

## Perspective

# Emerging Resistance Profiles of Newly Approved Antiretroviral Drugs

*The antiretroviral treatment goal in highly treatment-experienced patients is now suppression of viral replication to undetectable levels, a goal that can be achieved by strategic use of combinations that include newer antiretroviral drugs. Newer drugs in established classes that improve virologic response when added to optimized background therapy include the protease inhibitors darunavir and tipranavir and the second-generation non-nucleoside analogue reverse transcriptase inhibitor etravirine. New drugs from new classes that have proved active in treatment-experienced patients include the chemokine coreceptor 5 (CCR5) antagonist maraviroc and the integrase strand-transfer inhibitor raltegravir. Knowledge of the resistance patterns and predictors of response with these new agents and careful selection of background therapy are crucial to maximizing virologic response and preventing emergence of resistance. This article summarizes a presentation on emerging resistance profiles of newer antiretroviral drugs made by Eric S. Daar, MD, at an International AIDS Society–USA Continuing Medical Education course in Los Angeles in March 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).*

The goal of antiretroviral therapy in treatment-experienced patients is to achieve maximal suppression of HIV replication. As stated in the 2006 International AIDS Society–USA treatment guidelines (Hammer et al, *JAMA*, 2006), “Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment-experienced patients,” recommendations that are unchanged in the 2008 guidelines (Hammer et al, *JAMA*, 2008). Similarly, the latest US Department of Health and Human Services guidelines, issued in January 2008, state “In those with prior treatment and drug resistance, the goal is to resuppress HIV-1 RNA levels maximally and prevent further selection of resistance mutations, if possible” (Panel on Antiretroviral Guidelines for Adults and Adolescents, January 29,

2008). A major reason for redefining treatment goals in antiretroviral therapy–experienced patients is the availability of newer antiretroviral drugs from established and new drug classes. Effective use of these newer drugs depends on knowledge of predictors of response to given agents and the resistance consequences of failure that have been identified during the early experience with these drugs and included in recent IAS–USA guidelines and reviews on drug resistance testing (Hammer et al, *JAMA*, 2008; Hirsch et al, *Clin Infect Dis*, 2008).

### Protease Inhibitors

The availability and activity of the protease inhibitors (PIs) darunavir and tipranavir and the entry inhibitor enfuvirtide provided the first evidence that full virologic suppression could be achieved in highly treatment-experienced patients. In the Randomized Evaluation of Strategic Intervention in Multi-drug-resistant Patients with Tipranavir (RESIST) studies, which involved approximately 1500 heavily treatment-experienced patients, the addition of ritonavir-boosted tipranavir (tipranavir/ritonavir) to optimized background reg-

imens (OBRs; based on resistance data and including investigators’ choice of a ritonavir-boosted PI) significantly increased the rate of virologic response, including the rate of achieving plasma HIV RNA levels of less than 50 copies/mL at week 48, from 10% to 23% ( $P < .0001$ ) over OBR with comparator PI alone.

Enfuvirtide was added at physician discretion. Some patients were enfuvirtide-naïve, others were currently using the drug, and still others had prior experience, including those with no response during prior use. Among patients receiving enfuvirtide, response rates were 28% versus 14% for tipranavir/ritonavir versus OBR, respectively, and 21% versus 9%, respectively, among those not receiving enfuvirtide.

An analysis of virologic response at 24 weeks according to tipranavir resistance mutation score at pretreatment (based on 21 initially identified resistance mutations) was conducted in 718 patients receiving tipranavir/ritonavir. Among 144 patients with 0 or 1 mutation (median 0.7- to 0.9-fold change in susceptibility), the median decrease in HIV RNA level was 2.10  $\log_{10}$  copies/mL, compared with 0.89  $\log_{10}$  copies/mL in 242 patients with 2 or 3 mutations (median 1.1- to 1.4-fold change), 0.45  $\log_{10}$  copies/mL in 260 patients with 4 or 5 mutations (median 2.0- to 3.1-fold change), 0.49  $\log_{10}$  copies/mL in 68 patients with 6 or 7 mutations (median 3.3- to 3.9-fold change), and 0.08  $\log_{10}$  copies/mL in 4 patients with 8 or 9 mutations (median 14.7- to 52.5-fold change) (Baxter et al, *J Virol*, 2006).

