



A CME Newsletter

The 18th Conference on Retroviruses and Opportunistic Infections (CROI): ARV Therapies and Therapeutic Strategies

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

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Introduction

The 18th Conference on Retroviruses and Opportunistic Infections (18th CROI) was held in Boston, Massachusetts from February 27-March 2, 2011. This conference included presentations that discussed many important new insights into evolving treatment options for managing patients infected with HIV or hepatitis C virus (HCV), as described in this newsletter.

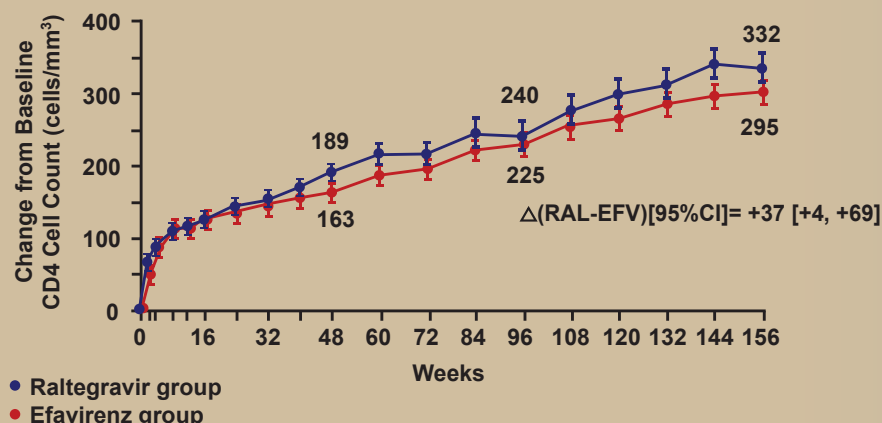
Treatment-Naïve Patients

STARTMRK: 156 Week Results

As patients with HIV continue to live longer, there is increased interest in determining the long-term effects of various antiretroviral (ARV) combinations. This issue is under investigation in STARTMRK, an ongoing study of 563 treatment-naïve HIV+ patients randomized to either raltegravir (RAL) or efavirenz (EFV), each with tenofovir (TDF)/emtricitabine (FTC), that is measuring efficacy endpoints and metabolic parameters [Rockstroh JK, et al. *Abst.* 542].

Long-term (156 week) results from STARKMRK were presented at CROI. It was reported that RAL provided greater virologic suppression and immunologic response after three years of treatment (Figure 1). Drug-related adverse events (AEs) occurred less often with RAL than EFV (49% vs. 80%; $P < 0.001$). Both drugs were generally well-tolerated, with few discontinuations due to AEs (5% RAL, 7% EFV). At week 156, RAL was reported to have less impact on fasting lipids than EFV. Fat changes, as measured by dual-emission X-ray absorptiometry (DEXA), were more favorable for RAL (total mean % change, +19 RAL, +31 EFV), with no patterns of fat loss after three years of treatment. These findings showed that the long-term tolerability and metabolic profile of RAL appeared to be favorable compared with EFV, when both were given with TDF/FTC.

Figure 1. Change from Baseline in CD4 Cell Count



Supported by an unrestricted educational grant from Merck & Co., Inc.

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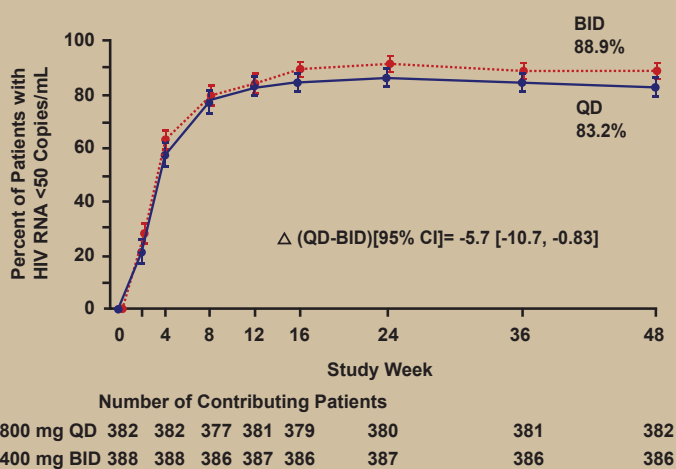
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QDMRK

The results of QDMRK, another study with RAL, were presented at CROI. This study was based on previous findings which suggested that once-daily RAL might be an effective alternative to twice-daily RAL in treatment-naïve HIV+ patients [Eron J, et al. *Abst. 150LB*]. QDMRK was a non-inferiority study with a prespecified -10% margin, in which treatment-naïve patients with HIV RNA levels >5,000 copies/mL and no resistance to TDF or FTC were randomized to receive RAL 800 mg QD vs. 400 mg BID, each with TDF/FTC. The primary efficacy endpoint in the study was percentage of patients with HIV RNA <50 copies/mL at week 48. A total of 770 patients were randomized and treated in QDMRK.

