Introduction

The 12th European AIDS Conference was held in Cologne, Germany from November 11-14, 2009. Presentations at this conference highlighted the latest original research in the field of HIV medicine and provided some significant new insights into treatments for HIV-infected patients. The most important presentations are briefly summarized in this newsletter.

Cost of Treating Patients with CD4+ Counts of 350-500 cells/mm³ Pursuant to the EACS Guidelines

A study was designed to determine the economic implications of treating all patients in the Spanish VACH Cohort (VACH) based on the when to start antiretroviral (ARV) therapy guidance contained in the European AIDS Clinical Society guidelines for managing HIV-infected adults (EACS Guidelines). [Abst. PS4/7] The VACH data for the study consisted of information from HIV-infected patients who were seen at least once between January 1 and December 31, 2008. The investigators selected asymptomatic individuals with CD4+ counts of 350-500 cells/mm³ who were either (1) older than 55 years, (2) hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infected, (3) had a plasma HIV RNA >100,000 copies/mL or (4) had a CD4+ count declining by >50-100 cells/mm³ per year. The analysis included 11,163 patients; 1497 of whom were ARV-naïve. Of these, 326 had CD4+ counts of 350-500 cells/mm³, and, based on recommendations from the EACS Guidelines, ARV treatment was indicated for 130 individuals. Thus, implementing ARV treatment in all patients recommended by the EACS Guidelines would involve a relatively small number of patients and a cost between 1,035,200.40 and 1,451,283.60€ per year depending on the treatment chosen, an increase of 0.6-0.9% in the annual cost of ARV treatment.

Ritonavir-boosted Protease Inhibitor Monotherapy

Several studies assessed the effects of monotherapy with darunavir/ritonavir (DRV/r), lopinavir/ritonavir (LPV/r), or atazanavir/ritonavir (ATV/r), with some concerns becoming apparent regarding this treatment strategy.

The randomized MONET trial assessed maintenance therapy with DRV/r. The study included 256 patients with an HIV RNA <50 copies/mL on HAART—57% protease inhibitor (PI) and 43% non-nucleoside reverse transcriptase inhibitor (NNRTI)—and no history of virologic failure. [Abst. PS4/1] Patients were randomized to receive 48 weeks of DRV/r (800/100 mg) once-daily (QD) with or without two nucleos(t)ide reverse transcriptase inhibitors (NRTIs). Using an intent-to-treat analysis, HIV RNA suppression rates to <50 copies/mL at week 48 were similar in the two groups: 84.3% in the DRV/r monotherapy arm and 85.3% in the DRV/r + two NRTI arm (lower limit 95% CI: -9.9%). DRV/r monotherapy also demonstrated non-inferiority based on various other sensitivity analyses, including an observed analysis, <200 copies/mL endpoint, and virological endpoints only.

In IMANI III, an open-label, pilot study, 31 patients with an undetectable HIV RNA ≥96 weeks on LPV/r (400/100 mg) twice-daily (BID) were switched to LPV/r (800/200 mg) QD. At week 48, 84% (26/31) had an HIV RNA <75 copies/mL (ITT, M=F). 1 subject was lost to follow-up and 4 patients had detectable HIV viremia. Importantly, 2 of the 4 patients who virologically failed developed significant PI resistance during LPV/r monotherapy.

The OREY study – a multicenter, open-label, single-arm, pilot study – assessed the efficacy and safety of ATV/r (300/100 mg) QD monotherapy for maintenance of HIV viral suppression. [Abst. PS4/6] The study included 61 HIV-infected patients with no prior
virologic failure while on HAART who immediately prior to study entry had to have been on HAART for ≥24 weeks with an HIV RNA <50 copies/mL and on ATV/r + 2 NRTIs for ≥8 weeks. A 48-week analysis revealed that 79% (48/61) and 67% (40/60) of patients maintained an HIV RNA <400 copies/mL and <50 copies/mL, respectively, after switching to once-daily ATV/r monotherapy and the mean change in CD4+ counts from baseline was 53 cells/mm³. After a significant period of low-level viral replication, 2 patients on ATV/r monotherapy developed the N88S mutation.

