Introduction

This newsletter describes presentations and discussions held during the continuing medical education Internet symposium ARV Therapies and Therapeutic Strategies. This program provided an update on important presentations on HIV and hepatitis C infection made during the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held on September 17-20, 2011 in Chicago, Illinois.1 The faculty panel for this program consisted of course director and moderator John Bartlett, MD from the Johns Hopkins University School of Medicine in Baltimore, Maryland, and panelists José Arribas, MD from Hospital de La Paz in Madrid, Spain, Calvin Cohen, MD from Harvard Medical School, in Boston, Massachusetts, Jürgen Rockstroh, MD from the University of Bonn, in Bonn, Germany and Andrew Zolopa, MD from Stanford University, in Palo Alto, California.

Studies in Antiretroviral-Naïve Patients

Dr. Arribas discussed STARTMRK, in which ARV-naïve patients were randomized to receive tenofovir (TDF)/emtricitabine (FTC) + raltegravir (RAL) BID or TDF/FTC + efavirenz (EFV).1 At baseline, >50% of the patients had >100,000 RNA copies/mL, and almost 50% had CD4 cell counts <200 cells/mm3. After 3 years of follow-up, 75% of patients in the RAL group had <50 copies/mL, compared with 68% in the EFV group (Figure 1). CD4 cell recovery was significantly better (~40 CD4 cells) with RAL than with EFV.

Figure 1. STARTMRK Results through 156 Weeks2

A subanalysis of STARTMRK examined outcomes based on different strata of baseline characteristics.1 The investigators determined the efficacy by treatment groups across different levels of viral loads and found no significant differences between the arms. However, with RAL, there was a non-significant decrease in virologic response as the viral load increased: from 94% for patients <50,000 copies to 84% for those with viral loads >250,000 copies.

Discussion: Dr. Cohen noted that these findings indicate RAL is on the borderline of superiority to EFV for the lower stratum (≤50,000 copies), and that 94% is an impressive finding. While there was a decline in the percentages, it started from 94% then reached the same level as EFV. Dr. Bartlett asked if these findings will motivate any of the panelists to change their practice. Dr. Arribas said no, as he considers both drugs to be excellent choices when treating an ARV-naïve patient with a very high viral load.
Dr. Arribas also discussed an analysis of STARTMRK that looked at outcomes in terms of the baseline CD4 cell counts. Regarding virologic success, there were no significant differences between EFV and RAL groups in patients who started therapy at CD4 cell counts of 50, between 50 and 200, or >200 cells/mm³. In data on CD4 cell count recovery, on the other hand, for the two higher CD4 levels (50-200 and >200 cells/mm³), the results favored RAL, but in patients with CD4 cell counts <50, there was no advantage to either drug.

In the SENSE trial, a small clinical trial in ARV-naïve patients (n=157), patients were randomized to receive two nucleoside reverse transcriptase inhibitors (NRTIs) and either etravirine (ETR) 400 QD or EFV 600 QD. The primary end point was neuropsychiatric adverse events up to week 12; the secondary end point was HIV RNA suppression at week 48.

The trial showed that CNS adverse events grade 1 to 4 were lower with ETR than with EFV. The efficacy of ETR QD and EFV (ITT analysis) was similar - about 75%. In the non-viral failure censored analysis, 92% in the ETR arm had an HIV RNA <50 copies/mL vs. 89% in the EFV arm.

An analysis presented at ICAAC characterized the impact of baseline mutations on the results of the SENSE trial. This analysis, baseline mutations were analyzed in two ways: with population genotyping and with an ultrasensitive allele specific PCR. For patients to enter the trial, their virus had to be genotypically sensitive to ETR and EFV, and not have any of the mutations considered related to primary resistance by the WHO list of mutations. However, there were patients who had mutations at baseline that were not on the WHO list, but were on the IAS-USA list of mutations, and this was more common in the ETR arm. Also, some protocol violators had mutations to NRTIs, but this was found only in the ETR arm. So, when the investigators re-analyzed the samples using an ultrasensitive PCR, they found one patient with the non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation K103N in the ETR arm and one patient in each arm with the NRTI mutation M184V. However, the investigators could not find an impact of these baseline mutations on patient response to either ETR or EFV. The investigators also examined the impact of the NRTI resistance mutations that were found only in the ETR arm, and found they had no impact. The investigators also reported finding that when patients failed with ETR, non-resistant mutations were found, while 3 of the 7 patients who failed on EFV had resistant mutations. These findings support the view that ETR has a higher genetic barrier than EFV.

