



ICAAC/IDSA* 2008 CME/CE Newsletter 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

ACCREDITATION AND DESIGNATION STATEMENTS



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Co-supported by an independent educational grant from Gilead Sciences Medical Affairs



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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 antivirals including those in Phase II/III, in ARV- naïve and experienced patients.

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 acknowledge any off label discussion in his presentation should it occur.

Dr. Ian Frank has disclosed that he will acknowledge any off label discussion in his presentation should it occur.

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 combined 48th Interscience Conference on Antimicrobial Agents and Chemotherapy and 46th Infectious Disease Society of America Meeting was held in Washington, DC from October 24-28, 2008. This conference provided some significant new insights into HIV therapeutics, the most important of which are briefly summarized in this newsletter.

REDEFINING THE OPTIMAL TIME TO START ARV THERAPY

While the current IAS and DHHS guidelines recommend starting therapy for HIV infection at CD4 counts of ≤ 350 cells/mm³, recent data have emerged indicating that there may be significant benefit to starting earlier. The NA-ACCORD group, comprised of 22 cohorts of HIV+ patients in the US and Canada, presented an observational study that assessed the risk of death associated with not starting anti-retroviral (ARV) therapy when the CD4 count is between 351-500 cells/mm³. The study evaluated all HIV+ individuals in these cohorts with a CD4 count of 351-500 cells/mm³ while in active follow-up from 1996-2006. These individuals were divided into 2 groups: Those that began ARV therapy within 1.5 years of their CD4 count being between 351-500 cells/mm³ (n=2,473) and with those that deferred therapy, and either began later or did not initiate ARV therapy (n=5,901). [Kitahata M, et al. Abst. H-896b] Patients were excluded if they had ever taken ARVs or had prior AIDS-related illnesses. All patients were initially included in the analysis, but were censored if they had not initiated ARV therapy within 1.5 years after reaching their target CD4 count. A mixture of ARV regimens were used, but significant proportions of both groups used either an unboosted PI (46% and 37%) or triple NRTI regimen (7% and 8%).

In comparison with starting HAART when the CD4 count is between 351-500 cells/mm³, deferral of HAART was associated with a significant increase in risk of mortality, and this was not affected by adjusting for IDU or hepatitis C virus infection. (Table 1)

Table 1: Multivariate Analysis of Risk of Death

	Relative Hazard (RH)*	95% Confidence Interval	P-value
Deferral of HAART at 351 - 500 cells/mm ³	1.7	1.4, 2.1	<0.001
Female Sex	1.1	0.9, 1.5	0.290
Older Age (per 10 years)	1.6	1.5, 1.8	<0.001
Baseline CD4 count (per 100 cells/mm ³)	0.9	0.7, 1.0	0.083

*Stratified by Cohort and Year

The 70% increased risk noted with deferring therapy until the CD4 count is ≤ 350 cells/mm³ is important and may influence clinical practice globally. Due to the limitations of observational studies, questions remain regarding what threshold of proof will be necessary to change clinical guidelines, and a large, randomized trial is being performed to assess this issue, but the strength of these data, in combination with other data that have demonstrated benefits to starting ARV therapy prior to the CD4+ count declining to ≤ 350 cells/mm³, may start to change clinical practice even before the results of that study are reported.

SUPERIORITY OF DARUNAVIR/r TO LOPINAVIR/r IN TREATMENT-NAÏVE PATIENTS

The ARTEMIS study compared once-daily (QD) ritonavir-boosted darunavir (DRV/r) to lopinavir/ritonavir (LPV/r) in treatment-naïve patients. Study subjects also received co-formulated tenofovir/emtricitabine (TDF/FTC) as the NRTI component of treatment. Forty-eight week results of this study were published this year [AIDS. 2008; 22(12): 1389-97], demonstrating that DRV/r was non-inferior to LPV/r, and leading to the recent FDA approval of DRV/r at a dose of 800/100 mg QD dose for treatment-naïve patients. Additional findings in that study were a lower incidence of diarrhea and lower triglyceride levels with DRV/r compared to LPV/r.

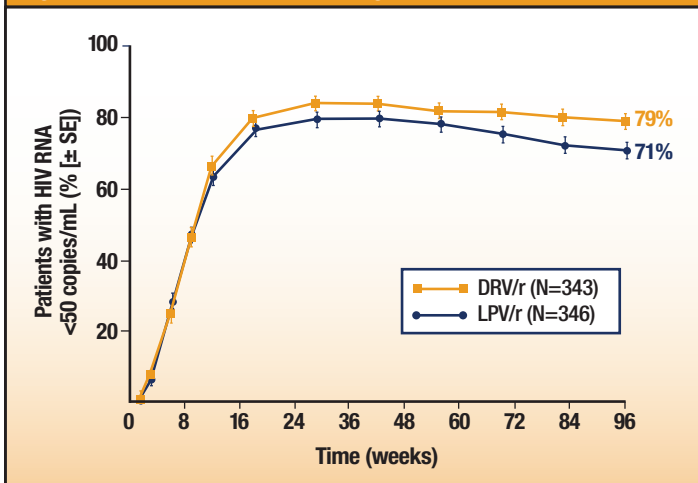
The 96 week follow-up data from this study were presented. [Mills A, et al. Abst. H-1250c] Six hundred eighty-nine treatment-naïve patients were enrolled, and randomized to receive either open-label DRV/r or LPV/r. The LPV/r could be taken QD or twice-daily (BID) depending on the approval for QD dosing at the study site; overall, 75% of LPV/r-treated subjects took it BID. Most patients started the study receiving LPV/r in capsule formulation, but by the end of the study, 86% had switched to the current tablet formulation.

