Drugs of the Future 2008, 33(8): 691-699

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.08.1206423

Review Article

The rise of second-generation non-nucleoside reverse transcriptase inhibitors: etravirine, rilpivirine, UK-453061 and RDEA-806

Mark Abdel-Malak, Christine Gallati, Shaker A. Mousa*

The Pharmaceutical Research Institute, Albany College of Pharmacy, 1 Discovery Drive, Rensselaer, NY 12144, USA.
**Correspondence: mousas@acp.edu*

CONTENTS

Abstract

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a crucial component of current highly active antiretroviral therapy (HAART) treatments for HIV-1 infection. One of the major limitations of the two most widely used NNRTIs, efavirenz and nevirapine, is their low genetic barrier to resistance, in addition to their undesirable side effects. The goal of current investigational NNRTI development is to create a safe, well-tolerated drug with a high genetic barrier to resistance that is active against known NNRTI-associated resistance mutations. This review discusses three investigational NNRTIs, rilpivirine (TMC-278), UK-453061 and RDEA-806, which are at different stages of development, as well as etravirine (TMC-125), a second-generation NNRTI that was recently granted accelerated approval by the FDA.

Introduction

Highly active antiretroviral therapy (HAART) was introduced in the 1990s, revolutionizing the treatment of HIV infection. HAART involves combining drugs from different classes with the goal of suppressing viral load and increasing $CD4^+$ cell counts. Drugs from existing and new classes have steadily continued to receive FDA approval since the introduction of HAART, resulting in the evolution and optimization of therapeutic drug combinations. Nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are the classes of drugs that currently comprise the core of HAART.

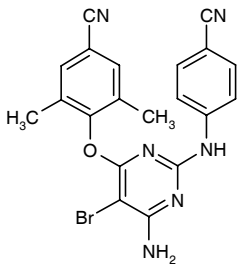
Current guidelines for HIV-1-infected adults recommend HAART regimens that include at least three drugs; the standard treatment usually consists of a combination of two NRTIs and an NNRTI or a ritanovir-boosted protease inhibitor (r/PI) (1). The guidelines do not recommend triple- or quadruple-class regimens containing both NNRTIs and PIs, as these regimens have failed to show additional benefits (1-3). Although both PI- and NNRTI-based HAART regimens are acceptable first-line treatments according to current guidelines, NNRTI-based regimens are the preferred first-line treatment for many patients. There are currently four FDA-approved NNRTIs: efavirenz (EFV), nevirapine (NVP), delavirdine (DLV) and etravirine (TMC-125). DLV is not recommended under current guidelines, as it is the least potent NNRTI (1), and it will therefore not be discussed in this review. Etravirine was recently granted accelerated approval by the FDA (January 18, 2008) and is indicated for use in combination with PI-based HAART for NNRTI-experienced patients (4). This review will provide an overview of the development of etravirine and other NNRTIs in the pipeline (Table I).

Current NNRTI therapy

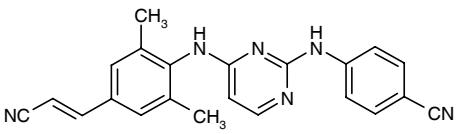
EFV-based HAART regimens are in many cases preferred over PI- and NVP-based regimens as first-line therapy. NVP or PIs may be selected over EFV, however, because the side effects associated with these agents are more tolerable for certain patients in comparison to the side effects associated with EFV. PI use has been associated with some undesirable side effects, including peripheral fat wasting, excessive central fat deposition (lipodystrophy), hyperlipidemia and insulin resistance (5).

Table I: Summary of second-generation NNRTI drugs on the market and in development.