In the Performance of Darunavir (TMC114)/ritonavir When Evaluated in Treatment-experienced Patients with Protease Inhibitor Resistance (POWER) studies, which involved more than 300 treatment-experienced patients, the addition of darunavir/ritonavir (600 mg/100 mg) twice daily to OBR increased virologic response ( $< 50$  cop-

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ies/mL at week 48) from 14% to 45% ( $P < .0001$ ) over OBR with comparator PI; response rates were 58% versus 11% among patients also receiving enfuvirtide, all of whom were enfuvirtide-naïve at pretreatment, and 44% versus 10% among those not receiving enfuvirtide (Clotet et al, *Lancet*, 2007). Eleven PI resistance mutations were associated with reduced response to darunavir/ritonavir. Virologic response occurred in 64% of 67 patients with no darunavir resistance mutations at pretreatment, 50% of 94 patients with 1 mutation, 42% of 113 patients with 2 mutations, 22% of 58 patients with 3 mutations, and 10% of 41 patients with at least 4 mutations (De Meyer et al, *Antivir Ther*, 2006).

Table 1 shows the current darunavir and tipranavir resistance mutations used in genotypic scoring. There are also evolving clinical cutoff values being generated for darunavir and tipranavir by each company performing phenotypic drug resistance testing. Some of the resistance mutations for the 2 agents are nonoverlapping, indicating that activity of 1 may be retained in the presence of resistance to the other. There are currently no data directly comparing darunavir and tipranavir. Consequently, for patients in whom both drugs are predicted to be active based on genotypic or phenotypic analysis, selection should consider convenience, tolerability, and experience of the physician.

The TMC114/r in Treatment-experienced Patients Naïve to Lopinavir (TITAN) trial compared darunavir/ritonavir with lopinavir/ritonavir, each plus OBR in treatment-experienced but lopinavir-naïve patients with plasma HIV RNA levels greater than 1000 cop-

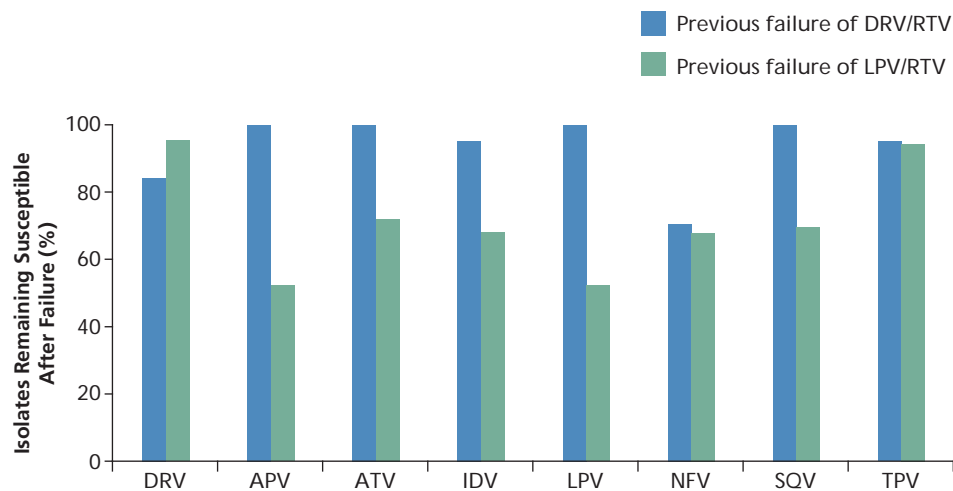


Figure 1. Percentage of patients in whom pretreatment isolates that were susceptible to protease inhibitors remained susceptible after virologic failure of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. APV indicates amprenavir; ATV, atazanavir; DRV, darunavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir. Adapted from De Meyer et al, CROI, 2008.