At baseline, study subjects were well matched, with 30% of the study population being female, and more than half non-Caucasian. The median CD4 count was around 220 cells/mm³, and 35% had an HIV RNA >100,000 c/mL. By week 96, 17% of the DRV/r group and 23% of the LPV/r had discontinued the study for a variety of reasons; this included 4% and 9% for adverse events in the DRV/r and LPV/r arms, respectively. At week 96, 79% of the DRV/r vs 71% of the LPV/r treated subjects had an HIV RNA < 50 c/mL. (Figure 1)



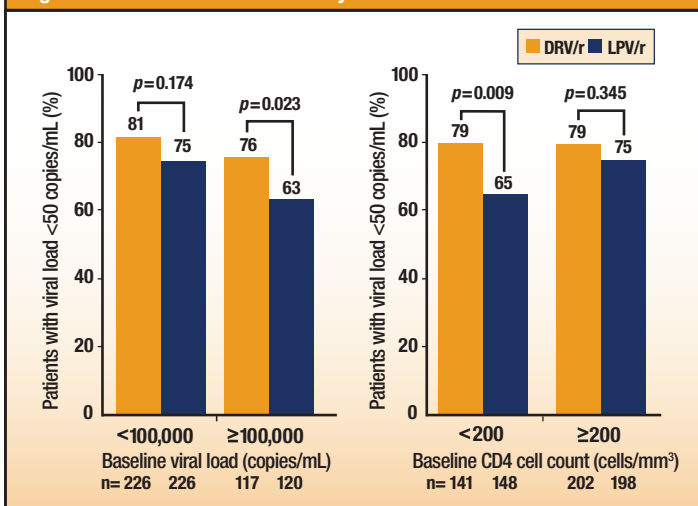
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Figure 1: ARTEMIS: Percent Achieving HIV RNA <50 c/mL at 96 weeks



Although the study was powered to demonstrate non-inferiority and did so with a difference in response of 8.4% ($p < 0.001$), these 96 week results meet criteria for DRV/r superiority as well, with a difference in response of 8.3% ($p = 0.012$). This DRV/r advantage was seen regardless of the criteria used for assessing response and the population assessed, including when the DRV/r was compared only to those LPV/r-treated patients who were taking the drug BID. Virologic failure was also less frequent in the DRV/r than the LPV/r arm (12% vs. 7%, $p = 0.0437$) and no patients in either arm developed PI mutations on failure. When analyses were conducted using the baseline stratification of $<$ or $\geq 100,000$ c/ml or $<$ or ≥ 200 cells/mm³, DRV/r suppression rates were significantly higher in the high viral load and low CD4 count patients. (Figure 2)

Figure 2: ARTEMIS: Outcomes by HIV RNA and CD4 Strata



CD4 responses did not significantly differ between arms (DRV/r +171 and LPV/r +188 cells/mm³), and the adverse event profiles between the two drugs were similar to that seen in the 48 week results—namely, significantly less diarrhea (4% vs. 11%, $p < 0.001$) and grade 2-4 increases in total cholesterol (18% vs. 28%, $p = 0.0016$) and triglycerides (4% vs. 13%, $p < 0.0001$) with DRV/r than LPV/r.

Overall, these results confirm that DRV/r + TDF/FTC is a highly effective and well-tolerated regimen for treatment-naïve patients, and validate the inclusion of the DRV/r as a recommended option in the latest version of the IAS-USA treatment guidelines [*JAMA*. 2008; 300(5): 555-70]. While LPV/r has the advantage of co-formulation and lower cost, DRV/r has a lower incidence of adverse effects and a higher virologic suppression rate at 96 weeks. The recent approval of the 400 mg DRV tablet—for a total daily dose of 4 pills daily when combined with 100 mg of RTV and TDF/FTC—offers a welcome new option for initial therapy.

COMPARISON OF RALTEGRAVIR AND EFAVIRENZ IN TREATMENT-NAÏVE PATIENTS

Standard initial therapy for HIV has consisted of two NRTIs plus either a PI or an NNRTI for many years. Results of this study, comparing the NNRTI efavirenz (EFV) to the integrase inhibitor raltegravir (RAL) may challenge that approach.

STARTMRK was a phase III, multicenter, double-blind, randomized clinical trial, into which 563 treatment-naïve patients, without evidence of baseline resistance on genotyping, were enrolled. Study subjects were randomized to receive either RAL (400 mg) BID or EFV QD; corresponding EFV and RAL placebos were also administered, and were given in a double-blind fashion. All study subjects also received fixed-dose, co-formulated TDF/FTC, so the total daily pill burden was 4 pills a day for all participants. The primary study endpoint was the proportion < 50 c/mL at 48 weeks.