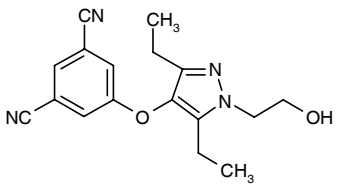
Drug	Source	Development status	Notes
Etravirine (TMC-125)	Tibotec	Approved by the FDA (1/18/08)	Approved for use in combination therapy for treatment-experienced patients
Rilpivirine (TMC-278)	Tibotec	In an ongoing phase IIb trial, different doses of rilpivirine will be compared to efavirenz in treatment-naïve patients	
UK-453061	Pfizer	Successfully completed a phase IIa trial in NNRTI-naïve patients; awaiting phase II/III trials	
RDEA-806	Ardea	Currently in phase II trials in NNRTI-naïve patients	
Dapivirine (TMC-120)	Tibotec	Development discontinued as a treatment for HIV infection	Possible utility as antimicrobial agent for preventing HIV transmission
MIV-150	Medivir/Chiron	Development discontinued as a treatment for HIV infection	Possible utility as antimicrobial agent for preventing HIV transmission



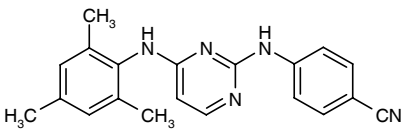
Etravirine



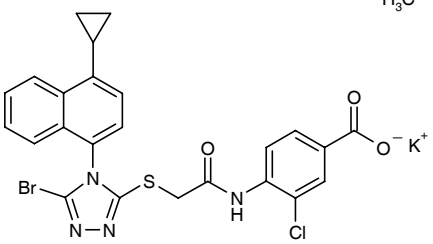
Rilpivirine



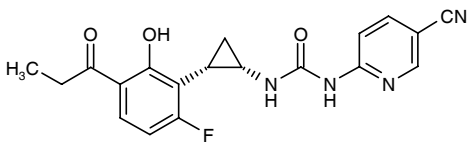
UK-453061



Dapivirine



RDEA-806



MIV-150

The results from a number of cohort studies and clinical trials have promoted the preferential use of NNRTIs, particularly EFV, in first-line treatment (6-9). One of the earliest and most definitive studies to suggest that EFV-based regimens were superior to PI-based regimens was a clinical trial conducted by Staszewski *et al.* in 1999 (6). This clinical trial compared EFV-, indinavir- (IDV; a PI) and combination EFV/IDV-based regimens. The EFV group showed significantly better viral load suppression and fewer adverse reactions than the other groups. The combination EFV/IDV group showed similar viral load suppression to the IDV group.

Another clinical trial conducted by Riddler *et al.* gave similar results (9). In this trial an EFV-based regimen was compared to a lopinavir- (LPV; a PI) based regimen and a combination EFV/LVP-based regimen. The EFV-based regimen again demonstrated superior viral load suppression and fewer adverse reactions in comparison to the LVP- and EFV/LVP-based regimens.

Although PI-based HAART regimens have demonstrated less efficacy than EFV-based therapies, they still have a crucial role in the treatment of HIV-1-infected patients who may not tolerate an NNRTI-based regimen. After experiencing virological failure or significant intolerance on an NNRTI-based regimen, a switch to a PI-based regimen can offer renewed suppression of viral load.

Limitations of current NNRTIs

The two major limitations of the currently available NNRTIs are crossresistance and safety problems. When

a patient is treated with an NNRTI, there is positive selection for HIV virus particles that have mutations in their reverse transcriptase genes which affect the binding of the NNRTI to the enzyme. When the NNRTI loses its ability to bind reverse transcriptase, the replication of those mutated HIV strains becomes unchecked and the viral load rebounds. The patient's body is then repopulated by new NNRTI-resistant HIV virus particles. Mutations causing single amino acid substitutions in critical regions of the reverse transcriptase gene are sufficient to produce resistance to EFV and NVP (10, 11). Patients treated with either EFV or NVP often develop crossresistance to the other drug because both EFV and NVP bind to the same region on reverse transcriptase. Mutations isolated in EFV-treated patients that confer crossresistance to NVP include: K103N, Y118L and G190S (11). K103N is by far the most frequently observed mutation in patients who are failing EFV treatment regimens. In one study, 90% of the subjects failing EFV regimens were reported to have this mutation. Common mutations isolated in NVP patients that confer crossresistance to EFV include: K101E, K103N and Y188L (12). Even single doses of NVP for the prevention of mother-to-child transmission during birth are sufficient to increase the prevalence of K103N and Y181C mutations leading to the development of NNRTI resistance. After a single dose of NVP, researchers found crossresistance mutations emerging in at least 65% of the women included in one study (13).

