



Post CROI* 2008 CME/CE Update

Assessing Best Practices in HIV/AIDS Therapy

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INTENDED AUDIENCE

Physicians, Pharmacists, and Registered Nurses who are involved in the care of persons with HIV infection.

LEARNING OBJECTIVES

Upon completion of this CME/CE activity, the participant should be able to:

- Explain how recent study results in antiretroviral therapy apply to clinical practice
- Discuss significant developments and strategies in antiretroviral therapy
- Describe recent antiretroviral toxicity, drug interaction, and side effect data and strategies for management

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Assessing Best Practices in HIV/AIDS Therapy

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OFF LABEL DISCUSSION

Dr. Calvin Cohen has disclosed that he will be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation. He will discuss all HIV Antivirals/All Combinations.

Dr. Edwin DeJesus has disclosed that he will not be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation.

Dr. Richard Elion has disclosed that he will not be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation.

Dr. Ian Frank has disclosed that he will not be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation.

Dr. Graeme Moyle has disclosed that he will not be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation.

Dr. Paul Sax has disclosed that he will not be discussing unlabeled/investigational use(s) of a drug(s) or device(s) in his presentation.



Assessing Best Practices in HIV/AIDS Therapy

INTRODUCTION

The 15th Conference on Retroviruses and Opportunistic Infections (15th CROI) was held in Boston from February 3-6, 2008. This conference provided some significant new insights into HIV therapeutics, the most important of which are briefly summarized in this newsletter.

WHAT ARE THE OPTIMAL THERAPIES FOR INITIAL ANTIRETROVIRAL THERAPY?

Immediately prior to the start of the 15th CROI some significant changes were made to the recommendations for initial antiretroviral therapy contained within the Department of Health and Human Services Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (<http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>). Most notably, the zidovudine (ZDV) and lamivudine (3TC) fixed-dose combination (FDC) was demoted to an "alternative" therapy and the abacavir (ABC) and 3TC FDC was promoted to a "preferred" therapy joining the tenofovir (TDF) and emtricitabine (FTC) FDC in that category. The Guidelines specifically note that ABC is only "for patients that test negative for HLAB*5701" and that all patients started on ABC should still be warned about and monitored for an ABC hypersensitivity reaction regardless of HLAB*5701 status.

Comparison of TDF/FTC and ABC/3TC FDCs

Several presentations at the 15th CROI provided new data which clinicians may find important in deciding on the optimal nucleoside analog (NA) combination. The HEAT study is the first prospective, randomized study to compare the two non-thymidine FDCs in combination with a RTV-boosted protease inhibitor (PI). [Smith K, et al. Abst. 774] In the study, 688 patients received either blinded ABC/3TC or TDF/FTC with lopinavir/ritonavir (LPV/r) soft gel caps (SGC) for 48 weeks and were switched to LPV/r tablets for the final 48 weeks. The median CD4+ count was about 200 cells/mm³ and HIV RNA level was 4.9 log₁₀ copies/mL (log), with a little over 40% having an HIV RNA level ≥100,000 copies/mL. Outcomes at 48 weeks are shown in Table 1 below and there were no significant difference between the 2 arms.

	ABC/3TC + LPV/r	TDF/FTC + LPV/r
ITT, M=F < 50 c/mL	68%	67%
ITT, M=F < 400 c/mL	75%	71%
CD4+ Count Δ	+201	+173

While in a previous trial, patients failing FTC had significantly lower rates of resistance than 3TC [Gallant J, et al. XVI IAC (2006). Abst. TUPE0064], in this trial more individuals failing on FTC had some evidence of FTC/3TC resistance, although

this difference was mainly composed of various mixtures and not statistically significant. Also, while no primary PI mutations were found on virologic failure, some secondary mutations occurred that have been included in LPV/r resistance scores (10V/F, 16E, 36I, 71T). [Parkin N, et al. AIDS 2003;17:955-961; King M, et al. Antimicrobial Agents and Chemotherapy 2007;51(9):3067-74]

The adverse event profile of both regimens was similar except for suspected ABC hypersensitivity (HSR) rates (4% with ABC/3TC vs. 1% with TDF/FTC). Two of the key safety analyses of the trial focused on differences in lipids and renal tolerability. As shown in Table 2, there were only minor differences in median renal function and lipids at 48 weeks, with TDF/FTC showing a slight advantage regarding lipid profiles and renal function being similar between the 2 arms with the Cockcroft-Gault formula and slightly higher in the ABC arm with the MDRD equation. Notably, proximal renal tubular dysfunction (PRTD) was rare in both arms, occurring in none of the patients on ABC/3TC and in <1% of those on TDF/FTC.

