



# HIGHLIGHTS

## POST IAS\* 2007 CME NEWSLETTER



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The audience for this program will primarily consist of internal medicine physicians, infectious disease specialists, and family physicians who actively manage patients living with HIV and AIDS.

### LEARNING OBJECTIVES

At the conclusion of this program, clinicians should be better able to

- Interpret how recent study results presented at the 4th IAS apply to clinical practice and can be used to improve clinical outcomes in treatment-naïve and treatment-experienced patients
- Discuss new developments and strategies for the management of patients living with HIV/AIDS as presented at the 4th IAS
- Apply updates presented at the 4th IAS regarding toxicity, drug interaction, and safety data

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## INTRODUCTION

The 4<sup>th</sup> International AIDS Society Conference on HIV Pathogenesis, Treatment (4<sup>th</sup> IAS) was held in Sydney, Australia, from July 22-25, 2007. This conference provided some significant new insights into HIV therapeutics, the most important of which are briefly summarized in this newsletter.

## TREATMENT OF ARV-NAÏVE INDIVIDUALS

There are three classes of agents used commonly in initial antiretroviral (ARV) regimens, an NRTI backbone and either a ritonavir (RTV)-boosted PI or an NNRTI. Since there may be tolerability or toxicity problems with these options, the addition of a new target, which would be potent and well tolerated, could serve to increase the options for patients starting ARV therapy.

Two studies, MERIT and Merck 004, evaluated the use of 2 new ARVs, maraviroc (MRV) and raltegravir (RAL), in ARV-naïve individuals. In both of these studies, the comparator arm was an efavirenz (EFV) regimen. One of the drugs, RAL, proved to be quite comparable to EFV in efficacy and to have some advantages regarding tolerability and adverse events, while the other, MRV, did not perform badly regarding efficacy and was reasonably well tolerated, but some key criteria indicate that it is not as potent as EFV. These studies are summarized and discussed below.

### The MERIT Study: Maraviroc in ARV-naïve individuals

This is an ongoing Phase 2B/3, double-blind study, in which MRV 300 mg twice-daily (BID) is being compared to EFV, both in combination with a co-formulated zidovudine/lamivudine (ZDV/3TC) backbone, in 721 treatment-naïve, R5-only, HIV-1 patients. (Saag M, WESS104) A MVC 300 mg once-daily (QD) arm was previously discontinued at week 16 due to underperformance during a planned analysis.

At baseline, the arms were similar, with baseline median CD4+ counts ranging from 241 to 254 cells/mm<sup>3</sup> and a mean viral load (VL) of 4.9 log<sub>10</sub> copies/mL. The key efficacy data at week 48, using an as-treated analysis, are summarized in **Table 1**.

	MVC	EFV
HIV RNA <400 copies/mL (%)	70.6	73.1
HIV RNA <50 copies/mL (%)	65.3	69.3
Mean Change CD4+ count (cells/mm <sup>3</sup> )	170	143

Using a non-inferiority margin of -10%, MVC proved to be similar (non-inferior) to EFV in the <400 copies/mL analysis, but it underperformed EFV in the <50 copies/mL analysis. In addition, MRV also underperformed relative to EFV in individuals with baseline viral loads >100,000 copies/mL. Taken as a whole, these data suggest, but do not establish, that EFV is more potent than MRV.

Another important factor to consider is the reasons for discontinuation of either the MRV or EFV regimen. Although the percentage of subjects discontinuing from the study prior to week 48 was similar in the MVC (26.9%) and EFV (25.2%) arms, the rate of discontinuation due to virologic failure was higher with MVC (11.9% vs 4.2%), while the rate of discontinuation due to adverse events was higher with EFV (4.1% vs 13.6%). Thus, while the individuals discontinuing EFV are likely to have little resistance and preserved ARV choices, those discontinuing MRV are likely to have resistance and a loss of ARV options.

Overall, there is no question of the great value of MCV in treatment-experienced population; but given the results of this naïve trial, and the current BID dosing schedule, it is difficult to justify the use of this regimen in ARV naïve patients, at least until more information is available to clarify why these differences in response were observed.

### Merck 004: Raltegravir in ARV-naïve individuals

This study compared RAL, an integrase inhibitor, with EFV in 198 ARV-naïve patients. (Markowitz M, TUAB104) There were four doses of RAL tested, 100, 200, 400 and 600 mg BID, and these were compared to EFV, with all patients receiving TDF/FTC as the NRTI backbone. In the arms, the mean viral load ranged from 4.6 to 4.8 log<sub>10</sub> copies/mL and mean CD4+ count from 271 to 338 cells/mm<sup>3</sup>.

