Introduction

The 17th Conference on Retroviruses and Opportunistic Infections (17th CROI) was held in San Francisco from February 16-19, 2010. This conference provided some significant new insights into HIV therapeutics, the most important of which are briefly summarized in this newsletter.

Earlier Initiation of ARV Therapy

Over the past few years, several studies have been presented and published that indicate that earlier initiation of antiretroviral (ARV) therapy decreases morbidity and mortality amongst HIV+ patients [Kitahata M, et al. New Engl J Med 2009;360:1815-26; Emery S, et al. JID 2008;197:1133-1144]. A number of studies reported on specific mechanisms that could be contributing to the pathogenesis of untreated HIV/AIDS, and, therefore, lend credence to the emerging trend of earlier initiation of ARV therapy, and one study assessed benefits of ARV therapy in newly-infected patients.

Studies Assessing Cardiovascular Risk

A cross-sectional study evaluated early functional risk factors for heart disease in 80 men with an undetectable HIV RNA on ARV therapy. These patients were drawn from the SCOPE cohort, in which patients began ARV in the chronic phase of HIV infection with lower CD4 counts, and the OPTIONS cohort, in which patients begin ARV therapy within 6 months of HIV diagnosis [Hsue P, et al. Abst. 707]. Cardiovascular (CV) risk was assessed using arterial stiffness (AS) by pulse wave analysis and carotid-femoral pulse wave velocity (PWV). After adjusting for both traditional CV risk factors and HIV-related covariates, nadir CD4 <350 cell/mm³ was independently associated with a significant increase in AS and PWV, indicating an increased CV risk. Other significant determinants of PWV in multivariate analysis included age, systolic and diastolic BP, and diabetes. Notably, AS was not affected by the duration of ARV therapy or exposure to protease inhibitors (PIs) or abacavir (ABC). These findings are provocative, in that they suggest that delays in initiating therapy may increases the likelihood of developing coronary artery disease, despite later use of effective ARV therapy.

A second study evaluated endothelial function by flow-mediated dilation (FMD) of the brachial artery and high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, in 98 HIV+ patients with an undetectable viral load (VL) on ARV therapy and 32 HIV- controls [Hsue P, et al. Abst. 708]. In the HIV+ patients, endothelial function was found to be impaired and hs-CRP levels were found to be more predictive of worsened endothelial function than traditional risk factors. Other significant determinants of PWV in multivariate analysis included age, systolic and diastolic BP, and diabetes. Notably, AS was not affected by the duration of ARV therapy or exposure to protease inhibitors (PIs) or abacavir (ABC). These findings are provocative, in that they suggest that delays in initiating therapy may increases the likelihood of developing coronary artery disease, despite later use of effective ARV therapy.

Therapeutic approaches to prevent non-AIDS-related events must account for the need for earlier treatment to limit viremia and inflammation, selection of agents that will not exacerbate these risks, and possibly additional agents to address the smoldering inflammation that persists despite effective ARV therapy.
CHARTER Study: Risk of HAND
To explore whether early initiation of ARV therapy may prevent HIV-associated neurocognitive disorders (HAND), the correlation between CD4 nadir and HAND was assessed in a multicenter cohort study, the CNS HIV ART Effects Research (CHARTER), which has comprehensive medical and neuropsychological evaluations of 1,525 HIV+ patients [Ellis R, et al. Abst. 429]. In the cohort, 799 patients (52.4%) were found to have HAND, 603 of whom did not have any neuropsychologic confounder, and 1080 patients (71%) were on ARV therapy, 589 with an HIV RNA <50 copies/mL. After adjusting for other predictors including plasma viral load, age, sex, ethnicity, and duration of HIV infection, HAND was found to be associated with CD4 nadir, with a higher CD4 nadir significantly associated with lower risk of HAND (Figure 1). Further, there was no threshold effect, with higher CD4 nadir conferring a lower risk of HAND at all levels; however, it should be noted that there was no stratification above 350 cells/mm³. Finally, HAND persisted in many patients despite effective ARV therapy, as evidenced by an undetectable HIV RNA and good immune reconstitution. These findings support early initiation of ARV therapy as it may prevent the onset of HAND, which in many patients who develop it, is not reversible with effective ARV therapy.