The investigators reported that at week 48, 83.2% of the QD patients, and 88.9% of the BID patients, achieved HIV RNA levels <50 copies/mL (Figure 2). In addition, 88 patients experienced virologic failure (non-response or rebound): 13.9% in the once-daily and 9.0% in the twice-daily groups. Based on their findings, the investigators concluded that both once-daily and twice-daily RAL in combination with TDF/FTC achieved high virologic response rates and similar immunologic effects with favorable tolerability and safety. However, once-daily dosing was found to not be non-inferior in virologic efficacy compared with twice-daily RAL.

Figure 2. Percentage of Patients with HIV RNA <50 copies/mL in QDMRK: QD vs. BID*



*All patients received TDF/FTC FDC

Central Fat Accumulation

Another study with treatment-naïve patients presented at CROI was A5224s. This study was a metabolic substudy of the A5202 4-arm trial of HIV-infected subjects randomized to abacavir (ABC/lamivudine (3TC) or TDF/FTC with open-label EFV or atazanavir (ATV)/ritonavir (r) [McComsey GA, et al. *Abst. 77*]. A5224s endpoints included changes from baseline to week 96 in visceral adipose tissue (VAT) and VAT:total adipose tissue (TAT) ratio by CT scan. Post-hoc endpoints included trunk fat (by DEXA scan).

The investigators randomized 269 subjects (85% male, 47% white non-Hispanics) to two arms. At baseline, the median HIV RNA was 4.6 log₁₀ copies/mL, CD4 was 233 cells/mL, trunk fat was 9.4 kg, VAT was 84.1 cm², and VAT:TAT was 0.31. They reported finding no significant evidence of an interaction between the nucleoside reverse transcriptase inhibitor (NRTI) and the EFV and ATV/r components of treatment in terms of trunk fat, VAT or VAT:TAT. The estimated mean percentage changes from baseline to week 96 in trunk fat and VAT for all subjects were 28% and 19%, respectively. No statistically significant differences were observed in mean percentage change in trunk fat, VAT or VAT:TAT between the NRTI arms (combining third drugs). Comparing ATV/r with EFV (combining NRTI), the estimated mean percentage change from baseline to 96 weeks in trunk fat was higher for ATV/r (36.5% vs. 21.1%; *P*=0.028 in intent-to-treat and 38.9% vs. 21.7%; *P*=0.028 in as-treated); estimated mean percentage change in VAT tended to be higher for ATV/r vs. EFV (26.6% vs. 12.4%; *P*=0.09 in intent-to-treat and 30.0% vs. 14.5%; *P*=0.10 in as-treated); however, estimated mean percentage changes in VAT:TAT were similar for ATV/r and EFV (-2.24% vs. -1.00%; *P*=0.67 in intent-to-treat and -0.43% vs. -0.40%; *P*=0.99 in as-treated). The results were similar for absolute changes in trunk fat, VAT and VAT:TAT.

The results presented on A5224s demonstrated that, compared to EFV, ATV/r use resulted in significantly larger mean percentage increases in trunk fat and a trend toward higher mean percentage increase in VAT. However, mean changes in VAT:TAT were similar, and increases in trunk fat and VAT were similar between the ABC/3TC and TDF/FTC arms.

Treatment-Experienced Patients

Dolutegravir and the VIKING Study

In the VIKING study, an ongoing, open-label, phase 2b study (n=27), the activity of 50 mg dolutegravir QD (DTG, S/GSK1349572), a novel integrase inhibitor, was investigated in HIV+ patients with RAL resistance. Because reduced activity was



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noted against virus with Q148+ associated mutations, a second cohort of patients (cohort II) was recruited to receive 50 mg DTG BID [Eron J, et al. *Abst. 151LB*]. In this second study, subjects with HIV RNA $\geq 1,000$ copies/mL with genotypic resistance to RAL and to ≥ 2 other ARV classes received DTG while continuing their failing regimen (without RAL) to day 11, after which the background regimen was optimized. Unlike cohort I, eligibility required at least 1 fully active ARV for day 11 optimization.

A total of 24 subjects (75% white, 75% male) were enrolled in this second cohort, with virus showing a median (range) fold change in susceptibility vs. wild type at baseline of >128 (0.8 to >128) to RAL and 2.7 (0.9 to 9.5) to DTG. Virus with similar genotypes were observed in cohort I subjects, with a DTG fold change range of 0.55 to 35, median 1.46. Median (range) baseline CD4 and plasma HIV RNA were 202 cells/mm³ (19 to 528) and 4.3 log₁₀ copies/mL (3.3 to 5.8), respectively for cohort II. Of subjects in cohort II, 23 (96%) achieved plasma HIV RNA <400 copies/mL (n=13) or ≥ 0.7 log₁₀ copies/mL decline (n=23) at day 11 (primary endpoint) compared with 21 of the 27 (78%) subjects in cohort I. All subjects in cohort II with Q148+ virus were found to have responded compared with 3 of 9 in cohort I. The mean reductions in plasma HIV RNA (log₁₀ copies/mL) at day 11 were reported to be -1.76 (SD=0.54) for cohort II (-1.57 for Q148+ virus) and -1.45 (SD=0.77) for cohort I (-0.72 for Q148+ virus).

