A CME Newsletter

ARV Therapies and Therapeutic Strategies

REPORTING FROM

The 19th Conference on Retroviruses and Opportunistic Infections (CROI)

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Introduction

This newsletter is based on discussions held during the continuing medical education Internet symposium ARV Therapies and Therapeutic Strategies. *This program provided an update on important presentations made during the 19th Conference on Retroviruses and Opportunistic Infections (CROI).**

Faculty panel and contributors for this program consisted of course director and moderator John Bartlett, MD from Johns Hopkins University School of Medicine, Baltimore, Maryland, and panelists José Arribas, MD from the Hospital de La Paz, Madrid, Spain, Calvin J. Cohen, MD, MS from Harvard Medical School, Boston, Massachusetts, David Cooper, MD from the University of New South Wales, Sydney, Australia, and Jürgen Rockstroh, MD from the University of Bonn, Bonn, Germany.

Search for a Cure

Several presentations at CROI addressed the issue of finding a cure for HIV infection. One of these involved the use of vorinostat (VOR), a histone deacetylase (HDAC) inhibitor.[1] The use of VOR is based on the view that proviral latency of HIV remains an obstacle to curing HIV infection, and that inducing the expression of latent genomes within resting CD4 cells may clear reservoirs of HIV. HDAC inhibitors such as VOR disrupt HIV latency in vitro; however, this effect has never been shown in HIV-infected patients. Therefore, a study was conducted to examine this issue.

In this study, HIV+ participants on ART who had stable viral loads (<50 copies/mL) provided resting CD4 cells via leukapheresis, which were exposed to VOR. If an increase in the frequency of HIV RNA expression was found, patients received 400 mg VOR at separate visits. VOR pharmacokinetics (PK), biomarker measures of HDAC inhibition in peripheral blood mononuclear cells (PBMCs), and measurements of unspliced HIV gag RNA in pools of 1 million resting CD4 T cells were quantified during VOR exposure.

The investigators reported on 5 men who were treated with VOR (medians: age, 45 years; CD4 counts, 562 cells/mm^3; 4 years of ART). VOR was well tolerated. Measures of PBMC cellular histone acetylation and chromatin-bound histone acetylation at the human p21 gene promoter increased <2-fold within 8 hours of VOR dosing. VOR PK was comparable to oncology studies. In each participant, HIV RNA levels increased significantly in pools of resting CD4 cells obtained after VOR dosing compared with baseline measurements. These findings were the first demonstration that a molecular mechanism known to enforce HIV latency can be successfully targeted, resulting in readily measureable HIV RNA expression in highly purified, resting CD4 cells. The study provided proof-of-concept for HDAC inhibitors as a therapeutic class for directly attacking and potentially eradicating latent HIV infection.

Another approach for attempting a cure for HIV is the use of zinc finger nucleases (ZFNs), which target CCR5, an important co-receptor for HIV entry. ZFN-mediated modification of this receptor in CD4 T cells may render a survival advantage in HIV infection. Researchers have previously reported preliminary data from two phase 1 studies of SB-728-T, a ZFN. At CROI, researchers reported additional data from two studies on SB-728-T, which addressed safety, effect on CD4 cells, persistence, trafficking, and effect on HIV.[2]

In a University of Pennsylvania study, 6 immunologic responders (IR) with CD4 ≥450 cells/mm^3 and 6 immunologic non-responders (INR) with CD4 ≤500 cells/mm^3 were infused with 1,010 cells. At week 4, the IRs underwent a 12-week HAART treatment interruption (TI). In a University of California, Los Angeles study, 9 INR (CD4 200-500 cells/mm^3) were enrolled into 3 cohorts that received 1x, 2x or 3x10^{10} cells. The median duration of follow-up for both studies was 232 days (range 56 to 561 days).

The combined findings were reported at CROI. The mean CD4 and SB-728-T counts increased by 1,533 cells/mm^3 (range 216 to 3,025) and 83 cells/mm^3, respectively, on Day 7 in IR and by 820 cells/mm^3 (range 133 to 4,467) and 19 cells/mm^3, respectively, in INR. Increases in CD4 over time correlated with SB-728-T engraftment. SB-728-T was detected in the gut mucosa of all 18 subjects biopsied. During TI, HIV RNA levels dropped ~0.8 to 2.1 log from their peak levels in 3 subjects. In one CCR5 Δ32 heterozygous subject with a viral set point of 165,000 copies/mL, viral load peaked at 6,247 during week 6 of TI and was undetectable by week 12. In the California study, PBMC HIV proviral DNA was evaluated. Samples with previously undetectable levels using traditional qPCR showed measurable proviral DNA. Three of 6 subjects with >11 months follow-up had an ~1-log decrease over time. Overall, it was reported that SB-728-T infusion increased CD4 counts, which persisted over time. In one subject with the highest level of CCR5 modification, viral load was controlled (<limit of detection) without HAART. These data suggest that in addition to the previously documented increases in CD4 cells, SB-728-T may also suppress HIV replication.