Figure 1. Odds Ratio for Cognitive Impairment by CD4 Nadir

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>CD4 Nadir</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>&lt;50</td>
</tr>
<tr>
<td>0.4</td>
<td>50-199</td>
</tr>
<tr>
<td>0.5</td>
<td>200-349</td>
</tr>
<tr>
<td>0.6</td>
<td>≥350</td>
</tr>
</tbody>
</table>

ACTG 5217/SETPOINT Study:
ARV Therapy in Newly-Infected Patients
ACTG 5217, the SETPOINT study, compared a 36 week course of ARV therapy with tenofovir (TDF), emtricitabine (FTC) and lopinavir/ritonavir (LPV/r) followed by treatment interruption versus no therapy in patients with HIV infection within the previous six months, testing the hypothesis that early therapy would modify the viral load set point compared to no therapy and forestall the need to resume treatment [C Hogan, et al. Abst. 134]. The primary endpoint of the study was the viral load set point at week 72, 36 weeks after stopping therapy in the treatment arm. Subjects in either arm could start or resume therapy if they experienced a CD4 <350 cells/mm³ at or after week 12, <200 cells/mm³ at any point, an HIV RNA >750,000 copies/mL at or after week 4 or >200,000 copies/mL at or after week 12, or symptomatic HIV infection. 130 subjects were enrolled in the study, with a median CD4 of 540 cells/mm³ and a median HIV RNA of 4.4 log₁₀ copies/mL. Following a DSMB review in June, 2009, the study was stopped because of a higher rate of disease progression in the no treatment arm. At the time of the DSMB review, 79 subjects had completed 72 weeks of study. By week 36, 27.5% of subjects in the no treatment arm reached criteria to start therapy, and by week 72 50% had met criteria for therapy. In contrast, only 10% of subjects in the early treatment group met criteria to restart therapy. The study was stopped due to futility - so many subjects in the no treatment arm had started therapy that the primary question of differences in viral load setpoint could not be determined. By comparing the time to resuming therapy for the early treatment after week 36 to the time to initiate therapy for the no treatment group from week 0, there was a delay in the time to resumption of therapy of 18 weeks that persisted over a 60 week period of time. Therefore, early treatment produced a marginal benefit compared to no treatment. The viral load set point 36 weeks after treatment discontinuation for the early treatment group (week 72) compared to week 36 for the no treatment group was 3.99 log₁₀ copies/mL vs. 4.37 log₁₀ copies/mL, a difference that was not statistically significant. So, early treatment followed by interruption modestly delayed the need for subsequent treatment, and therefore, there may be a slight advantage to early treatment of patients with acute infection. But the real story of this trial is that half of the people not initially started on therapy met criteria for starting therapy within the first 72 weeks of follow-up. Thus, early progression of HIV infection may be more rapid than we appreciate.

ARV Therapy in ARV-Naïve Patients
ACTG 5202: ABC/3TC vs. TDF/FTC and EFV vs. ATV/r
The first presentation was made of the final results of ACTG 5202 [Daar E, et al. Abst. 59LB]. This study which compared TDF/FTC with ABC/lamivudine (3TC) and atazanavir/ritonavir (ATV/r) with efavirenz (EFV) in 4 arms with 1800 patients already had produced notable results when the higher VL strata (> 100,000 c/mL at screening) was unblinded when the DSMB found approximately twice the number of virologic failures (VF) with ABC/3TC compared with TDF/FTC [Sax PE, et al. N Engl J Med 2009;361:2230-40]. The lower VL strata continued blinded and the open-label comparison of the anchor agents continued. The efficacy data presented included a breakdown of the higher VL comparison of ABC/3TC vs. TDF/FTC by anchor arm, demonstrating similar decreases in virologic efficacy of ABC/3TC compared to TDF/FTC with
either EFV or ATV/r. The comparison between ABC/3TC and TDF/FTC in the lower viral load strata surprisingly showed no significant or substantial difference in VF between the two arms with either anchor agents with the probability of being VF free at 96 weeks 88.3% for ABC/3TC and 90.3% for TDF/3TC when either was given with ATV/r and 87.4% for ABC/3TC and 89.2% for TDF/3TC when either was given with EFV. These differences were not significant. The comparison in VF between EFV and ATV/r over the entire study population (both VL strata) showed near equivalence between these two arm. The proportion of patients with VF who had resistance mutations was substantially higher in the EFV arms compared to the ATV/r arms regardless of dual NRTI backbone. CD4 changes were robust though somewhat lower in the EFV/TDF/FTC arm compared to the other three arms.