The ARIES study also addressed the issue of minority resistant species and the impact on response in ARV-naïve patients. In this study, all subjects started with ritonavir-boosted atazanavir (ATV/r) plus abacavir (ABC)/lamivudine (3TC); if patients had undetectable levels of virus at week 36, they either stopped the ritonavir and increased the dose to ATV 400 QD or continued with ATV/r. In the 3-year data, it was shown that unboosted ATV had the same virological efficacy whether it was used in an induction-maintenance type strategy or it was boosted. While all patients had to be sensitive to the drugs before they entered the trial, the investigators did ultrasensitive sequencing to find minority species that confer resistance. They found that of the 20 virological failures, only 5 had detection of mutations by ultradeep sequencing. The investigators concluded that if boosted protease inhibitors (PIs) are used, detecting minority species might not be as important as with other drugs.

Finally, Dr. Arribas discussed ECHO and THRIVE, two large clinical trials in ARV-naïve patients that compared EFV with rilpivirine (RPV). Efficacy data have shown non-inferiority of RPV vs. EFV. In an analysis presented at ICAAC, the investigators looked at the tolerability of both drugs during the first 12 weeks of treatment. They found that CNS adverse events during the first 12 weeks were lower with RPV than EFV. Overall, there were more adverse events in the EFV arm than in the RPV arm. Further, there was a lower incidence of rash and lipids were more neutral with RPV; however, there was no difference in the total cholesterol:HD ratio. These results indicate that clinicians have another option for treating ARV-naïve patients that, like ETR, can cause fewer CNS adverse events than with EFV.

**Studies in Antiretroviral Experienced Patients**

Dr. Zolopa started his presentation by discussing a study that examined data from almost 70,000 isolates that were sent to a lab for resistance testing. The analysis started in 2003 and the isolates were primarily from patients who were treatment experienced. The investigators found that the prevalence of resistance to PIs has dropped steadily from 2007 to 2010, the most recent year measured. This finding correlates with a continuous decrease in triple class resistance. These data indicate that patients with highly resistant virus are becoming less common.

Dr. Zolopa next discussed the VERITAS study, which consisted of 31 treatment experienced patients from Montreal, Canada. These patients were on 4 or 5 drug salvage regimens with suppressed HIV RNA and the investigators examined the effect of removing one of the inactive NNRTIs, based on their baseline resistance test. Of 31 patients, 29 stopped 3TC or FTC (because of a 184V mutation), 1 each stopped zidovudine (ZDV) and TDF. The investigators found that no patient had virologic rebound over the 24 weeks they were followed. Although this was a small study, the findings suggest that some NRTIs can be stopped, although Dr. Zolopa considers this an unresolved question.

Next, Dr. Zolopa presented data on resistance to RPV from the Monogram database, which consisted of the phenotypic profiles from clinical isolates that had single NNRTI mutations. The analysis excluded viruses with NRTI or PI mutations, to avoid any cross talk interfering with the analysis. There are 15 resistance association mutations (RAMs) that have been associated with a diminished response to RPV. These include K101E/P, E138K and Y181C/I/V. (Table 1) While the E138K mutation is a signature mutation, the 181 mutations seem to have a bigger impact then the 138 mutations; with the 181 mutations, over 3/4 were above the...
biological cut-off. The H221Y mutation seems to be active some of the time, but only 13% were above the biological cut-off. With K103N, which is probably the most frequently transmitted virus, only 7% of the isolates were above the biological cut-off.

