The Body

New Developments in HIV Drug Resistance and Options for Treatment-Experienced Patients

Coverage of the 4th European HIV Drug Resistance Workshop and the 12th Annual Conference of the British HIV Association

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Introduction

The emergence of drug resistant HIV in patients failing therapy is a result of two processes: the emergence of pre-existing genetic variants and the selection of drug-resistant virus as a result of selective pressure. There are a multitude of reasons for HIV's enormous genetic variability -- not only is the HIV reverse transcriptase (RT) error-prone, but there is also an absence of any enzymatic proofreading activity and a high rate of HIV replication in vivo. In patients who are maintained on a failing regimen, the insufficient potency of the treatment means viral replication is ongoing. This risks the accumulation of additional mutations as well as increasing cross-resistance.

Resistance continues to have substantial clinical relevance. Among viremic patients in the United States, 50% are estimated to harbor resistance to two classes of drugs and 13% to three.[1] Thus we are left with the challenge of assembling an active regimen for HIV-infected patients with varying degrees of resistance. Fortunately, the treatment landscape has been somewhat transformed in the last few years with the approval of enfuvirtide (T-20, Fuzeon), which belongs to the new fusion inhibitor class of HIV drugs, and the approval in the summer of 2005 of tipranavir (TPV, Aptivus), a potent protease inhibitor (PI) active in many patients with resistance to PIs.

In addition, at the 13th Conference on Retroviruses and Opportunistic Infections (CROI 2006) as well as the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment (IAS 2005), a multitude of agents in various stages of development were showcased. In the pipeline are not only new agents from existing drug classes -- such as TMC125 (etravirine), TMC114 (darunavir), TMC278, vicriviroc (SCH 417690, SCH-D) and maraviroc (UK-427,857) -- that are active in multidrug-resistant patients, but agents from a new class altogether -- the integrase inhibitors MK-0518 and GS 9137.

Keeping track of all the investigational HIV antiretroviral agents is a tall order for the busy practicing clinician. With new, improved agents being developed in currently approved drug classes and exciting compounds with novel mechanisms of action working toward U.S. Food and Drug Administration (FDA) approval, clinicians are struggling to see how these new drugs will best serve patients.

The greatest urgency is, of course, to find solutions for heavily treatment-experienced patients. Reviews of all the resistance data for drugs in advanced clinical development will help to identify new options for these patients. Additionally, a greater understanding of the interpretation of resistance assay results for recently improved drugs has relevance for routine clinical practice and will help refine the use of some of the more recently introduced antiretrovirals.

This article will review presentations from the 4th European HIV Drug Resistance Workshop, which took place on March 29-31, 2006 in Monaco. Among the highlights of this conference was research looking at ongoing issues regarding the understanding of resistance, particularly in the context of new drugs such as tipranavir and TMC114. The Workshop provided important additional detail on much of the new data presented at CROI 2006. Also reviewed here are presentations from the 12th Annual Conference of the British HIV Association, which took place on March 29 - April 1, 2006 in the United Kingdom.

Epidemiology of HIV Resistance

Surveillance data on drug resistance in treatment-experienced patients reveals a lot about not only the prevalence of resistance, but also the reasons behind the resistance. In France, a nationwide study by Dominique Costagliola and colleagues, samples were taken from HIV-infected patients in 28 specialized centers in France and one in Switzerland.

To be included in the study, patients were required to have an HIV RNA viral load greater

than 1,000 copies/mL and to be currently on antiretroviral therapy or on a treatment interruption of less than a month. In 2004, when this study was conducted, 80.3% of patients followed in French hospitals were receiving antiretroviral therapy and 21.3% were found to have viral loads of more than 1,000 copies/mL.

Samples were taken from 498 patients with viral loads greater than 1,000 copies/mL. The researchers then systematically looked for resistance mutations. The protease, RT and gp41 gene mutations were identified using the IAS-USA resistance testing panel. Genotype results were interpreted using the French ANRS (National Agency for AIDS Research) algorithm.

STUDY SNAPSHOT

Design:	Surveillance for prevalence of HIV drug resistance in treated HIV-infected patients with viral loads > than 1,000 copies/mL.
Population:	498 patients were enrolled, with 379 men and 113 women. Median age: 42.5. Median duration of HIV infection: 12 years.
Main Results:	Resistance to NRTIs occurred with the most frequency. The pattern of resistance reveals that most of the patients had initiated therapy years ago with NRTI monotherapy or dual therapy.
Significance:	A failing regimen should be changed immediately, and, if at all possible, at least two fully active drugs should be included in the new regimen.

Patients had been exposed to a median of nine antiretrovirals (range: 6-12) with 12% having received enfuvirtide. A median of four nucleoside/tide reverse transcriptase inhibitor (NRTI) mutations, four PI mutations and zero non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations were detected.

Resistance was observed to at least one antiretroviral in 88% of patients, to at least one NRTI in 77%, to one PI in 66%, to one NNRTI in 50% and to enfuvirtide in 7%. Overall, 19% of the patients had virus that retained susceptibility to only a single drug class. NRTI resistance occurred with the most frequency, suggesting that most of the patients had begun therapy years ago with NRTI monotherapy or dual therapy.[2]

These data are a sad reminder of the consequences of the era before HAART (highly-active antiretroviral therapy) when fewer than three potent drugs were combined. Although combination therapy is now the standard of care, it must be remembered that the principles of resistance remain the same. Patients who are left on a regimen with only one to two active drugs, or who are switched to a new regimen that includes drugs that are no longer active, are in effect being treated with only one to two agents and will suffer the same consequence as if they were taking monotherapy or dual therapy -- namely high-level cross-resistance.

Predicting Treatment Response Based on Resistance Scores

With up to 50% of treated patients estimated by some studies[1] to have HIV drug resistance, the use of genotype resistance testing to guide treatment decisions is becoming increasingly more important, especially for patients who are failing first- or second-line therapy.

Genotypic resistance results need to be interpreted in terms of the clinical impact of the mutations.[3,4] As such, many algorithms -- or genotypic resistance scores -- have been developed to help clinicians with such interpretation, thereby enabling clinicians to predict how well a patient may respond to a particular agent in a salvage setting. Freely accessible examples include the Stanford University HIV Drug Resistance Database and the French ANRS.

Unfortunately, even as new drugs become available to clinicians, the resistance data for them is often incomplete -- in part due to a need for the FDA to move these drugs quickly through the approval process so that HIV-infected patients with few treatment options can receive them in a timely manner.

Although preliminary resistance data are now included in the labeling of recently approved drugs, more data, and a better understanding of that data, is necessary. Only as larger and more diverse patient populations receive these drugs, and correlates of baseline resistance and virologic response are elucidated, can we fine-tune our ability to interpret resistance to these key antiretrovirals. A number of presentations at the 4th European HIV Drug Resistance Workshop offered improved insight into our ability to interpret resistance to some of these commonly used drugs.

Refinement of the Genotypic Resistance Score for Tipranavir

For a genotypic resistance score to be clinically valid, baseline genotypes must be correlated with the virologic response to treatment. Given that the FDA only recently approved tipranavir in July 2005, researchers are still figuring out which mutations will affect treatment response.

The genotypic score for tipranavir + ritonavir (RTV, Norvir) was previously derived from clinical isolates taken from patients who were participating in the phase 2 and 3 RESIST (**R**andomized **E**valuation of **S**trategic **I**ntervention in Multi-Drug Re**s**istant Patients with **T**ipranavir) trials, which were designed to assess the efficacy and safety of tipranavir in heavily treatment-experienced individuals.

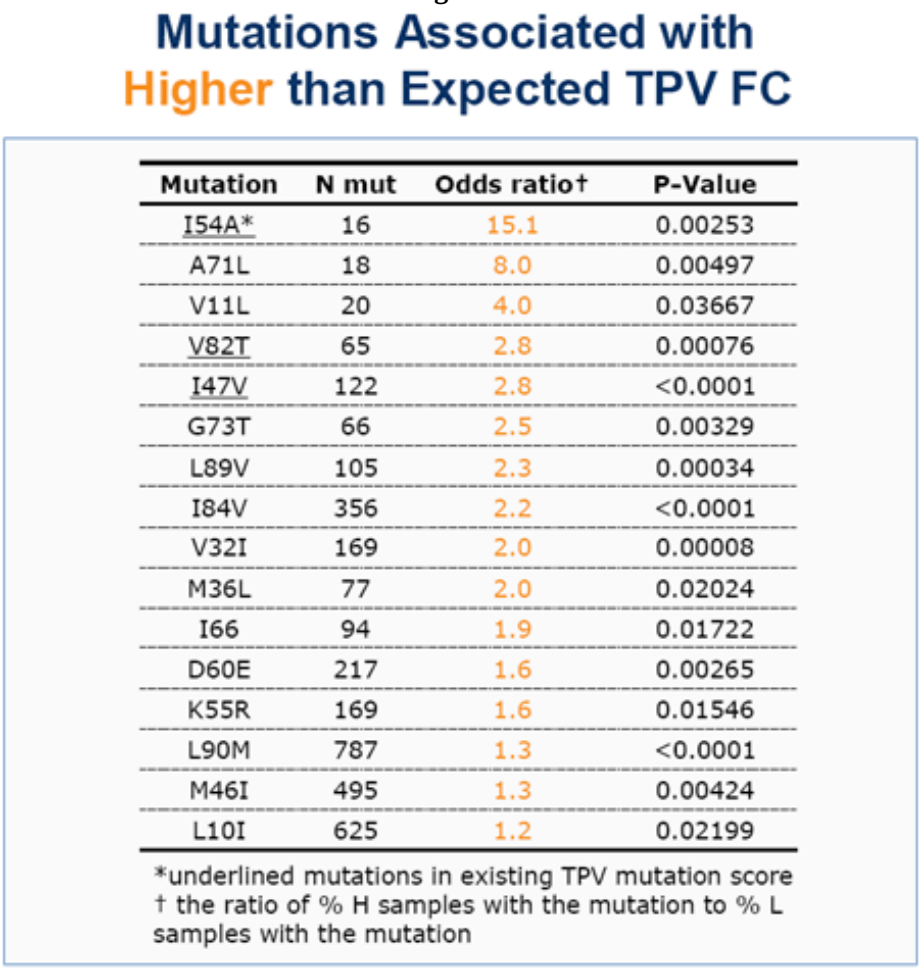
STUDY SNAPSHOT	
Design:	Analysis of data from the Monogram Sciences database.
Data Set:	HIV-1 isolates containing at least one PI-resistance mutation with no more than one mixture at any position.
Main Results:	A revised tipranavir mutation score that included new resistance mutations and that, with altered weighting of known mutations, better correlated with measured phenotypes and demonstrated lower phenotype-genotype discordance than the current mutation score.
Significance:	The revised tipranavir mutation score may more accurately predict the virologic response to tipranavir in heavily treatment-experienced patients.