**ACTG 5224s: Metabolic Substudy of ACTG 5202**

Accompanying the report of the final results of ACTG 5202 were the results of ACTG 5224s, the metabolic substudy that focused on bone and limb fat outcomes [McComsey G, et al. Abst. 106LB]. This substudy enrolled 269 subjects (69 TDF/FTC + EFV; 65 TDF/FTC + ATV/r; 70 ABC/3TC + EFV; and 65 ABC/3TC + ATV/r), who received DEXA scans at weeks 0, 24, 48, and 96 and abdominal CT scans at weeks 0 and 96. The primary comparisons were changes in hip and lumbar bone mineral density and ≥10% loss of limb fat. For each comparison interactions between the two NRTI and the NNRTI/PI components were tested, and because none were identified, comparisons were made of the TDF/FTC arm vs. ABC/3TC arms and of the EFV vs. ATV/r arms. At week 96, the percent change in lumbar spine bone mineral density was statistically lower in the TDF/FTC arms compared to the ABC/3TC arms (p=0.004) and in the ATV/r arms compared to the EFV arms (p=0.035). Changes in hip bone mineral density were a bit different – there was greater loss in the TDF/FTC arms compared to the ABC/3TC arms (p=0.025), but there were no difference between the EFV and ATV/r arms. 5.6% of subjects in the substudy (and 4.3% in the entire study) experienced a bone fracture, almost all of which were traumatic, and there was no difference in fracture rate by treatment assignment. The proportion of subjects with ≥10% limb fat loss from week 0 to 96 was 14.3% TDF/FTC + EFV, 15.6% TDF/FTC + ATV/r, 18.9% ABC/3TC + EFV, and 16.3% ABC/3TC + ATV/r, with no statistically significant differences between the NRTI components or the NNRTI/PI components. However, in the intent-to-treat (ITT) analysis, there was no difference between TDF/FTC and ABC/3TC regarding changes in limb fat, but there was a greater degree of fat gain in the ATV/r arms than the EFV arms (p=0.010); and, in the as-treated analysis, there was a greater absolute fat gain in the ABC/3TC arm compared to the TDF/FTC arm (p=0.023), and in the ATV/r arm compared to the EFV arm (0.041). Do these findings change our view of the choice among fixed NRTI combinations or EFV and ATV/r? Not likely. We’ve known that TDF is associated with a risk for loss of bone mineral density, and what was seen is consistent with previous data. Although there was more peripheral fat gain in the ATV/r group compared to EFV, peripheral fat increased in both groups. This data is similar to ACTG 5142 which showed an advantage of peripheral fat gain in the LPV/r compared to EFV arm. So there are subtle metabolic differences between NRTIs and boosted PIs with respect to changes in body fat composition.

**ACTG 5208/Octane Study: NVP vs. LPV/r**

Trial II of the ACTG Octane Study (A5208) compared nevirapine (NVP) to LPV/r, both with TDF/FTC, in treatment-naïve women with a CD4 < 200 cells/mm³ in southern Africa who had not received previous single-dose NVP [McIntyre J, et al. Abst. 153LB]. Trial I enrolled women with a history of single-dose NVP greater than 6 months prior to entry and showed that LPV/r was superior to NVP in that setting [Lockman S, et al. 16th CROI, Abst. 94LB (2009)]. In contrast, trial II demonstrated equivalence between the two treatment arms when time to VF or death was compared. Seventeen percent of women randomized to the NVP arm and 20% of women randomized to the LPV/r arm experienced this endpoint. Like many ACTG studies this trial has 2 primary endpoints, the second of which was the time to discontinuation of NVP or LPV/r. For this endpoint, there were significantly more discontinuations of NVP compared to LPV/r (28% vs. 9%) and half of the discontinuations on the NVP arm were due to adverse events (AEs). There were no discontinuations on the LPV/r arm due to an AE. The vast majority of AEs leading to discontinuation of NVP were hepatic events, rash or the combination of the two. Many of these were protocol mandated discontinuations due to the potential severity of these events in individuals on NVP. The equivalence of NVP to LPV/r in virologic efficacy is an important finding given that the most common initial regimen worldwide is NVP-based. However, the study also points out the potential risks of NVP-based therapy and the need for an alternative agent if toxicity occurs.