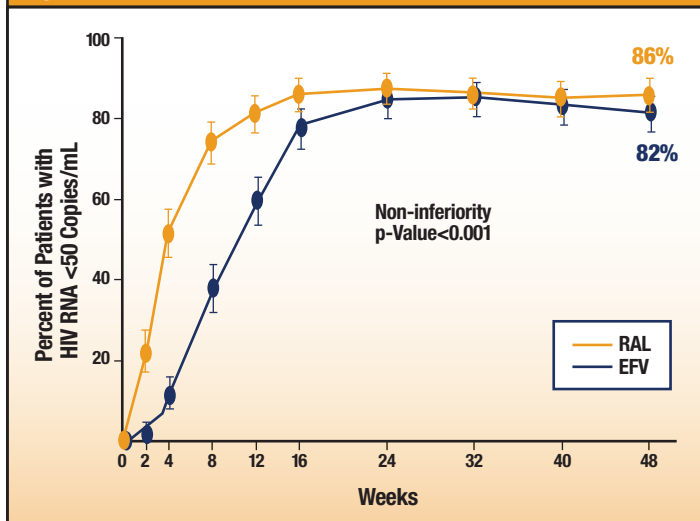
At baseline, study subjects overall were well matched. Approximately 80% were male, and more than half non-white. The mean HIV RNA was a little over 100,000 c/mL, and the CD4 count around 200 cells/mm³. At study entry, 53% had an HIV RNA $\geq 100,000$ c/ml, and 47% had a CD4 count < 200 cells/mm³. Subject disposition demonstrated low rates of study discontinuation, with 8.5% and 12.4% in the RAL and EFV arms, respectively, stopping the study, a non-significant difference.

At week 48, 86% of the RAL treated subjects and 82% of those receiving EFV had an HIV RNA < 50 copies; this difference demonstrated non-inferiority of RAL (95% -1.9, 10.3, $p < 0.001$). (Figure 3)



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Figure 3: STARTMRK: Percent with HIV RNA <50 c/mL at 48 weeks



As noted in the phase II study comparing RAL with EFV, the RAL-treated subjects had a faster decline in HIV RNA, with a quicker time to virologic response as defined by the protocol (log rank $p < 0.001$). There was also a greater CD4 response in the RAL arm, with an increase of 189 cells/mm³ for RAL and 163 cells/mm³ for EFV (95% CI: 4,47).

There were 12 virologic failures in the RAL-treated subjects, of which 9 underwent successful genotyping. Five of 9 had no resistance; of the 4 with resistance, all had genotypic resistance to RAL, with 3 also having M184V, the signature mutation to FTC. In the EFV arm, there were 8 virologic failures; out of the 6 patients with successful genotypes, 3 had EFV-resistance, and 1 also had M184V.

Using a broad definition of clinical adverse events, the study found that 90% of RAL vs 96% of EFV-treated subjects had such an event ($p = 0.002$). More importantly, there was a difference in adverse events attributable to the study drugs (44% for RAL, 77% for EFV, $p < 0.001$). By week 8, CNS toxicity was more common in EFV than RAL subjects (17.7% vs 10.3%, $p = 0.015$), and at the end of the study, changes from baseline total cholesterol, LDL cholesterol, and triglycerides all were lower in RAL vs. EFV recipients (each $p < 0.001$). The increase in HDL cholesterol, however, was greater in the EFV group ($p < 0.001$).

These results clearly show that RAL + TDF/FTC is comparably active to EFV + TDF/FTC in treatment-naïve patients, and therefore has major importance for clinical practice, as TDF/FTC/EFV (co-formulated as a single pill) is the most commonly-used initial therapy presently. One potential limitation to this study arose from the inevitable increase in pill burden to both study arms through the use of placebo—with the EFV arm increasing from potentially 1 pill daily to 4 pills taken on a BID basis—but this limitation is small

compared with the benefits of doing a double-blind study to assess tolerability in an unbiased fashion. Before there is widespread adoption of RAL for treatment-naïve subjects, some clinicians may wish to see longer term safety and tolerability data; nonetheless, these excellent results and the ongoing successful use of RAL in treatment-experienced patients clearly support the use of this agent earlier in HIV treatment strategies.

REANALYSIS OF MERIT STUDY USING TROFILE ES

The MERIT study was presented over a year ago. [Saag M, et al. 4th IAS, Abst. WESS104] This randomized trial compared the use of either EFV or maraviroc (MVC) with two NRTIs—primarily zidovudine (ZDV) and lamivudine (3TC)—in treatment-naïve patients. The HIV RNA <50 c/mL results for the BID MVC arm at week 48 were notable for a similar response to the EFV arm (65.3% vs. 69.3%, respectively); however, since the lower bound of the 95% confidence interval was slightly more than -10%, and the pre-specified limit to define non-inferiority was -10%, this study could not conclude that MVC was “non-inferior” to EFV. As a result, the use of MVC has been targeted to treatment-experienced patients.

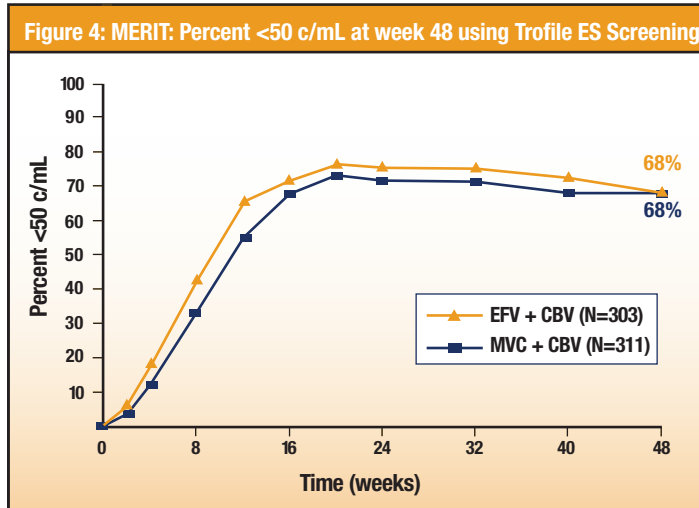
It is critical to note, however, that while the MERIT study intended to enroll a population of patients who had only CCR5-tropic virus, the original version of the Trofile assay—the tropism test performed by Monogram Laboratories—that was used in this study lacked the sensitivity to detect low levels of dual/mixed (D/M)-tropic virus populations, and this led to the enrollment of some patients who harbored D/M-tropic virus at baseline. Recently, an improved version of this assay, the Enhanced Sensitivity Trofile assay (“Trofile ES”), with a 30-fold improvement in sensitivity to detect D/M-tropic virus, was introduced and the original version is no longer commercially available. Since the use of the Trofile ES is likely to lead to the detection of more patients with D/M-tropic virus present, the use of this assay for screening might better select a population of subjects who would respond to MVC.