	ABC/3TC	TDF/FTC
Lipids		
Total Cholesterol (mg/dL)	+32	+23
Triglycerides (mg/dL)	+64	+38
LDL (mg/dL)	+8	-1
HDL (mg/dL)	+13	+11
Renal		
MDRD (mL/min/1.73 m ²)	+7	0
Cockcroft-Gault (mL/min)	+9	+6

HEAT revealed no clinically significant differences between the two thymidine-sparing FDCs. Virologic efficacy and immunologic improvement were statistically similar, as were all adverse events except ABC HSR. The use of HLA-B*5701 testing, which was not allowed in this study, may decrease the risk of ABC HSR, but the tolerability and safety of both combinations was outstanding, and the risk of any renal problems with TDF was remarkably low. Thus, either of these 2 combinations appears to be a reasonable choice and the decision of which to use should be based on the individual patient profile, rather than a new insight from this trial. Of course, as is discussed later in this newsletter, other information on risk profiles, especially regarding the potential cardiac risk of ABC, should be considered by clinicians as well when making this decision.

Comparison of ATV/r and LPV/r

The current DHHS Guidelines list RTV-boosted atazanavir (ATV/r) as a preferred PI regimen. To this point, however, the data supporting this recommendation has been limited

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to small studies without adequate regimens for comparison. At the 15th CROI, the CASTLE study compared ATV/r and LPV/r, with both given in combination TDF/FTC FDC, in 883 treatment-naïve patients. [Molina JM, et al. Abst. 37] The baseline demographics were balanced with a median CD4+ count of approximately 200 cells/mm³, median viral load on entry of 5.0 log, with approximately 50% ≥100,000 copies/mL.

There were no significant differences in overall virologic response or CD4+ cell increase. A confirmed virologic response to <50 and <400 c/mL occurred in 78% and 86%, respectively, with ATV/r and 76% and 82%, respectively, with LPV/r and CD4+ cells rose by 203 cells/mm³ with ATV/r and 219 cells/mm³ with LPV/r. Virologic responses were also similar in the 2 arms in patients with viral loads ≥100,000 copies/mL; however as shown in Figure 1, while ATV/r had similar efficacy across baseline CD4+ count strata, LPV/r efficacy significantly declined as the baseline CD4+ count declined.

LPV/r regarding efficacy, and also demonstrate some ATV/r advantages, such as fewer GI complaints and less need for lipid lowering therapy. Multiple PI comparison trials now offer insight for the selection of ritonavir(RTV)-boosted PI regimens. The KLEAN trial found RTV-boosted fosamprenavir (FPV/r) to be similar to LPV/r in efficacy, tolerability (13% vs. 11% grade 2-4 diarrhea) and lipid profiles [Eron J, et al. Lancet 2006;368:476-82]; the ARTEMIS trial demonstrated that once-daily RTV-boosted darunavir (DRV/r) performed as well, or better than, LPV/r and had a better adverse event profile [Clumeck N, et al. 11th EACS (2007). LBPS7/5.]. Given the need for and advantages to once-daily regimens, future clinical trials may need to compare once-daily regimens of ATV/r and DRV/r to assist clinical management.