ies/mL who had been on a stable anti-retroviral therapy regimen for at least 12 weeks. Darunavir/ritonavir met the criterion for noninferiority to lopinavir/ritonavir in virologic response (the primary study endpoint), defined as HIV RNA level less than 400 copies/mL at week 48 on per-protocol analysis (Madruga et al, *Lancet*, 2007). Darunavir/ritonavir also met criteria for superiority for proportions of patients with reductions to less than 400 copies/mL and less than 50 copies/mL at week 48 on intent-to-treat analysis. However, the proportion of patients with pretreatment susceptibility to the study PI to which they were assigned (darunavir or lopinavir) was higher in the darunavir group, and the statistical significance of the superiority was lost when analysis excluded patients with

resistance to their assigned treatment.

An analysis of proportions of patients retaining pretreatment susceptibility to other PIs after virologic failure while receiving darunavir/ritonavir or lopinavir/ritonavir plus OBR is shown in Figure 1 (De Meyer et al, CROI, 2008). The data suggest that patients for whom darunavir/ritonavir is failing are less likely to lose susceptibility to other PIs. Although some of the difference may reflect a higher pretreatment frequency of resistance to the assigned PI for those given lopinavir/ritonavir, the findings still provide support for the notion that darunavir/ritonavir could be used earlier in treatment-experienced patients with some assurance that future use of other PIs will not be overly compromised in cases of virologic failure.

Table 1. Genotypic Scoring for Darunavir and Tipranavir

Darunavir	V11I	V32I L33F	I47V
Tipranavir	L10V	I13V K20M/R/V	L33F E35G M36I K43T M46L I47V
Darunavir	I50V	I54L/M	G73S L76V I84V L89V
Tipranavir	I54A/M/V	Q58E H69K	T74P V82L/T N83D I84V

From Baxter et al, *J Virol*, 2006, and Clotet et al, *Lancet*, 2007.

## CCR5 Antagonists

HIV variants use chemokine coreceptors CXCR4 (X4 variants) or CCR5 (R5 variants) or both (X4/R5, dual-tropic variants) for target cell entry, and individuals with HIV infection may have a mix of variants. The Efficacy and Safety of Maraviroc Plus Optimized Background Therapy in Viremic, ART-experienced patients Infected with

CCR5-tropic HIV-1 (MOTIVATE)-1 and -2 trials examined the addition to OBR of the CCR5 antagonist maraviroc, either once or twice daily (dosing depended upon other drugs in the regimen), in 1049 highly treatment-experienced patients with no detectable CXCR4-utilizing HIV variants on pretreatment assay (approximately 50%-60% of screened patients) (Hardy et al, CROI, 2008). Virologic response defined as plasma HIV RNA level less than 50 copies/mL at 48 weeks occurred in 45.5% of patients in the OBR plus twice-daily maraviroc group and 43.2% in the OBR plus once-daily maraviroc group versus 16.7% of those receiving OBR only (both  $P < .0001$ ).

In a phase IIb study, 167 screened patients with detectable CXCR4-utilizing virus (ie, with dual/mixed or X4 only) or nonphenotypable virus entered the trial. Treatment consisted of the same 3 regimens as in the MOTIVATE trials: OBR plus maraviroc once or twice daily or OBR only (Goodrich et al, IDSA, 2007). At 48 weeks, there were no statistically significant differences between the OBR plus maraviroc regimens versus OBR only with regard to change in HIV RNA level ( $-0.62$  and  $-1.11$  vs  $-0.84$   $\log_{10}$  copies/mL, respectively) or change in CD4 + count ( $+65$  and  $+78$  vs  $+51$  cells/ $\mu$ L, respectively), suggesting that maraviroc is likely of little virologic benefit in patients with detectable CXCR4-using variants.