The results from the trial are shown in **Table 2** and demonstrate similar virologic efficacy between all RAL arms and the EFV arm, with no significant differences between the 5 arms of the study.

	Patient Number	<50 copies/mL	<400 copies/mL
<b>RAL</b>	100 mg	39	85 %
	200 mg	40	83 %
	400 mg	41	88 %
	600 mg	40	88 %
<b>EFV</b>	600 mg	38	87 %

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Similar CD4+ count improvements were also seen in all arms. The only difference noted between the arms was the rapidity of response in achieving viral suppression in the RAL arms. This was discussed in another poster (Murray JM, TUAB103), and the clinical significance is not clear.

Both compounds were well tolerated with fewer CNS side effects experienced in the RAL arms (13% vs 29%), and no serious AEs were reported in any of the groups. There was a significant difference in cholesterol elevation (−2.3 vs +20.7) favoring RAL, and the remaining lipid profile was entirely neutral for RAL.

Thus, in this study, RAL had similar efficacy and somewhat better tolerability than EFV. This is an impressive achievement, as few agents can match the efficacy or tolerability of an EFV-based regimen. The BID administration of RAL may limit its widespread use in initial therapy, but this study indicates that RAL may, with further study, become a solid alternative for initial ARV therapy.

### TREATMENT OF ARV-EXPERIENCED INDIVIDUALS

Important trials at this conference increased our knowledge of how to use drugs in the PI class and established that a second-generation NNRTI, etravirine (ETV, TMC125), is quite effective in treating ARV-experienced patients. The TITAN trial indicates that darunavir (DRV), which is commonly used in heavily treatment-experienced patients, may be a reasonable option in earlier lines of therapy. The DUET trial demonstrated the efficacy of etravirine (ETV) in heavily-experienced patients and further defined our knowledge of when and how to use this new NNRTI. Finally, additional data from 3 presentations refined our knowledge regarding the use of MRV in treatment-experienced patients and raised concerns regarding the potential for cross-resistance in the integrase inhibitor class.

#### TITAN: Darunavir + ritonavir (DRV/r) versus lopinavir/ritonavir (LPV/r) in treatment experienced patients

This phase III study compares DRV/r to LPV/r in patients with a viral load >1,000 copies/mL on a stable, failing ARV combination for at least 12 weeks. (Valdez-Madruga J, TUAB101 and *Lancet* 2007;370:49-58). The study enrolled 604 subjects who were randomized to open label LPV/r 400/100 BID — initially using the soft gel capsule, but later switches to the tablet were allowed when it became available — or DRV/r 600/100 BID, together with an optimized background, selected on the basis of a resistance test, that included at least two drugs among the NRTI and NNRTI classes. ENF and experimental drugs were not allowed.

Of the enrolled subjects, the median viral load was 4.35 log<sub>10</sub> copies/mL and CD4+ count 235 cells/mm<sup>3</sup>. Prior treatment was NRTI + NNRTI in

29% and NRTI + PI in 22%, with 46% having 3-class treatment experience. With respect to PI class experience, 32% of subjects had received no PI, 36% one, and 32% ≥ two; previous experience with LPV/r was an exclusionary criterion. The median number of primary PI mutations at baseline was 0 and the geometric mean fold-change of virus to DRV in the DRV group was 0.6 (range 0-37), with 2% having a fold-change >10 to DRV, while the fold-change of virus to LPV in the LPV group was 0.8 (range 0-74), with 10% of subjects having a fold-change >10.

Data from the 48-week primary endpoint of this 96-week study were presented, using per protocol, intent-to-treat analysis, and are summarized in **Table 3**.

**Table 3.**

	DRV/r	LPV/r	P value
<400 copies/mL (%)	77	67	<0.0001
<50 copies/mL (%)	71	60	0.005
Mean VL change (log <sub>10</sub> copies/mL)	−1.95	−1.72	0.046
CD4 increase (cells/mm <sup>3</sup> )	+88	+81	0.33

These findings demonstrate superiority of DRV/r over LPV/r in achieving a viral load <400 copies/mL and that significantly more patients in the DRV/r arm achieved a viral load <50 copies/mL. In addition, fewer patients in the DRV/r had virologic failure (10% vs 22%) and developed additional primary PI mutations (21% vs 36%) or lost active ARV drugs. Further, subgroup analyses were performed comparing outcomes by baseline CD4+ count, baseline viral load, number of sensitive drugs in the background combination, number of baseline primary PI mutations, and baseline lopinavir and darunavir fold-change. In each comparison, DRV/r was either non-inferior or superior to LPV/r. However, there is one cautionary note that must be stated in interpreting these virologic findings, and it relates to the baseline susceptibility of virus to each drug. Among the subjects with a baseline LPV/r fold-change of >10, only 28% achieved a viral load <50 copies/mL, and therefore a significant proportion of the poorer virologic outcomes in the LPV/r group may have been driven by the poor response to LPV/r in subjects with baseline phenotypic resistance.