In another study presented at CROI, researchers examined whether initiation of therapy during the early stages of HIV infection reduces the size and decay kinetics of the latent HIV reservoir and if it allows for a functional cure of HIV-1 infection that mimics natural viral control found in elite controllers (ECs). To study this question, they isolated CD4 cells from three patient types: 37 treatment-naïve ECs, 10 patients who initiated ART in the chronic phase of infection (chronic treated), and 8 patients initiating ART within 90 days of infection (early treated).[3] Levels of total, integrated and 2-long terminal repeat (2-LTR) HIV-1 DNA were measured. In addition, integrated HIV-1 DNA in acute treated patients was longitudinally measured in 3-year intervals, and decay kinetics was calculated using linear regression with first order kinetics. The investigators found that pre-treatment HIV-1 RNA levels and CD4 counts were not significantly different between the acute treated and the chronic treated cohorts. In comparison to chronic treated patients, levels of integrated and total HIV-1 DNA were significantly lower in ECs and patients treated during acute infection. 2-LTR circles were also more frequently detected in chronic treated (5/10) than ECs (3/37) and early treated subjects (1/8). In addition, the ratio between total and integrated HIV DNA was significantly lower in early compared with chronic treated patients and ECs.

According to the investigators, the study revealed that initiation of ART during the early disease process, followed by prolonged therapy for >10 years, reduced integrated and total HIV-1 DNA to levels observed in ECs. Moreover, extra chromosomal HIV-1 DNA was lower in early treated subjects, suggesting reduced residual HIV-1 replication in these patients. These data contribute increasing evidence that prolonged ARV initiated during primary infection may allow for a clinically significant reduction of HIV-1 reservoirs.

Early Treatment

A report at CROI described an effort to estimate the HIV+ in-care population and the number of HIV+ persons on ART who are virally suppressed. This assessment was conducted by the Medical Monitoring Project (MMP), which conducted clinical surveillance of HIV+ adults receiving medical care in 23 cities, states, and territories in the United States. Using a 3-stage design, MMP used probability-proportional-to-size methods to first select states or territories, followed by facilities that provide HIV medical care, and HIV+ adults seen at these facilities.[4] The sampling design allowed them to estimate the size of the HIV+ population receiving medical care in the United States between January and April 2009. MMP estimated that 421,186 HIV+ adults were receiving HIV medical care in the United States – or 44% of the estimated 941,950 persons diagnosed and living with HIV infection. Of those in care, 373,591 (88.7%) were prescribed ART in the past 12 months and the most recent viral load for 287,670 (70.9%) persons in care was ≤200 copies/mL. By race/ethnicity, blacks and women were less likely to be prescribed ART or achieve viral suppression than whites or men, respectively. While most of those in care were prescribed ART and achieved viral suppression, there are significant disparities by race and gender that need to be addressed.

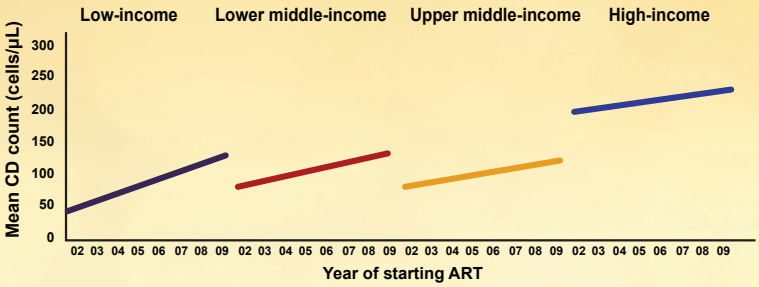
A study reported at CROI addressed the issue of life expectancy in people with HIV infection. Changes in life expectancy of HIV+ individuals in North America have not been well characterized, particularly since the availability of modern ART. To clarify this situation, a study was designed to estimate changes in life expectancy from 1996 to 2007 among HIV+ individuals in NA-ACCORD.[5] Investigators hypothesized that there had been an improvement in life expectancy of people with HIV infection over the study period, and that this life expectancy was approaching that of the general population. To test this hypothesis, investigators partitioned each individual's total person-time contribution and deaths into 5-year age categories at start of year, and by calendar era (1996 to 1999, 2000 to 2002, 2003 to 2005, and 2006 to 2007) to compute abridged life-tables and life expectancies at age 20 years. They also partitioned follow-up by sex, ethnicity, HIV risk group, and baseline CD4 (at the beginning of each calendar era). Over the study period, 65,484 individuals contributed 293,562 person-years and 8,105 deaths for an overall crude mortality rate of 27.6/1,000 person-years. The percentage of person-time after ART initiation increased from 58% in 1996-1999 to 82% in 2006-2007. Life expectancy at age 20 years increased from 26.7 to 52.3 years from 1996-1999 to 2006-2007. Men and women had comparable life expectancies in all periods, except the most recent: 54.7 years for men and 46.1 years for women. In all periods, those with a history of injection drug use had lower life expectancies than men who have sex with men (MSM), and blacks had lower life expectancies than whites and Hispanics. Over all years, life expectancy was lower in patients with baseline CD4 counts <100 cells/mm^3 (18.6 years) than those with CD4 >350 cells/mm^3

(42.2 years). These findings showed that in NA-ACCORD, a 20-year-old individual with HIV in North America could expect to live into his or her early 70s, a life expectancy only slightly lower than that of a person in the general U.S. population.