A5142: Predictors of Treatment Outcome

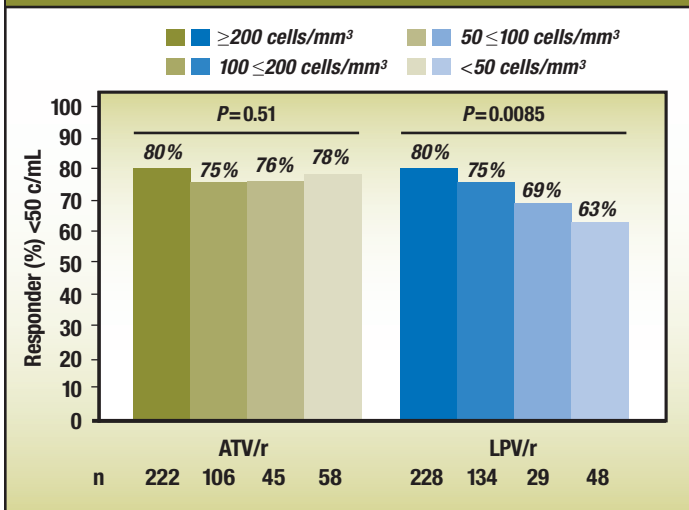
ACTG Study 5142 (A5142) was a prospective, randomized trial that enrolled 753 treatment-naïve patients and randomized them to either efavirenz (EFV) + 2 NAs, LPV/r + 2 NAs or LPV/r (533/133mg BID) + EFV. As presented initially at the 16th IAC, the primary virologic response endpoint overall favored the EFV + NAs group while the LPV/r treated patients experienced a statistically significant greater rise in CD4 cell counts, the clinical significance of which was unclear, and also had a lower risk of developing resistance if virologic failure did occur. [Riddler S, et al. 16th IAC (2006). Abst. THLB0204] Finally, the NA-sparing strategy and the TDF-treated patients had a comparably low risk of protocol-defined lipatrophy (>20% limb fat loss), while significantly higher risk occurred with EFV than LPV/r and stavudine (d4T) and ZDV than TDF. [Haubrich R, et al. 14th CROI (2007). Abst. 38]

At the 15th CROI, A5142 investigators evaluated the baseline predictors of the risk of virologic failure, treatment discontinuation (called "regimen completion"), and toxicity-related discontinuation among various study regimens. [Riddler S, et al. Abst. 776] Baseline factors evaluated in this analysis included sex, race, age, CD4 cell count, and HIV RNA. Cox proportional hazard models were used to analyze associations between these factors and outcome.

A shorter time to virologic failure was associated with younger age, female sex, lower CD4+ cell count, and black race. None of these parameters correlated with the likelihood of regimen completion.

Notably, there were differences in regimen outcomes by sex: females had a lower risk of virologic failure and a longer time to treatment-limiting toxicity on the LPV/r + EFV arm than other regimens, while males were more likely to have metabolic toxicities, especially on LPV/r. Finally, when subjects with baseline CD4 cell counts < 50 cells/mm³ were evaluated based on time for counts to exceed 200 cells/mm³, there were no differences among the three regimens.

Figure 1: CASTLE study: Responses by baseline CD4+ count



There were no reported differences in resistance between the two arms, and rates of virologic failure were similar. Both regimens were well tolerated with adverse event related discontinuations of 2% for ATV/r (<1% related to jaundice/hyperbilirubinemia) and 3% for LPV/r. There were similar rates of Grade 2-4 adverse events in both groups (26% vs 30%) with a lower incidence of treatment-related diarrhea (2% vs 11%) and less nausea (4% vs 8%) with ATV/r. There were significantly lower levels of total cholesterol, non-HDL cholesterol and triglycerides on ATV/r and this resulted in lower rates of ATV/r patients starting lipid lowering therapy (2% vs. 7%). Finally, like the HEAT study, this study also confirms the safety of TDF/FTC FDC with RTV-boosted PIs since there were only 2 discontinuations (0.2%) due to renal events.

This study provides greater confidence in the use of ATV/r. These data demonstrate at least equivalency of ATV/r and

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Results of other studies evaluating the influence of sex and race on treatment outcome have generally *not* shown an association once adjustment is made for other sociodemographic factors. While the A5142 results presented at the 15th CROI appear in conflict with those data, notably absent in this evaluation is a measure of economic status – in the United States, women and minorities with HIV are generally poorer than non-minority men with HIV, and hence have more barriers to care. The fact that the NA sparing regimen was overall best in the women in this study (but not in the men) underscores the importance of continuing to measure the impact of demographic factors on treatment outcome. One potential limitation of this finding is that only a third of the study subjects received a TDF-based NA regimen, and hence two-thirds were receiving more toxic NAs (d4T and ZDV) no longer listed as “preferred” in current treatment guidelines. Finally, it is reassuring that all three of these potent regimens were highly successful in bringing patients with severe immunosuppression above the clinically-relevant CD4 threshold of 200 cells/mm³.