**STARTMRK: Metabolic and Body Composition Data**

The STARTMRK study was a phase III, multicenter, double-blind, randomized clinical trial, in which 563 treatment-naïve patients without genotypic evidence of baseline resistance were enrolled. Study patients were randomized to RAL or EFV, both given in combination with TDF/FTC. Outcomes have been very similar between the 2 arms, and in an analysis presented at this meeting, metabolic and body shape changes were compared at 96 weeks.
Further, CD4 counts continued to increase in the RAL arm, with an increase from baseline of 164 cells/mm³ in the RAL arm vs. 63 cells/mm³ in the placebo arm at 156 weeks. Exploratory analyses evaluated the effects of different early virologic responses grouped into 3 categories: continuous suppression (all <50 copies/mL); low level viremia (all <400 with one or more >50 copies/mL) and not suppressed (intermittent >400 copies/mL). These analyses demonstrated that although the low level viremia patients had a significantly shorter time to loss of virologic response compared to the continuous suppression group, they still were able to maintain favorable virologic suppression and immunologic response through 156 weeks of therapy (Figure 4). These data are encouraging regarding the long-term effectiveness of RAL in triple-class resistant patients, even though they may have low level viremia on treatment.

Figure 4. Comparison of Virologic Suppression among Different Virologic Response Groups

VICTOR E3 & 4: Vicriviroc in Treatment-experienced Patients
Vicriviroc (VCV) is an investigational CCR5 antagonist that has shown promise in prior studies in treatment-experienced patients [Gulick R, et al. J Infect Dis. 2007;196(2):304-12; Zingman B, et al. 15th CROI, Abst. 39LB (2008)]. Presented here are the results of two larger identical Phase III studies comparing VCV to placebo in a treatment-experienced population [Gathe J, et al. Abst. 54LB]. A total of 721 patients with CCR5-tropic virus and documented resistance to ≥2 then available drug classes (NRTI, NNRTI, or PI) or ART experience of ≥6 months were enrolled. All patients received OBT, with randomization to VCV 30 mg daily or placebo. Approximately a third of study participants were female; the study population had a mean CD4 in the 200s cells/mm³ range and an HIV RNA of approximately 4.5 log₁₀ copies/mL. Notably different from other recent trials in this patient population was the high activity of the OBT, with 64% of subjects having ≥3 active drugs in their OBT and around a third using RAL and 40% DRV in the OBT.
At 48 weeks, 64% of the VCV and 62% of control group had an undetectable HIV RNA, hence not demonstrating superiority of VCV over placebo. In a protocol-specified subset analysis, however, study subjects with ≤2 active drugs in their OBT did show additional benefit of VCV (70% VCV vs. 55% placebo <50 c/mL, p = 0.02). No new safety concerns were identified during the trial, with importantly no evidence of an increase incidence in malignancy or seizures in patients receiving VCV. While this study did not overall demonstrate superiority of VCV over placebo, the results are hardly surprising since, in the current treatment era, most regimens can be crafted to contain at least 3 active drugs. The subset analysis does demonstrate that VCV can act as one of the active agents in a regimen, and the safety results are encouraging. Based on the results of this study, FDA approval for VCV in treatment-experienced patients will not be sought; however, studies of VCV in treatment-naive subjects are ongoing and will continue.