Since there was only a limited number of samples collected during these trials, there is a need to improve the ability of the genotypic score to predict the response to tipranavir

treatment. To this end, Eoin Coakley and colleagues performed phenotype and genotype assays on an independent set of clinical isolates obtained from the Monogram Biosciences database.[5] Their results were presented at the 4th European HIV Drug Resistance Workshop.

By analyzing a total of 1,411 new clinical isolates, Coakley and colleagues determined that the tipranavir mutation score derived from the RESIST data modestly correlated with the mean fold change (FC) in tipranavir susceptibility (linear regression coefficient: 0.51; *P* < .0001). Moreover, the researchers identified several additional mutations not included in the original mutation score that influenced phenotypic susceptibility to tipranavir.

Figure 1



Mutation	N mut	Odds ratio†	P-Value
I54A*	16	15.1	0.00253
A71L	18	8.0	0.00497
V11L	20	4.0	0.03667
V82T	65	2.8	0.00076
I47V	122	2.8	<0.0001
G73T	66	2.5	0.00329
L89V	105	2.3	0.00034
I84V	356	2.2	<0.0001
V32I	169	2.0	0.00008
M36L	77	2.0	0.02024
I66	94	1.9	0.01722
D60E	217	1.6	0.00265
K55R	169	1.6	0.01546
L90M	787	1.3	<0.0001
M46I	495	1.3	0.00424
L10I	625	1.2	0.02199

*underlined mutations in existing TPV mutation score
† the ratio of % H samples with the mutation to % L samples with the mutation

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Figure 2

Mutations Associated with Lower than Expected TPV FC

Mutation	N mut	Odds ratio†	P-Value
I50V	53	0.1	<0.0001
D30N	134	0.2	<0.0001
L76V	49	0.3	0.00303
L24I	93	0.3	<0.0001
V82I	46	0.4	0.04848
I50L	34	0.4	0.04168
I54L	133	0.5	0.00063
N88D	153	0.5	0.00005
M46L	201	0.6	0.00259
L10F	281	0.7	0.01981
K20R	234	0.7	0.04161
L10V	145	0.7	0.04127
M36I	549	0.8	0.03953
I13V	564	0.8	0.01566

*underlined mutations in existing TPV mutation score
† % of H samples with the mutation to % of L samples with the mutation

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These additional mutations correlated with FCs in phenotypic susceptibility that were either significantly higher than predicted, such as the L10I, V11L, V32I, M36L, M46I, K55R, D60E, A71L, G73T, I84V, L89V and L90M mutations, or significantly lower than predicted, such as the L10F, L24I, D30N, I50L/V, I54L, L76V, V82I and N88D mutations. By re-weighting the effect of certain mutations included in the original tipranavir score and by including these newly identified mutations, the investigators derived a new tipranavir mutation score that better correlated with the tipranavir FC (linear regression coefficient: 0.66) and showed reduced genotype-phenotype discordance using specific phenotypic cutoffs.

Although the revised tipranavir genotype algorithm might more accurately predict the response to tipranavir in heavily treatment-experienced patients, the algorithm is quite complex and does not fully capture the impact of all mutations affecting in vitro tipranavir susceptibility. Indeed, since it may be unclear what FC cutoff should be used to indicate decreased susceptibility, a clinical validation of this new score will be needed in order to assess its real usefulness.

Larger and more diverse populations must be studied to further improve our understanding of tipranavir resistance. Studies that include patients with a great variety of baseline genotypes and phenotypes and well documented virologic response data must be analyzed using appropriate statistical techniques. Once new genotypic scores and phenotypic cutoffs are derived, different datasets will be required to cross-validate these findings. Hopefully, efforts on both sides of the Atlantic will lead to these improved and validated interpretation scores.

The Value of Discussing Resistance Test Results With HIV Resistance Experts

As the case of the tipranavir resistance mutation score demonstrates, interpreting an HIV resistance test in light of various genotypic resistance algorithms can be a significant challenge, especially for clinicians who are not well versed in the importance of certain resistance mutations. A more accurate interpretation of genotypic, phenotypic and virtual phenotypic resistance tests might be had if an HIV resistance expert is consulted about the results, and it might ultimately lead to a better treatment decision, particularly in the case of salvage therapy.

To test the validity of this assumption, Joseph Llibre and colleagues conducted a multi-center, prospective study in which clinicians and HIV resistance experts partook in a conference call every six weeks to discuss suitable salvage therapy for 10 treatment-experienced patients each week. The final regimen chosen was based on their genotype and virtual phenotype test results, antiretroviral history, adherence to therapy and hepatitis B/C coinfection status.[6]

STUDY SNAPSHOT	
Design:	Prospective study involving 10 centers in Spain.
Population:	115 heavily treatment-experienced patients with a viral load > 1,000 copies/mL.
Main Results:	42% of patients achieved a viral load < 50 copies/mL and 59% achieved a viral load < 400 copies/mL when treated with a salvage regimen guided by experts in HIV genotype and phenotype resistance.
Significance:	Clinicians with limited knowledge of HIV resistance mutations might be able to better manage their treatment-experienced patients by consulting with HIV resistance experts regarding the interpretation of genotype and virtual phenotype test scores.

Prior to the conference call, the experts reviewed this information and returned an individualized report to all conference call participants detailing the recommended treatment regimen for each patient based on an interpretation of their resistance results and the other information.

A total of 115 patients were discussed during conference calls throughout the study. These patients had been infected with HIV for a median of 10 years, had been on antiretroviral therapy for a median of eight years, and had received a median of 5.9 prior regimens of antiretroviral therapy.

Overall, 60% of all patients in this study harbored five or more resistance mutations within the HIV RT sequence, 67% harbored five or more resistance mutations within the HIV protease sequence and the majority of patients were resistant to NNRTIs (74%). In addition to the specific NRTIs, NNRTIs and PIs recommended as salvage therapy for these patients, the expert panel recommended that 65% receive enfuvirtide and that 11% undergo a treatment interruption.

Nearly 75% of all patients were administered the advised salvage regimen. The remaining quarter did not take the advised regimen largely due to the burden of a complex treatment schedule or reluctance to inject enfuvirtide. After 24 weeks of treatment, 42% of the patients had a viral load below 50 copies/mL and 59% had a viral load below 400 copies/mL, which is impressive considering that the patients were very treatment-experienced and

harbored multidrug-resistant virus.

In this study, consultation between clinicians and HIV resistance experts achieved a high rate of viral suppression among a very heavily treatment-experienced population. Indeed, there was a considerable educational benefit to everyone hearing all the cases discussed during the conference calls: It provided all the participants with considerable training and updating.

Although we don't know how these patients would have fared without the expert consultation, since there was no control group, and even though "experts" in resistance can disagree, previous studies have shown that expert advice improves outcome.[3] Needless to say, the vast majority of providers would probably welcome discussion before deciding on treatment for their multidrug-resistant patients.

Interpreting Genotype Results for Patients With Low Viral Load

Tradeoffs exist when a clinician considers ordering a resistance test when HIV RNA levels are still very low (in the 50 - 1,000 copy range). Although we strive to detect and manage resistance as early as possible, technical and statistical limitations have challenged performing testing at very low viral loads. By increasing sample volume and optimizing the assay being used, many laboratories can now technically perform resistance testing at these very low levels. The question remains: To what degree do the results truly reflect a patient's viral population? The answer may not be clear cut.

Stone and colleagues showed that when HIV from paired blood samples is amplified and sequenced from patients with a viral load below 200 copies/mL, the sequences from the sample pairs are typically identical.[7] However, in some instances (2/11; 18%), the researchers observed significant genetic differences between the sequences, likely corresponding to HIV variants present in the host. Because differences can be detected in paired extractions in a minority of patients with a very low viral load, the finding of wild-type virus does not mean that there is not a mutant virus hidden, so interpretation should be undertaken with care.