Both PIs were well tolerated in the study, with only 7% of subjects discontinuing due to toxicity. Rash was observed more commonly in the DRV/r group (16% vs 7%), while diarrhea was more common in the LPV/r group (32% vs 42%). All other adverse events were similar between the two groups, including lipid elevations.

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These results confirm the potency and safety of DRV/r and indicate that in this population, in which 68% of patients had failed  $\geq 1$  PI, that DRV/r may lead to higher rates of viral suppression to  $<400$  and  $<50$  copies/mL, less virologic failure, and less resistance than LPV/r. While, as noted, there are some flaws in these data, these data certainly demonstrate that DRV/r may be a reasonable choice for patients with early PI failure.

**DUET Studies: ETV activity against NNRTI-resistant virus**

In a phase II study previously reported, ETV demonstrated potent activity in patients with documented NNRTI resistance with one or two NNRTI-associated mutations (Cohen C, 16<sup>th</sup> IAC [2006]. TUPE0061). At this meeting, the DUET-1 and DUET-2 studies, two large phase III studies testing ETV versus placebo in combination with DRV/r and optimized background therapy (OBT), were reported. In these trials, a total of 1203 subjects – all with documented NNRTI resistance – were randomized to receive ETV 200 mg BID or a placebo together with DRV/r and at least two investigator-selected ARVs from the NRTI class or enfuvirtide (ENF).

Notable baseline characteristics of the subjects are shown in **Table 4**. It should be noted that a majority of subjects had two or more NNRTI resistant mutations and the median fold-change of virus demonstrated clear phenotypic resistance to EFV and nevirapine (NVP).

	DUET 1		DUET 2	
	ETV	Placebo	ETV	Placebo
<b>Disease Characteristics</b>				
Viral load ( $\log_{10}$ c/mL)	4.8	4.9	4.8	4.8
% with VL $>100,000$ c/mL	39%	41%	37%	31%
CD4 count (cells/mm <sup>3</sup> )	99	109	100	108
<b>Baseline NNRTI mutations</b>				
0	9%	12%	16%	15%
1	25%	21%	19%	21%
2	28%	24%	26%	28%
3	17%	22%	19%	19%
4	21%	20%	20%	17%
<b>Median Fold Change IC50</b>				
TMC-125	1.6	1.4	1.6	1.7
Efavirenz	101.5	72.8	39.8	27.6
Nevirapine	74.3	73.8	77.3	74.3
Darunavir	5.6	6.1	6.7	7.0
<b>ENF experience</b>				
	31%	34%	49%	50%

The 24-week results of the study were reported and are summarized in **Table 5**. Overall, the addition of ETV to the optimized background therapy significantly increased the proportion of subjects achieving viral load reductions to  $<400$  and  $<50$  copies/mL. When the phenotypic resistance to DRV was 10-fold or higher, ETV increased the proportion of subjects achieving an undetectable viral load by 30% or more. In both studies, ETV significantly enhanced outcomes even when subjects had three or more NNRTI associated mutations.

	DUET 1		DUET 2	
	ETV	Placebo	ETV	Placebo
<b>% VL <math>&lt;50</math> c/mL</b>	56%	39%	62%	44%
<b>% VL <math>&lt;400</math> c/mL</b>	74%	51%	75%	54%
<b>% VL <math>&lt;50</math> c/mL by # baseline NNRTI mutations in subjects reusing or not using ENF</b>				
0	47%	42%	80%	50%
1	77%	45%	70%	44%
2	64%	38%	48%	41%
3	47%	34%	71%	28%
$\geq 4$	44%	21%	57%	15%
<b>% VL <math>&lt;50</math> c/mL by baseline DRV fold-change in subjects reusing or not using ENF</b>				
$>40$	33%	0%	43%	0%
10 – 40	56%	19%	50%	17%
$<10$	66%	47%	73%	52%
<b>Mean change in CD4+ count (cells/mm<sup>3</sup>)</b>				
	89	64	78	66

There were similar rates of AEs in the ETV and placebo groups. Rash was the most common AE with ETV (20% vs 10%); however, discontinuation due to rash occurred in only 2% of the ETV group. The incidence of central nervous system and psychiatric adverse events were similar, as were laboratory abnormalities.