In order to understand the implications of using the Trofile ES in a treatment-naïve population, stored samples from the screening period of MERIT were repeated using the Trofile ES, allowing a comparison of what might have been observed if the MERIT population were enrolled today and the more sensitive assay was used for patient screening. [Saag M, et al. Abst. H-1232a] All screening samples were rerun by Monogram Laboratories who was blinded to any clinical outcomes of the patients on the study. Based upon the Trofile ES results, 15% of patients (102/667) in MERIT were reclassified as having D/M-tropic virus instead of the original screening classification of only CCR5-tropic virus. As a result, the percent achieving virologic suppression at week 48 using an intent-to-treat analysis was now the same in



Assessing Best Practices in HIV/AIDS Therapy

both arms, with 68% in both arms achieving an HIV RNA <50 c/mL. (Figure 4) Based on this analysis, MVC BID would be considered noninferior to EFV as the confidence interval no longer crosses -10%.



Reassuringly these overall results are supported by the outcomes when stratifying the patient population by baseline viral load—as MVC and EFV performed similarly in both lower and higher viral load populations.

While these data are a retrospective look at a population rather than a formal prospective study using the Trofile ES assay, this reanalysis was done in a blinded manner to samples that were used in screening, and it appears to be a reasonable answer to what would be expected if the trial were repeated. It is not yet clear whether this new data is sufficient to lead to renewed interest in the use of MVC in initial therapy, especially in the context of other new data about initial therapy presented.

UPDATE ON FOSAMPRENAVIR/RITONAVIR 1400/100 QD

Boosted fosamprenavir at a dose of 1400/100mg QD (FPV/r100) was approved by the FDA for use in treatment-naïve patients based mainly on pharmacokinetic data, but questions remained regarding the long term efficacy, resistance consequences, metabolic advantages and overall benefit of this dose over the standard FPV/r 1400/200 dose (FPV/r200). Several presentations at this conference provided some answers with data collected on two randomized clinical trials: COL100758 and LESS.

COL100758

COL100758 is an open-label study conducted in treatment-naïve patients to evaluate the efficacy, safety, and tolerability

of FPV/r100 versus FPV/r200, when used in combination with ABC/3TC. The 48-week results were previously presented. [Hicks, C. et al., 11th EACS Abst. P5.7/01] A 96-week update was provided regarding the efficacy, resistance, safety and metabolic data from this study. [DeJesus E, et al., Abst. H-1246].

At Week 96, 78% and 66% of FPV/r100 versus 53% and 53% of FPV/r200 subjects achieved viral loads of <400 and <50 c/mL, respectively, by ITT, M=F analysis, and the CD4 gains in both arms were nearly identical. Since this is a pilot study, not powered statistically, *p*-values were provided only for descriptive purpose, and therefore, are not included here. Protocol-defined virologic failure occurred in 9% of FPV/r100 arm and 14% of FPV/r200 arm. None of these subjects selected for any major PI resistance mutation, and only 2 developed a significant new resistance mutation in RT (M184V or M184M/V mixtures). [Ross L, et al, Abst. H-360] The incidence of any treatment-related grade 2–4 adverse event was not significantly different between the two groups.

An interesting observation was the lack of significant improvement in lipid parameters with the use of FPV/r100. When these data were paired with measurements for adherence it was discovered that a lower adherence to ritonavir was observed in the FPV/r200 arm. Thus, it was postulated that this may have affected virologic responses in the FPV/r200, and could possibly have contributed to the lack of a difference between the arms with regard to changes in lipid parameters and incidence of AEs. The study also looked at changes in regional fat and bone mineral density (BMD) by total body DEXA obtained in 71 patients pre-treatment and at weeks 48, 72 and 96. [Wohl D, et al. Abst. H-2302] The median percent change in fat mass in all regions studied was not significantly different between the study groups. Comparing the FPVr100 and FPV/r200 arms, a >20% loss of fat was observed in upper limbs in 18% vs. 13% and in lower limbs in 15% vs. 6%; a >20% gain in trunk fat occurred in 38% vs. 45% of patients. No patient had simultaneous limb fat loss >20% and trunk fat gain >20%. BMD changes were small in both study arms.