Based on these findings, the investigators concluded that DTG continued to show activity against RAL-resistant virus and was generally well tolerated at a higher dose in this advanced population. Although the day 11 responses were numerically better in cohort II, the baseline fold change range in virus susceptibility to DTG for cohort II was more limited.

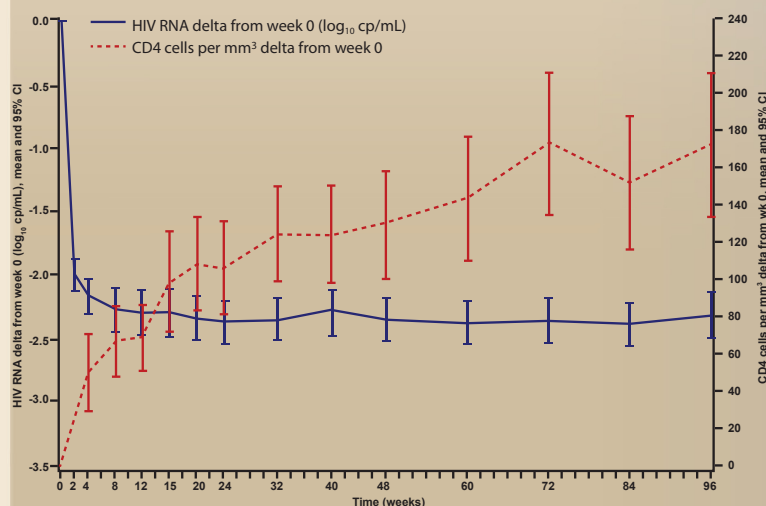
TRIO Trial

The ANRS 139 TRIO study was a phase II noncomparative trial that included 103 patients with multi-drug resistant HIV who received RAL + etravirine (ETV) + darunavir (DRV)/r +/- NRTIs or enfuvirtide (ENF). At week 48, patients were proposed to go through follow-up until week 96 to evaluate the long-term efficacy and safety of treatment. Follow-up visits were performed at weeks 60, 72, 84 and 96. The investigators recorded the change in HIV RNA, CD4 cells, and metabolic parameters [Fagard C, et al. *Abst. 549*].

100 patients were included in the extended follow-up. 89% were male, the median age was 45 years, and 41% had a history of AIDS. At week 0, the median CD4 count was 258 cells/mm³ and the HIV RNA was 4.2 log₁₀ copies/mL. Despite a low genotypic

sensitivity score at baseline (median 0.5), concern about the loss of efficacy was the reason for pursuing NRTIs in 74% of patients. Five patients (5%) experienced virologic failure after week 48; however, they all had HIV RNA measurements below 400 copies/mL and in four of these patients, the HIV RNA decreased to <50 copies/mL thereafter. The mean change in CD4 cell count from baseline to week 48 and week 96 was +130 cells/mm³ and +179, respectively (Figure 3). Mean change of HIV RNA from baseline to week 48 and week 96 was at -2.4 log₁₀ copies/mL and -2.3 log₁₀ copies/mL, respectively. The TRIO investigators stated that the RAL, ETV and DRV/r combination was highly effective and safe over ≥ 2 years of continuous treatment. None of the study participants interrupted treatment after week 48. Virologic failure was rare and occurred at low level viremia. They noted that whether background therapy with NRTIs could be safely discontinued in these patients is not known.

Figure 3. Mean Change in HIV RNA and CD4 Cell Count from Baseline



NRTIs and Salvage Therapy with Raltegravir

While NRTIs are often used in salvage therapy even if genotypic resistance tests (GRTs) indicate high-level resistance, the clinical benefit of additional NRTIs is not clear. Therefore, it is important to investigate the clinical benefit of these NRTIs because, if there is no benefit, patients might be over-treated with potentially toxic drugs; but if there is a clinical benefit and patients do not receive NRTIs, rapid selection of RAL resistance might occur.

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A study was designed to explore the role of additional NRTIs in salvage therapy with RAL [Scherrer A, et al. *Abst. 550*]. The study investigated the effect of <2 compared with 2 NRTIs on viral suppression at week 24 in salvage patients from the Swiss HIV Cohort Study (SHCS) who received RAL. Inclusion criteria were a GRT prior to RAL start and a HIV RNA level of >500 copies/mL. Intent-to-treat and per-protocol analyses were performed. Because patients with a better resistance profile and more remaining drug options tended to receive fewer NRTIs, the researchers performed a weighted analysis (marginal structural model). Weights were defined as the inverse of the probability for receiving <2 NRTI. This method created a pseudo-population, in which the probability for receiving <2 or 2 NRTIs was unrelated to baseline factors prognostic for treatment response. To analyze the outcome, a weighted logistic regression was performed adjusted for age, sex, risk group, ethnicity, cumulative genotypic sensitivity score (GSS) of the regimen, number of drug classes, baseline RNA, and CD4 cell count.