**ODIN Study: DRV/r Once- or Twice-daily in Treatment-Experienced Patients**

To assess the use of once-daily dosing of DRV/r in treatment-experienced patients who harbor viruses susceptible to DRV, investigators enrolled 590 treatment-experienced patients into ODIN, a prospective, randomized, non-inferiority trial [Cahn P, et al. Abst. 57]. Eligible patients needed to have no genotypic or phenotypic evidence of resistance to DRV; furthermore, they were required to have an HIV RNA >1000 copies/mL and a CD4 >50 cells/mm³. Randomization was to once- or twice-daily DRV/r and OBT, consisting of NRTIs only, was chosen based on resistance testing and at the discretion of the site investigators. The primary endpoint was proportion <50 copies/mL at week 48. At baseline, the two study groups were well balanced; the median baseline HIV RNA was 4.1 log₁₀ copies/mL and CD4 count was in the low 200s cells/mm³. Resistance testing done at baseline showed that the median number of PI mutations was zero in both treatment arms; overall, 45% of study subjects were PI naïve; in the remainder, the bulk of prior PI use was LPV/r or indinavir (IDV). 75% and 68% of the once- and twice-daily treatment arms respectively had 2 or more active NRTIs in their background therapy. At 48 weeks, 72.1% of the once-daily group and 70% of the twice-daily group had an HIV RNA < 50 copies/mL meeting the protocol-specified non-inferiority threshold of 12%. CD4 responses were similar between groups. In PK analyses, trough concentrations of DRV were higher in those receiving the drug twice daily, but this difference did not meet statistical significance and there was extensive overlap between the two groups. Rates of virologic failure did not significantly differ between treatment arms; there were two cases of virologic failure with emergence of additional resistance mutations in the once-daily group vs. none in the twice-daily group. Once-daily treatment was associated with slightly lower rates of GI side effects, and approximately half the incidence of grade 2-4 lipid elevations. Once-daily dosing of DRV/r has several advantages over giving the drug twice a day, including lower pill burden, lower cost, and a lower incidence of dose-dependent ritonavir (RTV) side effects such as gastrointestinal complaints and hyperlipidemia. The results of this study strongly suggest that once-daily DRV/r is a generally a suitable option for treatment-experienced patients who have DRV-susceptible virus. It is likely that the results would have been even better had inclusion of any of RAL, maraviroc (MVC), or etravirine (ETR) been allowed in the background regimen.

**New Drugs**

*Phase II clinical data for elvitegravir and cobicistat (GS-9350)*  
In the past few years, Gilead Sciences has presented data about the activity of their integrase inhibitor elvitegravir (EVG), with both phase I short term monotherapy studies and in combination therapy for treatment-experienced patients. These studies documented the activity of EVG as well the ability to dose it using RTV. In addition, Gilead has presented data about a novel booster agent, cobicistat (GS-9350), and its ability to boost the levels of both EVG and PIs such as ATV in a manner similar to what is observed using RTV. EVG and GS9350 were the focus of two phase II studies in treatment-naïve patients [Cohen C, et al. Abst. 58LB]. One study was a double-blind, randomized comparison of GS-9350 (n=50) to RTV (n=29) with all participants receiving open-label TDF/FTC + ATV (300 mg). The other study, which was also double-blind, compared the co-formulated EFV/TDF/FTC tablet (n=23) with a co-formulated TDF/FTC/EVG/GS-9350 tablet (n=48). The primary endpoint in both studies was a comparison of the percent achieving virologic suppression at week 24, with additional follow up planned to week 48. To be eligible, participants had wild type HIV based on screening resistance testing (NRTI, NNRTI and PI testing), a viral load >5000 copies/mL, a CD4 count >50 cells/mm³, and were negative for both hepatitis B and C virus. In both studies, there was nearly identical virologic response rates observed between the standard and the experimental arms. Response rates in the GS-9350 vs. RTV study were very similar at 24 weeks, with about 85% in each arm achieving an HIV RNA <50 copies/mL (ITT, M=F) and CD4 improvements in both arms of approximately 200 cells/mm³. Response rates in the EFV/TDF/FTC vs. TDF/FTC/EVG/GS-9350 study were also similar regarding immunologic (CD4+ increase of ~123 cells/mm³ in each arm) and virologic parameters (ITT, M=F: 83% vs. 90% <50 copies/mL; 95% CI -11%, +21.1%).
and non-inferiority was demonstrated regarding the TDF/FTC/EVG/GS-9350 arm. There were differences reported in the rates of all grade adverse events in the TDF/FTC/EVG/GS-9350 (35%) vs. EFV/TDF/FTC (57%) arms. As expected, most of these differences were due to differences in the frequency of EFV-related CNS events. For the GS-9350 vs. RTV study, rates were low and similar for adverse events comparing the two boosters, with only a somewhat higher rate of nausea seen on GS-9350 vs. RTV (10% vs. 3%) but fewer reports of diarrhea (6% vs. 10%). Further, laboratory adverse events were infrequent and similar in the randomized arms; lipids showed minimal differences in median increases across all study arms. There was a particular focus on changes in creatinine in the two studies and some differences were noted (Table 1).