As noted, in the MONET, IMANI III, and OREY studies the enrolled patients were virologically suppressed when they switched to a ritonavir-boosted PI (PI/r) monotherapy. In a phase 2, open-label trial, ARV-naïve patients initiated ARV therapy with DRV/r (800/100 mg) QD monotherapy. [Abst. PS4/4] To enroll, patients were required to have an HIV RNA between 10,000 and 100,000 copies/mL and a CD4+ count >100 cells/mm³. A total of 45 subjects were screened, with 38 screen failures due to their HIV RNA being too high or low or the presence of resistance associated mutations (RAMs). Of the 7 patients enrolled, all achieved a HIV decline of ≥1 log₁₀ copies/mL at week 4 of DRV/r monotherapy; however, most developed inadequate virologic responses in subsequent weeks and the trial was stopped.

These trials indicate some of the limitations of a PI/r monotherapy strategy. While the MONET study presented here indicates that switching patients with an undetectable HIV RNA to DRV/r QD monotherapy may be effective in most, the strategies used in the other studies—including LPV/r QD and ATV/r QD in virologically suppressed patients and DRV/r QD in ARV-naïve patients—were associated with relatively high rates of failure and, in IMANI III, with significant resistance concerns. Thus, this strategy should still be approached and used with some caution.

**Daranavir/r vs. Dual Ritonavir-boosted PIs in ARV-Experienced Patients**

The DVD study—a randomized, pilot study, conducted at 6 centers in the US—enrolled 24 patients with an HIV RNA <400 copies/mL ≥12 weeks while on 2 ritonavir-boosted PIs and ≥1 other ARV from another class (excluding NNRTIs). The enrolled patients were randomized to continue on their entry regimen or substitute DRV/r (600/100 mg) BID for the PIs. [Abst. PS4/2] After 24 weeks, the patients randomized to continue their entry regimen could cross-over to the DRV/r arm if their HIV RNA was <400 copies/mL, and 9 did so, and all patients on DRV/r were followed for an additional 24 weeks. The investigators found that at 24 weeks 100% of the patients in both arms maintained an HIV RNA <50 copies/mL. At 48 weeks, 92% (11/12) of patients randomized to switch to DRV/r maintained an HIV RNA <50 copies/mL, with 1 patient experiencing a blip. Of the 9 patients initially randomized to continue their entry regimen who crossed-over to the DRV/r arm at week 24, 1 patient with hepatitis B virus (HBV) co-infection discontinued at week 36 due to a grade 4 increase in ALT level and 88% (7/8) of the patients on therapy at week 48 had an HIV RNA <50 copies/mL. While there were no significant differences in lipids by study arm, treatment satisfaction improved after the switch to DRV/r. Finally, using DRV/r is cheaper than continuing 2 ritonavir-boosted PIs, and this may also be a consideration favoring this substitution strategy.

**The ARTEN Study: Analysis of Efficacy by Baseline Parameters and of Lipid Outcomes**

Two presentations highlighted analyses of the ARTEN trial, a trial comparing nevirapine (NVP) QD or BID to ATV/r QD, each combined with tenofovir (TDF)/emtricitabine (FTC) co-formulated tablets QD, in 569 ARV-naïve patients with CD4+ counts <250 cells/mm³ in women and <400 cells/mm³ in men. One analysis assessed efficacy and safety at week 48 by viral load (<100,000 or >100,000 copies/mL) and CD4+ count (<50 or ≥50 cells/mm³). [Abst. PE7.3/11] Using HIV RNA <50 copies/mL as the endpoint, NVP and ATV/r exhibited similar efficacy in patients with a HIV RNA >100,000 copies/mL (65% vs. 62%) or a CD4+ count ≥50 cells/mm³ (73% vs. 75%) at baseline; however, the efficacy of NVP was markedly lower in patients with an HIV ≤100,000 copies/mL (78% vs. 91%), driven mainly by discontinuations due to adverse events (16% vs. 1%), and in patients with a CD4+ count <50 cells/mm³ (39% vs. 57%), although there were too few patients in each of the arms with CD4+ counts <50 cells/mm³ to draw any firm conclusions. Another ARTEN analysis compared lipid profiles in the treatment arms. [Abst. PS10/3] Over 48 weeks, a somewhat more favorable lipid profile was seen with NVP than with ATV/r; however, the differences were relatively small and of unclear clinical significance (Table 1).