Another study at CROI assessed the characteristics of people initiating ART at CD4 >500 cells/mm^3 vs. >350 cells/mm^3 and examined new trends in ART initiation.[6] San Francisco residents aged ≥13 years diagnosed with HIV from 2004 to 2010 were included in the analysis (N=3,858). CD4 cell counts at the time closest to HIV diagnosis and ART initiation were used. Investigators found that among persons with CD4 >500 cells/mm^3 at diagnosis, median CD4 cell counts at ART initiation increased from 384 cells/mm^3 in 2004 to 623 cells/mm^3 in 2010 and the proportion initiating ART at CD4 >500 cells/mm^3 increased from 31% in 2004 to 89% in 2010. Among persons with CD4 >350 cells/mm^3 at diagnosis, median CD4 cell counts at ART initiation increased from 365 cells/mm^3 in 2004 to 504 cells/mm^3 in 2010 and the proportion initiating ART at CD4 >350 cells/mm^3 increased from 48% in 2004 to 92% in 2010. The mean drop in CD4 cell counts from diagnosis to ART initiation decreased from 135 cells/mm^3 in 2004 to 5 cells/mm^3 in 2010. Persons initiating ART at CD4 >500 cells/mm^3 were more likely to be white, MSM, non-poor, and diagnosed by private providers. Persons initiating ART at CD4 >350 cells/mm^3 were more likely to be older, white, MSM, non-poor, and diagnosed by private providers. The findings from this analysis provided evidence of the benefits of initiating ART at CD4 >350 cells/mm^3 and possibly at >500 cells/mm^3. They also exposed a new potential inequality for populations already disproportionately affected by HIV, including youth, black Americans, the poor, and those diagnosed at facilities other than private providers. The investigators noted that unless these gaps are closed through earlier diagnosis, care and ART initiation, there may be increasing health and survival disparities among persons living with HIV.

In another study of treatment trends, investigators analyzed data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) and Western European cohorts in the ART Cohort Collaboration (ART-CC) to determine trends in CD4 count at the start of ART worldwide in various low, middle, and high income countries.[7] A total of 309,435 patients from 48 countries were analyzed: 222,980 patients from sub-Saharan Africa (20 countries), 58,880 from Europe (7 countries), 16,733 from North America (2 countries), 5,797 from Asia/Pacific (12 countries), and 5,045 from the Caribbean, Central and South America (CCASA) (7 countries). Trends in median CD4 counts at start of ART from 2002, when ART was scaled up globally, were similar in low-income and upper middle-income countries (Figure 1). Median counts were higher in lower middle-income and highest in high-income countries. The investigators reported that 15 countries had median CD4 cell counts at the start of ART of ≥200 cells/mm^3: Australia, Brazil, Burkina Faso, Cambodia, Canada, France, Germany, Italy, Mozambique, Netherlands, Rwanda, Spain, Switzerland, UK, and the United States. No country had median CD4 counts ≥350 cells/mm^3. In all except high-income countries, median counts were higher and increased to a greater extent in women than men.

Figure 1. CD4 Cell Count at Start of ART According to Country Income 2002-2009



PrEP and Prevention

CROI included a presentation from the FEM-PrEP trial.[8] This oral pre-exposure prophylaxis (PrEP) study was a randomized, double-blinded, placebo-controlled trial conducted in 3 African countries (South Africa, Kenya, and Tanzania) of once-daily emtricitabine/tenofovir (FTC/TDF). The primary effectiveness endpoint was incident HIV infection during 52 weeks of follow-up. Primary safety endpoints included liver and kidney abnormalities and other adverse events. Participants attended screening, enrollment, and follow-up visits at 4-week intervals. HIV seroconverters were taken off product and followed for an additional 52 weeks.

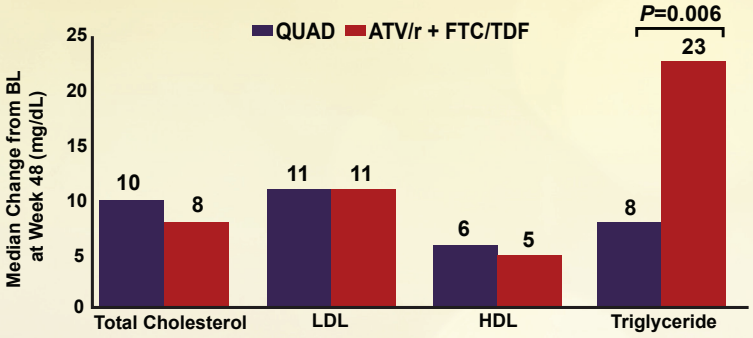
The study was stopped early after a planned interim analysis determined that the trial was unlikely to demonstrate a protective effect. Investigators found that 33 infections occurred in the FTC/TDF group and 35 in the placebo group – a 6% reduction in risk (P=0.81). Among pre-specified adverse event categories, only the rates of vomiting and nausea were significantly higher in the FTC/TDF arm. FTC resistance was detected in 5 seroconverters; 1 in the placebo arm and 4 in the FTC/TDF arm. Adherence by self-report and pill count data was higher than by drug level analysis. Among women assigned to FTC/TDF, drug was detectable in plasma in fewer than 50% of infected cases and uninfected controls matched on time of infection. The investigators concluded that adherence levels were too low to assess the efficacy of the PrEP regimen in the study population, and that intracellular drug level testing will give a clearer picture of adherence over time.