Table 1. Changes in Serum Creatinine and GFR (by C-G) in GS-9350 Studies

<table>
<thead>
<tr>
<th></th>
<th>EVG/GS-9350 + TDF/FTC n=48</th>
<th>EFV + FTC/TDF n=23</th>
<th>GS-9350 n=50</th>
<th>RTV n=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnCr Creatinine (All Grade 1)</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Δ Mean Serum Creatinine Baseline to Week 24 (mg/dL)</td>
<td>+0.14</td>
<td>+0.04</td>
<td>+0.18</td>
<td>+0.14</td>
</tr>
<tr>
<td>Δ Mean eGFR* Baseline to Week 24 (mL/min)</td>
<td>-18</td>
<td>-7</td>
<td>-15</td>
<td>-14</td>
</tr>
<tr>
<td>Mean eGFR* At Week 24 (mL/min)</td>
<td>111</td>
<td>126</td>
<td>102</td>
<td>111</td>
</tr>
</tbody>
</table>

Given these observations, Gilead explored the impact of GS-9350 given alone on the two mechanisms of creatinine clearance and found that the most likely mechanism for the observed increase in serum creatinine (and estimated GFR) associated with GS-9350 is an impact on the tubular secretion of creatinine, which accounts for about 15% of the renal clearance of creatinine. Taken together, these studies suggest that GS-9350, whether used to boost ATV, or used to boost the investigational integrase inhibitor EVG, results in high rates of virologic suppression, similar to standard of care regimens. Phase III development of both investigational compounds is planned starting in 2010.

Special Populations

Hepatic Safety of RAL in HIV and Hepatitis Co-infection

Patients with HIV and hepatitis co-infection have a significantly increased risk for developing hepatotoxicity following initiation of ARV therapy. Although this is partially due to immune reconstitution associated flares of underlying chronic hepatitis it also reflects the potential for liver damage by the various ARVs currently in use. With the recent introduction of new drug classes, such as the integrase inhibitors, the question arises how these drugs may perform in the hepatitis co-infected individual. To answer this question regarding RAL, an analysis was presented on the long-term hepatic safety and efficacy data from HIV+ patients with HBV and/or HCV co-infection who participated in the 3 Phase III studies of RAL, BENCHMRK 1 and 2 and STARTMRK [Rockstroh J, et al. Abst. 662]. In total, 743 individuals received RAL and 519 received comparator across the 3 studies. Hepatitis co-infection was present in 16% (114/699) of treatment-experienced pts (HBV=6%, HCV=9%, HBV+HCV=1%) and in 6% (34/563) of treatment-naïve patients (HBV=4%, HCV=2%, HBV+HCV=0.2%). Grade 3/4 liver enzyme elevations were observed more frequently in HBV or HCV co-infected patients than in HIV-mono-infected patients, but were not different between the RAL and control (Placebo or EVF) groups. In the BECNHMRK studies, ALT increases (defined as percent with grade 3 or 4 lab abnormalities and increased grade from baseline) were higher in HBV or HCV co-infected than in HIV-mono-infected patients receiving RAL (13% vs. 3.6%) or placebo (8.3% vs. 3.0%). In STARTMRK, increases in ALT were higher in the HBV or HCV co-infected group than in the HIV-mono-infected patient group (5.6% vs 1.5%) but comparable between hepatitis co-infected patients receiving RAL or EVF with TDF/FTC (5.6% vs 12.5%). Hepatobiliary adverse events were extremely rare in all 3 studies and did not differ between co-infected and HIV-mono-infected patients. Also, the rate of undetectability (HIV RNA < 50 copies/mL at week 96) did not differ between hepatitis co-infected and HIV-mono-infected study participants. Overall, RAL was efficacious and generally well tolerated up to 96 weeks in HIV-infected patients with HBV and/or HCV co-infection.

ARV Therapy in HIV/HCV Co-infected Patients Undergoing HCV Therapy with PEG-IFN and Ribavirin