Table 1. Impact of Genotypic Mutations on Phenotypic Susceptibility to Rilpivirine

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Median FC</th>
<th>Percent ≥ BCO</th>
<th>N</th>
<th>OR</th>
<th>FET</th>
<th>P-value</th>
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<tr>
<td>K101E</td>
<td>1.68</td>
<td>40</td>
<td>15</td>
<td>22.38</td>
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<tr>
<td>K101P</td>
<td>25.5</td>
<td>100</td>
<td>13</td>
<td>All Above BCO</td>
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<td></td>
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<tr>
<td>E138A</td>
<td>1.94</td>
<td>47.9</td>
<td>168</td>
<td>26.08</td>
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<td></td>
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<tr>
<td>E138G</td>
<td>2.25</td>
<td>33.53</td>
<td>10</td>
<td>50</td>
<td>0.00011</td>
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<tr>
<td>E138K</td>
<td>1.65</td>
<td>40</td>
<td>10</td>
<td>22.38</td>
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<td></td>
</tr>
<tr>
<td>E138Q</td>
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<td>75</td>
<td>8</td>
<td>100.78</td>
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<tr>
<td>Y181C/I/V</td>
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<td>77</td>
<td>56</td>
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</tr>
<tr>
<td>Y181I</td>
<td>3.79</td>
<td>76.9</td>
<td>52</td>
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<td>Y181V</td>
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<td>100</td>
<td>2</td>
<td>All Above BCO</td>
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<tr>
<td>H221HY</td>
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<td>100</td>
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<td>All Above BCO</td>
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<td></td>
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<td>H2231Y</td>
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<td>818</td>
<td>2.52</td>
<td>0</td>
<td></td>
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</tbody>
</table>

Discussion: Dr. Cohen noted one of the limitations of this analysis is that they isolated those who did not have NRTI mutations. His concern is that if somebody is rebounding on RPV, or when they have the 138K mutation, they probably have 184 as well. So it is not clear exactly what to do with these data – but he thinks they are interesting, and they support his assumption that we may be loosing the class, and that we may lose both RPV and ETR. Nevertheless, at least in this table, 40% had predicted elevations of their phenotype but 60% maintained apparent susceptibility based on the complexity of the gene. So, it is reasonable to be conservative but it is also reasonable to check the phenotype, because sometimes we have not lost the full activity of the drug.

Dr. Zolopa next discussed a study of patients on a single tablet regimen of EFV/TDF/FTC who switched to the new single tablet regimen of RPV/TDF/FTC.9 It is known that EFV is a potent inducer of the isoenzymes that induce the metabolism of RPV; it has been shown in healthy volunteers that it reduces drug levels to what appeared to be subtherapeutic levels in many cases. So, there is a concern that if patients switch from EFV/TDF/FTC to RPV/TDF/FTC, they will have subtherapeutic drug levels and virologic failure. In the study, patients who were well suppressed on EFV/TDF/FTC, with viral loads of <50 copies/mL over 8 weeks, were switched to RPV/TDF/FTC. The investigators looked at virologic outcomes at 12 weeks and at pharmacokinetic (PK) profiles and tolerability over 48 weeks.

Of those treated, all 49 (100%) maintained viral suppression. No patients had adverse events that led to the discontinuation of the new regimen. In the first couple of weeks, the drug levels for RPV were below a therapeutic level, but EFV drug levels remained high, and were considered therapeutic for about 4 weeks. In other words, as EFV is washed out, RPV levels slowly increase and patients maintained virologic suppression.

Next, Dr. Zolopa discussed the SWIFT study,10 in which patients maintained an ABC/3TC and boosted PI regimen for more than 3 months. To be in the study, patients had to be suppressed for more than 3 months with viral loads <200 copies/mL and no history of resistance to study drugs. There were 311 people enrolled in the study who were randomized 1 to 1 to either switching the ABC/3TC to FTC/TDF or continuing their regimen with ABC/3TC. They were followed for 48 weeks. There were no restrictions in terms of T cells or the boosted PI they were on. At week 48, the results from both treatment groups were almost numerically and statistically identical, but there were more virologic failures in the ABC/3TC arm. However, there was a lipid advantage to taking TDF: total cholesterol, LDL cholesterol, and triglycerides significantly declined (Figure 2).