Elvitegravir/Cobicistat/Tenofovir/Emtricitabine (Quad)

Investigators reported 48-week findings on Quad, a single-tablet regimen (STR) in development that consists of the integrase inhibitor elvitegravir (EVG), the pharmacoenhancer cobicistat (COBI), FTC, and TDF.[9] They compared Quad with

ritonavir-boosted atazanavir (ATV/r) plus fixed-dose FTC/TDF in treatment-naïve patients with HIV RNA ≥5,000 copies/mL and no resistance to ATV, FTC, or TDF. A total of 708 subjects were randomized: 90% male, 26% non-white, 39% with viral load ≥100,000 copies/mL. The primary objective was met: Quad was reported to be non-inferior to ATV/r + FTC/TDF, with 90% and 87%, respectively, having HIV RNA of <50 copies/mL at week 48. Among subjects with HIV RNA ≥100,000 copies/mL, response rates were similar (Quad 85%, ATV/r + FTC/TDF 82%). Virologic failure was infrequent (5%, in both arms). Median CD4 increases were similar as were discontinuation rates for adverse events (AEs). Among AEs occurring in ≥5% of subjects, AE associated with elevated bilirubin levels were significantly higher with ATV/r + FTC/TDF, and no AE were significantly higher in Quad. Median triglyceride increases were 8 mg/dL in Quad and 23 mg/dL in ATV/r + FTC/TDF (*P*=0.006) (Figure 2). Median BMD changes for hip favored Quad over ATV/r + FTC/TDF. The investigators concluded that the findings demonstrated high and comparable efficacy in Quad and ATV/r + FTC/TDF, with high virologic suppression rates in all subgroups.

Figure 2. Change in Baseline Fasting Lipids at Week 48



Investigators also reported the 48 week results from another Quad study, which compared the Quad combination with co-formulated efavirenz (EFV)/FTC/TDF as initial therapy for HIV infection.[10] In this study, treatment-naïve subjects with HIV were randomized 1:1 to blinded Quad or EFV/FTC/TDF once daily plus matching placebos. The primary endpoint was the proportion of subjects with HIV RNA <50 copies/mL at week 48 per the FDA snapshot algorithm (12% pre-specified non-inferiority margin).

Seven hundred subjects (89% male, 37% non-white, 33% with viral load >100,000 copies/mL) were randomized and treated in the study. The primary endpoint was met: Quad was found to be non-inferior to EFV/FTC/TDF, with 88% and 84%, respectively, having viral suppression at week 48. Among subjects with baseline HIV RNA >100,000 copies/mL, response rates were similar (Quad 84%, EFV/FTC/TDF 82%). Virologic failure rates at week 48 were 7% in both arms. At week 48, mean CD4 cell increase was 239 cells/mm^3 in Quad and 206 cells/mm^3 in EFV/FTC/TDF (*P*=0.009). Drug discontinuation rates for adverse events (AE) were similar in both arms. Total and LDL cholesterol increases at week 48 were significantly lower for Quad than EFV/FTC/TDF, but, like the differences with ATV/r + TDF/FTC shown above, these differences were not large enough to be of clinical significance.

Cardiac Risk and Prevention

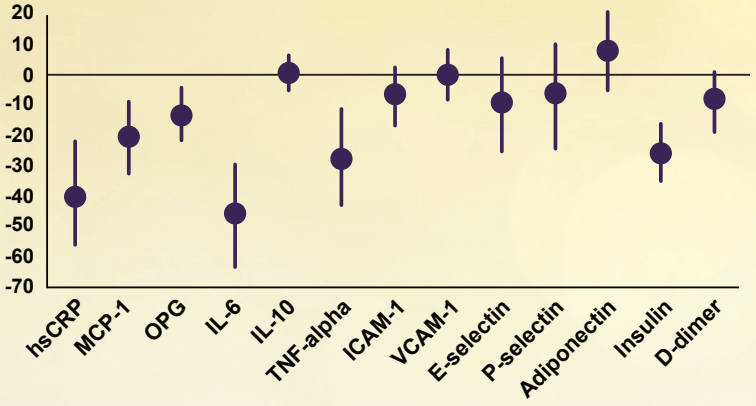
In a report on risk prevention in people with HIV infection, researchers evaluated whether statin therapy decreased the risk of serious non-AIDS defining events and all-cause mortality among subjects followed in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort.[11] This evaluation included 3,601 subjects who initiated ART but were not on a statin at ALLRT entry. The primary endpoint was time to first major clinical event. Differential statin effects by baseline covariates were evaluated. The cohort was 83% male, with median age of 39 years, and 21% Hispanic, 30% black, 47% white; median nadir and baseline CD4 counts were 180 and 346 cells/mm^3, respectively. Over 16,670 person-years of follow-up, 481 subjects initiated statins; 619 subjects experienced an event. Statin therapy was associated with an 18% reduction in time to first non-AIDS event or non-accidental death, although this finding was non-significant. A statistically significant 55% reduction was apparent for malignancy events. Confirmatory studies are needed to evaluate the statin-associated reduction in risk of cancer and other non-AIDS-associated morbidities.

In the SPIRAL study, investigators switched patients from a ritonavir-boosted protease inhibitor (PI/r) to raltegravir (RAL). In a substudy of SPIRAL, they measured whether there was a significant change in cardiovascular (CVD) biomarkers and sought to determine whether there was any correlation between changes in plasma lipids and changes in CVD biomarkers.[12] Patients in the study consisted of stable, HIV+ adults with HIV RNA <50 copies/mL for at least 6 months. Prior to switching, patients received a PI/r + 2 non-PI ARVs, and had no prior RAL use. Patients were randomized to receive either RAL or to continue on their PI/r. Biomarkers measured at baseline and at 48 weeks were: high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein-1 (MCP-1), osteoprotegerin (OPG), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), selectin E and P, adiponectin, insulin, and D-dimer. The lipids measured were triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol.