WHAT ARE THE OPTIMAL THERAPIES FOR TREATMENT-EXPERIENCED PATIENTS?

Safety and Efficacy of Etravirine in Treatment-Experienced Patients

Etravirine (ETR), a recently approved non-nucleoside reverse transcriptase inhibitor (NNRTI), was evaluated in the DUET studies, a pair of randomized, placebo controlled studies that enrolled triple class experienced patients with documented NNRTI resistance and at least three PI mutations. [Madruga J, et al. *Lancet* 2007;370:29-38 and Lazzarin A, et al. *Lancet* 2007;370:38-48] These studies demonstrated that ETR was significantly better than placebo when given with a DRV-containing regimen and an optimized background therapy (OBT) of NAs and enfuvirtide (ENF) as selected by the investigator. At the 15th CROI, the durability of response, as well as the longer term side effect profile of ETR was addressed through 48 week updates of the DUET studies. [Haubrich R, et al. *Abst.* 790 and Johnson M, et al. *Abst.* 791] While presented separately, the studies had essentially similar outcomes and the pooled results will be discussed here.

Duet 1 and 2 enrolled 617 and 591 patients, respectively, of whom 90% were male and 70% Caucasian. The baseline viral load and CD4+ count were about 4.8 log and 100 cells/mm³. About 95% of enrollees were naïve to DRV and 26% used ENF for the first time on this study. Using a phenotypic sensitivity score, about 17% had no fully active antiretrovirals in the background regimen, and 38% had only one fully active antiretroviral drug.

At week 48, 61% achieved a viral load <50 c/mL (ITT-TLOVR) on ETR, in comparison to 40% on the placebo arm ($p < 0.0001$). It was noted that the percent maintaining virologic suppression

at week 24 was essentially identically to what was observed at week 48. The CD4 response paralleled the outcomes in virologic suppression, with a mean increase of 98 cells/mm³ on ETR compared to a 73 cells/mm³ increase on the placebo arm ($p = 0.0006$).

Several subsets of interest from the 48 week data were also presented. Of patients given ETR or placebo who used ENF for the first time on study, 71% and 59%, respectively, achieved an HIV RNA <50 copies/mL ($p = 0.01$), while those who either did not use ENF or recycled it had response rates of 57% and 33%, respectively ($p < 0.001$). Another analysis explored the impact of the baseline phenotypic fold change of DRV combined with the overall number of active drugs in the regimen. In patients with a DRV phenotypic fold change <10, for each additional active drug in the OBT there was an approximate 15% increase in the percent achieving virologic suppression to <50 copies/mL on ETR: from 46% for PSS = 0 to 78% for PSS ≥ 2 . Interestingly, in the patients with a DRV phenotypic fold change <40 the results were similar: 33% for PSS = 0 and 82% for PSS ≥ 2 achieving a viral load <50 copies/mL. These data support the combination of ETR with DRV across a broad range of DRV susceptibility.

There were no new safety concerns noted at week 48 – with still the ongoing observation that there is about an 8% higher rate of rash on ETR than placebo, and a 2% higher rate of nausea. There were no noted consistent lab abnormalities observed other than about a 3% higher rate of elevated total cholesterol and triglycerides; however, LDL cholesterol elevations were the same as on placebo. In both DUET studies, about 2% discontinued for rash, and no case of grade 4 rash was observed on ETR in these studies, while one case of Stevens-Johnson syndrome was seen on the placebo arm.

These data support that ETR is clearly an active NNRTI in many patients despite a history of NNRTI use and resistance to the “first generation” NNRTIs (EFV, nevirapine [NVP] and delavirdine [DLV]). Perhaps the clearest illustration of the activity of ETR is in those patients with a highly-compromised background regimen. Of those who received no other active drugs on the ETR arm, with a >40 fold change resistance to DRV at study entry, 33% achieved and maintained an HIV RNA <50 copies/mL at week 48. Of course, adding more active antiretroviral drugs will improve outcomes – 82% had virologic suppression if they received two or more active drugs in the regimen in addition to ETR – but, the fact that a third of patients can achieve and maintain an undetectable viral load at week 48 on ETR with no other active antiretroviral drugs in the regimen should increase confidence in its use.