In addition, both arms saw a continued decrease in kidney function as measured by estimated glomerular filtration rate (eGFR), although it was significantly more on TDF than on ABC (P=0.012). However, these changes were within a normal range.

Figure 2. SWIFT: Change from Baseline in Fasting Lipids at Week 48

No significant difference between groups in total cholesterol/HDL ratio at Week 48

*P-values for between arm differences from Wilcoxon rank-sum test
TC = Total Cholesterol, LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein, TG = Triglycerides

Dr. Zolopa next reviewed some novel approaches for the treatment of experienced patients, starting with the monoclonal antibody ibalizumab (TMB-202). This monoclonal antibody binds to the conformational epitope on the CD4 cell, so it blocks HIV entry. It interferes with the interaction between gp120 and the CD4 receptor on the cell. A study presented at ICAAC was designed to determine the optimal dose for this therapy.11 The patients received one of two dosing schedules: either 800 mg IV every two weeks or 2 g every four weeks, then they were followed for 24 weeks. The subjects were triple class resistant patients, failing their current regimen, and they had to have at least one sensitive drug in their OBR. Viral loads were improved after treatment (Figure 3).

Complete information about this program, including faculty disclosures and CME credit information, is available at www.viraled.com
There were no statistically significant differences between treatment arms. So, there was some response from the drug, but the role of this drug in treatment remains unclear.

Figure 3. TMB-202: Primary Endpoint, ITT-MEF

There was an inverse correlation with the viral load after the ART period 4 weeks after the infusion. The investigators found CCR5 modified cells in these patients for >1 year. The investigators also found modified cells when they did biopsies of the intestine. Finally, there was an inverse correlation with the viral load after the ART was stopped and the number of these circulating cells. This approach is now moving into phase 1 and phase 2 studies.

Management Issues

Dr. Cohen discussed an analysis of a large Medicaid database that evaluated the relationship between the number of pills in an ARV regimen and hospitalization risk. The study used diagnostic codes and pharmacy refill data and, while the database had tens of thousands of HIV patients, the investigators were able to identify almost 2,000 patients who received the only single tablet regimen (STR) that was available at that time (FTC/TDF/EFV) and compare them to 6,000 patients who received a multi-pill regimen. The investigators found that there was a significant advantage to those who were taking an STR in terms of adherence. Further, the investigators reported that those who were receiving an STR had a 25% lower risk of hospitalization. Even when they limited the analysis to the treatment naïve patients, there was a 25% lower hospitalization rate in populations in which the STR approach would be the ideal drug choice.

Next, Dr. Cohen discussed a study from The Chelsea and Westminster Group that looked at the reasons for switching ARV therapy in 472 treatment-naïve patients who were started on EFV/TDF/FTC. The patients were mostly a gay, white male population whose CD4 cell counts were about 300 cells/mm³ and whose viral load was low. Almost all patients had an undetectable viral load after 6 months of treatment. The investigators found that while only 6 patients had virologic failure, 19% stopped taking EFV/TDF/FTC in their follow-up. These discontinuations were mainly due to CNS toxicities, hepatotoxicity, and rash. Dr. Cohen noted that 16% of the interruptions of EFV/TDF/FTC were in the first 12 weeks, and half in the first year. There was another 36% in year 2 – a time when some double-blind trials have suggested that EFV toxicities are gone and are equal to placebo – suggesting that maybe the patients had symptoms that were not related to EFV, but clinicians were considering that it might be the EFV that was causing the symptoms.

Dr. Cohen next discussed the issue of proteinuria in patients on a TDF-based regimen with a PI, which was addressed in a small trial with 21 patients, all of whom had proteinuria without known etiology other than use of TDF. The patients were on a TDF/FTC and boosted PI regimen that apparently had additional renal complications compared with TDF/FTC used with a NNRTI. The patients were on TDF on average for about 4 years. The intervention in the study consisted of stopping TDF/FTC and replacing it with RAL while maintaining the PI. The investigators reported that 14 of 21 patients had a decline in urinary protein; however, there were a few patients who continued to show an increase, suggesting that this is a heterogeneous group in which TDF was relevant to their proteinuria in some but not all patients. Dr. Cohen said these findings suggest that if a clinician is struggling with a patient with significant proteinuria, RAL might be an alternative in this two drug approach for some of those patients.

