48-week data from both of these studies demonstrated that DRV/r and ATV/r were non-inferior to LPV/r regarding virologic outcomes, the 96-week extension demonstrates that DRV/r and ATV/r are both superior to LPV/r, and there were some interesting details in these studies trying to explain why those differences occurred out at 96 weeks. Further, there were other benefits to DRV/r and ATV/r over LPV/r, for example, less diarrhea and better lipid profiles. So, these data indicate that LPV/r may no longer be the preferred boosted PI in treatment-naïve patients.

Also, a systematic review was presented, which included nearly 5000 patients in 12 trials, of TDF/FTC vs. abacavir (ABC)/lamivudine (3TC) in studies that used RTV-boosted PIs as the third agent. (Hill A, et al. Abst. H-1254) The aggregate results of the review favored TDF/FTC, and this was especially impressive when one looks at the individuals treated with LPV/r, and there, the effect was really quite strong (Figure 2).

This study also looked at another important question about RAL, which is, what is its potential as a QD agent? It was noted in BENCHMRK, in which RAL was given twice-daily (BID), that RAL pharmacokinetics (PK) were a very poor predictor of outcome in that those patients with the lowest quartile of RAL exposure did about as well as those in the highest quartile of exposure (Figure 3). It’s a very puzzling finding. Well, some in vitro data showed that if you remove RAL 8 hours after the cell has been infected with HIV you still see a significant inhibition of viral replication at 24 hours (Figure 4). This finding, which is not what we would see with other ARVs, may be explained by irreversible binding of RAL to the pre-integration complex. So, with RAL, once it binds to its target it continues to work, even if drug levels in the plasma fall to zero. So, this study gives us some understanding of why the activity of RAL is much longer than its PK would
We also saw a lot of focus on the enhanced-sensitivity Trofile® assay, which has now replaced the standard Trofile® assay and is the only assay available. In particular, the Trofile ES® was shown in ACTG 5211, a treatment-experienced trial using vicriviroc (VCV), and in the MERIT study, a treatment-naïve trial using maraviroc (MVC), to be more sensitive than the standard Trofile® assay (which it has now replaced) at detecting dual/mixed (D/M) virus. (Su Z, et al. Abst. H-895; Saag M, et al. Abst. H-1232a) This is important since D/M patients are likely to fail on a CCR5 antagonist, and, when they were removed from the cohorts in these studies, the results are much better (Figure 5). This means that the Trofile ES® does predict reasonably well who might be at risk for failure of a CCR5 antagonist and should add to clinician confidence that when the patient screens R5-only that it is safe to use a CCR5 antagonist.

There was a little bit of data about some new drugs that are entering into phase 2/phase 3. I’ll briefly mention one of them, the maturation inhibitor bevirimat (BVM). It’s the only oral drug in a novel class that’s being developed right now. What we learned is that patients who lack a certain GAG polymorphism that decreases BVM activity, which is true of about 62% of patients, had a mean 1.08 log_{10} c/mL reduction in HIV RNA. (Lalezari J, et al. Abst. H-891) Then if we take a look at the subset that had the right exposure to the drug, Cmin > 20 μg/ml, that group had a 1.26 log_{10} c/mL reduction, suggesting that this drug is on the pathway to focusing on who are the patients most likely to benefit.

**JB:** Edwin, do you want to tell us about some of the management issues regarding the treatment of HIV infection and what we learned?

**Edwin DeJesus, MD (ED):** So John, there were several presentations at this conference addressing management issues in HIV infected patients. I presented the results of two studies in which virologically suppressed patients were switched to a single tablet regimen (STR) containing co-formulated EFV, FTC and TDF. The first was A1073, and, in this study, virologically suppressed patients that were already taking a stable regimen, and had no history of regimen failure, were randomized to either switch to the STR or stay on their current regimen (SBR). (DeJesus E, et al. Abst. H-1234) This study showed equal continued efficacy in the 2 arms, indicating that virologically-suppressed patients can change to the STR without compromising virologic control. The downside of this approach is that patients that switch medications may need to get used to their new regimen, especially the well known CNS adverse events that are associated with the use of EFV. So, we learned from this study that we can safely switch virologically suppressed patients with no prior history of treatment failure to the STR, but that we need to be aware that CNS symptoms can occur, and although for the most part they are mild, they may require further intervention in some patients.