Another presentation focused on the prevalence in the population of NNRTI mutations relevant to the activity of ETR. [Picchio G, et al. *Abst.* 866] Using the Virco database of over 226,000 samples received since January, 1999, about

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90,000 isolates were found to meet one of two definitions of having NNRTI resistance. Analyzing this cohort for the presence of mutations known to confer resistance to ETR, 40% had no ETR resistance mutations observed, 37% had only one ETR mutation, and 16% had two ETR mutations. Only 7% had three or more ETR mutations, and this cutoff has been useful to define those who had a significantly decreased response rate to this drug. Of interest, also noted was a decline in the prevalence of both the Y181C mutation and the G190A mutation over the past decade, two common mutations that are relevant to the activity of ETR. These data indicate that the vast majority of virus resistant to the "first generation" NNRTIs (EFV, NVP, DLV) should remain sensitive to ETR and that high level resistance to ETR is uncommon.

Safety and Efficacy of Darunavir in Treatment-Experienced Patients

In the past year, a randomized study known as TITAN, which compared the activity of boosted DRV/r and LPV/r in LPV/r-naïve, treatment-experienced patients, has been presented and published. [Madruga J, et al. Lancet 2007; 370:49-58] This study enrolled 595 patients, the majority of whom were PI experienced (36% 1 PI, 32% >1 PI). At week 48, there were twice as many virologic failures (VF) on LPV/r (65/297 [21.9%]) as on DRV/r (31/298 [10.4%]). Presented at the 15th CROI was an analysis of the incidence of NA and PI resistance mutations at the time of failure, as well as a phenotypic analysis of the cross resistance implications of the resistance patterns observed [DeMeyer S, et al. Abst. 874].

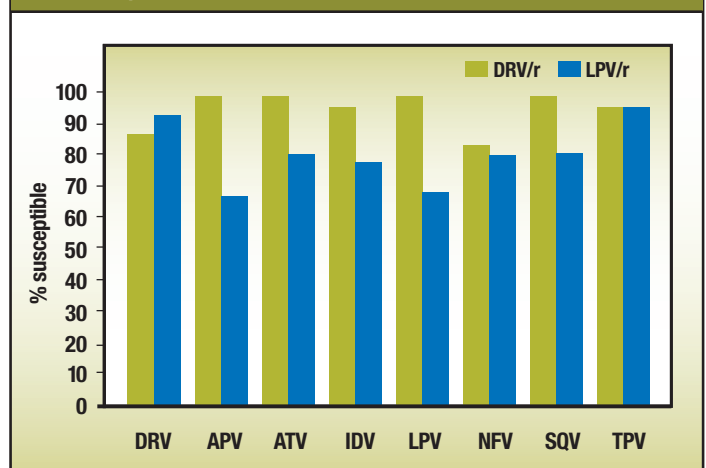
Genotypic resistance data was collected on most of those with VF (DRV/r 28/31; LPV/r 56/65). There were 6 on DRV/r and 20 on LPV/r that developed new primary PI mutations. Similar trends were observed for development of new NA mutations (4 on DRV/r vs. 15 on LPV/r). Of the 6 on DRV/r who developed new PI mutations, the new PI mutations (n) that were observed included V32I (3), I47V (2), L76V (2), I54L (1). One person on DRV/r had L90M observed at screening and at the time of failure. The pattern of new PI genotypic resistance for LPV/r was as follows: M46I (6), M46L and L76V (4), L33F (2), I47A (2), I47V (2), V82A (2), I84V (2), and V32I, I50V, I54M (1). One person on LPV/r had M46I at screening and at failure.

A phenotypic analysis was done of these genotypic resistance mutations to analyze the loss of additional drug options. It was noted that three of the VF on DRV/r lost susceptibility to DRV, while 13 on LPV/r lost susceptibility to LPV. Further, there was additional cross resistance to other PIs observed for those who were viremic on LPV/r versus what was observed with DRV/r [Figure 2]. Of note, most PIs, including LPV/r, were determined to be active in all patients after failure on the DRV/r arm, while those failing on LPV/r had some

degree of loss of susceptibility to several of the available PIs, including a small number who developed DRV resistance.