130 patients were included in the study, of whom 58.5% (n=76) received <2 NRTIs. NRTIs were often replaced by other drug classes; percentages with ≤1, 2, 3 additional classes were 68.5%, 27.8%, 3.7% (2 NRTI) and 34.2%, 55.3%, 10.5% (<2 NRTI, *P*-exact <0.001). The activity of non-NRTI treatment components were lower in the 2 NRTI group (median GSS: 2 [1.5 to 2.5]) compared to the <2 NRTI group (2.5 [2 to 3], *P*-Wilcoxon <0.001). The median contribution of each NRTI to the overall GSS was 0.5 in both groups (*P*=0.134). The administration of <2 NRTI was associated with a worse viral suppression rate. The investigators stated that these findings suggested that even partially active or inactive NRTIs contribute to treatment response, and thus NRTIs with partial activity may play an important role in salvage therapy.

Treatment Issues

Causes of Death in HIV

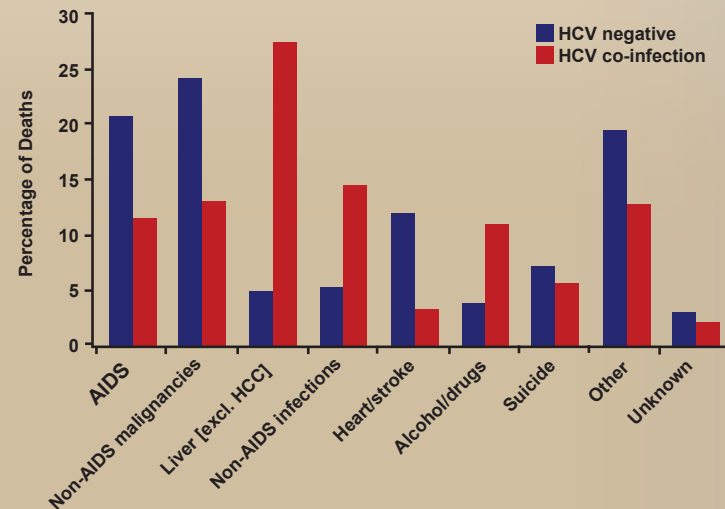
As the treatment of people with HIV infection has changed, so has the cause of death. It is important to characterize these changes, because information on causes of death can influence priorities in medical care and preventive measures. Given the importance of this information, researchers sought to describe characteristics of participants in the SHCS who died between 2005 and 2009, and determine their cause of death [Ruppik M, et al. *Abst. 789*].

The researchers found that a total of 459 of 9,053 SHCS participants died between 2005 and 2009. The underlying causes of death were: non-AIDS-defining malignancies (n=87, 19.0%), including hepatocellular carcinoma, n=13 (2.8%); AIDS (n=74, 16.1%);

liver diseases (excluding hepatocellular carcinoma) (n=68, 14.8%); non-AIDS-defining infections (n=42, 9.2%); heart disease and stroke (n=35, 7.6%); alcohol and substance use (n=33, 7.2%); suicide (n=29, 6.3%); other (n=77, 16.7%); and unknown (n=14, 3.1%). Causes of death are shown in Figure 4, stratified in patients with (n=202) and without (n=244) HCV co-infection. Median age at death increased from 45 years (IQR 41 to 52) in 2005 to 49 (44 to 56) in 2009; median CD4 counts increased from 257 (118 to 429) cells/mm³ in 2005 to 321 (157 to 519) cells/mm³ in 2009.

An important finding of the study was that malignancies were the most frequent underlying cause of death (total of non-AIDS + AIDS-malignancies = 25.5%), whereas AIDS-related deaths decreased to 16%. The researchers noted that HCV co-infection substantially influenced the distribution of causes of death.

Figure 4. Cause of Death in HIV+ Patients: HCV Negative and HCV Co-infection in SHCS



Abacavir and MIs

The issue of a possible association of ABC therapy with increased risk of myocardial infarction (MI) has been raised by several observational studies and one randomized controlled trial (RCT). However, other RCTs and the safety database maintained by the manufacturer of ABC do not support this association. To provide more information on this issue, the FDA conducted a trial-level meta-analysis of RCTs in which ABC was randomized as part of

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a combined ARV regimen to determine the effect of ABC on the risk of MI [Ding X, et al. **Abst. 808**].