The second study that I had the opportunity to present regarding switching patients to the STR was an extension of Gilead 934 (GS 934). (DeJesus E, et al. Abst. H-1235) GS 934 randomized patients to either TDF and FTC or zidovudine (ZDV) and 3TC, both in combination with EFV. Those patients were followed in these arms for three years, and the results, which have already been published, showed that the TDF and FTC arm outperformed the ZDV and 3TC arm in many efficacy and safety endpoints. (Arribas J, et al. JAIDS 2008;47(1):74-8) At the end of three years, patients were offered the opportunity to participate...
in an extension phase of the study during which all patients were placed on the STR, and those are the data I presented here. Overall, the patients did very well and maintained virologic suppression. (Figure 6) Patients already taking TDF and FTC plus EFV did well because they continued to take their same medications and just switched to taking one co-formulated tablet QD instead of two. For patients taking ZDV and 3TC plus EFV there were several advantages to switching to the STR, which included simplification of the regimen from BID to QD with fewer pills and some had improvements in CD4 count, lipids and lipoatrophy. Like in AI073, some patients developed minor tolerability issues after switching to the STR, but, in general, these events were rare, mild and transient and none of them resulted in study discontinuation.

Figure 6: Virologic outcomes in GS 934 Extension

**JB:** Paul, you’ve talked about the NA-ACCORD study, tell us how that’s likely to impact clinical practice?

**PS:** Well, it’s a good question because we already have a lot of signals that starting therapy earlier is better, and probably the strongest signal came from the SMART study demonstrating that non-AIDS complications were more common in people off therapy. (SMART Study Group. NEJM 2006;355:2283-96) And now, we’re seeing that in multiple cohort studies that non-AIDS complications are more common in people off therapy. What was missing was the piece on mortality: we didn’t have data that survival was better for people starting earlier, and that’s what this study gives us. It gives us strong evidence, maybe not conclusive, but strong evidence that starting therapy with a CD4 count >350 cells/mm$^3$ improves survival. I think one question that remains is whether observational data is enough, or do we need a randomized trial? I think one of the biggest concerns with an observational study, like the NA-ACCORD study, is that the patients who start with a higher CD4 count may be different from the patients who don’t. For example, are they the kind of patients who take better care of themselves by not smoking, exercising, eating well, etc. and have better access to health care. So, whatever patient behavior it might be, is getting ARV therapy at a higher CD4 count a marker for good health behavior that predisposes this group to have better survival? And, only a randomized trial can truly answer that, but if we can’t do a randomized trial, I think these observational data are compelling.

**CC:** I think that ultimately, the central question is not, what we think, but what do clinicians around the world need as proof to know the answer to this question. And, observational studies and expert opinion have occasionally gotten it wrong. My sense is that clinicians have a need to see it rather than just infer it, and that only a randomized study will adequately answer the question of when it is best to start ARV therapy.

**JB:** What is the role for RAL as initial therapy in treatment-naïve patients?

**PS:** Well, if we make our clinical decisions based on clinical trials data and clinical experience, you’d have to conclude that RAL should be part of the mix for initial therapy. The STARTMRK study demonstrates that RAL is every bit as good as EFV and in some ways better, and the only caveat one has is that this is still a relatively new drug class and we don’t have any real sense of its long-term safety. And, there have already been patients that we have seen in our practice for whom RAL has been the best third drug to use.

**CC:** When resistance analyses are done on the few percent of patients who fail, and we’re talking about 5% of the entire cohort, we see that the amount of resistance is similar between the RAL and EFV arms. So, while RAL is a great drug to create suppression, like EFV, it is also vulnerable to resistance in patients who don’t achieve suppression. I think that’s going to be part of the discussion about using RAL or a boosted PI given the data which indicate failure with a boosted PI does not lead to PI resistance.

**PS:** One thing that has been striking about the clinical use of RAL in treatment-experienced patients is the rarity of virologic failure, and when one polls busy HIV clinicians around the country and asks them how many patients with RAL failure and probably resistance are you managing, the number is surprisingly small. One wonders though if it’s expanded to use in a patient population who maybe is not quite so motivated or doesn’t understand the consequences of resistance quite so much, whether we will see more resistance.