These data demonstrate that there are multiple factors to consider when selecting a PI in treatment-experienced patients. While the response rates to both PIs were high, these data indicate that there are fewer VFs observed on DRV/r, and those who have VF on DRV/r have fewer PI and NA resistance mutations than those who fail on LPV/r. Finally, as shown in Figure 2, these data clarify that unlike LPV/r, the resistance that occurs as a result of the earlier use of DRV/r rarely impacts other PIs, as nearly all patients with VF on DRV/r had complete phenotypic susceptibility to other PI options. While in both cases there were active PIs available, there were a greater number of PI options with the earlier use of DRV/r.

Figure 2: TITAN Study: Percent of isolates remaining susceptible to other PIs upon VF on DRV/r or LPV/r



PI evaluated by phenotype (Antivirogram®)

Safety and Efficacy of Raltegravir in Treatment-Experienced Patients

At the 14th CROI, the presentations of the two phase III raltegravir (RAL) studies in heavily treatment-experienced patients ushered in the integrase inhibitor class. [Cooper D and Steigbigel R, et al. 14th CROI (2007). Absts. 105aLB and 105bLB] At the 15th CROI, these investigators updated the results of these studies by providing 48 week data. [Cooper D and Steigbigel R, et al. Absts. 788 and 789]

In the BENCHMRK-1 and -2 trials, nearly 700 heavily treatment-experienced patients were randomized to receive an OBT plus either RAL (400 mg BID) or placebo. All had documented resistance to the three major drug classes (NRTI, NNRTI, and PI) at entry; remarkably more than half the study population had a genotypic sensitivity score of 0 or 1, indicating severely restricted conventional options for therapy. Background treatment was selected based on results of resistance testing and prior treatment history, and could

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include ENF as well as the newer PIs tipranavir (TPV) and, if available, DRV.

The 48 week results are shown in Table 3.

Table 3. BENCHMARK 48 week outcomes		
	<50 copies/mL (combined BENCHMARK 1 and 2)	CD4 increase (BENCHMARK 1/BENCHMARK 2)
RAL + OBT	64%	120/98
Placebo + OBT	34%	49/40

P<.001 for all comparisons between RAL and placebo

A combined analysis of the two studies demonstrated strikingly different results with RAL and placebo when the genotypic sensitivity score (GSS) or phenotypic sensitivity score (PSS) was 0, i.e., there were no predicted active drugs. An HIV RNA <50 copies/mL at week 48 was achieved in 45% and 3%, respectively, with a GSS of 0 and 51% and 2%, respectively, with a PSS of 0. Inclusion of additional active agents – most notably DRV or ENF or both – augmented responses to RAL. While ENF use was slightly, but not significantly, more effective than DRV when combined with RAL (80% vs. 69%), the criteria for assessing DRV susceptibility had not been established at the time of these studies and, in most cases, another RTV-boosted PI was included in the regimen with ENF.

Overall, there were few adverse events leading to drug discontinuation, and there was no increased risk of malignancy for RAL in these studies or when additional data from phase II studies were included. When virologic failure on RAL occurred, it often was accompanied by resistance using one of two primary residues, Q148 or N155, in combination with at least one other mutation.

Overall, these results are encouraging for clinicians and patients alike, as they suggest that initial virologic responses to RAL will be sustained especially if it is combined with other active agents. As shown in this study, DRV and/or ENF, can significantly improve outcomes when included in the OBT, and other agents, including ETR and, in patients documented to have R-5 only virus, maraviroc (MRV), are likely to have a similar effect. The low rate of drug-discontinuation due to adverse events – comparable to or lower than placebo – is also good news, as is the absence of an increased incidence of malignancies, allaying an earlier concern. As increasing numbers of patients receive treatment with this agent from the newest drug class, further long-term follow-up of these patients will be critical in assessing the long term safety and efficacy of the drug.