Clinical Implications of HIV Drug Resistance to Therapy With Approved Antiretrovirals

Atazanavir

Atazanavir (ATV, Reyataz) is now widely used in PI-naive patients due to both its convenient dosing and reduced lipid-related toxicity. Although ritonavir-boosted atazanavir has been shown to have activity in patients harboring mild to moderate PI resistance, data suggest this is not the drug of choice for patients with significant PI resistance.

So the question remains: Just how much PI resistance can boosted atazanavir safely overcome? This has been the focus of much research in recent years since, although clinicians are eager to use a convenient and less toxic PI, above a certain threshold of resistance, other more potent PIs with higher genetic barriers might make better choices.

Ada Bertoli and colleagues from several HIV treatment centers in Italy sought to identify the determinants for atazanavir failure among a large cohort of multiply failing patients.[8] Of the 355 patients who had a baseline viral load of at least 500 copies/mL and who were included in the analysis, 200 (56.4%) were treated with a boosted 300-mg atazanavir-containing regimen, whereas 155 (43.6%) received a 400-mg unboosted atazanavir-

containing regimen.

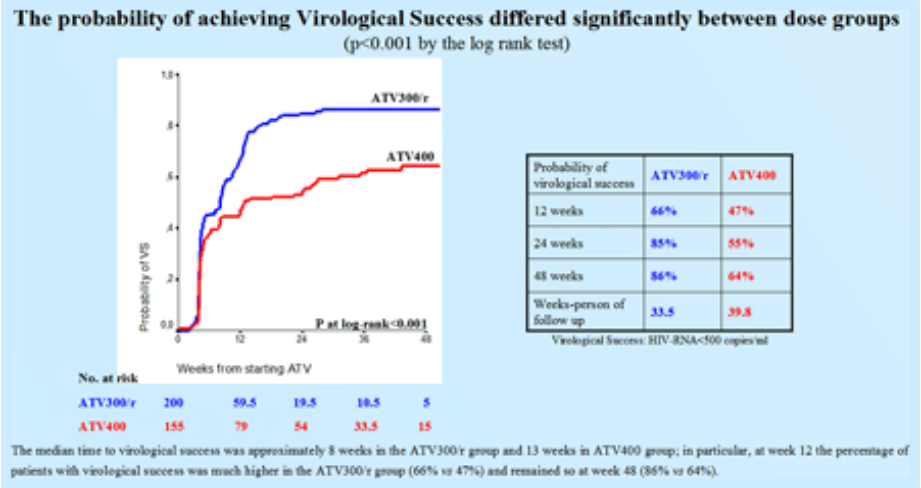
STUDY SNAPSHOT	
Design:	Comparison of unboosted 400-mg atazanavir-containing regimen to boosted 300-mg atazanavir-containing regimen in HIV-infected treatment-experienced patients.
Population:	355 patients treated with atazanavir-containing regimens.
Main Results:	Compared to unboosted atazanavir-based regimens, boosted atazanavir-based regimens were associated with virologic response and immunologic recovery.
Significance:	Boosted atazanavir is still active in the presence of less than eight atazanavir-specific IAS-mutations together with novel protease mutations potentially associated with resistance to PIs.

Significantly more patients who received boosted atazanavir achieved a viral load below 500 copies/mL versus those who received unboosted atazanavir -- 85% versus 63% at 48 weeks. Similarly, patients on boosted atazanavir achieved a CD4+ cell count increase of 97 cells/mm^3 versus an increase of only 20 cells/mm^3 for those on atazanavir alone. In addition, the boosted-atazanavir group had a significantly shorter time to virologic response than the unboosted-atazanavir group -- with a median time to virologic response of eight weeks versus 13 weeks for the unboosted-atazanavir group.

Not surprisingly, patients who received the boosted regimen had a better chance of attaining viral suppression according to multivariate analysis. Factors predicting a poor virologic response to atazanavir included more advanced disease (U.S. Centers for Disease Control and Prevention stage C), a higher baseline viral load and more extensive exposure to PIs.

A median of 7.5 PI mutations correlated with virologic failure among those taking boosted atazanavir, whereas a median of only five PI mutations correlated with failure in those receiving the unboosted drug. Perhaps of most interest, the 69M mutation, which is a novel protease mutation potentially associated with PI resistance, significantly predicted a two-fold increased chance of virologic success (adjusted hazard ratio: 1.98; 95% confidence interval: 1.14-3.17).

Figure 3



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Although this study does not establish any comparison with other PIs, it allows us to take home the message that boosted atazanavir-based approaches might still have some activity in treatment-experienced patients with fewer than eight mutations, as well as that the presence of a new mutation (69M) may predict higher activity.

Tenofovir

Tenofovir (TDF, Viread) has gained widespread use in both treatment-naive and treatment-experienced patients. This agent has had excellent success when combined with agents from other drug classes, although there have been disappointing results when it has been used in particular NRTI-only combinations. In terms of tenofovir resistance, it is an evolving story. We still don't know the answers to the following questions: What are all the resistance pathways to the drug? How prevalent are they and to what degree do mutations selected by tenofovir affect other NRTIs? An example is the effect of mutation L74V on tenofovir. As this is a signature mutation for didanosine (ddI, Videx) and abacavir (ABC, Ziagen), its effect on tenofovir is of major interest. The data have been somewhat conflicting, with laboratory studies showing no effect on tenofovir susceptibility, but statistical analyses linking the presence of L74V with a poorer response to tenofovir. A number of studies at the 4th European HIV Drug Resistance Workshop provided additional insight into tenofovir resistance.

Although prior analyses have shown that K65R and certain thymidine analog mutations (TAMs) can reduce the response to tenofovir, McColl and colleagues performed a more in-depth analysis of the specific mutations affecting the response to tenofovir.[9]

STUDY SNAPSHOT

Design:	Expanded analysis of the specific mutations affecting response to tenofovir.
Population:	566 patients from two randomized trials in which tenofovir was added to a stable antiretroviral regimen when patients' viral load exceeded 400 copies/mL.
Main Results:	Two patterns of TAMs were statistically defined. Treatment response to tenofovir decreased for HIV with three or more TAMs in the 41-67-210-215 pattern. Multivariate analyses confirmed these four TAMs and additionally identified the L74V mutation as a significant predictor of reduced response to tenofovir therapy. In this study, the L74V mutation is associated both with multiple TAMs and the development of K65R. M184V is a predictor of improved tenofovir response (~0.1 $\log_{10}$ decrease).

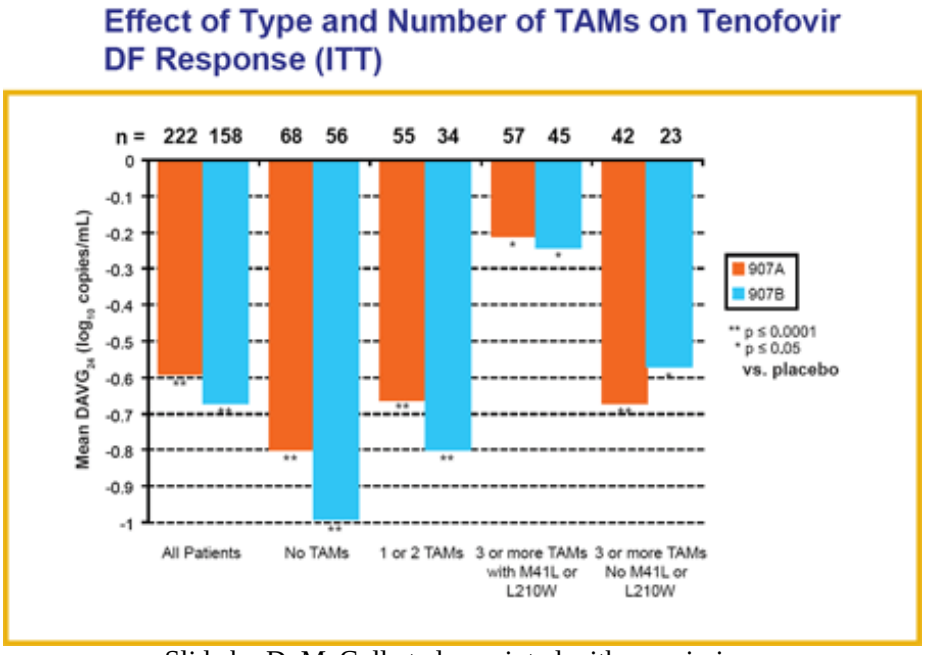
A total of 566 patients from two randomized trials (studies 902 and 907, which focused on the use of tenofovir in salvage therapy), in which tenofovir was added to a stable antiretroviral regimen when patients' viral load exceeded 400 copies/mL, were included in the current expanded analysis.

Twelve mutations within the HIV RT, including L74V, were significantly associated ($P < .05$) with a diminished viral response to tenofovir. In an adjusted multivariate analysis, four TAMs -- M41L, D67N, L210W and T215Y -- and the L74V

mutation significantly and independently predicted a poor response to tenofovir.

The correlation between L74V and a diminished virologic response is surprising considering that this mutation is completely susceptible to tenofovir in vitro. However, the researchers noted that the presence of the L74V mutation was usually accompanied by the K65R mutation and multiple TAMs -- mutations known to decrease the response to tenofovir.