Next, Dr. Cohen reviewed a study that was conducted in response to a concern by the FDA, which identified limitations in some of the demographic information in RAL studies. Specifically, studies that supported FDA approval of RAL had <20% females and <15% African Americans, so the FDA requested a study to provide additional experience of RAL in diverse patient populations. Merck responded by conducting a broad single cohort study, in which patients could be either treatment naïve or treatment experienced and leaving the regimen because of intolerance or viremia. For this study, the new regimen had to contain RAL in combination with an optimized background. The study included 97 patients switched for failure, 88 switched for intolerance to their current regimen, and a small number of treatment naïve patients. About half of the patients were female and about 80% of the subjects were black. The investigators reported minimal differences in the results of the RAL-containing regimens regardless of gender or race and this was true for all patients, whether they belonged to the failure group, the intolerance switches, or the treatment-naïve groups and even if they pooled all patients. There were
also no differences by gender or race in terms of adverse events. Dr. Cohen asked if the study found a difference in RAL processing or PK by race and/or by gender. The reason this is an important question is that studies over the past decade have shown that a lower percentage of African Americans are suppressed than non-black populations. Is this an adherence issue, or is this a PK issue with processing? The data with RAL from the REALMRK study showed no evidence of a difference by race or gender in terms of the RAL PK. This finding suggests that if there is a difference in drug performance, it is due to behavioral causes, not drug characteristics.

Dr. Cohen reviewed a study on pre-exposure prophylaxis (PrEP). The study was done in Chicago at the Core Center. The investigators surveyed 359 HIV-negative heterosexuals in a sexually transmitted disease clinic who were at high risk of HIV exposure. The subjects were mostly single, black men, and 79% had an educational level of high school or less. In this group, 21% reported anal sex with their female partners. This study was done before the results of the Pre-exposure Prophylaxis Initiative (iPrEx) trial were known, but done in anticipation of it. The investigators asked a simple question to these subjects: Would you take a pill for PrEP, and 83% said yes. The biggest predictor of those who were reluctant to take PrEP was a low education level. Clinicians have been curious why they are not hearing more of a demand from patients for PrEP. Dr. Cohen suggested that maybe if clinicians ask them, patients would be willing to try PrEP.

### Hepatitis C—Co-infection Issues

Dr. Rockstroh discussed hepatitis co-infection issues. The first study he reviewed was from Spain, which involved a cohort of patients who had HIV and hepatitis C virus (HCV) co-infection. In this study, 210 patients received HCV-specific therapy that consisted of pegylated interferon (PegIFN) + ribavirin (RBV) therapy. The patients received regular liver stiffness measurements by FibroScan, so investigators were able to measure regression of liver fibrosis in patients who received HCV therapy compared with those who had not. The study found that patients who achieved sustained virologic response (SVR) had the most decrease of liver stiffness, but that even patients who did not achieve SVR demonstrated a benefit in terms of fibrosis compared with those who were not treated. Clinicians can use these findings to tell patients that even if they do not respond to therapy or achieve clearance, it will probably provide some benefit, such as delaying fibrosis, and maybe newer drugs will be available to help them in the future.

Dr. Rockstroh also addressed the risk of interactions between drugs for HIV and HCV infection that are metabolized by similar pathways. He stressed that the first question clinicians need to ask today when a patient walks into a clinic is: “Which HIV drug is he or she on and can I combine it with an HCV protease inhibitor?” To help answer these questions, he discussed interaction data that were presented at ICAAC on telaprevir (TVR) and RAL. He said it was reassuring to see in a healthy volunteer trial that there was no significant interaction between the two drugs, as TVR levels remained virtually unchanged with the co-administration of RAL and there was only a 31% increase in AUC of RAL. Dr. Rockstroh noted that there is evidence of an interaction between TVR and NNRTIs. Unfortunately, only EFV has been studied, so there is no information on ETR or RPV. If patients combine TVR with EFV, clinicians need to do a dose adjustment and increase the dose to 3 tablets of TVR TID (for a total of 1,250 mg). The patient may still have lower TVR levels but it will be in a range that is probably clinically acceptable.