For this meta-analysis, a literature search was conducted for all clinical trials that included a randomized ABC treatment arm. The FDA reviewed the results to identify RCTs that met the following criteria: conducted in adults; sample size >50 subjects; status completed; not a pharmacokinetic trial and not conducted in Africa. The Mantel-Haenzel method, with risk difference and 95% confidence interval, was used for the primary analysis based on trial-level summaries; unit of analysis was the subject and the stratification factor was the trial. For trials with more than 2 arms, ABC vs. non-ABC arms were compared. Data from 26 RCTs conducted from 1996 to 2010 were used in the analysis: 16 trials from the drug manufacturer database, 5 from the AIDS Clinical Trials Group, and 5 from academic centers. A total of 9,832 subjects were included in the study (5,028 ABC, 4,804 non-ABC) and 47 (0.47%) MI events were reported (25 [0.5%] ABC, 22 [0.46%] non-ABC).

Based on their analysis, the researchers reported that no significant difference was detected between the 2 groups in terms of developing an MI. A stratified odds ratio sensitivity analysis using 18 trials (8 trials with no MI in either treatment group were excluded) similarly found no statistically significant association between MI and ABC. The FDA investigators concluded that their meta-analysis of RCTs did not show an association between increased risk of MI and use of ABC.

PI-Based HAART and Preterm Delivery

Another issue that has been raised by some investigators is the possible association between protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) in pregnancy and preterm deliveries (PTDs). This association has been reported in some observational studies, but not others. Researchers studied this question in a randomized trial discussed at CROI that compared ARV regimens among pregnant women [Powis K, et al. **Poster 746**].

In this study, HIV-infected, HAART-naïve pregnant women with CD4 cell counts >200 cells/mm³ were randomized between 26 and 34 weeks gestation to PI-based (lopinavir [LPV]/r + zidovudine [AZT]/3TC) or triple NRTI (ABC/AZT/3TC) HAART as part of a clinical trial to prevent mother-to-child transmission (PMTCT) of HIV infection. Inclusion criteria for the analysis required delivery of a live, singleton infant. Spontaneous preterm labor or rupture of membranes was a requisite for all deliveries taking place preterm (<37 weeks gestational age).

In the study, a total of 530 women (267 in PI and 263 in NRTI groups) received a median of 11.3 weeks of HAART before delivery. PTD rates were higher in the PI group (21.4% vs. 11.8%, $P=0.003$) (Table 1). PI-based HAART was therefore found to be a significant risk factor for PTD. Weight gain during late pregnancy, measured by mean change in maternal body mass index (BMI) in the first month after HAART initiation, was lower in the PI vs. the NRTI group (0.3 vs. 0.5 kg/m², $P<0.001$); however, change in BMI one month after HAART initiation was not significantly associated with PTD. Neither infant hospitalization nor mortality in the first six months of life differed by the maternal HAART regimen received. Based on these findings, the investigators concluded that the use of PI-based HAART for PMTCT in resource limited settings may require additional obstetrical and neonatal care to avoid adverse consequences from PTDs.

Table 1. Rates of PTD by Treatment Arm and Gestational Age at HAART Initiation

Gestational Age at HAART Initiation	Triple NRTI (n)	% Preterm	PI-based (n)	% Preterm
26 to 28 weeks	177	10.2%	180	21.7%
29 to 31 weeks	44	13.6%	63	19.1%
32 to 34 weeks	42	16.7%	24	25.0%
Total	263	11.8%	267	21.4%

Predictors of Response: Gender and Race/Ethnicity

Women and racial/ethnic minorities comprise the majority of HIV-infected persons in the United States. To better understand the impact of gender and race/ethnicity (R/E) on treatment outcomes, researchers evaluated the impact of sex and R/E on clinical outcomes in the A5202 study [Smith K, et al. **Abst. 536**].

The A5202 study randomized treatment-naïve HIV-infected individuals to ATV/ritonavir (ATV/r) or EFV, with either TDF/FTC or ABC/3TC. Associations of sex and R/E with time to virologic failure (VF), safety and tolerability events were analyzed. Analyses focused on third agent comparisons (ATV/r vs. EFV) and within each of the ABC/3TC and TDF/FTC arms. The investigators reported that of 1,857 participants, 17% were female (F), 40% white non-Hispanic (W), 33% black non-Hispanic (B), and 23% Hispanic (H). Blacks patients had lower baseline CD4 (24% vs. 13% <50 cells/mm³, $P\leq 0.001$) and viral load (63% vs. 46% <50,000 copies/mL, $P\leq 0.001$) than whites, while Hispanics were not statistically different from white patients.



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Compared to white race, black race was associated with increased VF risk, while Hispanics had VF risk similar to whites. Women who received ATV/r had an increased risk of VF with either NRTI backbone than women who received EFV. When ATV/r was compared to EFV, there was no significant difference in time to safety or tolerability events by sex. Blacks, but not Hispanics, were more likely to report <100% adherence than whites. The percentage reporting <100% adherence at week 8 in R/E groups were the following: in ABC/3TC arms, 5.6% whites, 12.4% blacks and 8.0% Hispanics; in TDF/FTC arms, 5.6% whites, 10.5% blacks and 9.2% Hispanics.