Figure 4



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K65R development was rare, with a frequency of only 2.6% among all patients. Of potential importance, the M184V mutation correlated with a significantly improved response to tenofovir (P = .004). These results support the use of lamivudine (3TC, Epivir) in a salvage regimen, even if M184V is present, because its maintenance will increase the activity of tenofovir in this setting. It is important to highlight that L74V alone will not have much impact on the antiviral activity of tenofovir. In these studies, L74V was always accompanied by TAMs or K65R.

The use of tenofovir/emtricitabine (TDF/FTC, Truvada) has been widely accepted in initial first-line therapy. These data on the apparent positive impact of the mutation M184V on tenofovir activity provide additional support for the use of tenofovir/emtricitabine in the salvage setting as well.

Although clearly all drug resistance should be avoided, data are accumulating to suggest that once the M184V mutation has been selected and the virological activity of the very potent NRTI lamivudine and emtricitabine (FTC, Emtriva) regrettably lost, some clinical benefit can apparently still be derived by continued use of these drugs. This, of course, has been suggested for many years for zidovudine (AZT, Retrovir), and now we see the data mounting for tenofovir as well.

In vitro data clearly show the presence of mutation M184V mitigating the effect of TAMs on tenofovir susceptibility, and now the clinical evidence appears to be accumulating as well. Since maintaining M184V requires lamivudine or emtricitabine to be continued in the regimen, the use of tenofovir/emtricitabine in the salvage setting to improve tenofovir

activity may often be an acceptable choice.

STUDY SNAPSHOT	
Design:	An HIV-1 sequence database (N = 118,240) of virus collected from 2001 to 2005 was queried for combinations of K70E with K65R, L74V, TAMs1 (M41L/L210W/T215 F/Y), TAMs2 (D67N/K70R/T219Q/E), E44D/A, V118I, 69Ins, 69A/D/N/S, Y115F, the multidrug resistance complex Q151M-A62V/V75I/F77L, F116Y (MDRQ151M), and M184V/I, as well as combinations of those mutations with K70R and the wild-type amino acid at position 70 (70wt).
Main Results:	K70E represents an alternative resistance pathway from K70R, separate from TAMs2 and K65R. It is linked with M184V, MDR-Q151M and Y115F and occurs in the background of a large number of NRTI mutations.
Significance:	As more data accumulate, interpretation algorithms may need to consider this mutation when determining resistance to tenofovir.

In a related tenofovir study, Van Houtte and colleagues determined that the K65R and K70E mutations that confer resistance to tenofovir develop through independent pathways, as no HIV isolates among a panel of over 118,000 analyzed harbored both mutations within the same sequence.[10] K70E was typically found in conjunction with the M184V, Q151M and Y115F mutations, indicating that the development of this mutation might play a compensatory role in improving viral fitness. K70E represents an alternative resistance pathway from K70R, separate from TAMs2 and from K65R. K70E is associated with modest resistance to tenofovir.

There is a need to assess if this pathway is selected more according to the HIV subtype. Although not commonly encountered, it is prudent to monitor for this mutation and to consider it when evaluating resistance to tenofovir. As more data accumulate, interpretation algorithms may need to consider this mutation when determining resistance to tenofovir.

The Impact of Emerging Resistance Mutations on Treatment Response

In highly treatment-experienced patients there is the risk of developing K65R and therefore a possibility of a reduced response to tenofovir in patients harboring the L74V mutation. However, these observations cannot be extrapolated to treatment-naive patients who are experiencing their first confirmed virologic failure with the L74V mutation. Descamps and colleagues[11] examined whether the K65R mutation was present as a minority variant where L74V was the major variant selected upon virologic failure of first-line abacavir/lamivudine (ABC/3TC, Epzicom, Kivexa)-based HAART approaches.

The results of this study show that the selection of K65R minor viral variants is not a common phenomenon in abacavir/lamivudine-containing HAART. Indeed, they have demonstrated that the M184V mutation alone or in association with the L74V mutation remains the signature resistance pathway of abacavir/lamivudine-based therapies. These findings are important because they tell us that in treatment-naive patients, those failing abacavir/lamivudine might be rescued with tenofovir + zidovudine-based approaches.

The Impact of New Antiretrovirals on Treatment Options for Multidrug-Resistant Patients

The magnitude and duration of virologic responses to currently approved antiretroviral agents are significantly reduced in treatment-experienced patients in comparison with treatment-naive patients. As such, agents that are highly potent against drug-resistant HIV and that can confer long-term viral suppression while still being tolerable represent ideal salvage therapies for treatment-experienced patients. Major conferences in late 2005 and early 2006, including CROI 2006, cast a spotlight on an encouragingly large number of such agents in the development pipeline.[12] Several studies presented at the 4th European HIV Drug Resistance Workshop and the 12th Annual Conference of the British HIV Association provided a closer look at two of these drugs in particular: TMC114 and TMC125. In addition to presenting safety and efficacy data, these studies also delved more deeply into how the extent of baseline and developing resistance mutations can impinge on the response to novel and approved antiretrovirals.

TMC114

In the summer of 2006, TMC114 may become the newest PI approved in the United States. Given its demonstrated activity in treatment-experienced patients, there is a great amount of interest not only in the extent of the drug's efficacy and safety, but in its resistance profile as well -- particularly in comparison to other recently approved PIs. Several recent studies attempted to elucidate these issues.

Further Positive Results for TMC114: The POWER 3 Study at Week 24

In 2005, three presentations on the POWER (**P**erformance **O**f TMC114/r **W**hen **E**valuated in triple-class-experienced patients with PI **R**esistance) 1 and 2 studies documented the intrinsic activity of TMC114 in PI-experienced patients.[13-15] Based on the dramatic, positive results of these studies, the single-arm POWER 3 study[16] was opened up for additional participants to receive the highest study dose of TMC114 -- 600 mg twice daily (with 100 mg twice daily of ritonavir) -- in combination with an optimized background regimen.

Twenty-four week data from POWER 3, conducted by Jean-Michel Molina and colleagues, were presented at the 12th Annual Conference of the British HIV Association. In all, 327 patients were enrolled in POWER 3, of whom 303 were newly recruited to receive TMC114, while 24 patients entered after being on the control arms of the POWER 1 and 2 trials. These were all triple-class-experienced patients with an extensive prior treatment history. Interestingly, 31% of the POWER 3 patients had already received tipranavir. Similar to POWER 2, 30% of the patients had previously received enfuvirtide. Patients had high-level PI resistance, reporting a median of three primary PI mutations and a median of nine PI-associated mutations at entry.

Results for POWER 3 confirm what was reported in the POWER 2 study results. At week 24, 65% of the patients maintained a viral load at least 1 log copies/mL below baseline, and there was a corresponding mean CD4+ cell count increase of 80 cells/mm^3.

Also interesting is the breakdown of patients who achieved maximal viral suppression to below 50 copies. In total, 40% of the POWER 3 patients achieved maximal suppression at week 24 -- and the single best predictor of this response was the degree of baseline phenotypic resistance to TMC114. For example, 50% of trial participants with a phenotype of less than 10 fold at baseline achieved maximal suppression, as compared to a 17%

response for those with a more than 40-fold resistance at baseline.

Fortunately, 170 of the 238 patients (about 71%) entering this study had a FC below 10 fold, suggesting that many triple-class-experienced patients will still show a response to TMC114. The study authors also noted that phenotype was more predictive of virologic response than the number of PI mutations.

Table 1

HIV RNA Response Rates* by Baseline Characteristics in Week 24 Data From the POWER 3 Trial		
Baseline Characteristics	**n**	**Response Rate n, (%)**
TMC114 FC		
≤ 10	170	85 (50)
10-40	33	3 (9)
> 40	35	6 (17)
CD4+ cell count (cells/mm^3)		
< 50	74	16 (22)
50-100	37	10 (27)
100-200	49	27 (55)
≥ 200	82	44 (54)
Primary PI mutations		
1	17	6 (35)
2	32	19 (59)
3 or more	194	71 (37)
Susceptible NRTI in the optimized background regimen		
0	86	25 (29)
1	91	44 (48)
2 or more	58	24 (41)
Use of enfuvirtide		
Previously enfuvirtide-naive	53	24 (45)
Enfuvirtide re-used	49	13 (27)
Enfuvirtide not used	144	61 (42)
Prior use of tipranavir		
Yes	81	25 (31)
No	165	73 (44)
* HIV RNA response rates defined as HIV RNA < 50 copies/mL		

In addition, the use of enfuvirtide was found to be of benefit -- more so for study patients who were taking the drug for the first time. Among these enfuvirtide-naive patients, 45% achieved a viral load of less than 50 copies/mL, compared to 27% who had used enfuvirtide in the past and continued to take it during the POWER 3 study.

Of great interest was the virologic outcome in patients who had prior tipranavir exposure and resistance. The drop in viral load among this subset was 1.38 log copies/mL, similar to the overall response of 1.74 log for all patients who participated in POWER 3.

STUDY SNAPSHOT	
Design:	Single-arm, open-label, non-randomized, 24-week safety and efficacy study of TMC114 + ritonavir.
Population:	327 patients with triple-class experience and extensive treatment history.
Main Results:	Viral load reduction of at least 1 log in 65% of patients; mean CD4+ cell increase of 80 cells/mm^3.
Significance:	With FDA approval possibly slated for summer 2006, TMC114 appears to be a safe, effective, durable PI for patients with triple-class experience.