Data from subjects screened for the MOTIVATE-1 and -2 studies ( $n = 2560$ ), the Study of the Consequences of the Protease Inhibitor Era (SCOPE) trial ( $n = 186$ ), and the AIDS Clinical Trials Group (ACTG) 5211 study ( $n = 391$ ) showed that in treatment-experienced patients, the proportion without detectable CXCR4-using variants ranged from 49% to 60%, whereas dual/mixed variants were detected in 39.5% to 47% and X4-only in 0.5% to 4% (Coakley et al, 2nd International Workshop on Targeting HIV Entry, 2006; Hunt et al, *J Infect Dis*, 2006; Wilkin et al, *Clin Infect Dis*, 2007). In contrast, the absence of detectable CXCR4-using virus is more common in patients with earlier, untreated HIV infection. In treatment-na-

ive study populations ranging in size from 299 to 1428 patients, this was seen in 81% to 88%, with dual/mixed variants in 12% to 19%, and X4-only variants in less than 1% (Brumme et al, *J Infect Dis*, 2005; Moyle et al, *J Infect Dis*, 2005; Demarest et al, ICAAC, 2004; Coakley et al, 2nd International Workshop on Targeting HIV Entry, 2006).

The original phenotypic coreceptor tropism assay that was validated in many of the studies listed above was reported to be virtually 100% sensitive for detecting variants that use CXCR4 (X4 and dual-tropic variants) when they constitute 10% or more of the viral population, with sensitivity declining for smaller minority populations.

Reflecting the issue of assay sensitivity, approximately 5% of patients without detectable CXCR4-using variants at screening for the MOTIVATE trials using the original tropism assay had evidence of dual/mixed variants at the trial entry assessment, a phenomenon that has been consistent across studies in this area. Among this subset of patients, an HIV RNA level of less than 50 copies/mL was observed at week 24 in only 27% of patients receiving OBR plus maraviroc once daily, 18% of those receiving OBR plus maraviroc twice daily, and 18% of those receiving OBR alone.

By comparison, response rates were 50% in both OBR plus maraviroc groups versus 26% in the OBR-only group in those patients without detectable CXCR4-using variants at screening and at pretreatment (van der Ryst et al, ICAAC, 2007; Lewis et al, CROI, 2008). An enhanced assay has replaced the earlier version, with data indicating that it has 100% and 81% sensitivity to detect CXCR4-using virus present at frequencies of 0.3% and 0.1%, respectively, detecting these variants in about half of the 5% of cases that were missed at the time of screening when using the earlier assay (Su et al, *Antivir Ther*, 2008; Trinh et al, *Antivir Ther*, 2008).

The selection for, or emergence of, CXCR4-using variants appears to be an important pathway to virologic failure in patients initially responding to maraviroc. At week 48 in the MOTIVATE-1 trial, approximately 50% of patients

in the maraviroc once-daily group and 63% in the twice-daily group with available data had evidence of CXCR4-using variants at the time of virologic failure (Hardy et al, CROI, 2008). Clonal analysis over time in individual patients with virologic failure indicates that this largely reflects the selection for preexisting but undetected CXCR4-using variants under CCR5 antagonist treatment. With cessation of CCR5 antagonist treatment, the CXCR4-using variants often become undetectable by the standard tropism assay (Lewis et al, *Antivir Ther*, 2007).

Although data are currently limited, a potential implication of these findings is that a response would be unlikely to a different CCR5 antagonist in those patients who experience virologic failure while receiving a CCR5 antagonist that is associated with the detection of CXCR4-using variants. True drug resistance of R5 variants—in which the virus utilizes the CCR5 receptor despite the presence of a CCR5 antagonist—also occurs and is responsible for some proportion of virologic failure (Coakley et al, *Curr Opin Infect Dis*, 2005; Westby et al, *J Virol*, 2006; Mori et al, *Antivir Ther*, 2007). Mutations in the V3 loop of HIV gp120 have been associated with maraviroc resistance, although patterns of amino acid changes differ among patients. The resistance is manifest as a plateau effect in percent inhibition of virus at increasing drug concentrations in vitro. No assays are yet clinically available to identify maraviroc resistance.