A total of 233 patients (119 RAL, 114 PI/r) remained on their allocated therapy for 48 weeks and had sera available. Triglycerides and total, LDL-, and HDL-cholesterol significantly decreased in the RAL group relative to the PI/r group, while total-to-HDL cholesterol ratio remained unchanged. As seen in Figure 3, there

were significant decreases in hsCRP (-40%, $P<0.0001$), MCP-1 (-20%, $P=0.0003$), OPG (-13%, $P=0.0024$), IL-6 (-46%, $P<0.0001$), TNF-α (-27%, $P=0.0011$), insulin (-26%, $P<0.0001$), and D-dimer (-8%, $P=0.0187$) in the RAL group relative to the PI group, while IL-10, ICAM-1, VCAM-1, selectin E, selectin P, and adiponectin remained unchanged. Lipid and biomarker changes at 48 weeks were not correlated. Switching from PI/r to RAL decreased biomarkers associated with inflammation, insulin resistance, and hypercoagulability, but did not modify biomarkers associated with endothelial dysfunction. Reductions in biomarkers were unrelated to lipid changes. These data confirm that RAL is likely to be one of the most cardiac friendly ARVs.

Figure 3. Median Difference of Percentage Change in Biomarkers: RAL minus PI/r



The ACTG A5202 study randomized 1,857 treatment-naïve subjects to blinded abacavir/lamivudine (ABC/3TC) or FTC/TDF with open-label EFV or ATV/r. The substudy ACTG A5224s compared changes in inflammation markers from baseline to week 24 in ABC/3TC vs. TDF/FTC-containing arms.[13] Secondary endpoints included changes from baseline to week 96 and comparisons of EFV- vs. ATV/r-containing arms. A5224s included 244 A5202 subjects: 85% male, 48% white non-Hispanic, median age 39 years, HIV-1 RNA 4.6 $\log_{10}$ copies/mL, CD4 240 cells/mm^3. The investigators reported that there were no significant interactions between the NRTI and the EFV and ATV/r components for the inflammation markers at weeks 24 or 96. Soluble tumor necrosis factor receptors (sTNFR)-I and -II, TNF-α, and the adhesion molecules sVCAM-1 and sICAM-1 decreased significantly at weeks 24 and 96, without significant differences between regimen components at either time point. At week 24, ABC/3TC-containing arms had a greater mean fold-change in hsCRP than TDF/FTC (1.43 vs. 0.88), which remained significant at week 96. A post-hoc analysis did not detect a differential NRTI effect between subjects with (n=168) and without (n=68) HIV-1 RNA <50 copies/mL at week 24. At week 24 (but not week 96), EFV-containing arms had a greater mean fold-change in hsCRP than ATV/r. IL-6 decreased significantly at week 24 in the TDF/FTC arms but not in the ABC/3TC arms. At week 96, however, similar decreases were seen in both NRTI arms. Changes in IL-6 were not significantly different between ATV/r and EFV arms at either time point. The investigators concluded that sTNFRs and adhesion molecules decreased following treatment initiation and did not significantly differ by regimens. Less favorable effects were seen on hsCRP and IL-6 when initiating ABC/3TC vs. TDF/FTC and on hsCRP with EFV vs. ATV/r.

In a previous analysis, investigators from the D:A:D study found that the cumulative exposure to lopinavir (LPV) and indinavir (IDV), but not saquinavir or nelfinavir, was associated with an increased risk of myocardial infarction (MI). An association with ATV usage and MI has not been investigated, because of the limited follow-up time among persons exposed to ATV. However, sufficient person-years of follow-up (PYFU) have now accrued among those exposed to ATV to permit the D:A:D investigators to examine the association between ATV and the risk of MI and stroke.[14] To investigate the association between cumulative exposure to ATV and MI and stroke, the D:A:D investigators used Poisson regression after adjusting for known demographic and clinical confounders, cumulative exposure to ARV drugs, and recent exposure to NRTIs. Follow-up started on the date of enrollment in the D:A:D study and ended at the earliest of a new MI/stroke, death, 6 months after last clinic visit, or February 1, 2011. A sensitivity analysis was performed to investigate a potential modifying association with the latest bilirubin level, included as a categorical covariate, based on the inverse association between bilirubin level and risk of cardio- or cerebrovascular events (CVE) reported in HIV– persons. There were a total of 844 cases of MI and 523 strokes. Longer exposure to ATV was not associated with an increased risk of either event in multivariable analyses. Further adjustment for the latest bilirubin level, in the subgroup of cohorts that provide these data, had no impact on the size of the association with either MI or stroke. The investigators concluded that ATV was not associated with an increased risk of CVE, suggesting that previously reported associations in the D:A:D study with LPV and IDV are unlikely to reflect a class-wide association.

Neurocognitive Issues

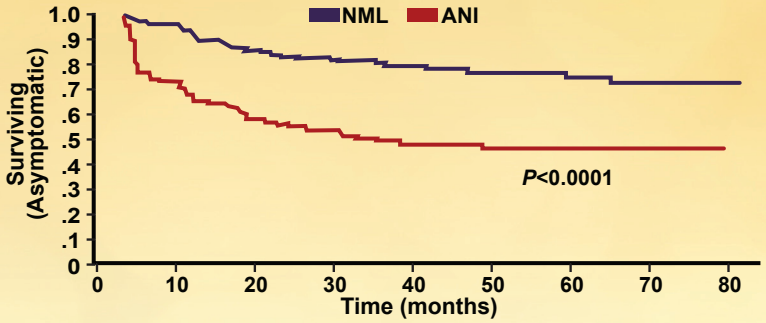
Another important topic presented at CROI was neurocognitive health in people with HIV infection. In one report at CROI, researchers sought to determine the prevalence and predictors of neurocognitive decline over 18 to 42 months in a group of HIV-infected patients treated at 6 university-affiliated clinics in the CNS HIV Anti-retroviral Therapy Effects Research (CHARTER) study.[15] Participants received comprehensive laboratory,

neuromedical, and neurobehavioral assessments every 6 months and published norms for change were used to generate overall change status at each study visit. Survival analysis was used to examine the predictors of time to neurocognitive decline over 18 to 42 months.