The high rate of successful outcomes in this trial is due to the fact that the use of ETV led to the majority of subjects receiving two or more active agents, an essential strategy for the selection of an ARV combination for patients with resistant virus. Clearly, ETV fills an important gap in our therapeutic armamentarium – the ability to use an

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NNRTI after a patient has already failed on a previous agent within the class.

### **MOTIVATE studies: Maraviroc in treatment-experienced patients**

At the 2007 Conference on Retroviruses and Opportunistic Infections (CROI), the initial 24-week data from the MOTIVATE 1 and 2 studies were presented. In these studies, the efficacy and safety of MRV were assessed in heavily treatment-experienced patients with R5-only HIV-1. At each of the 2 MRV doses tested (150 mg QD and 150 mg BID), MRV combined with an optimized background therapy (OBT) was very active, with an average decline in viral load (VL) of approximately 1.9 log<sub>10</sub> copies/mL from baseline to week 24 in both treatment arms. (Lalezari J, 14<sup>th</sup> CROI [2007]. 104bLB; Nelson M, *Ibid.* 104aLB)

Two subanalyses of the combined pooled data from these studies were presented at this conference and demonstrated (1) that increased drug activity in the OBT improves the chance that a patient treated with MRV will achieve an undetectable VL (van der Ryst E, WEPEB115LB) and (2) that while MRV QD and BID dosing are equally safe, higher rates of virologic suppression occurred in the BID arm in patients with no active drugs in OBT, low baseline CD4+ count, or high baseline HIV-1-RNA. (Gulick RM, WEPEB116LB) Thus, it appears that in treatment-experienced patients, MRV should be combined with as many active drugs as possible and preferentially used BID.

### **Cross-resistance of the integrase inhibitors raltegravir and elvitegravir**

One of the important strengths of the integrase inhibitor (INI) class of ARVs is that it is not cross-resistant with other ARV classes. As a result, studies involving the 2 drugs in this class that are in advanced clinical trials, RAL and elvitegravir (EVG), have demonstrated that they maintain full potency in patients with significant prior ARV treatment and resistance to other classes of ARVs.

One of the potential downfalls of the INI class, however, is that resistance may develop relatively rapidly after virologic rebound and be associated with loss of activity of both EVG and RAL. A small pilot study presented proposed to evaluate the clinical responses from patients with virologic rebound on EVG/ritonavir (EVG/r) who were then treated sequentially with RAL. (DeJesus E, TUPEB032) In the study, patients with virologic failure taking EVG/r (under the guidance of the ongoing GS-USA-183-0105 study) were given the option to mono-substitute EVG/r with RAL 400mg BID for one week without any change to the background regimen. As of day 8, the background regimen was optimized in any manner based on patient history and prior resistance testing. Baseline safety data, CD4, HIV-1 RNA, PR/RT phenotype and

genotype, replication capacity and samples for INI genotyping were obtained at weeks 1, 2, and 4 and monthly thereafter until week 24.

The viral load declines after one week of RAL mono-substitution were 0.16 to 0.29 log<sub>10</sub> copies/mL in the first 2 patients enrolled. These results suggest a lack of RAL efficacy, likely mediated by cross-resistance with EVG. The initial mutation patterns that were observed in these patients did not follow the primary mutation patterns originally described in the EVG *in vitro* data (principal mutations E92Q or T66I), but they are consistent with *in vitro* data collected from the GS-US-183-0105 study, in which ~1/3 of patients with virologic rebound did not follow one of these 2 main mutation pathways. In addition, one patient developed the INI mutation N155H at virologic rebound on EVG/r, which has also been observed in patients failing RAL. Another interesting finding is that after a switch to RAL, one of the patients had persistence of the Q148R mutation, but the G140C mutation that was initially present evolved to G140A, which has been previously identified to be selected by RAL *in vitro*, suggesting an evolution toward a pattern that is more characteristic of RAL failure.

When the initial results for these 2 patients were known, the study was halted. While further research may be needed, based on these data it appears that failure of one INI will result in a significant fold reduction in response to the other INI and lead to rapid viral evolution to further decrease susceptibility to the INI being used.

## **ARV TOXICITY ISSUES**

Long-term success with ARV therapy requires maintenance of adherence and avoidance of toxicities. As newer, simpler and potentially less toxic ARVs have become available, modification of ARV regimens has become a popular and increasingly well studied means of managing and potentially preventing treatment related toxicity and adherence issues. Further, new data may allow clinicians to use HLA-B\*5701 testing to screen patients and avoid most cases of abacavir (ABC) hypersensitivity reactions.