Safety results for this study were similar to those noted in prior reports on this drug. There was new onset of diarrhea (14%) and nausea (10%); 75% of the adverse events reported were graded mild/moderate. Among the most common grade 3 or 4 lab abnormalities was increased amylase, which was reported in 7% of the participants. Elevated lipase was only seen in 3% of participants, however. Grade 3 or 4 elevated liver function tests were seen in only 2% of participants.

There were minimal changes reported in lipid fractions compared to baseline, with the exception of a drop in triglycerides for those who entered while taking lopinavir/ritonavir (LPV/r, Kaletra). There was a very low rate of treatment discontinuation due to adverse events (2%). POWER 3 had no control arm, so no comparison of adverse effects is possible.

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This study confirms the exciting results reported from the POWER 1 and 2 studies. It is reasonable to anticipate that a majority of drug-resistant patients -- even those with triple-class experience -- could receive some benefit from TMC114, especially when the drug is combined with other active antivirals. The safety profile of TMC114 continues to be reassuring as well, with no new adverse events observed in this study as compared to the earlier, smaller POWER 1 and 2 studies.

Who Can Benefit Most From TMC114 + Ritonavir? Examining the Genotypic and Phenotypic Data

A key challenge for clinicians faced with new treatment options is a precise understanding of which patients are most likely to benefit, and which factors contribute to ensuring the best activity from a novel compound. Anton Pozniak and colleagues combined data from the POWER 1, 2 and 3 studies to assess which baseline factors could predict which patients would have the greatest (or least) likelihood of virologic success when starting a regimen containing TMC114.[17] Several interesting lessons came out of this look at the data, which were presented at the 12th Annual Conference of the British HIV Association.

In POWER 1, 2 and 3, there were a total of 458 patients who received TMC114 and 124 control patients. Previous analyses[13-15] of the four doses tested in POWER 1 and 2 demonstrated that the best response was to the 600-mg, twice-daily dose; those who received only this dose were the focus of this analysis.

STUDY SNAPSHOT	
Design:	Analysis of pooled data from the POWER 1, 2 and 3 studies to gauge factors affecting efficacy of TMC114 600 mg + ritonavir 100 mg.
Population:	582 treatment-experienced patients (458 receiving TMC114 + ritonavir; 124 controls).
Main Results:	Baseline phenotype (TMC114 FC) is best predictor of TMC114 + ritonavir virologic success; number of active drugs in regimen also important.
Significance:	Data gives providers the ability to assess the likelihood that prescribing TMC114 + ritonavir will be effective in their treatment-experienced patients.

One interesting finding of this analysis -- the percentage of patients who achieved a viral load of less than 50 copies/mL -- demonstrates the activity of TMC114 among treatment-experienced patients. For patients on TMC114, 42% achieved maximal viral suppression. By comparison, for those not on TMC114, even if the control regimen contained a PI predicted to be active by baseline resistance testing, only 24% of patients achieved this degree of suppression. Not surprisingly, only 7% achieved a viral load of less than 50 copies/mL if they were on a PI to which, according to resistance testing, they were not susceptible.

The multivariate analysis of response showed that the baseline phenotypic FC to TMC114 was the single best predictor of virologic response (defined as a viral load below 50 copies/mL). A FC below 10 was associated with a 50% response, compared to a 25% response rate for a FC of 10 to 40, and 13% for a FC of more than 40. (It was also noted that a FC of more than 10 was associated with having 10 or more PI-resistance mutations.)

Fortunately, 255 of 366 patients (about 70%) for whom FC data were available had a FC below 10. As noted in the POWER 3 analysis above, this finding suggests that the majority of triple-class-experienced patients have the potential to receive the most benefit from TMC114.

Another factor predicting virologic response was the number of other active antivirals in the regimen. For example, only 26% of all POWER study participants achieved a viral load of less than 50 copies/mL if the regimen contained *no* active antivirals, whereas 46% achieved a viral load of less than 50 if they had at least one other active antiviral.

One additional interesting finding noted that if someone was on a nucleoside that resistance testing predicted to be active, he or she had a slightly greater virologic response rate (51%) compared to patients who had no active NRTIs but instead used enfuvirtide (43%). However, this analysis did not control for degrees of baseline TMC114 resistance, which could reasonably be expected to differ in these two populations and could thus account for the observed disparity in virologic success.

It is worth adding that, among the subset of patients who had both an active NRTI(s) and

enfuvirtide, the rate of suppression was 53% -- a similar rate to that of patients who had an active NRTI but did not receive enfuvirtide.

These data reassure and inform practitioners as to which patients can be predicted to have the best response to TMC114. The authors concluded that 600 mg TMC114 + 100 mg ritonavir twice daily was consistently more active than any control PI used by this PI-experienced cohort, regardless of the predicted susceptibility to another PI. They noted that baseline phenotype was the best predictor of response, though other factors were also important, including having at least one other active drug in the regimen. It is surprising that some NRTIs could have retained activity in this heavily-pretreated population, but that was confirmed by resistance testing to be the case for 165 of the participants who used TMC114 without enfuvirtide.

STUDY SNAPSHOT	
Design:	Retrospective analysis of three TMC114 clinical trials -- POWER 1, 2 and 3.
Population:	215 heavily treatment-experienced patients who received 600 mg TMC114 + 100 mg ritonavir twice daily plus an optimized background regimen (excluding enfuvirtide).
Main Results:	TMC114 FC > 10 predicted a poorer virologic response to treatment and was strongly correlated with ≥ 10 PI-resistance mutations at baseline. Identification of select resistance mutations present at baseline and that emerged during treatment to reduce the TMC114 virologic response.
Significance:	Despite a reduced virologic response to TMC114 in a subset of patients, isolates from viral rebounders who were sensitive to tipranavir at baseline remained susceptible to tipranavir, suggesting another treatment option for such individuals.

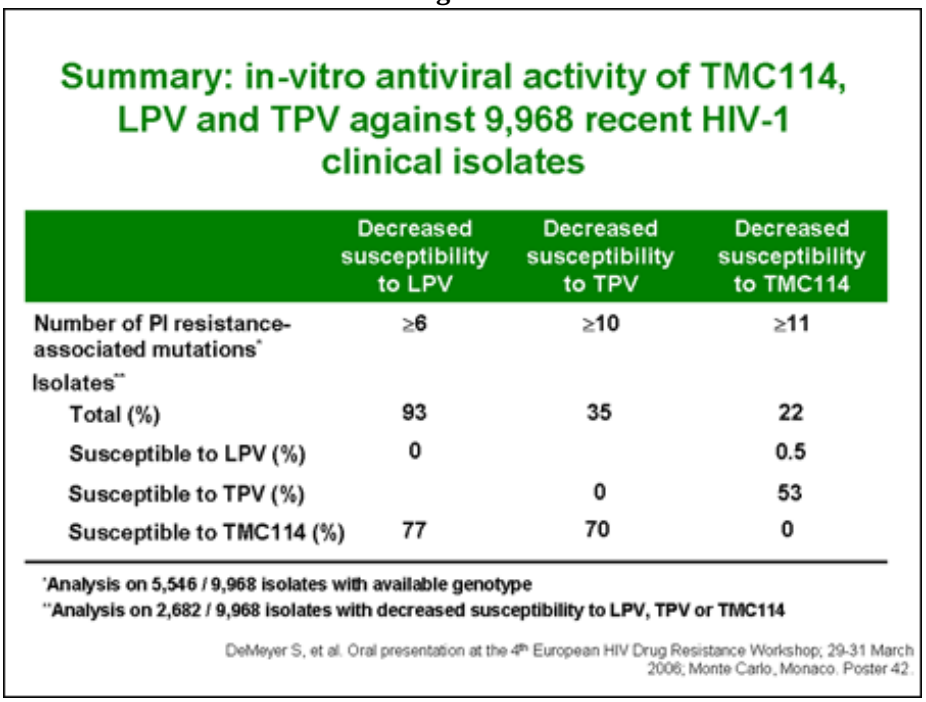
Another TMC114 resistance analysis was conducted by Marie-Pierre de Béthune and colleagues, on behalf of the manufacturer of TMC114, and presented at the 4th European HIV Drug Resistance Workshop.[18] de Béthune et al carried out an analysis of all patients who received 600 mg TMC114 + 100 mg ritonavir twice daily in the three POWER studies; patients who received enfuvirtide as part of their optimized background regimen were excluded. The investigators were specifically interested in identifying the genotypic and phenotypic factors associated with a diminished ability to achieve a viral load below 50 copies/mL.

Among the 215 patients assessed, the number of PI-resistance mutations present at baseline was eight. The baseline TMC114 FC emerged as the strongest predictor for virologic response. Patients with a TMC114 FC less than 10 demonstrated a much better virologic response than those with a FC above 10, which was strongly associated with the presence of 10 or more PI-resistance mutations. Moreover, the presence of the V11I, V32I, I47V or I54L/M mutations at baseline also correlated with a poorer virologic response, although the response was still higher than that observed in control patients who did not receive TMC114. Interestingly, isolates containing these mutations tended to contain more PI-resistance mutations overall than isolates without these mutations. Not surprisingly, the development of some of these mutations during treatment -- V32I, I47V and I54L -- in addition to other mutations -- L33F and L88V -- also compromised patients' virologic response and were implicated in at least 10% of all failures. Patients experiencing virologic rebound displayed a median TMC114 FC increase of 8.14-fold.