The investigators concluded from these findings that black race was associated with increased risk of VF compared with white race, possibly related to lower adherence and higher rate of third drug tolerability endpoints. Female sex was associated with increased VF on ATV/r compared to EFV, with differences in safety, tolerability and adherence not appearing to explain the difference. These results provide clinicians with insights they may be able to use to develop regimens and interventions tailored to patients at higher risk for treatment failure.

Experimental Agents

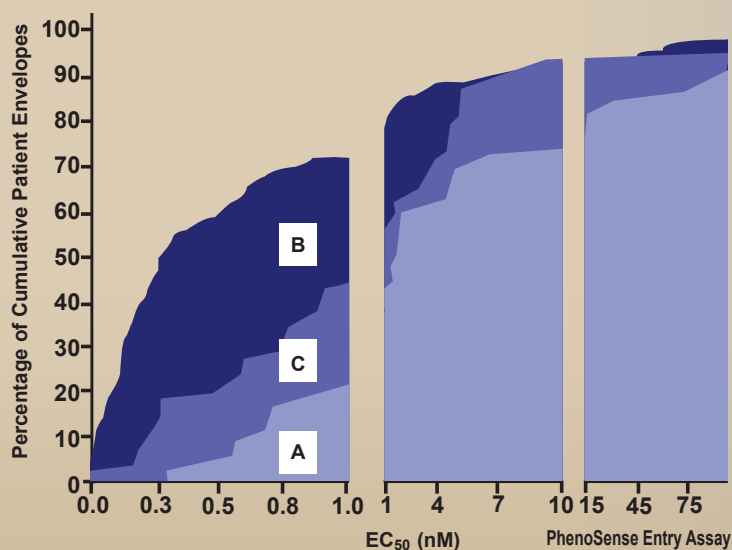
BMS-626529

CROI also included information on promising ARVs in development. One of these was BMS-626529 (529), a next-generation HIV-1 attachment inhibitor (AI). In a study reported as CROI, the activity of 529 against laboratory HIV strains was examined in T cell lines with/without 40% human serum (HS) [Nowicka-Sans B, et al. *Abst. 518*]. In this study, clinical isolates were examined in freshly prepared peripheral blood mononuclear cells (PBMCs) and the susceptibility of patient-derived envelopes was tested.

Investigators reported that 529 binds directly to gp120 and inhibits the binding of soluble CD4 to gp120, with an IC_{50} of 14 nM. The displacement of [3H]BMS-626529 from gp120 by excess soluble CD4 required about 8 hours. 529 exhibited a spectrum of activity against clinical isolates of HIV-1 within and between subtypes and is active against both R5 and X4 viruses. In a screen of 157 subtype B and 36 C viruses, 93% to 94% of viruses from both subtypes exhibited EC_{50} <10 nM, with 73% of the clade B and 42% of the clade C viruses exhibiting EC_{50} of less than 1 nM (Figure 5). Similar ranges were observed with clades A, AG, BF, F, and F1. It was also reported that in combination with 24 marketed and investigational anti-HIV agents, 529 provided synergistic or additive antiviral effects. The investigators concluded that 529 is a potent and selective member of the novel

class of AIs that is superior to the previous clinical candidate BMS-488043. The favorable antiviral profile of BMS-626529 supports further development of its oral prodrug, BMS-663068.

Figure 5. Activity Against Clinical Envelopes



Zinc Finger Nuclease-disrupted CD4 T cells

Despite adherence to effective ARV treatments, some aviremic HIV+ patients on HAART continue to exhibit low CD4 counts. Researchers have suggested that low-level cryptic viral replication in mucosal tissues may deplete progenitor cells, contributing to poor immunologic outcomes. The use of CD4 adoptive transfer therapies has demonstrated limited persistence of infused cells. However, researchers have hypothesized that gene modification of circulating CD4 cells could make them resistant to HIV. Preclinical research has shown that zinc finger nuclease mediated CCR5 disrupted (ZFN-M-R5-D) CD4 cells provide protection against R5 tropic infection, due to the fact that CCR5 is a major co-receptor of HIV entry. To learn more about this approach, a study was conducted to assess the safety, engraftment, persistence, CD4 count and homing to gut mucosa of SB-728-T (ZFN-M-R5-D CD4 cells), in aviremic HIV subjects [Lalezari J, et al. *Abst. 46*].

In this open-label, single-arm study, 6 aviremic HIV+ patients on HAART with CD4 counts of 200-500 cells/mm³ were enrolled in 2 cohorts: 1x10¹⁰ and 2x10¹⁰ total cells. Subjects were followed weekly for 1 month and then monthly for 11 months post-infusion.