### **Switching to Thymidine-sparing therapy**

One of the current focuses of ARV therapy switching studies is a switch away from thymidine analogues, such as ZDV, to combinations of once-daily, non-thymidine NRTIs. Previous studies such as MITOX (Martin A, *AIDS* 2004;18:1029-36) and RAVE (Moyle GJ, *AIDS* 2006;20:2043-50) had focused on using this approach to manage clinically evident lipodystrophy. Two studies of this nature, SWEET and BiCombo, were reported during the IAS meeting.

The SWEET study is a comparison of 234 subjects randomized equally to either continue co-formulated ZDV/3TC BID or switch to co-formulated

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tenofovir plus emtricitabine (TDF/FTC) QD each with continued EFV in individuals stable on the therapy for  $\geq 6$  months with a viral load  $< 50$  copies/mL. (Moyle GJ, WEPEB028) Subjects received a median of 36 months prior therapy with ZDV/3TC, with 86% having received no other prior thymidine analogues. Participants were well matched for baseline characteristics.

At 24 weeks, the switch to TDF/FTC arm maintained VL  $< 50$  copies/mL and the analyses rates of viral suppression (ITT Missing = Failure or Switch = Failure) were 89.7% vs 94.0% for ZDV/3TC arm vs TDF/FTC arm, respectively (treatment difference 4.3%, 95% confidence interval (CI) of  $-2.7\%$  to  $11.3\%$ ,  $p = 0.34$ ). The key outcome measures for the study through week 24 are shown in **table 6**. Switching to TDF/FTC was associated with significant increases in hemoglobin (Hb) and significant declines in total cholesterol and triglycerides.

$-2\%$ ,  $14\%$ ). These differences were largely attributed to a higher discontinuation rate in the ABC/3TC group due to suspected ABC hypersensitivity reactions. Viral rebound to  $\geq 200$  copies/mL was observed in four individuals in the ABC/3TC group, but none in the TDF/FTC group. Changes in CD4 cell count were  $+44$  and  $-2.7$  cells/ $\text{mm}^3$  for the ABC/3TC and TDF/FTC groups, respectively ( $p = 0.032$ ). Changes in lipids from baseline to week 48 indicate statistically significant declines in all lipid parameters, including HDL, with the switch to TDF/FTC relative to ABC/3TC. (**Table 7**) Changes are, however, modest in nature. In a sub-study of 47 individuals who underwent DEXA scanning at baseline and at week 48, there was no difference in total or limb fat or bone mineral density reported. Also, no differences were observed between changes in creatinine or estimated GFR. Thus, switching to TDF/FTC and ABC/3TC both

**Table 6.**

	Baseline		Wk 24 Change from Baseline		
	ZDV/3TC	TDF/FTC	ZDV/3TC	TDF/FTC	
Median CD4 (cells/ $\text{mm}^3$ )	393	415	21	-8	$p = 0.20$
Mean Hb (g/dL)*	14.0	14.1	0.10	0.46	$p < 0.001$
Median total cholesterol**	5.08	5.47	-0.06	-0.39	$p = 0.008$
Median LDL-c**	2.99	3.25	-0.09	-0.10	$p = 0.42$
Median HDL-c**	1.30	1.31	-0.02	-0.03	$p = 0.82$
Median Triglycerides**	1.32	1.60	0.05	-0.24	$p < 0.001$

\* LOCF = Last Observation Carried Forward  
 \*\*mmol/L

These data indicate that switching from ZDV/3TC to TDF/FTC in persons receiving EFV maintains virologic control and leads to improvements in hemoglobin and key lipid parameters. Further analysis of DEXA scan assessments of limb fat changes through week 48 and assessments of adherence and quality of life are ongoing.

The BiCombo study evaluated 333 individuals stable on therapy with a 3TC-based regimen who were randomized to switch to either TDF/FTC ( $n = 166$ ) or co-formulated ABC plus 3TC (ABC/3TC) ( $n = 167$ ) with continuation of the third agent in their regimen. (Martinez E, WESS102) The most common previous NRTI regimen was ZDV/3TC ( $n = 107$ ), and other NRTI regimens included stavudine (d4T) plus 3TC ( $n = 48$ ), TDF plus 3TC ( $n = 100$ ), ABC plus 3TC ( $n = 30$ ) and didanosine (ddI) plus 3TC ( $n = 54$ ). As a result, 34% of those in the TDF/FTC arm simply switched 3TC to FTC, and 7% of those in the ABC/3TC arm maintained the same ARV agents and simply modified the formulation.