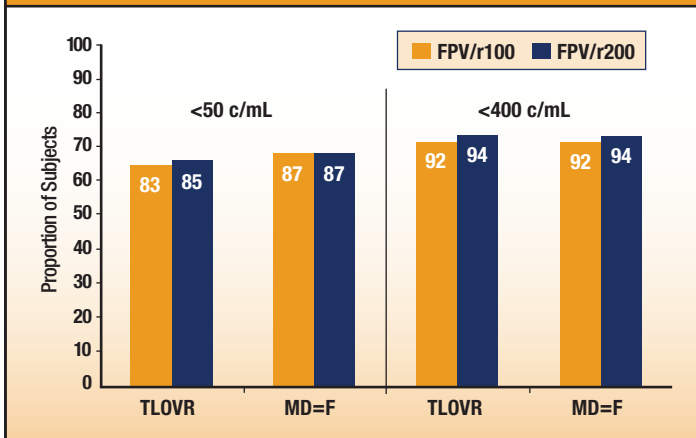
LESS

This phase IIIb, open-label study enrolled 210 virologically suppressed patients on a full dose of FPV/r 1400/200 (taken QD or divided BID) and randomized them to continue their current dose or switch to FPV/r100. [Cohen C, et al. Abst. H-1250e] The results at week 24 are depicted in Figure 5 and demonstrate continued suppression after the switch to FPV/r100.

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Figure 5: LESS: Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL and <400 c/mL by Week 24, ITT-E Population

The proportion of subjects who were not failures at Week 24 was similar regardless of their baseline regimen (FPV/r200 QD or BID) or previous treatment (no previous PI use, unboosted PI, or boosted PI). Only one subject (FPV/r200 arm) experienced protocol defined virologic failure during the 24 week study period, and no major PI mutations emerged. Overall, both regimens were generally well tolerated and no subject experienced a treatment-related SAE. Lipid changes were similar between the treatment groups.

The data presented in these studies, which demonstrated that FPV/r100 has comparable virologic, immunologic and safety outcomes when compared to FPV/r200, are reassuring about the long term safety and durability of FPV/r100.

ANTIRETROVIRAL OUTCOMES IN CLINICAL PRACTICE

It is often said that patients receiving ARV therapy through clinical trials have better treatment outcomes than patients followed in routine clinical practice because of selection bias that excludes patients from trial participation who have characteristics or behaviors perceived to be associated with poorer adherence. Several cohort studies were presented that evaluated antiviral response rates in clinical practice, with direct or indirect comparisons to clinical trials.

Treatment-naïve Patients

A retrospective analysis assessed response to ARV therapy in 452 patients starting HAART from 1996 to 2005; 305 were followed through clinical practice and 147 participated in clinical trials. [Forrester, J, et al. Abst. H-1257] The proportions of subjects with durable virologic suppression were similar in the clinical practice and clinical trials groups, 45% vs. 50%, respectively ($p=NS$). However, there were more opportunistic infections and greater rates of hospitalization and death in the clinical practice group. The authors conclude that there were no differences in long-term virologic suppression between patients treated in their clinical practice or

enrolled in clinical trials, but patients in clinical practice had greater severity of illness; and, by excluding subjects with more comorbidities or illness from participation in clinical trials, critical data may be lost that is necessary to inform outcomes regarding the entire spectrum of patients in care.

Treatment-experienced Patients

For treatment experienced patients better virologic outcomes have come on the heels of the availability of ARVs in new classes, as well as a next generation NNRTI (etravirine [ETR]) and 2 next generation PIs (DRV/r and tipranavir/r). The performance of RAL, DRV/r, or ETR in clinical practice was reported in two studies. Beginning in July 2006, a prospective analysis assessed factors associated with achieving an HIV RNA <50 c/mL in 87 triple-class experienced patients starting a new ARV regimen who did not participate in a clinical trial. [Mugavero M, et al. Abst. H-1262] Overall, 52% achieved an HIV RNA <50 c/mL after 24 weeks of therapy; however, 66% of subjects that received either DRV/r or RAL, and 70% (19/27) that received both DRV/r and RAL, achieved that level of virologic suppression. In a multivariate analysis, a low baseline viral load and receipt of DRV/r and RAL were the factors most likely to predict complete virologic suppression. A second study evaluated virologic response rates in patients who were given RAL and ETR through expanded access programs prior to FDA approval. [Kerrigan H, et al. Abst. H-1263] 53 subjects were evaluated, with a median baseline HIV RNA of 4.36 log₁₀ c/mL and CD4 count of 171 cells/mm³, and a mean of 5 PI mutations. The new ARV combination included DRV/r in 83% of subjects, LPV/r in 4%, ATV/r in 2% and, no PI in 11%. At Week 24, 50/53 subjects (94%) had a HIV RNA <75 c/mL and 96% were <400 c/mL. Outcomes did not differ by number of ETR-associated mutations, though few subjects had 3 or more mutations that predicted lower response rates in the DUET studies. These two studies confirm other reports that the new ARV agents perform as well in the clinic as they do in clinical trials.

Overall Improvement in Success Rates

The chronologic trend in virologic suppression rates among patients on HAART from 2001 through 2006 was analyzed using two databases, the HIV Research Network, a database of 19 clinical sites across the U.S., and the Massachusetts cohort, a database including patients from 21 publicly funded clinics. [Hirschhorn L, et al. Abst. H-1261] Both cohorts included patients entering care and those already in care. In the HIV Research Network, the proportions of subjects with persistent virologic suppression and those with their last HIV RNA <400 c/mL increased from 34% and 53%, respectively, of 11,595 patients in 2001 to 51% and 67%, respectively, of 9,816 patients in 2006. While in the Massachusetts cohort the proportions of subjects with persistent virologic suppression and those with their last



Assessing Best Practices in HIV/AIDS Therapy

HIV RNA <400 copies/mL increased from 49% and 63%, respectively, of 809 patients in 2001 to 68% and 82%, respectively, of 857 patients in 2006. Importantly, from 2003 there were no differences in virologic suppression rates by racial group, reversing the lower rates of virologic suppression among racial minorities compared to Whites seen in 2001 and 2002. These data document the temporal improvement in HIV treatment outcomes with recent improvements in ARV therapy, and parallel improved virologic suppression rates in clinical trials.