Adverse events associated with the use of EFV and NVP are also an important limitation that could be improved upon in future NNRTIs. Adverse events characteristic of EFV use include a variety of neuropsychiatric phenomena, such as dizziness, somnolence, insomnia, abnormal dreams such as nightmares, amnesia, agitation, depersonalization, hallucinations and euphoria. Dermatological complications are also common with EFV use, ranging from erythema and pruritus to Stevens-Johnson syndrome and toxic epidermal necrolysis (1).

NVP is notorious for hepatotoxicity-related adverse events. These side effects range from elevated hepatic enzymes to hepatitis or hepatic failure. This is of particular concern in the treatment of HIV patients coinfected with hepatitis B and C. Hepatotoxicity secondary to NVP treatment commonly occurs early in therapy and more frequently in female patients. NVP-induced hepatotoxicity is correlated with higher baseline $CD4^+$ cell counts; females with $CD4^+$ cell counts exceeding 250 cells/μl and males with $CD4^+$ cell counts exceeding 400 cells/μl are at greater risk (1, 14).

The limitations of EFV and NVP have stimulated interest in the development of new, second-generation NNRTIs. It is hoped that these investigational NNRTIs will be associated with more tolerable side effects, as well as antiviral activity against HIV-1 with NNRTI-associated resistance mutations. Second-generation NNRTIs in development include rilpivirine (TMC-278; Tibotec), RDEA-806 (Ardea) and UK-453061 (Pfizer). A number of NNRTIs that looked promising in preliminary clinical trials and *in vitro* studies have now had their development halted because they proved to be ineffective or dangerous (or both) in clinical trials. This list of drugs includes DPC-083, DPC-961 and DPC-963 (Bristol-Myers Squibb), atevirdine (Pfizer), capravirine (Pfizer/Agouron), PNU-142721 (Pfizer), GW-5634 and GW-678248 (GlaxoSmithKline), emivirine (Coactinon®; Triangle Pharmaceuticals), HBY-097 (Bayer, sanofi-aventis), loviride (Janssen), BILR-355BS (Boehringer Ingelheim), (+)-calanolide A (Sarawak MediChem), dapivirine (TMC-120; Tibotec) and MIV-150 (Medivir, Chiron). Although dapivirine and MIV-150 are no longer being considered as therapeutic agents for the treatment of HIV infection, they are currently being investigated for their utility as antimicrobial agents for the prevention of HIV transmission.

Etravirine (TMC-125), which is marketed under the name Intelence™, is the first second-generation NNRTI to receive FDA approval. On January 18, 2008 it was granted accelerated approval by the FDA for the treatment of NNRTI-experienced patients. Etravirine has shown activity against HIV-1 strains with the K103N mutation in the clinical setting. Etravirine had been available since 2006 through the U.S. Expanded Access Program for the treatment of HIV-1-infected individuals who had exhausted all licensed NNRTI therapies and were experiencing virological failure or intolerance to their current antiretroviral regimen (4).

Etravirine

Etravirine is a diarylpyrimidine that binds directly to HIV-1 reverse transcriptase and interferes with its global binding hinge mechanism, thereby disturbing the enzyme's motion (15). In early *in vitro* studies etravirine demonstrated potent activity against HIV-1 strains harboring the K103N and Y181C mutations, as well as activity against the wild-type virus (16, 17). It is believed that etravirine has an inherent molecular flexibility, allowing it to bypass these common enzyme mutations and remain bound to reverse transcriptase (16, 18).

While the results from these *in vitro* studies were, indeed, very exciting, later clinical trials revealed that the presence of other NNRTI-associated resistance mutations could decrease the virological response to etravirine. These mutations include: V179D, V179F, V179T, Y181V and G190S. Additionally, a decreased virological response was also associated with the presence of three or more of the following mutations: V90I, A98G, L100I, K101E/P, K103N, V106A/I/M, V108I, V179D/F, Y181C/I/V, Y188C/H/L, G190A/S and P225H. Tibotec recently stated that it expects virological failure with etravirine to result in crossresistance to EFV and NVP. Studies have shown that virological failure on an etravirine-containing regimen is commonly associated with the appearance of the NNRTI resistance-associated mutations V179F, V179I, Y181C and Y181I. Less commonly observed NNRTI resistance mutations include K101E, K103N, V106I/M, V108I, Y188L, V189I, G190S/C and R356K (19).