## Integrase Strand-transfer Inhibitors

In the Blocking Integrase in Treatment-experienced Patients with a Novel Compound Against HIV, Merck (BENCHMRK)-1 and -2 trials, approximately 700 treatment-experienced patients received the integrase strand-transfer inhibitor raltegravir 400 mg twice daily or placebo plus OBR. In BENCHMRK-1 ( $n = 350$ ), plasma HIV RNA level was reduced to less than 50 copies/mL in 65% of raltegravir patients versus 31% of placebo patients ( $P < .001$ ) at 48 weeks (Steigbigel et

al, *N Engl J Med*, 2008). Rates of virologic failure for raltegravir versus placebo were 15% and 51%, respectively, in BENCHMRK-1, and 15% and 48%, respectively, in BENCHMRK-2 (Steigbigel et al, *N Engl J Med*, 2008).

The primary genotypic pathways to raltegravir resistance have been identified as mutations at codons 155 and 148 and to a lesser extent at codon 143 (Cooper et al, *N Engl J Med*, 2008). These key mutations are associated with minor mutations that result in a marked increase in raltegravir 50% inhibitory concentration (Figure 2). The codon N155H and codon Q148 mutations infrequently occur together. A

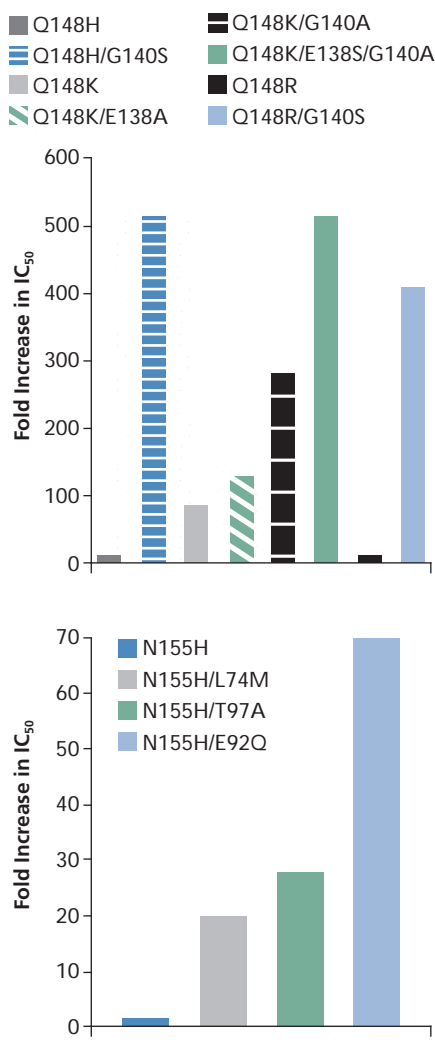


Figure 2. Fold increases in raltegravir 50% inhibitory concentration (IC<sub>50</sub>) with key Q148H/K/R (top) and N155H (bottom) mutations and associated minor mutations. Adapted from Hazuda et al, *Antivir Ther*, 2007.

high frequency of resistance is found in patients having virologic failure while using raltegravir and the investigational integrase inhibitor elvitegravir. Among 94 patients in BENCHMRK-1 and -2 with nonresponse of viral rebound that underwent genotypic testing, 64 (68%) had detectable mutations associated with raltegravir resistance. Of these, 27 (29%) had a mutation at codon 148 and 38 (40%) at codon 155 (Cooper et al, *N Engl J Med*, 2008). These findings emphasize the need to use such drugs selectively and to ensure that background therapy is truly optimized.

Failure also occurs rapidly during treatment with the investigational integrase inhibitor elvitegravir in the absence of adequate background therapy (Figure 3) (Zolopa et al, ICAAC, 2007). Further analyses of patients receiving elvitegravir/ritonavir 125 mg/100 mg in a phase IIb trial showed that E92Q, E138K, Q148H/K/R, and N155H were the most common mutations (38%), with other mutations including S147G (32%) and T66I/A/K (18%) (McColl et al, *Antivir Ther*, 2007). The mutations were associated with a mean greater-than-150-fold increase in the 50% inhibitory concentration (range, 1.2- to 301-fold increase). Also, replication of mutants was decreased by 50% compared with

that of wild-type virus. The effect of a single integrase mutation on susceptibility to raltegravir and elvitegravir and the effect of clinical mutation patterns with elvitegravir treatment on raltegravir susceptibility are shown in Table 2. The data indicate substantial cross-resistance between these drugs (McColl et al, *Antivir Ther*, 2007).