Despite the diminished response to treatment in a subset of patients -- mostly those harboring 10 or more PI-resistance mutations -- all isolates from patients experiencing virologic rebound that were found to be sensitive to tipranavir at baseline remained so.

Indeed, related data presented at the 4th European HIV Drug Resistance Workshop by DeMeyer and colleagues, also representing the manufacturer of TMC114, found that more than half (53%) of the nearly 600 isolates with decreased sensitivity to TMC114 included in their genotypic and phenotypic profiling analysis remained sensitive to tipranavir.[19] By contrast, only 0.5% of these isolates remained susceptible to lopinavir (LPV). On the flip side, 77% of the isolates resistant to lopinavir and 70% resistant to tipranavir remained susceptible to TMC114.

Figure 5



Slide by S. DeMeyer et al; reprinted with permission.

These data indicate that TMC114 and tipranavir share no, or only very limited, cross-resistance, which offers up a potential back-up salvage therapy should one or the other fail in treatment-experienced patients. However this is a hypothesis based on in vitro data -- the ability to sequence tipranavir + ritonavir and TMC114 + ritonavir still needs to be assessed in clinical trials.

Comparison of TMC114 + Ritonavir and Tipranavir

Any examination that involves both TMC114 and tipranavir cannot help but raise a larger question: Which of the two would make a better choice for salvage therapy? As both of these drugs have been developed for a similar use -- the suppression of HIV in patients with a history of PI resistance -- it is inevitable that clinicians will attempt to compare these two compounds on several measures.

In the absence of a randomized, head-to-head comparison study, one must use other means to assess the relative strengths and weaknesses of these two PIs. The most obvious way to do so is to directly compare the data from available studies on each drug -- in this case, the POWER 1 and 2 studies (for TMC114) and the RESIST 1 and 2 studies[20] (for tipranavir).

As these studies had many overlapping enrollment criteria, Andrew Hill and Graeme Moyle decided to conduct this analysis,[21] which is the first formal effort to assess, from the available data, both the similarities and differences that there may be when comparing TMC114 and tipranavir. Their analysis, presented at the 12th Annual Conference of the British HIV Association, compared the week-24 virologic response across all four studies using publicly available data.

STUDY SNAPSHOT	
Design:	De facto comparison of TMC114 and tipranavir, achieved by cross-analyzing data from the POWER and RESIST studies.
Population:	Triple-class-experienced patients with at least one primary PI mutation (201 from POWER; 1,159 from RESIST).
Main Results:	Data comparison suggests that TMC114 has greater antiviral activity than tipranavir.
Significance:	While these results seem to favor TMC114, head-to-head trials are necessary in which patients have susceptibility to both drugs.

The RESIST studies enrolled 1,159 people, while the POWER trials enrolled 201. As noted above, the RESIST and POWER studies had similar eligibility criteria. For instance, both allowed patients who had a viral load of more than 1,000 copies/mL and at least one primary PI mutation to enroll. Resistance testing was done at baseline (using the same test). However, because the RESIST studies were somewhat more restrictive in the resistance patterns defined for eligibility, there were some limitations as to the PI-resistance profile of the participants.

In all four studies, an optimized background regimen was constructed, with the optional use of enfuvirtide. NNRTIs were allowed in the RESIST studies (and used in 17% of the patients), while they were excluded from the POWER studies.

The baseline demographics were very similar across all four studies, as were the baseline HIV RNA data (4.6 log copies/mL in the POWER studies; 4.8 log copies/mL in the RESIST studies). Median CD4+ cell counts at baseline were also similar (153 cells/mm^3 in POWER; 155 cells/mm^3 in RESIST).

The level of treatment experience among patients was also well-matched between the POWER and RESIST studies. In both groups there was a median of four prior PIs used, and similar numbers of patients had prior experience with enfuvirtide (17% POWER; 12% RESIST). At baseline, there was a median of three PI mutations seen in both series of studies. By phenotype, again there were similarities: For example, there was a more than 79-fold resistance to lopinavir in the POWER studies, compared to an 87-fold resistance in the RESIST studies. There were similarities when comparing the FC to that of the other PIs as well, including tipranavir (1.8 POWER; 1.7 RESIST). As there were differences in the percentage of patients using enfuvirtide both overall and for the first use, Hill and Moyle conducted one subset analysis to compare the results while controlling for enfuvirtide use.

The POWER studies compared four doses of TMC114, but only one dose -- 600 mg with 100 mg ritonavir twice daily -- is being developed in phase 3 studies. Thus, this twice-daily dose was used for comparison against the results from the RESIST studies of tipranavir, in which 500 mg tipranavir was administered with 200 mg ritonavir twice daily.

In both series of studies, the newer PIs (i.e., tipranavir and TMC114) showed a significant

activity advantage over the comparator PI arm. Hill and Moyle also noted that the response to the control or comparator PI arm was found to be extremely similar between POWER and RESIST -- regardless of whether virologic response was measured using the percentage of patients with:

1. a viral load reduction of 1 log copies/mL or more,
2. a viral load under 400 copies/mL or
3. a viral load under 50 copies/mL.

For example, 19% of the patients in the POWER studies and 16% in the RESIST studies had their viral load fall below 400 copies/mL on the comparator PI arm; 21% of the patients in the POWER studies and 18% in the RESIST studies had at least a 1-log copies/mL reduction in viral load compared to baseline by week 24. This comparison serves to strengthen the authors' contention that these two cohorts were sufficiently similar at baseline as to make it reasonable to compare the responses of patients to each of the newer PIs.

Accordingly, Hill and Moyle presented several analyses of the response to tipranavir versus TMC114. In these analyses, TMC114 appeared to have greater activity based on several outcome measures. For example, TMC114 patients experienced a 1.9-log copies/mL decline in viral load from baseline, versus a 0.8-log copies/mL drop in viral load among the tipranavir patients.

Other analyses showed consistent differences, all of which appeared to favor TMC114. For instance, 48% of the patients in the POWER studies experienced a viral load reduction to less than 50 copies/mL, compared to 23% of patients in the RESIST trials.

Table 2

Benefit of TMC114 + Ritonavir or Tipranavir + Ritonavir Over Control PI in Week 24 Efficacy Data From the POWER and RESIST Trials						
	POWER			**RESIST**		
Parameter	**TMC114 + Ritonavir**	**Control PI**	**TMC114 + Ritonavir Benefit [95% CI]**	**Tipranavir + Ritonavir**	**Control PI**	**Tipranavir + Ritonavir Benefit [95% CI]**
n	99	102	--	582	577	--
$\geq$ 1 $\log_{10}$ HIV RNA reduction (%)	71	21	+50 [39 - 61]	40	18	+22 [17 - 27]
HIV RNA < 400 copies/mL (%)	60	19	+41 [30 - 52]	34	16	+18 [13 - 23]
HIV RNA < 50 copies/mL (%)	48	14	+34 [22 - 44]	23	9	+14 [10 - 18]

log_{10} HIV RNA reduction (SD for POWER trials)	-1.90 (1.25)	-0.49 (0.89)	-1.41 [1.14 - 1.68]	-0.8	-0.25	-0.55 [0.43 - 0.67]
Mean CD4 + cell count rise (cells/ mm^3) (SD for POWER trials)	+98 (120)	+17 (107)	+81 [52 - 110]	+34	+4	+30 [19 - 42]
SD = standard deviation CI = confidence interval						

Within the subset of patients that used enfuvirtide, the comparison again consistently favored TMC114. For example, for patients who used enfuvirtide for the first time after enrolling in these studies, 64% in the POWER study had their viral loads fall below 50 copies/mL, while 36% of RESIST participants achieved this degree of suppression. The statistical comparison focused on the magnitude of the difference between the comparator arm and the newer PI, using the absolute difference within a 95% confidence interval. For all of Hill and Moyle's analyses of virologic activity, there was statistically greater activity seen among patients on TMC114 than tipranavir.

Hill and Moyle conclude that the data show statistically greater activity of TMC114 than tipranavir when each drug is pitted against a comparator PI. This suggests that TMC114 may be a more active agent than tipranavir in treatment-experienced patients, since the magnitude of the benefit of the newer PI versus the comparator arm consistently favored TMC114. This trend was seen even when controlling for the use of enfuvirtide.

The authors argue that their approach to comparing TMC114 and tipranavir was valid, as the inclusion criteria and design were similar between the POWER and RESIST studies, as were the baseline characteristics on several important measures, including predictors of response other than the PI used. However, there are always limitations to the strength of the conclusions one can make when comparing across trials. One analysis not done here that would also be of interest is a comparison of outcomes when both drugs were predicted to have activity, rather than looking at overall outcomes. It is certainly possible that there is greater retained activity to TMC114 given a broad spectrum of highly PI-resistant virus. However, there also may be greater similarity in the response rates for TMC114 and tipranavir when each drug is used "appropriately" -- i.e., in those predicted to have susceptible virus to that PI.

As a result of this research (as well as that by Eoin Coakley,[5] summarized earlier in this article), more refined algorithms have been developed in order to predict which patients are most likely to respond virologically to TMC114 or tipranavir. While the FC to tipranavir was similar at baseline in the POWER and RESIST studies, it is possible that there were greater numbers of patients enrolled in the RESIST trials for which current algorithms would suggest reduced activity from tipranavir. Because the criteria to determine such thresholds were in part identified as a result of these studies, it is clear that the question posed by this analysis can only be rigorously and fairly answered by future randomized, comparison studies that directly compare TMC114 and tipranavir in PI-experienced patients

whose resistance profile predicts that both PIs are fully active at study entry.