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The investigators reported that infusions were generally well tolerated, with only mild adverse events. CD4 counts increased in all subjects at day 14 (range, 35 to 1,038 cells/mm³) and were sustained at all time points for 5 of the 6 subjects (mean increase of 208, 86, 233, 911, and 210 cells/mm³). R5-disrupted cells were detected in the rectal mucosa of all subjects at all assessed time points.

These findings demonstrated that ZFN-disrupted CD4 T cells can be processed at a clinical scale achieving R5 modification rates of up to 36%. Successful engraftment of SB-728-T was observed in all subjects. The levels of persistent engraftment on day 90 was 6- to 40-fold greater than previously reported. Homing of these cells to the gut mucosa was observed in all subjects tested, suggesting these cells traffic normally. In addition, increases in total CD4 counts were seen in 5 subjects at all time points. These findings suggest that ZFN-M-R5-D CD4 T cells can bolster CD4 cell counts even in HIV+ patients with undetectable viral load, which may provide an important addition to treatment options.

Treatment of HCV Infection

Boceprevir Pharmacology

There was a report at CROI on the clinical pharmacology of boceprevir (BOC), an HCV NS3 protease inhibitor [Kasserra C, et al. *Abst.* 118]. Multiple-dose studies of BOC were conducted in healthy subjects to determine the metabolic pathways used in BOC metabolism/elimination and drug interactions, using probe drugs and medications likely to be co-administered in patients who are infected with HCV.

The investigators reported that they did not observe any clinically relevant changes in BOC exposure when co-administered with peginterferon (PegINF) alfa-2b, TDF, or drosiprone (DRSP) + ethinyl estradiol (EE). There was a slight reduction in BOC AUC (0-8h) and C_{max} (19% and 8%, respectively), and a 44% decrease in BOC C_{min} when co-administered with EFV. Ketoconazole (KCZ) increased BOC exposure (131%, AUC); however, ritonavir and clarithromycin had minimal effects on steady-state BOC exposure. Ritonavir decreased BOC AUC by 19% and clarithromycin (in the presence of diflunisal) increased BOC AUC by 21%. There was no clinically relevant change in PegINF alfa-2b exposure when co-administered with BOC. BOC also had no notable effect on TDF AUC or renal clearance, but it was reported to increase TDF C_{max} by 32%. BOC slightly increased EFV AUC (0-24h) and C_{max} (20% and 11%, respectively), increased DRSP AUC (0-24h) and C_{max} (99% and 57%, respectively) and decreased EE AUC (24%), with no effect on EE C_{max}. Midazolam (MDZ) plus

steady-state BOC resulted in increased MDZ exposure: 177% C_{max} and 430% AUC_{0-24 h}.

Based on these findings, the investigators concluded that CYP3A4 and P-gp do not contribute substantially to BOC metabolism and/or elimination; they noted that increased exposure to BOC with KCZ suggests involvement of another non-CYP3A4-mediated pathway. The increase in MDZ supports the view of BOC as a strong, reversible inhibitor of CYP3A4. Radiolabeled data suggest a primarily hepatic-mediated clearance of BOC. Therefore, the researchers concluded that no BOC dosage adjustment is needed with co-administration of PegINF alfa-2b or TDF. BOC did not affect the exposure to DRSP or EE in a manner likely to reduce contraceptive efficacy. The clinical implications of a reduced BOC trough concentration when co-administered with EFV are unclear.

SPRINT-2 Results

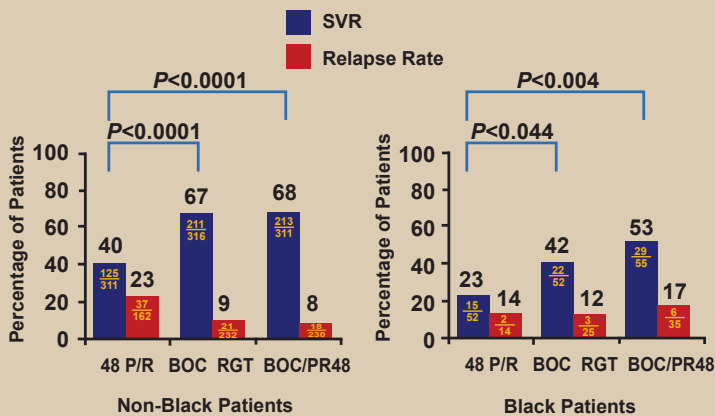
It has been reported that sustained virologic response (SVR) is <50% in HCV genotype-1 patients treated with standard therapy, especially those of African descent. SPRINT-2 assessed the safety and efficacy of pegylated interferon alfa-2b/ribavirin (P/R) ± BOC in genotype-1 patients [Sulkowski M, et al. *Abst.* 115]. This phase 3, double-blind, randomized study compared a 4-week lead-in treatment (LI) period with P/R, followed by either: (1) P/R + placebo for 44 weeks (48 P/R) or (2) response-guided therapy – BOC + P/R for 24 weeks with an additional 20 weeks of P/R if detectable HCV RNA during weeks 8 to 24 (LI + 24 BOC/P/R ± 20 P/R) or (3) BOC + P/R for 44 weeks (LI + 44 BOC/P/R). Interferon was dosed 1.5 µg/kg subcutaneously weekly; the RBV dose was weight-based (600 to 1,400 mg/day) divided twice daily, and the BOC dose was 800 mg TID. Patients with detectable HCV RNA at week 24 were discontinued for futility. The primary efficacy endpoint was SVR 24 weeks post-therapy in all patients receiving ≥1 dose of any study medication. Non-black (cohort 1) and black (cohort 2) patients were enrolled and analyzed separately per protocol.