SWITCHING VIROLOGICALLY SUPPRESSED PATIENTS TO EFV/FTC/TDF

The co-formulation of EFV/FTC/TDF (STR) has significantly simplified the treatment of HIV infection and the long-term efficacy and safety of this regimen has been demonstrated. [Arribas JR et al. *JAIDS* 2007; 47: 74-78]. Questions still remain, however, whether treatment-naïve patients originally started on other regimens, and now virologically suppressed, benefit from a treatment simplification by switching their current regimen to the STR. Two large studies prospectively evaluated the efficacy, safety and tolerability of this therapeutic strategy.

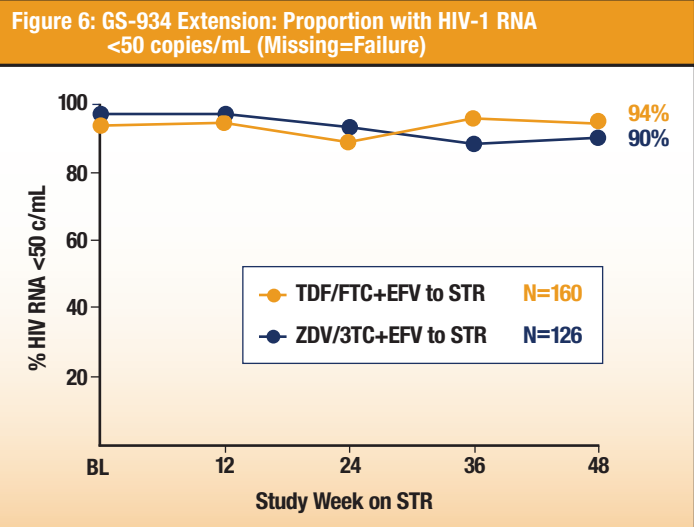
In a multicenter, open-label study, 300 patients with no history of virologic failure and an HIV RNA <200 c/mL on a stable NNRTI- or PI-based regimen were randomized to stay on their baseline regimen (SBR) or change to STR. [DeJesus E, et al. Abst. H-1234] Baseline characteristics were well balanced between both treatment groups with about half of the study participants taking an NNRTI versus a PI at baseline.

At week 48, the percentage of patients maintaining an HIV RNA <50 c/mL was similar in both treatment groups (87% STR vs. 85% SBR, *P*=NS) and only 4 patients developed virologic failure (3 STR vs. 1 SBR). The overall incidences of AE's in the STR arm, as well as the rate of AE's leading to study discontinuation, were higher in the STR versus the SBR arm. This was mainly driven by central nervous system AE's associated with the use of EFV and there were no significant differences between arms regarding median estimated glomerular filtration rate (GFR) calculated by both Cockcroft-Gault (CG) and Modified Diet in Renal Disease (MDRD). The STR group experienced mild improvement in total triglyceride levels and 85% reported that the STR was "much better" than their previous regimen.

The second study to evaluate a switch-simplification strategy was an extension of the GS-934 study. [DeJesus E, et al. Abst. H-1235] After the initial 144-week randomized phase, in which patients took EFV + TDF/FTC or EFV + ZDV/3TC, all patients with an HIV RNA <400 c/mL were offered a switch to the STR.

The proportion of patients maintaining an undetectable HIV RNA was very similar in both treatment groups. (Figure 6)

The incidence of EFV associated AE's was very low (<2%) and all AE's in general were mild, grade ≤2, and no drug-related AE resulted in study discontinuation.



Patients switched from a ZDV-containing regimen to the STR had a modest improvement in lipid parameters and a mild improvement in CD4+ count (+21 cells/mm³) and limb fat levels (0.2 Kg). There were no elevations in serum creatinine, phosphorus or further decline in the median estimated GFR after switching to STR.

Treatment guidelines are very clear about the initiation of ARV treatment and about what patients can benefit from initiation of ARV treatment with the lowest pill burden and dosing schedule. These two studies now provide important reassurance that the simple regimen of EFV/FTC/TDF can also be used as a treatment strategy to simplify and potentially improve ARV therapy in virologically suppressed patients.

TENOFOVIR METABOLIC EFFECTS IN HEALTHY VOLUNTEERS

Antiretroviral agents have been associated with changes in lipids and insulin sensitivity. Among the PIs ritonavir (RTV), indinavir (IDV) and LPV/r have been associated with insulin resistance in healthy volunteers whereas atazanavir (ATV) and atazanavir/r (ATV/r) have not. [*JAIDS* 2008; 49(Suppl 2): S86-92] As reported at this conference, differences in lipids have also been observed between PIs in clinical studies such as CASTLE and ARTEMIS, which favor regimens (ATV/r or DRV/r) involving lower doses of RTV. Insulin resistance also has been reported to develop with stavudine (d4T) and ZDV/3TC therapy and cumulative exposure to these agents may be associated with increased risk of type 2 diabetes mellitus. [*Diabetes Care* 2008; 31: 1224-9.].