### Table 1. Lipid Differences Between NVP and ATV/r in ARTEN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Difference in mean changes from baseline [NVP-ATV/r (95% CI)]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>5.1 (0.2 to 10.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-29.8 (-43.4 to -16.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>5.7 (3.9 to 7.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>5.3 (1.2 to 9.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>TC:HDL-c ratio</td>
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<td>0.0001</td>
</tr>
<tr>
<td>ApoA1 (g/L)</td>
<td>0.10 (0.06 to 0.14)</td>
<td>0.0001</td>
</tr>
</tbody>
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**Raltegravir in Combination with Abacavir/Lamivudine**

A prospective, open-label, pilot study assessed the efficacy and safety of raltegravir (RAL, 400 mg) BID plus abacavir (ABC)/lamivudine (3TC) co-formulated tablets QD in 35 ARV-naïve patients. [Abst. PE7.2/1] The median HIV RNA and safety of raltegravir (RAL, 400 mg) BID plus abacavir (ABC)/lamivudine (3TC) co-formulated tablets QD in 35 ARV-naïve patients. [Abst. PE7.2/1] The median HIV RNA and...
CD4+ count in the enrolled patients were 4.8 log_{10} copies/mL and 301 cells/mm³, respectively, and 34% and 20% had an HIV RNA ≥100,000 copies/mL and CD4+ count <200 cells/mm³, respectively. A planned interim analysis at week 24 revealed that ABC/3TC + RAL has potent antiretroviral activity (Figure 1) and resulted in a mean CD4+ count increase of 193 cells/mm³. In addition, the regimen was very well tolerated, with no significant adverse events and very modest lipid changes.

**Figure 1.** Virologic response at 24 Weeks in Study of RAL + ABC/3TC

**CARDS Study: Switching to Raltegravir + Atazanavir**

The CARDS study tested the efficacy of combining RAL (400mg) BID with unboosted ATV (300mg) BID in 24 RAL-naïve patients with no PI resistance and not on a proton pump inhibitor. [Abst. LBPE4.3/5] Most patients switched off of a PI-based regimen (20) and the reasons for switching included toxicity (10), tolerability (9) or resistance (5) issues. The primary objective of the study was a pharmacokinetic (PK) assessment of ATV and RAL, and secondary objectives included efficacy, safety, tolerability and toxicity. A PK analysis at 2 weeks and a planned interim analysis at week 24 revealed that the RAL + ATV regimen used was highly effective. At 24 weeks, 100% of patients had an HIV RNA <50 copies/mL, the mean CD4+ count increase was 116 cells/mm³, and there were no clinically significant adverse events or laboratory abnormalities. Further, the regimen generally exhibited favorable pharmacokinetics regarding both RAL and ATV; however, it should be noted that 18% of the patients had an ATV trough level below the minimal effective concentration of 150 ng/mL. Thus, while this regimen appears effective and safe, clinicians should exercise some caution given the patients with sub-therapeutic ATV levels. Nevertheless, that all patients maintained virologic suppression was reassuring and the significance of the trough ATV concentrations will be determined by additional follow up of this cohort.