TMC125

There is a critical need for a second-generation NNRTI that has the dosing simplicity of currently available NNRTIs and that can be used in sequence. The NNRTI TMC125, which has been engineered to have a high genetic barrier to resistance, is one such candidate -- in fact, it is the only candidate currently in phase 3 clinical trials.

TMC125 Effective Against NNRTI Resistance Through 48 Weeks: Study TMC125-C223

Data documenting the activity of TMC125 for at least 24 weeks were first presented at the 10th European AIDS Conference in Dublin, Ireland, in November 2005.[22,23] However, due to concerns about the durability of response for a new NNRTI in NNRTI-resistant patients, there has been interest in ensuring that any initial activity observed would endure. Data from a study documenting the preserved activity of TMC125 in combination with a variety of background regimens were presented at the 12th Annual Conference of the British HIV Association.[24]

To participate in this study, patients were required to have NNRTI resistance and at least three primary PI mutations. This is a group of patients for whom new treatment options are particularly critical given their broad cross-resistance. The study design was somewhat distinct, based in part on the known pharmacokinetic (PK) interactions at the time the study was underway.

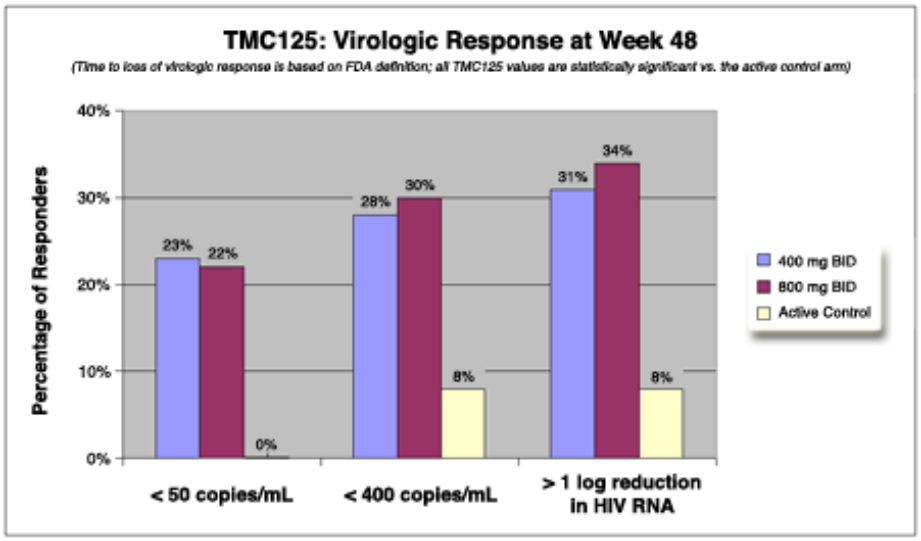
STUDY SNAPSHOT	
Design:	TMC125-C223 is a randomized, controlled trial assessing safety and efficacy of TMC125 in experienced patients.
Population:	199 patients with NNRTI resistance and at least three PI mutations.
Main Results:	TMC125 activity is durable through 48 weeks, with acceptable safety profile; concerns raised about continuing previous NNRTI-based therapy in face of virologic failure.
Significance:	TMC125 may provide a durable new option for patients with clear NNRTI resistance.

This was a triple-arm, randomized, controlled comparison of one of two doses of TMC125 (400 mg or 800 mg, each administered twice daily) given in combination with a background regimen. The background regimen was comprised of investigator-selected NRTIs; clinicians who chose to add a PI could only use lopinavir/ritonavir, a choice based on then-available PK interaction data. Clinicians were also allowed to use enfuvirtide in the regimen. The control arm was prescribed the best regimen that could be constructed from the available antivirals at the time.

In all, 159 people were randomized to one of the two TMC125 doses, and 40 were randomized to the control. The median baseline CD4+ cell count was about 100 in all arms, and the median baseline HIV viral load was about 4.7 log copies/mL. The results at week 48 validate what had previously been observed at week 24. In fact, 88% of those who had a viral load of less than 50 copies/mL at week 24 in this study maintained this degree of suppression at week 48.

Patients in this study had significant cross-resistance to current treatments, as demonstrated by the fact that, in the control arm, median viral load had only dropped by 0.14 log copies/mL at week 48. However, patients in the arm taking the 800-mg, twice-daily dose of TMC125 had a viral load that was 1.01-log copies/mL lower at week 48, and patients in the arm taking the 400-mg, twice-daily dose of TMC125 had a viral load that was 0.88-log copies/mL lower. At week 48, 22% of the patients on the higher dose of TMC125 had a viral load of less than 50 copies/mL, compared to none on the control -- a highly significant difference.

Figure 6

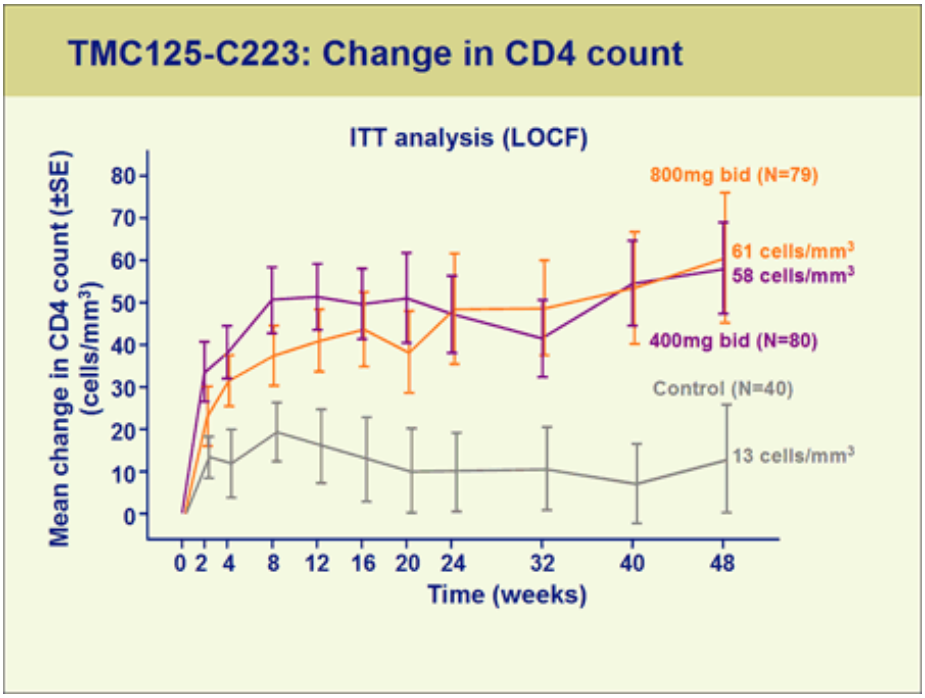


Click to enlarge

Just as they had at week 24, patients who had one or more active antivirals in their regimen in addition to TMC125 experienced a greater virologic response at week 48: with more than a 1-log copies/mL decline, in fact, versus a 0.6-log copies/mL decline when there were no other active antivirals. (In this subset of patients, there was no change in viral load within the control arm.)

This is an interesting finding: It is consistent with the concept of a better genetic barrier to resistance for TMC125, and suggests that there can be a durable response to this NNRTI even if the remainder of the regimen is minimally active. Not surprisingly, there was a significantly better CD4+ cell increase (about 60 cells/mm^3) at week 48 in patients on the TMC125 arms, compared to a 13 cells/mm^3 increase for patients on the control arm.

Figure 7



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In terms of safety issues, one way to examine these data is to compare the rates of specific events and note which were more frequent on the TMC125 arms versus the control arm, rather than only noting how often a specific adverse event was observed. However, this comparison gets complicated when one takes into account that patients spent much more time overall on the TMC125 arms than on the control arm (given that 78% of all control patients discontinued treatment by week 48 due to virologic failure, versus 9% of TMC125 patients). As a result, patients on the TMC125 arms also had more time to develop side effects.

Nonetheless, in this all-grade summary, there was a higher rate of many adverse events in the TMC125 arms compared to the control arm.

Table 3

Safety Overview of TMC125 in Patients With NNRTI Resistance and ≥3 Primary PI Mutations		
Most Common Adverse Events	**All TMC125 n (%) N=159**	**Active Control n (%) N=40**
Median Treatment Duration	**48 Weeks**	**18 Weeks**
Diarrhea	35 (22)	6 (15)
Any rash	32 (20)	3 (8)
Injection site reaction	32 (20)	10 (25)
Pyrexia	32 (20)	4 (10)
Fatigue	25 (16)	6 (15)
Headache	25 (16)	2 (5)

Nausea	24 (15)	6 (15)
Lymphadenopathy	22 (14)	4 (10)
Insomnia	21 (13)	4 (10)

- Safety comparisons confounded due to high rate of treatment discontinuation in control group, leading to substantial difference in treatment duration between groups.
- Adverse events reported in 99% of patients in TMC125 groups and in 78% of the control group.
- Both TMC125 doses were equally well tolerated.