The investigators reported that 99 (22.7%) participants experienced neurocognitive decline, 266 (61%) remained neurocognitive stable, and 72 (16.5%) improved over 18 to 42 months. The survival analysis showed that younger age, female gender, severe non-HIV co-morbidities, lower current CD4 counts, higher plasma and CSF viral loads, higher AST, urine toxicology positivity, methamphetamine history, and current major depressive disorder were univariable predictors of earlier neurocognitive decline. Multivariable Cox regression modeling using the univariable predictors as co-variates yielded a model with Hispanic ethnicity, severe co-morbidities, being off ART, and low CD4 count, in combination, as significant predictors. The investigators concluded that neurocognitive decline is highly prevalent in patients with HIV infection and that it is independently predicted by baseline neurological co-morbidities, immunocompromise, and being off ART.

In another CHARTER study, researchers investigated neurocognitive decline in a group of HIV-infected individuals with and without HIV-associated neurocognitive disorders (HAND) to determine if having asymptomatic neurocognitive impairment (ANI) – the most common HAND diagnosis – confers risk of progression to symptomatic HAND. In this study, 347 CHARTER participants with up to 90 months of follow-up were selected, based on being normal (NML), with no neurocognitive impairment and no self-reported or observed declines in everyday function (n=226), or having ANI (n=121), in which patients are neurocognitively impaired but have no self-reported or observed declines in everyday function.[16] Participants completed neuromedical, laboratory, neurocognitive, and both self-report and performance-based measures of everyday functioning approximately every 6 months. The investigators found that ANI increases the risk for symptomatic HAND, based on self-report, performance-based functional impairment, or self-report or performance-based measures (Figure 4). They reported that individuals with ANI have increased relative risk of approximately 3 to 5 (depending on method of functional determination) for earlier development of symptomatic HAND compared with cognitively normal individuals. ANI was a significant predictor of earlier functional decline, even after correcting for other baseline differences. Earlier decline to symptomatic HAND was more likely in women with substance abuse and other comorbidities, and who had lower nadir CD4 cell counts, AIDS, and HCV co-infection at baseline, and lower CD4 cell counts during follow-up. Because ANI can be harbinger of future HAND worsening, cases of ANI warrant increased monitoring.

Figure 4: Risk of Symptomatic HAND and ANI: Self-Report or Performance-based Measures



Another study on neurocognitive issues that was presented at CROI was designed to determine whether initiating ART at higher CD4 cell counts benefits neurocognitive functioning. Subjects in the study (N=79) consisted of HIV+ patients in Pune, India, with a CD4 cell count >350/mm^3. Patients were randomized to immediate (n=35) or deferred treatment (n=44). All participants completed a full NP battery at baseline and at one-year follow-up. NP performance was summarized using unadjusted mean scaled scores (mSS), a normalized score that puts all scores on the same metric (higher scores indicate better performance). The two groups were similar with respect to age, education, gender, and disease stage, and had comparably high current CD4 cell counts. On average, participants started treatment on the day they were tested. At baseline, the mSS for the deferred treatment group was 9.0 vs. 9.7 for the treated group (P=0.06). All participants in the treated group attained virologic suppression by their second visit. In a multivariable model, improvement in mSS was predicted by the interaction of group and baseline mSS (P=0.02) and time on treatment (P=0.002). Treated participants with the lowest baseline mSS and longest period of treatment demonstrated the most improvement. Whether the participants started treatment prior to baseline was not a significant predictor. ART initiation at higher CD4 cell counts appeared to be beneficial to the central nervous system. ART was most beneficial for those who demonstrated worse NP performance at baseline.

New Drugs for HIV

New findings on GS-7340, a prodrug of tenofovir in development for HIV, were presented at CROI. GS-7340 was studied in a randomized, partially blinded, placebo and active-controlled, dose-finding, 10-day monotherapy study conducted to compare 3 different doses of GS-7340 (8, 25, and 40 mg once daily), open-label TDF (300 mg once daily), and GS-7340 placebo in

HIV-1-infected subjects with HIV-1 RNA ≥2000 copies/mL, no genotypic resistance to TDF, and CD4 cell count ≥200 cells/mm^3.[18] The primary endpoint was time-weighted average HIV-1 RNA change from baseline after 10 days of treatment (DAVG10d). Plasma and intracellular PBMC PK were also assessed. Thirty-eight subjects (97% male, mean HIV-1 RNA 4.50 $\log_{10}$ copies/mL, mean CD4 478 cells/mm^3) were randomized and treated (n = 9, 8, 8, 6, and 7 in the GS-7340 8, 25, and 40 mg, TDF 300 mg, and placebo group, respectively). Median $DAVG_{10d}$ ($\log_{10}$ copies/mL) in the GS-7340 8-mg group was greater than that in the placebo group and similar to that in the TDF group. $DAVG_{10d}$ in the GS-7340 25- and 40-mg group were greater than that in the TDF group. No TDF resistance mutations were detected. Plasma tenofovir exposures across the GS-7340 groups were ~80% to 97% lower vs. TDF. Antiviral activity was associated with GS-7340 AUC, with 25-mg dose/exposure providing near-maximal activity. There were no clinically significant laboratory abnormalities or drug-related serious adverse events. GS-7340 25 mg and 40 mg demonstrated superior antiviral efficacy to TDF 300 mg. GS-7340 has the potential to be more efficacious with an improved safety margin, and is thought to be easier to co-formulate, compared with TDF.