**Comparing Tenofovir/Emtricitabine and Abacavir/Lamivudine**

Two presentations compared TDF/FTC and ABC/3TC co-formulated tablets. The first reported the results of a meta-analysis of two randomized trials, BICOMBO and STEAL, which enrolled 333 and 357 HIV patients, respectively. In both studies, the patients enrolled were stable and virologically suppressed on 1 NRTI + 3TC plus either a PI or NNRTI and were randomized to TDF/FTC or ABC/3TC, with continuation of the PI or NNRTI. At 96 weeks, ABC/3TC was found to be virologically non-inferior to TDF/FTC (Figure 2). In addition, while there was no difference by randomized arm in renal function, ABC/3TC was associated with greater increases in lipid levels and a greater frequency of significant adverse events, most due to cardiovascular disease events in the STEAL study.

**Figure 2.** Virologic failure in BICOMBO and STEAL (RD = Difference in proportions, ABC/3TC minus TDF/FTC)

The ASSERT study is an open-label, randomized study comparing TDF/FTC + efavirenz (EFV) with ABC/3TC + EFV in 385 HLA-B*5701-negative, ARV-naïve patients. [Abst. PS10/1] The primary analysis compared kidney and bone toxicities, as well as cardiovascular risk markers, over 48 weeks; however, data regarding efficacy were also presented. Virologic success rates using a TLOVR analysis were significantly higher in the TDF/FTC arm than the ABC/3TC arm (77% vs. 67% <400 copies/mL and 71% vs. 59% <50 copies/mL), driven in part by discontinuations due to suspected ABC hypersensitivity reactions. Kidney function remained stable in both arms, with similar changes in estimated glomerular filtration rates from baseline; however, there was a mild deterioration of one surrogate marker of proximal tubule function in the TDF/FTC arm which was of uncertain clinical significance. The assessment of bone toxicities found that the TDF/FTC arm had increased bone turnover and greater decline in bone mineral density than ABC/3TC in the hip (-3.6% vs. -1.9%, p<0.001) and spine (-2.4% vs. -1.6%, p=0.036), a finding...
that has previously been reported in trials of TDF-containing regimens. The cardiovascular assessment demonstrated that hs-CRP remained stable and IL-6 improved in both groups, and that while TDF was generally associated with lower lipid elevations than ABC/3TC, there was no significant difference in the total cholesterol:HDL cholesterol ratio.

Taken together, the data from the combined analysis of BICOMBO and STEAL and the ASSERT study indicate that both TDF/FTC and ABC/3TC are relatively effective at suppressing HIV viremia, with ASSERT indicating TDF/FTC may be somewhat more efficacious due to differences in toxicity profiles and clinician management. Further, some toxicity concerns may exist for both of these combinations, although the kidney data in ASSERT are reassuring regarding the limited effect of both ABC/3TC and TDF/FTC on kidney function.

**BASIC Study: Saquinavir/r and Atazanavir/r Combined with TDF/FTC**

The BASIC trial study randomized 120 ARV-naïve patients to saquinavir (SQV)/r (2000/100 mg) QD or ATV/r (300/100 mg) QD, both combined with TDF/FTC. The primary analysis compared differences regarding lipids, glucose/insulin sensitivity, body composition and kidney function, however, efficacy data were also reported. [Abst. LBPS10/6] At entry, the mean CD4+ count was 234-249 cells/mm³ and HIV RNA was 4.7-4.8 log₁₀ copies/mL. At 48 weeks, using an intent-to-treat analysis, the SQV/r and ATV/r arms were similar regarding HIV RNA <50 copies/mL (76% vs. 79%) and CD4+ count increase (190 vs. 161 cells/mm³). Modest changes in lipids and glucose/insulin sensitivity were seen in both groups, without any significant differences. There were, however, some significant differences regarding body composition. Only the ATV/r subjects experienced significant increases from baseline in lean body mass, limb fat, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), with a significantly greater increase in limb fat (p=0.03) and VAT (p=0.04) in the ATV/r arm compared with the SQV/r arm. A lesser decrease in estimated glomerular filtration rate was observed with ATV/r by Cockcroft-Gault calculation but not by the Modified diet in Renal Disease (MDRD) method. The study revealed that when combined with TDF/FTC, SQV/r and ATV/r are both effective and well tolerated once-daily regimens, but there may be some important differences between ATV/r and SQV/r regarding changes in body composition.