Next, Dr. Rockstroh addressed research on interactions between TVR and PIs frequently used for HIV. He noted that a recent report indicated that TVR levels are substantially changed by PIs. This is particularly true with lopinavir (LPV), as seen in Figure 4, which shows that the AUC of TVR drops by 54.3%. This interaction appears to be clinically meaningful, so clinicians should not co-administer these two drugs. The drug that was used in pilot trials and that appears to have the least impact on TVR is boosted ATV, which causes a 20% drop in AUC that is considered clinically acceptable. There is a lower decline in AUC with DRV than with LPV but it is still substantial.

Dr. Rockstroh also addressed the effect of TVR on HIV PI levels, and noted that when given with TVR, there is a 40% reduction in DRV levels. This could be a cause for concern, particularly in the patient who has received DRV because of prior resistance, in which case we want to be sure to maintain an adequate drug level. So, in view of existing data, Dr. Rockstroh concluded that when treating HIV/HCV co-infected patients, the data support the use of boosted ATV, EFV (with a dose increase in TVR), and, given the data presented at ICAAC, the possibility of using RAL.

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**Figure 4. Mean Telaprevir PK Profile with PIs**

![Graph showing mean telaprevir PK profile with PIs](image-url)
may overcome some drug interactions, because it could be metabolized this way over that enzyme cascade rather than the cytochrome pathway and so the interaction data at CROI with regard to low-dose ritonavir and BOC was reassuring, with little variation, which was probably not clinically significant. With EFV, there is a substantial decrease in BOC levels of around 50%; however, it is unclear if this decrease is clinically meaningful. There are some data from mono-infection trials that separated drug levels into quartiles; if we took the lowest quartile, that did not have a difference in cure rates compared to high quartiles. So, higher drug levels did not lead to higher cure rates. This suggests that when the patient has a lower drug level in that particular drug combination, it would not be clinically meaningful.

Next, Dr. Rockstroh discussed an algorithm for treating a patient with newly diagnosed chronic HCV genotype 1 infection. The first step is to assess fibrosis stage. If there is very little or no fibrosis, then treatment can usually be deferred; the patient has time to wait and to discuss options. If the patient has an IL28B CC genotype—which correlates with a greater interferon responsiveness—then that could be a reason to start treating, because the likelihood of the patient responding is very high, and clinicians may try using only PegIFN and RBV, so the patient can avoid the issue of drug-drug interactions presented by triple drug therapy for HCV. If patients have more advanced fibrosis stages, then Dr. Rockstroh said that triple therapy is indicated, particularly in patients with META VIR fibrosis scores of F2 and F3, which indicates a liver that is prone to cirrhosis. For patients with a META VIR score of F4, Dr. Rockstroh stressed that therapies for this patient group are difficult to administer. He recommends that an HIV/HCV co-infected patient with cirrhosis should be treated by clinicians experienced with this type of patient and preferably in combination with a transplant program.

Another issue Dr. Rockstroh addressed was the treatment of patients who have a history of prior treatment who did not respond. As shown in Figure 5, he divided patients into either naïve, relapser or non-responder categories and then listed approaches depending on their fibrosis stage. If a patient is treatment naïve and has a low fibrosis score, then treatment can be deferred—it is an individual decision. If the patient is a relapser, there clearly is an argument for treatment, because relapers in all trials are the patients who respond best, so there is a high likelihood that they are going to be cured with available HCV PIs. In patients who are non-responders and have a low fibrosis score, the treating clinician should consider that they are not likely to respond favorably. With the high risk of resistance development, and pilot trials with co-infected patients not finished, it would make sense to wait for some more data to emerge, and for more potent or better tolerated, easier to take drugs to become available then to treat the patient now.

References