Safety and Efficacy of Maraviroc in Treatment-Experienced Patients

The MOTIVATE 1 and 2 studies were the main registrational studies for MCV, the first approved CCR5 inhibitor, and led

to its approval for use in the heavily treatment-experienced population. These studies evaluated triple-class experienced patients with documented R5-only virus at screening and randomized them to receive placebo, MVC QD, or MVC BID, in combination with an OBT consisting of 3–6 antiretrovirals. The 48 week results of both studies have been presented independently demonstrating virologic and immunologic efficacy and a similar safety profile compared to placebo. [Lalezari J, et al. 47th ICAAC (2007), Abst. H-718a; Fätkenheuer G, et al. 11th EACS (2007), Abst. PS3/5] At the 15th CROI, the results were presented of a planned analysis of pooled, 48 week data from the two MOTIVATE studies. [Hardy D, et al. Abst. 792]

The combined dataset has a total of 1,049 patients who each received at least one dose of MVC QD (n=414), MVC BID (n=426), or placebo (n=209). The efficacy results demonstrated that both MVC dosages were effective at week 48 with 45.5%, 43.2% and 16.7%, respectively, achieving an HIV RNA <50 copies/mL. The benefits of MVC were also demonstrated in subgroups of patients with high screening viral loads or low baseline CD4+ cell counts. In addition MVC demonstrated a similar safety profile compared to placebo. These data reaffirm the efficacy and safety of MVC in patients with R5-only virus and support its use in treatment experienced patients.

CCR5 Antagonists in Development

Vicriviroc (VCV) is another CCR5 entry inhibitor with a mechanism of action similar to MVC, but with a pharmacokinetic profile that allows for a true once-daily administration when RTV-boosted. It is the investigational CCR5 inhibitor most advanced in clinical development, currently in phase 3, but is not yet available under expanded access.

Data from a new clinical trial using VCV in heavily treatment-experienced patients, Victor-E1, were presented at the 15th CROI. [Zingman B, et al. Abst. 39LB] In this phase 2, double-blind, placebo controlled trial, 2 dosages of VCV (20 mg and 30 mg once-daily) were compared to placebo in 116 R5-only, triple class experienced patients. All patients also took an OBT that included 2 active drugs in 43% and DRV/r in 23% of subjects. The efficacy of VCV appears comparable to MVC, with 56%, 53% and 14% of patients on VCV 30mg + OBT, VCV 20mg + OBT and Placebo + OBT, respectively, achieving an HIV RNA <50 copies/mL at week 48, and, as with other antiretroviral agents, that efficacy declining significantly as the number of active drugs in the OBT declines. There were also no clinically significant differences in the safety profile between VCV and placebo groups, so these data supported the selection of 30 mg once daily for Phase 3 studies. These data are also in harmony with the results previously seen from ACTG 5211, which also demonstrated the efficacy of VCV in a treatment-experienced population. [Gulick R, et al. 4th IAS (2007), Abst. TuAb102]

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Other investigational CCR5 entry inhibitors are in development including INCB 9471, presented at last year's IAS meeting, showing a half life over 60 hours and HIV-1 reductions of 1.81 logs over 14 days of monotherapy [Cohen C, et al. 4th IAS (2007), Abst. TUAB106]; and two other agents introduced at this conference. The first was a Pfizer compound (PF-232798) self proclaimed as a second generation oral CCR5 antagonist [Dorr P, et al. Abst. 737] and the other was another Schering compound (SCH532706) that needs boosting with RTV (just as VCV does) but produced viral load reductions of 1.662 logs after 2 weeks of monotherapy. [Pett S, et al. Abst. 38]

Thus far, the availability of MVC has only impacted marginally the treatment for heavily treatment experienced patients, however it is quite reassuring to know that the CCR5 inhibitors as a class remain viable, and that there are other agents in development that can potentially change treatment paradigms as we know them today.

IMPORTANT ANTIRETROVIRAL ADVERSE EVENT DATA

Cardiovascular Risk with Abacavir and Didanosine

The interest in lipids in studies relates to the importance of lipids to future cardiovascular (CV) risk. Concern regarding CV, or more specifically, myocardial infarction (MI) risk has focused mainly on the role of PIs based on data from the on-going D:A:D cohort study. Despite the known association of thymidine analogues (ZDV and d4T) with dyslipidemia and insulin resistance, the question of whether they may also be associated with an increased risk of MI has not been previously examined.