While some studies have indicated that TDF has limited effect on insulin sensitivity, the 'gold standard' for

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Assessing Best Practices in HIV/AIDS Therapy

evaluation of insulin sensitivity and peripheral glucose disposal is the hyperinsulinemic euglycemic clamp. A randomized, double-blinded, placebo-controlled study that utilized a two-sequence, two-period crossover design investigated the impact of TDF on insulin sensitivity and lipids in healthy HIV-negative volunteers. [Randell P, et al. Abst. H-2307] Metabolically normal, non-obese healthy males were randomized to receive either 2 weeks of TDF 300mg QD followed by 2 weeks of placebo or placebo initially followed by TDF. Fasting lipids and a euglycemic clamp were performed at baseline, after 2 weeks and after 4 weeks (2 weeks after tablet switch). Seven received TDF followed by placebo and nine received placebo followed by TDF. No significant change in the glucose disposal rate after 2 weeks of TDF was seen. There was a significant reduction in the mean total and LDL cholesterol following 2 weeks of TDF compared to placebo. These data indicate that, unlike thymidine analogs, TDF does not affect insulin sensitivity and results in modest (9%), but statistically significant, lipid lowering effects, reducing the key atherogenic parameters of total and LDL cholesterol. This anti-lipid effect warrants further investigation.

ANTIRETROVIRAL THERAPIES IN DEVELOPMENT

Studies of a number of antiretrovirals in Phase I/II development were presented, and these data give a good picture of which drugs are moving ahead in clinical development.

Bevirimat

This is the only orally available drug in a completely new drug class that is in active investigation. Bevirimat (BVM) is a "maturation inhibitor" which interferes with one of the last steps in the assembly of a "mature" infectious virus particle. In a phase II, placebo-controlled study, the safety and efficacy of BVM in heavily treatment-experienced patients was better defined. [Lalezari J, et al. Abst. H-891] The study enrolled 88 patients with detectable HIV levels, most of whom were on a stable, but failing, ARV regimen. They were given a range of doses and preparations of BVM, including tablets and a liquid preparation, QD for 14 days. Since data indicate that mutations in the viral GAG region affect the activity of BVM, the virus population of each patient was characterized with the use of a GAG gene resistance assay. BVM was well tolerated with few adverse events that were more frequent than the placebo group. Overall, the patients who received BVM had a mean decrease in HIV RNA of 1.08 log₁₀ c/mL vs. 0.2 log₁₀ c/mL on placebo, and when the analysis is restricted to those who achieved a BVM target PK exposure, there was a 1.26 log₁₀ c/mL decline noted. Finally, it was also noted that over 60% of patients have a virus with the GAG genotypic pattern that leads to a response to BVM. This drug continues to be developed based on these results, and a phase 3 study is planned which will use a tablet formulation of BVM and GAG screening for polymorphisms associated with decreased BVM activity.

Elvucitabine

Elvucitabine (ELV) is similar in structure and profile to 3TC and FTC, but appears to be more potent so that a much lower dosage is needed to gain the full antiviral effect. Prior phase I, monotherapy studies documented an approximate 1.9 log₁₀ c/mL decline in HIV RNA at day 28 of therapy. A randomized comparison of ELV vs. 3TC in combination with TDF and EFV in 77 treatment-naïve individuals used a double-blind design for the first 12 weeks, followed by an open label period for a total of 48 weeks. [DeJesus E, et al. Abst. H-892] The mean baseline CD4 count and HIV RNA of the population enrolled was about 320 cells/mm³ and 4.8 log₁₀ copies/mL, respectively. In the first 12 weeks there was a higher number of discontinuations on the ELV arm although there were several, apparently unrelated, reasons to account for this. The additional open-label follow-up from week 12 to 48 provided more reassuring data, with only one discontinuation considered potentially related to a toxicity of ELV (severe neutropenia). In terms of efficacy, there were similar rates of suppression between ELV and 3TC noted and nearly all patients on study had an HIV RNA <50 c/mL by week 48. As expected there was either NNRTI or NRTI resistance observed in the few patients who had virologic failure. These data support that ELV may be an alternative drug to 3TC. Whether there are sufficient advantages to this drug favoring ELV instead of 3TC or FTC are not clear from these data; other studies are ongoing to assess the impact of ELV in patients who harbor the M184V mutation.

RDEA806

RDEA806 (RDEA) is an NNRTI with in vitro activity against HIV with the K103N mutation, the most common mutation after EFV failure. In a dose-ranging study, 48 HIV+ male patients, who were either treatment-naïve or off therapy after minimal prior ARV use, were randomized to 7 days of one of four doses of RDEA versus placebo. [Moyle G, et al. Abst. H-893] Day 8 log₁₀ c/mL HIV RNA changes were: placebo +0.2, 400mg BID -1.8, 600mg QD -1.5, 800mg QD -1.8 and 1000mg QD -1.8. All patients in the 400mg BID, and 800mg and 1000mg QD groups achieved at least 1 log₁₀ c/mL decline in HIV RNA. A clear PK/PD relationship was observed with all patients achieving a 20ng/ml exposure achieving a ≥1log₁₀ c/mL decline in viral load. The mean elimination T_{1/2}, consistent with volunteer studies, was 8.5-12.1hrs. Based on β-hydroxycortisol/cortisol ratios no CYP3A induction was observed. A dose-dependent change in uric acid was observed. Adverse events were seen at similar frequency and intensity in the RDEA and placebo arms and no subject discontinued due to adverse events. These data support the continued development of this drug in phase II; however, the relative merits of this drug versus other "second generation" NNRTIs is yet to be defined.