As seen with other NNRTIs, a higher proportion of the patients had a report of rash while on TMC125 (20%, versus 8% of the control patients) -- although it should be noted that only three people had a grade 3/4 rash that could potentially be attributed to TMC125, and that the rash led only 4% of patients to permanently discontinue TMC125. Lab abnormalities of grade 3 or severity that occurred on the TMC125 arms were pancreatic lipase (8%) and elevated creatinine (4%). There was only one serious adverse event (pancytopenia) on the higher dose of TMC125, and three other events on the lower dose.

In sum, TMC125 has documented durable activity in patients who have clear NNRTI resistance, and has a reasonable safety profile as well. Although the three currently approved NNRTIs (delavirdine [DLV, Rescriptor], efavirenz [EFV, Sustiva, Stocrin] and nevirapine [NVP, Viramune]) have no validated approach to successful "sequencing," it is clear that TMC125 will have preserved activity despite NNRTI resistance.

Effect of Baseline Resistance on TMC125 Response

Based on the 24-week outcome data from the TMC125-C223 study, Johan Vingerhoets and colleagues retrospectively analyzed all patients who received the 800-mg twice daily dose of TMC125 to determine the effect of baseline resistance on the virologic response to treatment.[25] Their analysis was presented at the 4th European HIV Drug Resistance Workshop.

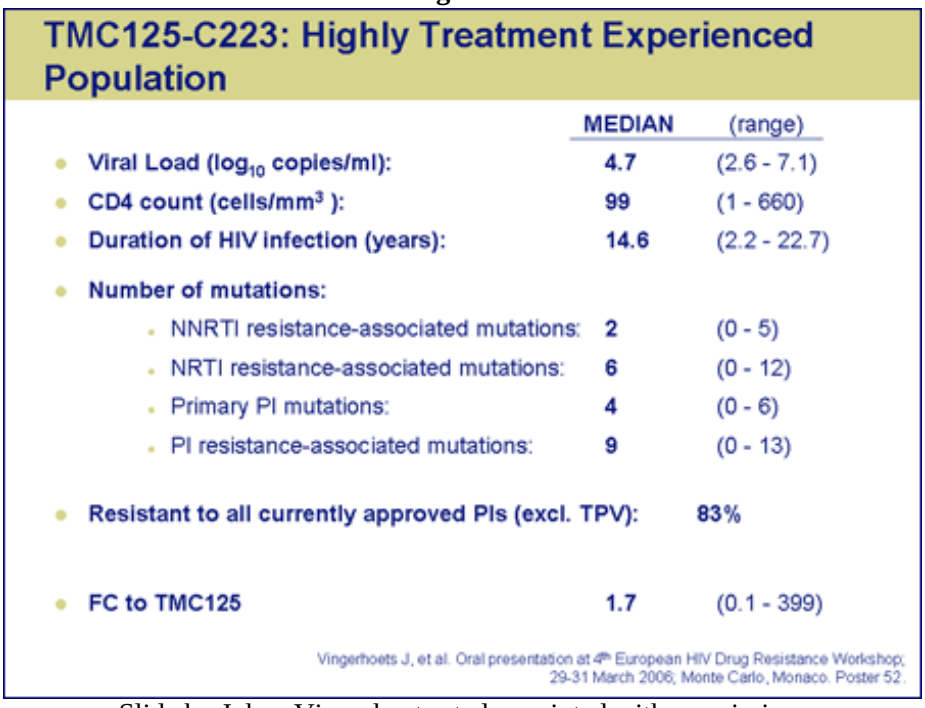
STUDY SNAPSHOT

Design:	Retrospective analysis of the phase 2 TMC125-C223 trial to investigate the baseline resistance parameters and virologic response associated with the number of baseline NNRTI mutations.
Population:	79 heavily treatment-experienced patients who received TMC125 800 mg twice daily plus an optimized background regimen.
Main Results:	Patients with fewer than three NNRTI-resistance mutations achieved at least a 1-$\log_{10}$ reduction in viral load as opposed to patients with three or more mutations. An increasing number of NNRTI-resistance mutations correlated with a decreased virologic response.

Significance:	TMC125 represents the first NNRTI to be effective against HIV in patients with extensive NNRTI resistance.

The 79 patients included in the analysis harbored a median of four PI-resistance mutations and two NNRTI-resistance mutations. Only 17% of the patients showed some phenotypic susceptibility to a PI, and the median FC to efavirenz and nevirapine was 41 and 61, respectively.

Figure 8



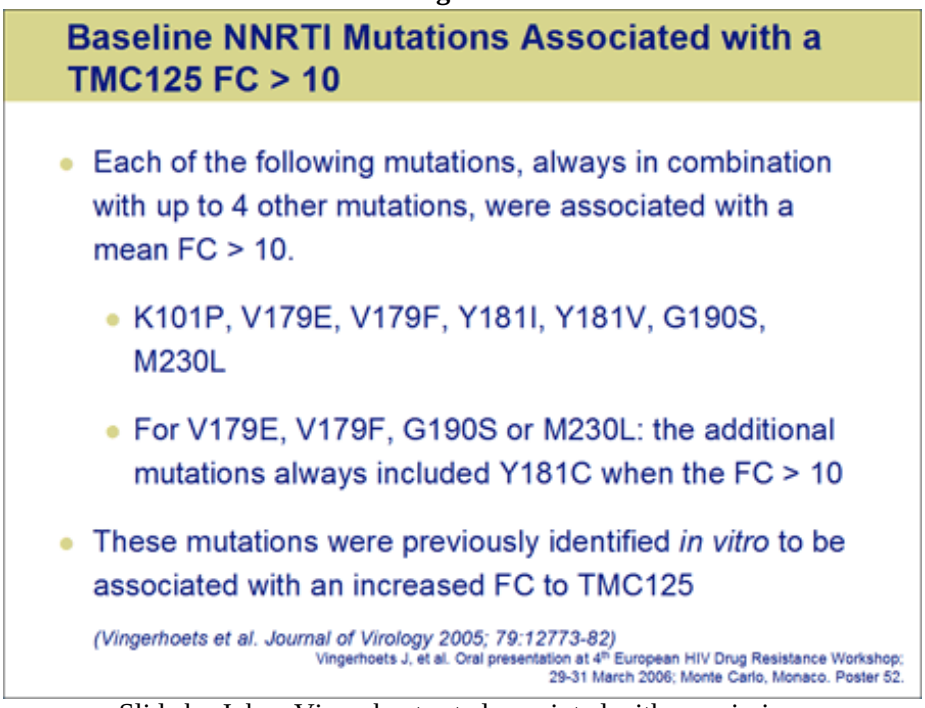
Slide by Johan Vingerhoets et al; reprinted with permission.

The researchers determined that patients with fewer than three NNRTI-resistance mutations achieved a viral load reduction of at least 1 $\log_{10}$ copies/mL, whereas those with three or more mutations achieved a mean reduction of only 0.86 $\log_{10}$ copies/mL -- though still substantially greater than the reduction observed in the control group (0.19 $\log_{10}$ copies/mL).

Table 4

Virologic Response to TMC125 at Week 24 Based on the Number of NNRTI Mutations Present at Baseline	
Number of NNRTI Mutations at Baseline	**Virologic Response, $\log_{10}$ copies/mL**
0	-1.82
1	-1.65
2	-1.00
$\geq$ 3	-0.66

Figure 9



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These findings demonstrate that TMC125 maintains significant activity against HIV even in the presence of some NNRTI-resistance mutations. No other NNRTI has demonstrated such potency in a salvage setting. Even in patients with K103N (the most frequent mutation that appears when an efavirenz-based approach fails), a more than 1.5-log decrease can be achieved with TMC125.

However, based on these and other data, it is now critical to consider interrupting NNRTI-containing regimens at the time of virologic failure in order to minimize the risk of selecting for a greater number of NNRTI mutations, which appears to undermine the activity of this new compound. Phase 3 studies are well underway and will further characterize the future role of this new antiviral.

Conclusion/Closing Comments

The treatment of drug-experienced patients -- many of whom started therapy in the pre-HAART era -- remains one of the key challenges for clinicians. Our hope for durable HIV RNA suppression lies in newer drugs and drug classes with improved resistance characteristics. Although studies of recently approved and investigational agents have shown greatly improved results in this patient population, clearly not all have benefited equally from these new therapies. It is urgent that we define the resistance characteristics of these drugs; determine clinically relevant genotypic and phenotypic patterns and levels; and compare these with other drugs of the same class.

The 4th European HIV Drug Resistance Workshop and the 12th Annual Conference of the British HIV Association were two important venues where recently generated data on such issues were presented and discussed. Refinement of our understanding of important salvage drugs such as tipranavir and tenofovir, and insight into the resistance of drugs in advanced clinical development such as TMC125 and TMC114 were presented. Mechanisms and early reports on resistance to investigational new drug classes such as the CCR5 and integrase

inhibitors were also discussed and there were examinations of updates on new resistance technologies and epidemiology studies and their clinical relevance.

But many questions remain unanswered. Can we really extrapolate data from different studies in attempt to compare tipranavir and TMC114 -- or have we learned that this is an unwise practice and that we require true comparative studies? Which and how many NNRTI mutations will preclude or substantially reduce any durable response from TMC125 in NNRTI-experienced patients? What will be the incidence and clinical impact of resistance to CCR5 inhibitor therapy?

Hopefully future meetings will address these important questions.

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