Another drug under investigation is dolutegravir (DTG), a once-daily, unboosted integrase inhibitor (INI). It was studied in SPRING-1, a multicenter, partially blinded, phase 2b, dose-ranging study with treatment-naïve HIV-infected adults randomized 1:1:1:1 to receive DTG 10, 25, or 50 mg or EFV 600 mg every day with TDF/FTC or ABC/3TC and stratification based on screening HIV-1 RNA (viral load) and NRTI selection.[19] The primary endpoint was proportion of subjects with viral load <50 copies/mL at week 16, with a planned analysis at week 96. Two hundred and five subjects received study drug: 86% male, 20% non-white, and 26% >100,000 copies/mL viral load. At week 96, the proportion of subjects with viral load <50 copies/mL (TLOVR) was 88% for the DTG 50 mg dose vs. 72% for EFV. Responses in the DTG 10 mg and 25 mg arms were 79% and 78%, respectively. There were no cases of protocol-defined virologic failure (PDVF, confirmed viral load >400 copies/mL) on the DTG 50 mg arm through 96 weeks; no new cases of PDVF occurred on any arm between weeks 48 and 96. No genotypic or phenotypic evidence of INI or NNRTI resistance was observed through week 96 in any of the treatment arms. The median change from baseline in CD4 cells in the combined DTG arms trended higher for DTG (combined) (+338.5 cells/mm^3) vs. EFV (+301 cells/mm^3) (P=0.155). No new safety issues occurred between week 48 and week 96. Through 96 weeks, fewer grade 2 to 4 drug-related AEs were reported on DTG (11%) than EFV (24%).

HCV/HIV Co-infection

Another important issue discussed at CROI was HIV/HCV co-infection, a problem for approximately one third of all HIV-infected individuals. The presentations at CROI included a SVR12 interim analysis of an ongoing study (Study 110) of telaprevir (TVR) in combination with pegylated interferon-alfa-2a (PegIFN-α-2a) + RBV in genotype 1 HCV treatment-naïve HIV+ patients.[20] Patients in each part were randomized into 2 groups: (1) TVR 750 mg every 8 hours + PegIFN 180 µg/week + RBV 800 mg/day for 12 weeks followed by 36 weeks of PegIFN + RBV and (2) placebo + PegIFN + RBV for 48 weeks. The TVR dose was 1,125 mg every 8 hours when the ART regimen included EFV. In part A of the study, patients had no concurrent ART. In part B, patients were on stable, predefined ART with either an EFV- or an ATV/r-based regimen. There were 62 patients randomized; 60 received ≥1 dose, 13 in part A, 47 in part B; 44 patients reached week 24 on the study drug. The mean age was 46 years; 88% were male, 27% were African American, 68% had HCV subtype 1a, and 3.3% had cirrhosis. At baseline, 92% and 81% of part A and B patients had HCV RNA ≥800,000 IU/mL, respectively; mean CD4 counts were 690 cells/mm^3 and 562 cells/mm^3, respectively. Two patients experienced HCV RNA breakthrough on TVR (one with EFV, one with ATV/r). There were no HIV RNA breakthroughs. Absolute CD4 counts declined from baseline in both groups, although CD4 percentage remained unchanged. Bilirubin adverse events occurred more frequently in ATV/r patients (27% vs. 0%). No severe rashes were reported. Three treated patients in part B experienced an adverse event that led to discontinuation of 1 or more study drugs. TVR pharmacokinetics was comparable across ART regimens. The pharmacokinetics of ART when co-administered with TVR resulted in changes consistent with drug interaction studies in healthy volunteers. At 12 weeks post-treatment (SVR12), substantially higher on-treatment responses were observed in chronic genotype 1 HCV/HIV co-infected patients treated with a TVR-based regimen than placebo – 74% vs. 45% . TVR exposures were comparable across ART regimens. Safety and tolerability of TVR in combination with PegIFN + RBV was comparable to that previously observed in HCV-mono-infected patients.

Another study with HCV/HIV co-infected patients involved the use of the HCV protease inhibitor boceprevir (BOC).[21] In this study, patients with untreated HCV genotype 1 infections and HIV RNA <50 copies/mL were randomized in a 2:1 ratio to receive (1) PegIFN-2b + RBV (600 to 1,400 mg/day, according to weight) + BOC 800 mg 3 times daily, or (2) PegIFN + RBV and placebo for 44 weeks. The individuals in the BOC arm had a 4-week lead-in of PegIFN + RBV before staring BOC. The primary objective of the study was to compare the efficacy of BOC + PegIFN2b/RBV to PegIFN2b/RBV alone in previously untreated

genotype 1, chronic HCV patients co-infected with HIV. The secondary objectives included evaluating the safety of BOC + PegIFN2b/RBV, defining predictors of SVR, such as epidemiologic factors, disease characteristics and on-treatment response, and assessing the steady state PK of BOC using population-based PK modeling. The SVR12 analysis found that HCV-HIV co-infected patients who were previously untreated had higher rates of HCV response on BOC: 61% of patients on BOC + PegIFN2b/RBV had undetectable HCV RNA vs. 27% of patients on PegIFN2b/RBV alone. Compared to the control group, BOC patients were more likely to have anemia, pyrexia, asthenia, decreased appetite, dysgeusia, vomiting, and neutropenia. The safety and tolerability profile was consistent with that observed in HCV-mono-infected patients.