Assessing Best Practices in HIV/AIDS Therapy

HEPATITIS CO-INFECTION

Liver Fibrosis and CD4+ Percentages and Counts

CD4+ counts can be blunted in HIV patients with cirrhosis due to hypersplenism and splenic sequestration. A study evaluated the relationship between hepatic fibrosis and discordance between CD4+ counts and percentages to determine whether earlier stages of liver disease impact CD4+ cell populations. [Claassen C, et al. Abst. H-2313] The study was a cross sectional analysis, involving 392 injection drug users with chronic hepatitis C infection (HCV), comparing the relationships between discordant absolute CD4+ counts and CD4+ percentages and liver fibrosis by Fibroscan scores, a measurement of hepatic elasticity. In both HIV+ and HIV-uninfected individuals, the stiffer the liver and the more alcohol consumed, the more likely the CD4+ percentage would be higher relative to the absolute CD4+ count. ARV therapy reversed this relationship, increasing the chance that the CD4+ percentage would be lower than the absolute CD4+ count. The data suggest that when evaluating CD4 count changes in HIV patients with chronic liver disease, clinicians should consider changes in both CD4+ percentage and absolute counts.

BENEFITS OF ARV THERAPY IN CO-INFECTED PATIENTS

Decreased Hepatic Fibrosis with HBV Therapy

ARV therapy appears to influence the course of hepatitis virus infection in HIV patients, and HIV treatment guidelines now endorse consideration of ARV therapy for all patients with chronic hepatitis B (HBV) co-infection, irrespective of CD4+ count. A study evaluated progression of hepatic fibrosis in HIV/HBV patients on ARV therapy with activity against HBV (TDF + 3TC or FTC) and found improvements of liver fibrosis in 57% of 65 patients with baseline and follow-up evaluations after a mean of 24 weeks of therapy. [Teixeira T, et al. Abst. H-2315] Worsening of hepatic fibrosis was seen in 34%, and was associated with hepatitis delta virus (HDV) co-infection, higher ALT levels, and greater CD4+ count recovery, suggesting immune reconstitution inflammatory responses as a mechanism for worsening liver disease.

ARV Therapy Leads to Better Response to HBV Vaccine

HBV vaccination of HIV patients appears to be ideally performed after ARV therapy has been initiated. A multivariable analysis evaluated factors associated with development of a protective HBV vaccine response in patients who received at least one dose of HBV vaccine. [Landrum M, et al. Abst. H-2314] Among 626 patients vaccinated, 35% were responders. Patients not on ARV therapy had a significantly reduced odds of a vaccine response, irrespective of CD4+ count (0.25, 0.12-0.51 for those with CD4+ count <350

cells/mm³; 0.53, 0.30-0.91 for those with CD4+ count \geq 350 cells/mm³). In contrast, patients on ARV therapy with CD4 counts <350 cells/mm³ had the same odds of responding as did those on ARV therapy with counts >350 cells/mm³ (0.60, 0.26-1.41).

ARV Therapy Decreases Necroinflammatory Activity in HIV/HCV Patients

A cross-sectional study evaluated factors associated with necroinflammatory activity of the liver in HIV/HCV co-infected patients with a CD4+ count >350 cells/mm³ who had a single liver biopsy. [Pascual Pareja J, et al. Abst. H-2319] Lower scores of necroinflammation were associated with less alcohol consumption, lower ALT levels, and receiving ARV therapy at the time of liver biopsy (but not total time on ARV therapy). There was no association with viral load <400 copies/mL, current or nadir CD4+ count, or HCV viral load. These data add to a growing body of evidence supporting antiretroviral therapy in all HCV co-infected patients.

TREATMENT OF HCV

Failure of Induction with High Dose Ribavirin

Ultimately, treatment of HCV is the preferable method for forestalling liver disease progression, but rates of sustained virologic response to standard interferon and ribavirin (RBV) have been disappointing in co-infected patients, especially those with HCV genotypes 1 or 4. In an effort to find more effective therapies for HCV, a trial compared higher dose RBV (2 grams per day) for the first four weeks of treatment with weekly erythropoietin support versus standard dose RBV (1–1.2 grams per day) for the entire treatment period, both with standard doses of pegylated interferon. [Soriano V, et al. Abst H-2321] Unfortunately, the strategy was unsuccessful—among the 175 randomized subjects, there was no difference in rapid virologic response—perhaps because there was no statistically significant difference in trough RBV concentrations between the two treatment groups.

Metabolic Abnormalities Affect HCV Treatment Response

HIV/HCV co-infection is associated with insulin resistance and dyslipidemia. Data from a study that evaluated 96 HIVC/HCV co-infected patients demonstrated that pre-treatment metabolic abnormalities influence HCV treatment outcomes. [Nasta P, et al. Abst H-2318] The odds of achieving a rapid virologic response, an end of treatment response, or a sustained virologic response decreased significantly with higher pre-treatment triglyceride levels (>150 mg/dL) or insulin resistance. Whether these metabolic derangements are a cause of poorer treatment outcomes or a sign of functional liver disease that is a marker of poorer treatment outcomes was not determined.



Assessing Best Practices in HIV/AIDS Therapy

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