In summary, etravirine has antiviral activity in EFV- and NVP-experienced patients; its efficacy, however, is

dependent upon the presence of particular NNRTI-associated resistance mutations, as well as the variety/quantity of NNRTI-associated resistance mutations that have been acquired. In addition, the utility of etravirine will probably be limited by the fact that its use can result in crossresistance to EFV and NVP.

Currently, it is not recommended that etravirine be administered alone or with NRTIs only (4, 19). Instead, etravirine will probably be added to standard PI-based regimens in addition to two NRTIs. Current guidelines do not recommend triple-class HAART regimens, but in light of the clinical data reviewed in this article, this recommendation will most likely be modified to reflect the utility of etravirine, as well as emerging drugs from other classes.

TMC125-207

The TMC125-207 study was a small (n=16) open-label phase IIa trial that included patients with phenotypic resistance to NVP or EFV who were failing NNRTI-based HAART (20). This 7-day trial was designed to assess the short-term efficacy and safety of etravirine. All subjects received 900 mg of etravirine twice daily in place of their current NNRTI. The mean viral load decay rate was determined to be 0.13 $\log_{10}$ copies/ml/day of HIV-1 RNA and the mean decrease from the baseline viral load was 0.86 $\log_{10}$ copies/ml of HIV-1 RNA. After 7 days, 88% of the patients achieved a viral load decrease of > 0.5 $\log_{10}$ copies/ml of HIV-1 RNA from baseline, but only 44% were able to achieve decreases of > 1.0 $\log_{10}$ copies/ml. One patient developed the K103N/K mutation during the trial, but still demonstrated a significant decrease in HIV-1 viral load. Only 2 patients (12.5%) achieved viral loads of < 400 copies/ml of HIV-1 RNA, and none of the subjects attained a reduction in viral load to < 50 copies/ml of HIV-1 RNA or demonstrated significant increases in $CD4^+$ cell count. These failings were attributed to the short duration of the study, as well as the lack of immunological compromise in the pool of subjects.

TMC125-208

TMC125-208 was a randomized, double-blind, placebo-controlled phase IIa trial conducted in treatment-naïve subjects (n=19) (21). This study assessed the drug's efficacy as monotherapy over 7 days. The subjects were randomized into two groups, one receiving 900 mg etravirine twice daily and the other placebo. The decay rate of HIV-1 RNA was significantly greater in the etravirine group compared to placebo (0.33 $\log_{10}$ copies/ml/day of HIV-1 RNA *vs.* 0.02 $\log_{10}$ copies/ml/day of HIV-1 RNA; $p < 0.001$). This decay rate was more than double that reported in the TMC125-207 trial. The average decrease in viral load from baseline in the etravirine group was also significantly greater than in the placebo group (1.99 $\log_{10}$ copies/ml of HIV-1 RNA *vs.* 0.06 $\log_{10}$ copies/ml of HIV-1 RNA; $p < 0.001$); all patients in the etravirine group achieved a decrease in viral load of > 1 $\log_{10}$ copies/ml, whereas none of the subjects in the TMC125-207 trial attained this level of reduction.

Additionally, a significantly larger proportion of patients in the etravirine group were able to achieve viral loads of < 400 copies/ml of HIV-1 RNA in comparison to the placebo group (67% *vs.* 0%; $p < 0.001$). A number of patients in the etravirine group, but not the placebo group, had their viral loads reduced to < 50 copies/ml of HIV-1 RNA (17% *vs.* 0%; $p < 0.001$). This clinically important benchmark was not achieved in the TMC125-207 trial. The subjects who received etravirine also showed significantly higher $CD4^+$ cell counts than the placebo group ($p = 0.016$). The etravirine group experienced a mean increase in $CD4^+$ cell count from baseline of 104 cells/μl, whereas the $CD4^+$ cell count in the placebo group showed a slight decrease. These results are in contrast to the TMC125-207 study, which found no significant increase in $CD4^+$ cell counts. The more favorable response to etravirine in this trial in comparison to the TMC125-207 trial can probably be attributed to the fact that the patients in this study were NNRTI-naïve, whereas the patients in the TMC125-207 were treatment-experienced.