By week 48, treatment failure occurred in 19% and 13% of ABC/3TC and TDF/FTC recipients, respectively (estimated difference 5.9%, 95% CI

**Table 7.**

Variable	ABC/3TC		TDF/FTC		P
	N	Median (IQR)	n	Median (IQR)	
$\Delta$ TG (mg/dL)	117	0 (-34 to 28)	124	-16 (-63 to 9)	0.01
$\Delta$ Cholesterol total, (mg/dL)	120	12 (-6 to 26)	126	-9 (-31 to 6)	0.001
$\Delta$ LDL (mg/dL)	104	7 (-6 to 24)	106	-4 (-25 to 8)	$< 0.001$
$\Delta$ HDL (mg/dL)	114	0 (-4 to 8)	118	-4 (-9 to 2)	$< 0.001$

appear to be effective and safe options, with some lipid advantages in the TDF/FTC arm.

### Switching PI therapy

Another focus of switching studies is to modify the choice of PI to improve dosing frequency, manage GI and lipid toxicity, and reduce RTV exposure. The SWAN study (Gatell J, *CID* 2007;44:1484-92) was the largest study to evaluate switching from a PI or PI/r to atazanavir (ATV),

and in that study, ATV without RTV was given unless TDF was present, in which case ATV/r was given. Non-inferiority to continuation of PI or PI/r therapy was observed from a virological standpoint and improvements in lipid and GI tolerability were noted. However, despite these data, concerns persist about the efficacy of ATV without RTV, with most physicians preferring to prescribe ATV/r.

The AtaZip study evaluated 265 individuals with viral loads <200 copies/mL for at least 6 months who were randomized to either continue LPV/r BID (n = 127) or switch to ATV/r QD (n = 121). (Mallolas J, WEPEB117LB) Patients were well matched for baseline characteristics with a median CD4+ cell count of approximately 450 cells/mm<sup>3</sup>, 20% having previously experienced one or more PI failures, 20% with a baseline LDL >130 mg/dL, and 80% male.

A similar number of patients in each group completed the study. Protocol defined treatment failure was observed in 17% of ATV/r and 20% of LPV/r recipients (estimated difference -2.3%, 95% CI -12, 8), meeting the predefined confidence intervals for non-inferiority of ATV/r to LPV/r. Adverse events led to discontinuation of 5% of patients in each group. Virological failure, defined as HIV RNA ≥200 copies/mL, was uncommon and occurred in 5% and 6% of ATV/r and LPV/r recipients, respectively. Changes in CD4+ cell count did not differ. While HDL remained unchanged, a favorable shift in LDL and statistically significant decreases in total cholesterol and triglycerides were observed in the switch to ATV/r relative to continuing LPV/r. (**Table 8**). This trial demonstrates that switching from LPV/r BID to ATV/r QD may be reasonable since it was safe and effective and conferred some lipid advantages.

**Table 8.**

	<b>ATV/r</b>	<b>LPV/r</b>	<b>P Value</b>
TG, mg/dL	-51 (-29%)	-3 (-1%)	<0.0001
Total Chol, mg/dL	-19 (-9%)	-4 (-2%)	<0.0001
LDL-c, mg/dL	-8 (-7%)	-2 (-3%)	0.163
HDL-c, mg/dL	-3 (-6%)	-2 (-3%)	0.375

**Using HLA-B\*5701 screening to prevent abacavir hypersensitivity reactions**

Up to this IAS meeting, the association between clinically diagnosed ABC hypersensitivity reactions (ABC HSR) and the presence of a positive HLA-B\*5701 test was in the region of 40% to 50% in whites and less in blacks, who express this allele more rarely and have less ABC HSR. (Lucas A, *J Antimicrob Chemother* 2007;59:591-3) Two studies presented at this conference indicate that this screening test may be

more accurate than previous studies have indicated and may lead to this test being the first pharmacogenetic screen used in HIV to individualize therapy.

SHAPE is a retrospective case control study that looked at 130 white and 69 black patients who had been clinically diagnosed as having had an ABC HSR. (Saag M, WEAB305) To confirm the ABC HSR diagnosis, all were tested with a skin patch test (SPT) that contained ABC. Thirty-two percent (42/130) of whites and 7% (5/69) of blacks tested positive and were considered immunologically confirmed cases of ABC HSR. One hundred percent of the immunologically confirmed cases were HLA-B\*5701 positive, while only 44% and 14% in the white and black groups, respectively, with clinically diagnosed but immunologically unconfirmed ABC HSR tested positive.