Research on drug interactions with BOC and various ARVs were reported at CROI. In one open-label, drug interaction study with BOC and 3 different boosted PIs, 39 healthy adult subjects received BOC (800 mg 3 times a day) for 6 days.[22] After a 4-day washout, subjects received ATV/r (300/100 mg every day), LPV/r (400/100 mg twice a day), or darunavir/ritonavir (DRV/r) (600/100 mg twice a day) on days 10 to 31. Subjects received concomitant BOC (800 mg three times a day) on days 25 to 31. It was found that co-administration of BOC with an HIV-PI/r was generally well tolerated, with no serious adverse events. Concomitant BOC treatment decreased the exposure of all 3 HIV PIs, with $AUC_{0\text{-last}}$, C_{max}, and C_{min} GMR (90% CI) of ATV 0.65 (0.55 to 0.78), 0.75 (0.64 to 0.88), and 0.51 (0.44 to 0.61); of LPV 0.66 (0.60 to 0.72), 0.70 (0.65 to 0.77), and 0.57 (0.49 to 0.65); and of DRV 0.56 (0.51 to 0.61), 0.64 (0.58 to 0.71), and 0.41 (0.38 to 0.45), respectively. Co-administration with BOC also decreased the exposure of ritonavir in all 3 HIV-PI groups, with ritonavir AUC_t decreasing 34%, 22%, and 27% in the ATV, LPV, and DRV cohorts, respectively. Co-administration with ATV/r did not alter BOC AUC_t, but co-administration with LPV/r and DRV/r decreased BOC AUC_t 45% and 32%, respectively.

In a second drug interaction study – an open-label, randomized, two-period, cross-over phase I trial in 22 healthy volunteers – investigators measured interactions between BOC and RAL.[23] Subjects were randomly assigned to BOC 800 mg three times a day for 10 days plus a single dose of RAL 400 mg on day 10 followed by a washout period and a single-dose of RAL 400 mg on day 38, or the same medication in reverse order. After observed intake of BOC and RAL with a standardized breakfast, blood samples were collected during an 8-hour and a 12-hour period, respectively. GMR and 90% CI were calculated for RAL AUC_{last} and C_{max} after log-transformation of within-subject ratios. A 90% CI within the 0.80 to 1.25 range indicates no clinically meaningful effect of BOC on RAL PK. No serious adverse events were reported. The geometric mean (95% CI) of RAL AUC_{last} and C_{max} for RAL + BOC vs. RAL alone were 4.27 (3.22 to 5.66) vs. 4.22 (3.19 to 5.59) mg.h/L and 1.06 (0.76 to 1.49) vs. 0.98 (0.73 to 1.31) mg/L, respectively. GMR (90% CI) of RAL AUC_{last} and C_{max} for RAL + BOC vs. RAL alone was 1.01 (0.85 to 1.20) and 1.09 (0.89 to 1.33). The investigators concluded from these findings that BOC did not affect RAL exposure.

Taken together, the data presented at CROI indicated that both BOC and TVR are very effective for treating HCV in HIV/HCV co-infected patients. Drug interactions and adverse events remain a challenge, and, of the DHHS Guidelines preferred ARVs for ARV-naïve patients, RAL appears to be the only agent that has no significant interaction with BOC or TVR.

HCV in the Future

Researchers are investigating new strategies for treating HCV, including new agents and interferon-free regimens. In PROTON, GS-7977 with PegIFN + RBV achieved >90% SVR in patients infected with HCV genotype (GT) 1, 2, or 3. In ELECTRON, GS-7977 and RBV (without PegIFN) given for 12 weeks achieved 100% SVR in HCV GT 2/3 patients. Two additional cohorts were enrolled in ELECTRON – GT1 treatment-naïve patients and GT1 prior null responders (defined as <2 log_{10} reduction in HCV RNA at week 12 of a PegIFN/RBV regimen) – to evaluate the response of this PegIFN-free regimen.[24] For 12 weeks, 20 null responders and 25 treatment-naïve, non-cirrhotic HCV GT1 patients received 400 mg GS-7977 + RBV. As reported at CROI, by week 2, mean HCV RNA decline from baseline was 5.54 log_{10} IU/mL in the GT1 null responders and 4.87 in the GT1 treatment-naïve patients (compared with 5.31 log_{10} in GT2/3 treatment-naïve patients); 78% of GT1 null responders and 71% GT1 treatment-naïve patients were below the limit of detection (<LOD, 15 IU/mL) at 2 weeks (compared with 80% of treatment-naïve GT2/3 patients). All patients in both cohorts were <LOD at week 4 (i.e., 100% rapid viral response). No virologic breakthrough was observed during treatment with GS-7977, suggesting a high barrier to resistance; however, most (9/10) null responders relapsed soon after the end of the 12 weeks of treatment with GS-7977 + RBV, with the exception of a young white woman with an IL28B CC genotype and the lowest fibrosis score. The investigators concluded that future studies of GS-7977 in GT1 prior null responders would require longer treatment duration or the addition of another DAA.

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