## Nonnucleoside Analogue Reverse Transcriptase Inhibitors

Etravirine was designed to retain activity against virus with the characteristic nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) K103N resistance mutation. The DUET-1 and -2 trials examined the addition of etravirine to OBR containing darunavir/ritonavir (with at least 2 nucleoside analogue reverse transcriptase inhibitors, with or without enfuvirtide) in approximately 1200 treatment-experienced patients (Lazzarin et al, *Lancet*, 2007; Madruga et al, *Lancet*, 2007). A statistically significantly higher proportion of patients receiving etravirine had HIV RNA level reduction to less than 50 copies/mL at week 48 than did the patients receiving placebo (61% vs 40%,  $P < .0001$ ).

As has been consistently shown in trials of newer drugs in highly treat-

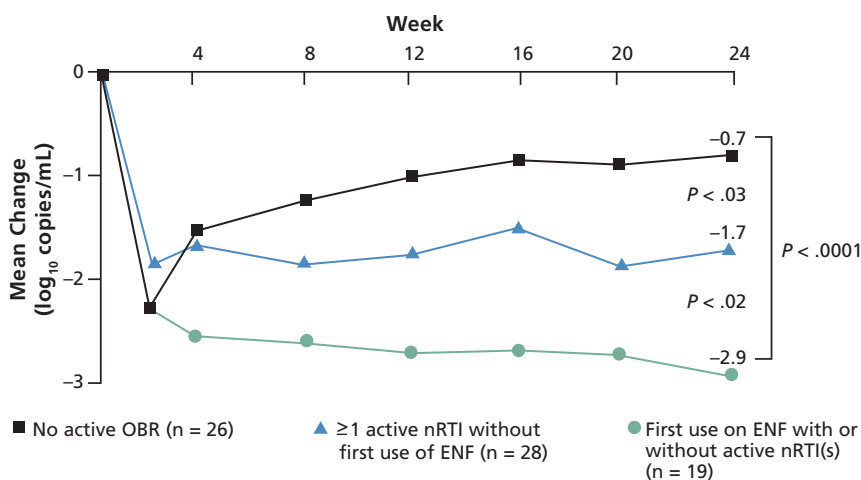


Figure 3. Mean change from pretreatment plasma HIV RNA level in patients receiving the investigational drug elvitegravir 125 mg with ritonavir 100 mg according to activity of optimized background regimen (OBR). Data from patients receiving elvitegravir/ritonavir after addition of a protease inhibitor were excluded. ENF indicates enfuvirtide; nRTI, nucleoside analogue reverse transcriptase inhibitor. Adapted from Zolopa et al, ICAAC, 2007.

**Table 2.** Cross-resistance Between Raltegravir and Elvitegravir<sup>a</sup> Based on Single Integrase Mutations and Clinical Mutation Patterns with Elvitegravir<sup>a</sup>

Fold Change in IC <sub>50</sub> of Mutant Viruses: Single Integrase Mutations									
	T66I	E92Q	E138K	G140S	S147G	Q148H	Q148H	Q148H	N155H
Raltegravir	1.4	6.0	0.9	2.0	1.0	20	34	30	23
Elvitegravir <sup>a</sup>	15	33	0.7	5.0	8.0	6.4	67	118	38

Fold Change in IC <sub>50</sub> of Mutant Viruses: Clinical Elvitegravir <sup>a</sup> Mutation Patterns					
	T66I/ S147G	T66I/ E92Q	E92Q/N155H	G140S/Q148H	E138K/S147G/ Q148R
Raltegravir	2.5	33	135	>1000	34
Elvitegravir <sup>a</sup>	46	145	166	>1000	175

<sup>a</sup>Investigational drug.Adapted From McColl et al, *Antivir Ther*, 2007.

ment-experienced patients, virologic response rates even in placebo-treated patients were increased according to the number of active drugs in the background regimen. Rates for etravirine versus placebo were 33% and 0%, respectively, in patients with no active drugs, 60% and 26%, respectively, in those with 1 active drug, and 76% and 61%, respectively, in those with at least 2 active drugs (Haubrich et al, CROI, 2008; Johnson et al, CROI, 2008). Such findings again stress the importance of ensuring that the background regimen is as active as possible to achieve and maintain suppression and prevent resistance to new agents.