**CASTLE Study: Effects of Atazanavir/r and Lopinavir/r with TDF/FTC on Body Composition**

The CASTLE study found that ATV/r had superior efficacy to LPV/r through 96 weeks of treatment. The CASTLE lipodystrophy substudy was designed to characterize metabolic and body composition changes during treatment. [Abst. LBPS 11/6] Patients taking LPV/r had greater mean increases in total cholesterol, non-HDL cholesterol, LDL cholesterol, and triglyceride compared with patients taking ATV/r. Subjects were assessed at baseline, week 48 and 96 by DEXA scan (for trunk and limb fat) and single slice CT scan (for VAT and SAT). Total weight, as well as limb, subcutaneous and visceral fat, increased in both groups. At week 96 in the substudy, 5% (5/106) of patients in the ATV/r group had experienced a ≥20% decrease in limb fat from baseline, compared with 7% (5/70) of patients in the LPV/r group. Changes in subjects’ body composition were influenced by baseline CD4+ count, body mass index (BMI) and randomized group. In low BMI (<22 kg/m²) patients, ATV/r resulted in significantly greater gain in SAT and VAT compared to LPV/r. A trend to greater limb fat gain was also seen in the subjects with ATV/r compared to LPV/r. In patients with advanced HIV disease (CD4+ counts <50 cells/mm³) ATV/r resulted in a significantly greater gain in limb fat and SAT compared to LPV/r. In high BMI (>27 kg/m²) patients, trends to greater gains in SAT and limb fat were seen with LPV/r compared to ATV/r.

Thus, some potentially clinically important differences regarding lipids and body composition are emerging regarding ATV/r and LPV/r indicating that ATV/r may have more favorable effects on lipids and body shape changes than LPV/r.

**Long-Term Safety of Vicriviroc**

By analyzing data from two 48-week phase II trials (ACTG 5211 and VICTOR E-1) and their open-label extensions, investigators assessed the safety of vicriviroc (VCV), an investigational CCR5 antagonist, in highly treatment-experienced patients receiving a PI/r containing regimen. [Abst. BPD 1/9] A total of 205 patients were enrolled in the 2 trials, and 196 received 12 or more weeks of VCV treatment, with a mean duration of 116 weeks. While different VCV doses (5-30 mg) were used at trial initiation, all patients ultimately received VCV 30mg QD during the long-term follow-up period. Treatment-emergent adverse events that occurred in ≥5% of patients included bronchitis (12%), upper respiratory tract infection (11%), increased bilirubin (10%), bronchitis (9%), increased AST (8%), increased ALT (7%), herpes simplex (6%), urinary tract infection (6%), influenza (5%), and pneumonia (5%). Liver abnormalities included 1 cirrhosis, 1 steatosis, 3 hepatomegaly/ hepatosplenomegaly and elevated ALT, AST, and bilirubin in 15, 17 and 21, respectively. In general, AST/ALT elevations were mild and considered by investigators not to be VCV related. All hyperbilirubinemia was associated with VCV use and did not involved AST/ALT elevation. The number and types of malignancies observed were generally those that would be expected in patients with advanced HIV disease. These data support the long-term safety of VCV and did not establish that there were any specific VCV-related toxicities.
Switching to Raltegravir

Several presentations assessed the outcomes of patients who were switched to RAL and found this to be a safe, effective strategy that may improve patient quality of life.

The EASIER study (ANRS-138) examined the impact on health-related quality of life in virologically suppressed patients with multidrug-resistant HIV. [Abst. PE 7.2/2] The open-label trial randomized 170 patients who had been stable on a regimen that included ENF and had an HIV RNA <400 copies/mL to continue receiving the ENF-containing regimen or to switch the ENF to RAL while continuing on the rest of the regimen. At week 24, the investigators noted a significant improvement of health-related quality of life scores related to pain and social and physical functioning in patients who switched from ENF to RAL (Figure 3).