DUET-1 and DUET-2

The DUET-1 and DUET-2 trials are both large (n=615 and n=593, respectively) ongoing trials investigating etravirine in treatment-experienced patients failing antiretroviral therapy (22, 23). Both studies are multinational, randomized, double-blind, placebo-controlled phase III trials. All subjects had at least one NNRTI resistance-associated mutation and at least three primary PI mutations at the time of screening. Subjects in the control groups received placebo, while the intervention groups received 200 mg of etravirine twice daily. Additionally, all patients received ritanovir-boosted darunavir (darunavir/r), optional enfuvirtide (a fusion inhibitor) and NRTIs selected on the basis of resistance profiles at screening. The findings presented were taken from the 24-week interim reports of each trial, as the studies are ongoing.

In the DUET-1 trial, a significantly larger proportion of the subjects in the etravirine group achieved a viral load of < 50 copies/ml of HIV-1 RNA compared to the subjects in the placebo group (56% *vs.* 39%; $p < 0.005$). The etravirine patients also achieved a significantly larger mean decrease from their baseline viral load in comparison to the placebo group (2.41 $\log_{10}$ copies/ml of HIV-1 RNA *vs.* 1.70 $\log_{10}$ copies/ml of HIV-1 RNA; $p < 0.0001$). Additionally, subjects in the etravirine group also experienced a significantly larger increase in mean $CD4^+$ cell count as compared to the patients in the placebo group (+89 cells/μl *vs.* +64 cells/μl; $p = 0.0002$).

In the DUET-2 trial, a significantly larger proportion of the patients in the etravirine group achieved viral loads of < 50 copies/ml of HIV-1 RNA at 24 weeks compared to the placebo group (62% *vs.* 44%; $p = 0.0003$). These results not only paralleled but exceeded the results from the DUET-1 trial. Similar results in the etravirine arm were

also achieved with regard to mean total reduction in viral load from baseline. A significantly greater mean decline in viral load was seen in the etravirine group in comparison to the placebo group (2.34 $\log_{10}$ copies/ml of HIV-1 RNA *vs.* 1.68 $\log_{10}$ copies/ml of HIV-1 RNA; $p < 0.0001$). In contrast to the DUET-1 trial, no significant difference in mean $CD4^+$ cell count changes from baseline was detected between the etravirine group and the placebo group (+78 cells/μl *vs.* +66 cells/μl; $p = 0.3692$).

To ensure that optional enfuvirtide use was not a confounding variable in achieving endpoints, a separate analysis was also conducted that stratified the subjects in each group into three categories: 1) *de novo* enfuvirtide users; 2) enfuvirtide reusers; and 3) those who did not use enfuvirtide at all. In the DUET-1 trial, significantly more *de novo* enfuvirtide users achieved a viral load of < 50 copies/ml of HIV-1 RNA compared to those in the control group who reused or did not use enfuvirtide (55% *vs.* 33%; $p < 0.0001$). In contrast, no significant difference in the proportion of patients achieving viral loads of < 50 copies/ml of HIV-1 RNA was found between the etravirine group and the control group in patients who received enfuvirtide *de novo* (59% *vs.* 56%; $p < 0.7935$). The *de novo* use of enfuvirtide in addition to darunavir/r thus produced an improvement that appeared to be on a par with the *de novo* use of etravirine plus darunavir/r.

TMC125-C223

The TMC125-C223 trial is an ongoing multicenter, open-label, partially blinded, randomized phase IIb clinical trial investigating etravirine in treatment-experienced subjects with at least one NNRTI mutation and at least three PI mutations (24). Subjects received etravirine (400 or 800 mg) plus at least two of the following: an NRTI, LPV/r or enfuvirtide. Patients in the control group received at least three of the following: NRTI(s), PI(s) and enfuvirtide.