Initially a total of 13 mutations were found to confer reduced etravirine susceptibility: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. Response rates according to the number of these mutations present at pretreatment were 75% in the 40% of patients with no mutations, 60% in the 30% of patients with 1 mutation, 58% in the 16% of patients with 2 mutations, 41% in the 8% of patients with 3 mutations, and 25% in the 6% of patients with at least 4 mutations (Cahn et al, ICAAC, 2007). Thus, the presence of at least 3 mutations was associated with a response rate comparable to that seen with the addition of placebo to OBR; this 3-mutation threshold for loss of activity for etravirine has also been observed in analyses using established non-etravirine-specific NNRTI

mutations (excluding K103N). More recently, further study has demonstrated that 17 mutations may be associated with reduced phenotypic susceptibility to etravirine. Furthermore, some mutations have a greater effect on susceptibility than others, allowing for the creation of a weighted mutation score to further enhance the ability to predict the likelihood of a given individual's virus being susceptible to this drug and how that might influence the patient's ultimate response to therapy (Vingerhoets et al, *Antivir Ther*, 2008).

Based upon the initial mutations reported to be associated with reduced etravirine response, it was found that 14% of patients receiving etravirine in the DUET trials had at least 3 resistance mutations at pretreatment. Moreover, the prevalence of virus with at least 3 etravirine mutations was reported to be relatively low in other cohorts, such as 30% in a study in Thailand (n = 158) (Sungkanuparph et al, CROI, 2008), 10% in a study in Nigeria (n = 214) (Taiwo et al, CROI, 2008), 9.3% in a study in Spain (Llibre et al, CROI, 2008), and 7.3% in a large commercial (Virco Lab, Inc) database (n = 226,491) (Picchio et al, CROI, 2008). Thus, although pretreatment resistance to etravirine and other second-generation NNRTIs in development may be relatively uncommon, it is clearly a real phenomenon, and careful genotypic analysis is warranted when use of these drugs is considered.

Phenotypic cutoff values for etravirine are also being developed (Vingerhoets et al, *Antivir Ther*, 2008).

## Conclusion

The goal of therapy in antiretroviral drug-experienced patients is to achieve a viral load below the limits of assay detection. The availability of new drugs in existing and new classes has increased the likelihood of achieving this goal. Defining resistance patterns for new drugs in existing classes allows for optimization of their use in antiretroviral drug-experienced patients. Defining how resistance develops to new drugs in new classes is key to understanding the risks of virologic failure. The strategic use of antiretroviral drugs to enhance successful suppression of virus is the best way to avoid resistance to new agents and new classes.

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## Update on The Chikumbuso Project

As attendees to our Continuing Medical Education courses know, the International AIDS Society–USA has been selling colorful hand-crocheted tote bags made of recycled plastic bags by the women of Lusaka, Zambia, to support the Chikumbuso Project. This project is the 2008 International AIDS Society–USA Charitable Partner, and it supports medical care and social programs for widows, orphans, and grandmothers in the Ng’ombe township whose lives have been impacted by HIV and AIDS.

The IAS–USA is pleased to report that as of September, 2008, sales of the bags at our courses have raised more than \$25,000 directly for the Chikumbuso Project. We thank the many attendees of our courses who have purchased

these bags and/or made additional donations to the project. The final chance to purchase a bag will be at our CME course in New York on October 3, 2008. Additional donations can be made at any time by mailing a check made out to “Second Baptist Church” (with “Chikumbuso Project” in the memo field) to:

Second Baptist Church  
146 Pendleton Hill Road  
North Stonington, CT 06359

Further information is available by contacting Linda Wilkinson at [chikumbusoproject@yahoo.com](mailto:chikumbusoproject@yahoo.com).

The International AIDS Society–USA is actively seeking a new Charitable Partner for 2009.