PREDICT-1 is a prospective study that enrolled almost 2,000 ABC naïve patients from 314 centers in Europe and Australia and randomized them to ABC standard of care (SOC), where any clinically suspected HSR's were retrospectively screened for HLA-B\*5701, and to a prospectively screened arm in which individuals positive for HLA-B\*5701 were not allowed to take ABC. (Mallal S, WESS101)

ABC HSR was clinically diagnosed in 7.8% and 3.4% in the SOC and screened arms, respectively. As in SHAPE, those patients with clinically diagnosed ABC HSR were given a SPT, and while 2.7% were confirmed positive in the SOC arm, none were positive in the screened arm. The negative predicted value of HLA-B\*5701 screening for immunologically confirmed HSR was 100%. There were quite a few HLA-B\*5701 positives in the SOC arm who were not SPT positive, so the positive predictive value was only 48%.

If applicable to all populations, these studies indicate that if testing for HLA-B\*5701 is widely utilized, it could virtually eliminate ABC HSR, while denying ABC to only a very few individuals who test HLA-B\*5701 positive, but would not subsequently develop ABC HSR.

**PHARMACOKINETIC STUDIES**

**ARAs lower rilpivirine levels**

In the pharmacokinetic (PK) studies presented at IAS, there was another reminder that ARAs must be used cautiously in HIV+ individuals since they may adversely affect the levels of some ARVs. It has already been well documented that ARAs, especially proton pump inhibitors, can affect ATV and indinavir (IDV) levels (Fulco PP, *Ann Pharmacother* 2006;40:1974-83), and it now appears that they may also affect levels of one of the newest NNRTIs, rilpivirine (RPV, TMC 278).

\*This coverage is not sanctioned by the conference organizers and is not an official part of the conference proceedings.

In an industry sponsored study of 24 HIV negative volunteers, a single dose of RPV (150 mg) was given alone or 2 hours after, 12 hours after or 4 hours before a single dose of famotidine (FAM, 40 mg). (Van Heeswijk R, TUPDB01) The maximum concentration ( $C_{max}$ ) and the area under the curve (AUC) of RPV given 2 hours after FAM were reduced by 85% and 76%, respectively; however, when it was given 12 hours after or 4 hours before the FAM there were no significant changes in RPV levels. The effect of FAM on RPV is similar to that seen with unboosted ATV and the effect will presumably be the same or greater with proton pump inhibitors (PPIs). TMC278 will need to be dosed separately from ARA's and as it is dosed once-daily, that should be feasible.

### Hepatic impairment does not affect DRV levels

In a study looking at RTV-boosted DRV in 32 volunteers with mild to moderate hepatic impairment, defined as Child Pugh class A and B,

respectively, DRV PK showed little change from healthy volunteer data and no dose adjustment should be necessary. There was a 50% increase in RTV AUC and a 2-fold increase in RTV minimum concentration  $C_{min}$  in subjects with moderate impairment. (Sekar VJ, TUPDB05)

### Etravirine and elvitegravir PK studies

There was no significant drug-drug interaction between Etravirine (ETV, TMC125) and RAL (Anderson MS, TUPDB02) or atorvastatin (Schöller-Gyüre M, WEPEA106), nor was there any significant interaction between Elvitegravir (ELV), an Integrase Inhibitor entering into phase 3 trials, and TPV (Mathias A, TUPDB06), DRV (Mathias A, TUPDB03) or fosamprenavir (FPV; Ramanathan S, WEPEB014).

## INSTRUCTIONS FOR RECEIVING CREDIT

To successfully complete this activity and receive CME credit, participants must

- Read the entire newsletter
- Fax the completed Post-test Answers and CME Evaluation Form to 215-504-5226 by June 30, 2008
- Score at least 70% on the post-test

Your CME certificate will be e-mailed to you within 4 weeks.

## POST-TEST

Choose the letter that best answers and/or completes the following, and mark your answers on the Evaluation Form.