Figure 3. EASIER Study: Significant Changes of Quality of Life from Baseline

In a retrospective study, outcomes in 46 patients who switched from ENF, PIs, or EFV to RAL were evaluated. [Abst. PE7.2/3] The patients studied had been on salvage regimens for ≥3 months with an HIV RNA <40 copies/mL and had a median of 11.8 years of prior ARV therapy and 6 prior ARV regimens. The ARVs that were switched to RAL were mainly ENF (28%) and PIs (44%) and the main reasons for making the switch were convenience and/or adverse events. Based on previous genotypic resistance data available for 28 patients, there were 1 to 3 active drugs in the switch regimen. After a median of 30 weeks following the switch, the regimens (N) included DRV/r in 79%, etravirine in 73%, ENF in 48% (18% de novo), and MVC in 2%. The GSS for the regimen used, excluding RAL, was 0 in 12%, 1 in 57% and ≥2 in 27%. The Primary end point of the study was proportion of patients with an HIV RNA <40 copies/mL at week 24, with virologic failure defined as an HIV RNA >400 copies/mL at or after week 24. A genotypic resistance test was performed for any HIV RNA >40 copies/mL at week 24 and at the last point where the HIV RNA was >40 copies/mL. At week 24, 64% of patients had a plasma HIV RNA <40 copies/mL. Between weeks 24 and 48, 8 more patients achieved an HIV RNA <40 copies/mL and 8 patients continued to have low persistent viremia with an HIV RNA of 40-400 copies/mL; no RAL resistance was observed in these groups. Eight patients experienced virologic failure, and integrase inhibitor mutations were detected in 6. A GSS of zero was predictive of an HIV RNA >40 copies/mL at week 24 by multivariate analysis (OR=20.9, 95% CI: 2.215.1) and was associated with RAL resistance by univariate analysis (OR=14.2, 95% CI: 2.1-94.7).

Thus, as in the switch studies discussed above, the GSS should be considered before using RAL in a salvage regimen, and use of RAL should be avoided if the GSS is <1.

Raltegravir in Highly Treatment-Experienced Patients

An observational study included 67 patients with triple-class resistance and a plasma HIV RNA >1000 copies/mL who started RAL with a new optimized background therapy (OBT). [Abst. PE 7.2/6] The patients studied had a CD4+ count of 177 cells/mm³, a median HIV RNA of 4.3 log₁₀ copies/mL, and a median mutation number of 7, 1 and 13 for NRTIs, NNRTIs and PIs, respectively. Optimized background regimens included DRV/r in 79%, etravirine in 73%, ENF in 48% (18% de novo), and MVC in 2%. The GSS for the regimen used, excluding RAL, was 0 in 12%, 1 in 57% and ≥2 in 27%. The Primary end point of the study was proportion of patients with an HIV RNA <40 copies/mL at week 24, with virologic failure defined as an HIV RNA >400 copies/mL at or after week 24. A genotypic resistance test was performed for any HIV RNA >40 copies/mL at week 24 and at the last point where the HIV RNA was >40 copies/mL. At week 24, 64% of patients had a plasma HIV RNA <40 copies/mL. Between weeks 24 and 48, 8 more patients achieved an HIV RNA <40 copies/mL and 8 patients continued to have low persistent viremia with an HIV RNA of 40-400 copies/mL; no RAL resistance was observed in these groups. Eight patients experienced virologic failure, and integrase inhibitor mutations were detected in 6. A GSS of zero was predictive of an HIV RNA >40 copies/mL at week 24 by multivariate analysis (OR=20.9, 95% CI: 2.215.1) and was associated with RAL resistance by univariate analysis (OR=14.2, 95% CI: 2.1-94.7).

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