D:A:D is a collaboration of 11 prospective cohorts, which includes data on 33,347 patients. Thus far, during over 157,912 person-years of follow-up, there have been 517 MIs reported. Poisson regression analysis was used to assess the effect of cumulative, recent (current or within last 6 months) and past (>6 months ago) use of thymidine analogues, ABC, didanosine

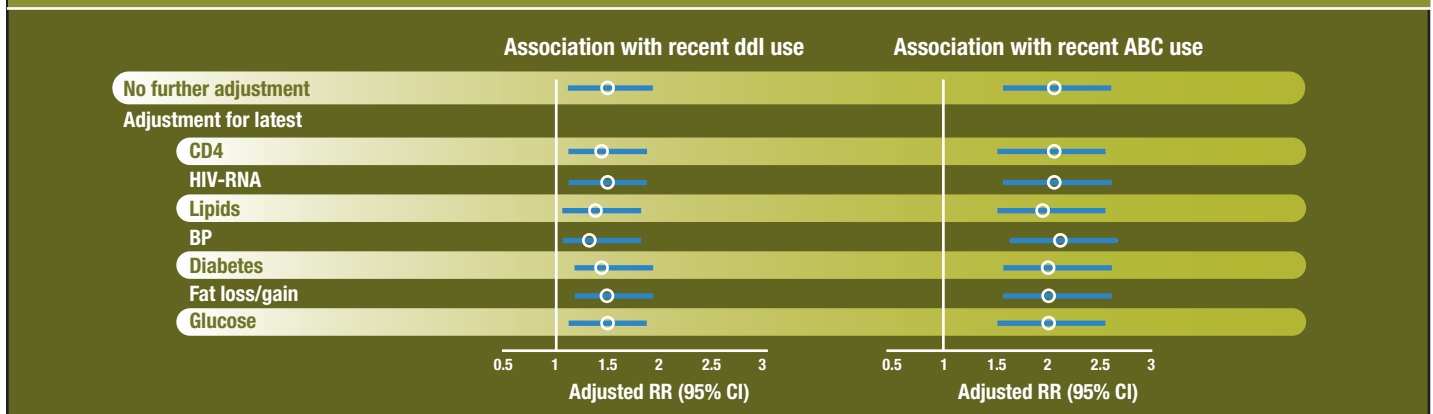
(ddl), and 3TC on the risk for MI or stroke after adjustment for demographic, known CV risk factors, cohort, calendar year, body mass index (BMI) and use of other antiretrovirals. Of note, TDF and FTC use were not assessed in the analyses. [Sabin C, et al. Abst. 957c]

Not surprisingly, 98% of MIs occurred among patients exposed to at least 1 NA. Neither cumulative nor recent use of the d4T, ZDV or 3TC was associated with risk of MI. An unexpected finding was that cumulative use of either ABC or ddl was associated with an increased risk of MI (relative risk [RR]/year of use: ABC=1.14 [95% CI, 1.08 to 1.21, $p<0.01$]; ddl=1.06 [1.01 to 1.12, $p=0.03$]. This risk of cumulative exposure to these drugs is similar to that described for PIs in previous publications.

Further models suggested recent but not past use of ABC and ddl was associated with elevated risk of MI (ABC RR=1.90 (1.47 -2.45, $p<0.01$); ddl RR=1.49 (1.14 to 1.95, $p<0.01$). [Figure 3] Risk of MI appeared to decline after drug discontinuation, suggesting the effect was independent of established CV risk factors. In those patients with low, moderate and high predicted Framingham CV risk, the absolute rates of MI (per 1000 person-years) for patients with recent ABC versus no recent ABC were 3.3 vs 1.2, 9.8 vs 7.1 and 31.3 vs 11.2, respectively, indicating a similar increase in risk with ABC in all strata. The risks of MI associated with recent ABC and ddl use remained after adjustment for age, current HIV-RNA levels, CD4 count, diabetes and lipids. [Figure 3]

This represents a potentially important safety signal with ABC and ddl that warrants further investigation. The data arise from a single cohort study and have not been reported by other groups and the authors specifically warn of potential biases that may explain the observations. Of specific note, no biologic mechanism by which ABC may be associated with MI, but not stroke, has been proposed. The hypothesis generating has just begun.

Figure 3: D:A:D Study: Adjusted MI Risk with Recent ddl and ABC Use



All data also adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by cART use and cumulative exposure to other ARVs.



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