1. In the MERIT study, comparing the maraviroc and efavirenz arms
  - a) Maraviroc achieved non-inferiority regarding <400 copies/mL
  - b) Maraviroc achieved non-inferiority regarding <50 copies/mL
  - c) Maraviroc arm had fewer virologic failures than the EFV arm
  - d) All of the above
2. Regarding the virologic outcomes in the Merck 004 study
  - a) The raltegravir arms were inferior to efavirenz
  - b) The raltegravir arms were superior to efavirenz
  - c) The raltegravir arms and efavirenz arm were similar
3. Based upon data presented at the 4th IAS, it appears that the 2 integrase inhibitors currently in advanced development, raltegravir and elvitegravir, have significant cross-resistance
  - a) True
  - b) False
4. In the TITAN trial, darunavir/ritonavir was more likely than lopinavir/ritonavir to
  - a) Achieve a viral load <50 copies/mL
  - b) Achieve a viral load <400 copies/mL
  - c) Reduce the risk of new PI mutations
  - d) All of the above
5. In the TITAN trial, darunavir/ritonavir was less well tolerated than lopinavir/ritonavir
  - a) True
  - b) False
6. In the DUET study, the use of etravirine significantly increased the number of patients that achieved a viral load
  - a) <400 copies/mL
  - b) <50 copies/mL
  - c) Both of the above
7. In the DUET study, the primary side effect associated with etravirine was
  - a) Nausea
  - b) Diarrhea
  - c) CNS
  - d) Rash
8. In the SWEET trial, switching from zidovudine/lamivudine to tenofovir/emtricitabine resulted in significant improvements in all of the following except:
  - a) Hemoglobin
  - b) Cholesterol
  - c) Triglycerides
  - d) HDL cholesterol
9. In the AtaZip trial, switching from lopinavir/ritonavir to atazanavir/ritonavir resulted in significantly improved levels of all of the following except:
  - a) Total cholesterol
  - b) Triglycerides
  - c) HDL cholesterol
  - d) None of the above
10. SHAPE and PREDICT-1 indicate that
  - a) All individuals positive for HLA-B\*5701 develop abacavir hypersensitivity
  - b) Some individuals positive for HLA-B\*5701 develop abacavir hypersensitivity
  - c) Some individuals negative for HLA-B\*5701 can still develop abacavir hypersensitivity
  - d) None of the above

**Post-test Answers & CME Evaluation Form**

**Fax this form to 215-504-5226 by June 30, 2008**

**Participant Information**

First Name \_\_\_\_\_  
 Last Name \_\_\_\_\_ Degree \_\_\_\_\_  
 Address \_\_\_\_\_  
 City \_\_\_\_\_ State \_\_\_\_\_ Zip \_\_\_\_\_  
 Telephone \_\_\_\_\_ Fax \_\_\_\_\_  
 E-mail (CME certificate sent by e-mail) \_\_\_\_\_  
 Rush Medical College Alumnus \_\_\_\_\_ Year of Graduation \_\_\_\_\_

Indicate the number of credits that you are requesting for this educational activity. You should only claim credit commensurate with the extent of your participation in the activity. \_\_\_\_\_ credits

Please evaluate the level of achievement of this CME activity. Match the number on the right to the questions and fill in the appropriate box according to the following scale:

- 5 = Excellent    4 = Good    3 = Fair    2 = Poor    1 = Unsatisfactory

Evaluate how well this activity addressed the stated objectives:

1. Interpret how recent study results presented at the 4th IAS apply to clinical practice and can be used to improve clinical outcomes in treatment-naïve and treatment-experienced patients
2. Discuss new developments and strategies for the management of patients living with HIV/AIDS as presented at the 4th IAS
3. Apply updates presented at the 4th IAS regarding toxicity, drug interaction, and safety data

Please use the following scale to respond to the following questions:

Agree					Disagree
5	4	3	2	1	

In thinking about implementing these objectives, rate the following:

4. My patient mix is appropriate for the strategies.
5. My office and practice systems can accommodate these changes.
6. My patients will have trouble complying with these changes/strategies.
7. These changes are too time consuming.
8. I am so comfortable with my current approach, it will be difficult to change.
9. My current office and practice systems are very difficult to change.
10. The medication's procedures discussed are not available for my patients.

In thinking about the issues raised in this educational activity, rate your degree of agreement with each statement below:

11. On average, I utilized the patient care treatment strategies described in this educational activity prior to my participation in this educational activity.
12. I plan to implement the patient care treatment strategies described.
13. This CME activity was free of commercial bias for or against any product. (If you perceived any bias please provide specific comments below.)
14. The course satisfied your reason for taking it.
15. The course was well organized and presented.
16. Please comment on the strengths/weaknesses of this activity, future topics, improvements, etc.

\_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

**Post-test Answers**

Check the best answer for each question.

1. A  B  C  D
2. A  B  C
3. A  B
4. A  B  C  D
5. A  B
6. A  B  C
7. A  B  C  D
8. A  B  C  D
9. A  B  C  D
10. A  B  C  D

**Evaluation Responses**

	Excellent	Good	Fair	Poor	Unsatisfactory
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Agree			Disagree	
4.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
5.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
6.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
7.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
8.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
9.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
10.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
11.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
12.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
13.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
14.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
15.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>
16.	5 <input type="checkbox"/>	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>