**JB:** Well, let me ask you the old question: With a drug like raltegravir, should we save it for a downstream need?

**PS:** I’ve never been a big fan of the sequencing argument. So I would say no, I think we should use our best drugs up-front because they can work for years.
CC: They might work for decades.

ED: Well, on the other hand, we can argue that we have very good regimens to initiate treatment-naïve patients without the use of RAL, and given that RAL is fairly new, there is an argument to save it, and learn a little bit more about it, before widespread use in treatment-naïve patients.

JB: With darunavir, what are the differences in dosing for initial therapy and for treatment-experienced patients?

PS: Yes, that's a good point. The 96-week ARTEMIS data which were shown here, uses the recently approved DRV/r dose of 800 mg DRV and 100 mg RTV QD, which is a lower dose of DRV and RTV than is used for treatment-experienced patients (600/100 mg BID). The efficacy of DRV/r 800/100 mg QD is unquestionable, and there exists good PK data to support this QD dosing. I do want to say about these 96-week results, one important point is that DRV/r was better than LPV/r not just because of adverse events or nonspecific dropouts; when one looked at the results based solely on virologic failures, there were fewer virologic failures in the DRV/r arm than the LPV/r arm.

JB: So Cal and Edwin, what do ARTEMIS and CASTLE studies mean to you in terms of selection of a PI-based regimen for initial therapy in 2008?

ED: Well, I agree with Paul that we should not be saving the best drug for later. I mean, we have several PIs; there is very little reason that we need to boost the PI with 200 mg of ritonavir with the data that we have collected in these studies. So with that said, there is very little reason in my mind to use LPV/r because it’s using 200 mg of RTV. So, I will favor the use of ATV/r or DRV/r QD in a PI-naïve patient.

CC: In terms of deciding, I guess I’d only add one or two more points. One is the patient in whom co-formulation is important, either because they travel a lot to hot climates and then the RTV capsule might be heat vulnerable, or the forgetting issue. If we look at those patients in whom that’s not a factor, I would agree that ATV/r and DRV/r have great data and the question is going to be how to choose between them. I think what Paul already mentioned earlier is interesting, and that is that the superiority of DRV/r over LPV/r includes a difference in fewer virologic failures. In the CASTLE study, the difference of ATV/r over LPV/r isn’t virologic superiority; it seems to be perhaps some tolerability issues that show up more at low CD4s.

JB: Are we at the point now where we can say it’s no longer appropriate to sequence boosted PIs?

PS: Certainly, the data on the rarity of PI resistance upon virologic failure with boosted PIs could make one very comfortable that one can just use whatever effective PI you want up-front, and not worry about the issue of salvage. The days of accumulating multiple PI resistance mutations should be over because we understand better how to manage our virologically failing patients.

ED: In addition, we have new drugs that we can use in the rare event that a patient develops significant PI resistance.

JB: Edwin, tell us what you would do with regard to switching therapy in patients who are virologically suppressed?

ED: I think that the data is very clear that we can switch virologically suppressed patients, but we need to make sure that the patients do not have any evidence of prior failure or baseline resistance mutations. With that said, there appear to be multiple benefits to switching a patient from a more complex or toxic regimen to co-formulated EFV, TDF and FTC

CC: I would actually say one more thing, which is that I’m impressed that the study worked given that there were two things that I think could have gone wrong with the switch study. One is we didn’t necessarily have baseline resistance tests on all the patients who entered, and if there is widespread non-nucleoside (NNRTI) resistance, this switch would not have worked, and yet, it worked. And so, obviously, whatever NNRTI resistance is floating in the population, either it doesn’t matter when you do a switch study in suppressed patients, or it’s at a low rate in the majority of our patients, I think that’s one compelling thing.

PS: Yes. The patients that we follow who have never failed treatment are a special subset for whom virtually everything works. Switching can be done with little risk of virologic failure, and really, it’s the toxicities you’re sorting out after the switches.

JB: Thanks very much Paul, Cal and Edwin.