At week 24 a higher proportion of patients in the control group (75%) discontinued early due to virological failure compared with the 400- (6.3%) and 800-mg (5.1%) etravirine groups. A significantly larger proportion of patients in the 400- and 800-mg etravirine groups reduced their viral load to < 400 copies/ml of HIV-1 RNA compared to the control group (30% and 38%, respectively, *vs.* 7.5%; $p = 0.018$ and $p = 0.002$, respectively), but the 400- and 800-mg etravirine groups did not have significantly larger proportions of subjects achieving viral loads of < 50 copies/ml of HIV-1 RNA in comparison to the control group (21.3% and 17.7%, respectively, *vs.* 7.5%; $p = 0.133$ and $p = 0.218$, respectively). This contrasts with the results of the DUET-1 and DUET-2 trials, in which a significantly higher proportion of patients achieved viral loads of < 50 copies/ml of HIV-1 RNA at week 24 compared to the control groups. Patients in the 400- and 800-mg etravirine groups also achieved significantly greater reductions in viral load from baseline in comparison to those in the control group (1.04 $\log_{10}$ and 1.18 $\log_{10}$ copies/ml of HIV-1 RNA, respectively, *vs.* 0.19 $\log_{10}$ copies/ml of HIV-1 RNA; $p = 0.005$ and $p < 0.001$, respectively), with a significantly higher proportion of patients in the 400- and 800-mg etravirine groups attaining viral load reductions > 1 $\log_{10}$ copies/ml HIV-1 RNA from baseline compared to the control group (36.3% and 41.8%, respectively, *vs.* 7.5%; $p = 0.005$ and $p < 0.001$, respectively). No significant increases in $CD4^+$ cell counts were detected.

TMC125-C277

The TMC125-C277 trial was a multicenter, randomized, active-controlled, open-label, exploratory trial that was prematurely discontinued. The study was performed on PI-naïve HIV-1-infected patients who were failing an NNRTI-based regimen. Subjects in this study were randomized to receive either 800 mg etravirine plus two NRTIs or a PI plus two NRTIs. Premature termination of the trial was required because the virological response in the etravirine group was lower than that in the PI group. A greater proportion of subjects in the PI arm achieved a viral load of < 50 copies/ml of HIV-1 RNA after 12 weeks of treatment compared to the etravirine arm (52% *vs.* 22%). Additionally, a greater proportion of subjects in the PI arm achieved a > 1 $\log_{10}$ reduction in viral load from baseline. Immunological outcomes were also better in the PI arm. The average increase in $CD4^+$ cell count in the etravirine group was +38 cells/μl, while the average for PI patients was +92 cells/μl. It is believed that baseline NRTI and NNRTI resistance, as well as lack of PI experience in these subjects, explained the inferior virological response observed in the etravirine arm (25).

Safety

The most definitive conclusions with regards to the safety of etravirine can be drawn from the long-term, large-scale DUET trials. In both the DUET-1 and DUET-2, there were similar rates of adverse events (any cause) in both the etravirine and the control groups. No significant differences were observed in the rate of neuropsychiatric events reported between the etravirine group and the control group in either DUET-1 or DUET-2 (36, 37). Treatment-emergent adverse events occurring in ≥ 10% of patients included nausea, diarrhea and headache and occurred at similar frequencies in both the etravirine and control groups (22, 23).

In DUET-1, a significantly greater proportion of patients receiving etravirine experienced rash compared to the control group (20% *vs.* 10%; $p < 0.0001$). All of the rashes were mild, with the exception of 4 cases (1%) of grade 3 rash in the etravirine group. Six (2%) patients in the etravirine group required treatment discontinuation due to rash. In the DUET-2 trial, however, no significant difference in the frequency of rash was found between the etravirine group and the control group (14% and 9%, respectively; $p = 0.0723$), although 7 patients in the etravirine group terminated the trial due to rash compared to none in the placebo group.

In the DUET-1 trial, 4 (1%) patients receiving etravirine died compared to 8 (3%) patients in the placebo group; however, none of these deaths were attributable to etravirine according to the study investigators (22). In the DUET-2 trial, 4 patients (1%) receiving etravirine died compared to 7 (2%) patients in the placebo group. Similarly, none of these deaths were deemed to be related to etravirine by the study investigators (23).

The discontinued TMC125-C277 trial is of interest in terms of adverse events, because it allows for the direct comparison of a PI-based regimen with etravirine-based treatment. The etravirine group had a significantly lower incidence of diarrhea (3% *vs.* 25%) (25). However, although etravirine may be better tolerated than PIs, its inferior efficacy in this trial is more important in determining the utility of this drug.