The investigators enrolled 938 non-black and 159 black patients in the study: 92% had >400,000 IU/mL HCV RNA. SVR in cohort 1 was significantly higher ($P < 0.0001$) in both BOC arms vs. the control arm (Figure 6). SVR in cohort 2 was also significantly higher ($P = 0.04$) in both BOC arms vs. control. At the end of the LI period, ~25% of patients had <1 log decline in baseline HCV RNA. Regardless of week 4 decline, SVR was consistently higher in the BOC arms than control. Anemia was reported in 29% of controls vs. 49% in BOC arms but rarely led to treatment discontinuation.

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Figure 6. SVR and Relapse Rates (ITT)



Telaprevir and ARVs

Three trials discussed at CROI were conducted on HIV/HCV-negative, healthy volunteers to evaluate interactions between telaprevir (TVR) and ARVs [van Heeswijk R, et al. *Abst.* 119]. In 2 studies, volunteers received 2 treatments: TVR, followed by a washout and ATV/r or LPV/r, or DRV/r or fosamprenavir (FPV)/r for 20 days with co-administration of TVR from day 11 onwards, or vice versa. In a third study, volunteers started TVR for 7 days then EFV/TDF for 7 days after a washout. Next, volunteers received one of two treatments: TVR 1,125 mg every 8 hours for 7 days with EFV/TDF daily for 7 days, followed by TVR 1,500 mg every 12 hours and EFV/TDF once daily for 7 days without a washout, or the reverse: TVR 1,500 mg every 12 hours and EFV/TDF once daily for 7 days, then TVR 1,125 mg every 8 hours for 7 days with EFV/TDF daily for 7 days.

At the conclusion of the three studies, the investigators found that various interactions were observed between TVR and ritonavir-boosted PIs. TVR slightly increased blood levels of ATV/r, and ATV/r slightly decreased levels of TVR, but these interactions were not deemed clinically relevant. An interaction between EFV and TVR was reported, but a higher dose of TVR (1,125 mg q8h) largely offset this interaction, so this higher dose of TVR combined with EFV (or a standard dose of TVR 750 mg q8h with ATV/r) is now being studied in HIV/HCV-coinfected patients. Significant interactions occurred in subjects receiving TVR with LPV/r, DRV/r, and FPV/r, so TVR treatment for HCV is not currently being evaluated in people taking these ARVs.

Telaprevir in HIV/HCV Co-infected Patients

Infection with HCV remains a major cause of morbidity and mortality in HIV-infected patients. A study presented at CROI described an interim analysis of a study in which researchers investigated the safety, viral kinetics, and efficacy of treatment with TVR and PegIFN α 2a/RBV in HIV/HCV genotype 1 co-infected, interferon-naive patients. The study had two groups: the first group consisted of patients who were not receiving ARV therapy, while the second group received ARV therapy with TDF/FTC with either EFV or ATV/r [Sulkowski M, et al. *Abst.* 146LB]. Patients in each group were randomized to two groups: TVR 750 mg every 8 hours + PegIFN alfa-2a 180 μ g/week + RBV 800 mg/day for 12 weeks followed by 36 weeks of PegIFN alfa-2a + RBV (TVR/PR groups), or placebo + PegIFN alfa-2a/RBV for 48 weeks. The TVR dose was 1,125 mg every 8 hours when the ARV regimen included EFV.

An interim analysis was performed on 59 of 60 patients. Discontinuations due to AEs occurred in 2 patients (3%) in the TVR/PR groups vs. 0 in the placebo group. No significant changes in CD4 decrease or in HIV RNA level were observed in patients who received either ARV therapy regimen compared with controls. Substantially more patients receiving a TVR-based regimen achieved undetectable HCV RNA at weeks 4 and 12 (Figure 7). The safety and tolerability of TVR/PR was consistent with that previously observed in HCV mono-infected patients; no novel adverse events were detected. The investigators stated that these data are encouraging for the treatment of HCV/HIV co-infected patients, and the study is ongoing for assessment of SVR.

Figure 7. Undetectable HCV RNA at Week 12