Various studies have demonstrated significant drug-drug interactions as well as overlapping toxicities between commonly used NRTIs for HIV therapy and interferon (IFN)/ribavirin (RBV) combination therapy. As a consequence didanosine (ddI) is contraindicated in patients with cirrhosis and should be avoided in patients with less severe liver disease. Stavudine (d4T) and zidovudine (AZT) should also be avoided if possible due to increased rates of lipoatrophy and anemia. More recently, competitive phosphorylation between the guanosine nucleoside analogues ABC and RBV has been hypothesized to further compromise anti-HCV treatment efficacy. To assess this, a large Spanish cohort analyses in 1,701 patients with HIV/HCV co-infection receiving PEG-IFN/RBV was presented investigating the effect of
accompanying antiretroviral drugs on SVR [Berenguer J, et al. Abst. 663]. Overall, 641 (38%) patients achieved a sustained virological response (SVR). Three factors were independently associated with increased odds of SVR: HCV genotype 2 or 3, HCV-RNA level < 500,000 IU/mL, and absence of AIDS. No difference was observed in overall SVR rates between co-infected patients on or off ARV therapy (43.7% vs 36.9%, p=0.144). With the exception of regimens including AZT, the effect of other NRTI backbones, including those with ABC, had no significant effect on SVR. This may be explained, in part by findings from the PARADIGM study, which showed that rates of anemia reported as adverse event in HIV/HCV co-infected patients undergoing HCV combination therapy were significantly higher in patients receiving concomitant AZT [Rodriguez-Torres M, et al. Abst. 664]. As a consequence, concomitant use of AZT was associated with an increase in the rate of RBV dose modifications among patients randomized to 1000/1200mg per day of RBV (25% versus 45%) and resulted in a small increase in the rate of withdrawal from the study for safety reasons. In summary, the concomitant use of AZT along with RBV treatment should be avoided, whereas ABC or TDF plus 3TC/FTC appeared to have no significant impact on outcome of HCV combination therapy.

**Pharmacokinetics**

**ARV Penetration into Genital Secretions**

There is concern about the penetration of ARV drugs into both the male and female genital tract, which may impact sexual and vertical transmission, persistent viral replication and emergence of ARV drug resistance. Several studies evaluated the penetration of recently approved agents, RAL, DRV and MVC into the cervicovaginal fluid (CVF) and semen. In a French study, 14 HIV positive women, virologically controlled on a stable RAL containing regimen were evaluated with paired plasma and CVF samples which were collected 13-14.5 hours after the last RAL dose was taken [Cyril C, et al. Abst. 608]. All patients had undetectable CVF HIV RNA, but two of them had low detectable plasma HIV (between 50 – 200 copies/mL). RAL concentrations were 93 (48-167) ng/mL in plasma and 235 (135-775) ng/mL in CVF, which is about 2.3 fold those in plasma and 16 fold higher than the IC50 for wild type HIV-1. This high level of RAL penetration into the CVF is likely to explain local virologic control. In another study, eight healthy male volunteers were given RAL twice-daily for 4 days plus a single dose on day 5 [Bonora S, et al. Abst. 609]. On day 5, plasma and semen samples were collected 2-4 (n=4) or 11-12 (n=4) hours after the last RAL dose (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (N=8)</th>
<th>2-4 HRS (N=4)</th>
<th>11-12 HRS (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEMINAL PLASMA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEMINAL PLASMA/BLOOD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This study showed a variable but high degree of RAL penetration into the seminal fluid of healthy volunteers. Semen to plasma concentration ratio was higher at the end of the dosing interval suggesting accumulation and persistence of RAL in this compartment.

In another presentation, DRV concentrations in plasma and seminal fluid were analyzed in HIV+ patients on a DRV-containing regimen [Lambert-Niclot S, et al. Abst. 610]. In the study, 47 men participating in the MONOI study (23 on DRV 600/100 mg monotherapy, 24 on DRV 600/100 mg plus 2 nucleosides) donated paired samples of plasma and seminal fluid at days 0 and 48. Total and free fraction blood plasma and total seminal plasma DRV concentrations were measured 12 hours and 15.9 hours, respectively, after the last DRV dose. The seminal plasma/blood plasma ratio for DRV concentrations was 8.6% (5.7-22.2%) and, after correction for protein binding, the DRV seminal plasma concentration was 6 fold above the DRV EC50 of wild type HIV-1. Notably, however, HIV RNA was detectable in 6 seminal plasma samples in different patients, although it was undetectable in the corresponding blood plasma samples.

For MVC, a PK analysis was conducted to determine the exposure in semen and rectal tissue [Brown K, et al. Abst. 85]. In the study, 12 healthy volunteers, STD free and sexually abstinent during the study, were treated with MCV for 8 days. Plasma, semen and rectal biopsies were obtained at different time intervals. MVC exposures in semen were found to be 38% lower than in plasma, but rectal MVC exposures were 10-fold higher than CVF and 2-fold higher than in plasma. Investigators theorized that this finding is likely due to MVC fecal elimination and mucosal trapping.

The availability of multiple agents with good genital penetration may help virologic control and ameliorate the issue of ARV resistance. These data also suggest that we cannot extrapolate drug exposure in genital secretions in men and women.