Emerging safety data on etravirine have revealed a comprehensive list of adverse events, which were mostly minor and/or transient. Common etravirine adverse events are gastrointestinal (nausea, diarrhea), dermatological (rash) and neurological (headache) in nature. Etravirine appears to be devoid of some of the notorious side effects of EFV and NVP, as these trials typically found little neuropsychiatric and hepatotoxic adverse events with etravirine use. Etravirine is similar to both EFV and NPV in that it may produce rash of varying severity, ranging from erythema and pruritus to Stevens-Johnson syndrome or toxic epidermal necrolysis.

Discussion of etravirine trials

The TMC125-C223 and DUET trials have shown that the addition of etravirine to a second-line PI-based HAART regimen can provide notable benefits; etravirine can bolster the antiviral activity of a PI-based regimen even after a patient experiences virological failure while receiving an EFV- or NVP-based regimen. This can be attributed to etravirine's ability to bind reverse transcriptase proteins that have common NNRTI resistance-associated mutations such as K103N and Y181C.

The results from the other studies reviewed, especially the TMC125-C277 trial, indicate, however, that etravirine should probably be used as an adjunct to traditional second-line, PI-based HAART therapies. Although etravirine has activity against mutant viruses resistant to EFV and NVP, its efficacy is decreased in NNRTI-experienced patients, as demonstrated by a comparison of the results from the TMC125-207 and TMC125-208 trials. The TMC125-207 study included patients with phenotypic NNRTI resistance to NVP or EFV who were failing NNRTI-based HAART, whereas the TMC125-208 study was conducted in treatment-naïve subjects. The mean viral load decay rate of the patients receiving etravirine in the TMC125-208 trial was more than double that seen in the TMC125-207 trial. Greater proportions of patients achieved viral loads of < 400 copies/ml of HIV-1 RNA and < 50 copies/ml of HIV-1 RNA in the etravirine group in the TMC125-208 trial in comparison to the TMC125-207 trial. Etravirine-treated patients also showed increases in $CD4^+$ cell counts in the TMC125-208 trial, while none of the patients in the TMC125-207 trial had detectable increases in $CD4^+$ cell counts. All treatment endpoints appear to be improved when exposure to other NNRTIs is limited, as confirmed by the discontinued TMC125-C277 trial.

In the TMC125-C277 trial, which included NNRTI-experienced subjects, the PI-based regimens used were markedly more effective than the etravirine-based regimens. The results from this study are the basis for the manufacturer's recommendation that etravirine be administered with other drugs. The results from the DUET studies provided a strong case for the use of triple-class HAART regimens in certain situations (*i.e.,* the combination of etravirine + PI + NRTIs as second-line therapy for NNRTI-experienced patients). The current guidelines discourage the use of triple-class HAART regimens. These guidelines reflect studies that investigated the combination of EFV + PI + NRTI(s) or NVP + PI + NRTI(s), which found that these regimens provided no additional benefit in comparison to traditional HAART regimens. In the coming years we may see changes made to these official guidelines as etravirine finds its niche in HAART therapy.

Another goal of second-generation NNRTI development was increased safety and tolerability. At the present time, it is not known how the side effects and risks of treatment with etravirine measure up to those associated with other NNRTIs, as there have been no studies directly comparing EFV and NVP to etravirine. The DUET trials, however, have shown that the addition of etravirine to a PI-based regimen does not significantly affect the tolerability and safety of the regimen as a whole. As research continues and the use of etravirine expands, we will gain a better idea of the risks and side effects associated with this drug in comparison to the more established HAART drugs.

Rilpivirine

Rilpivirine (TMC-278), like etravirine, belongs to the diarylpyrimidine class of compounds. Rilpivirine has been shown to have *in vitro* activity against both wild-type and resistant mutated strains of HIV-1, including the L100I, K103N, Y181C, Y188L, K103N+Y181C and L100I+K103N mutants. *In vitro* studies also suggest that rilpivirine has a higher genetic barrier to resistance than the available NNRTIs (26, 27).

Efficacy

The antiviral activity, pharmacokinetics, tolerability and safety of rilpivirine as monotherapy were assessed in the TMC278-C201 trial in antiretroviral-naïve HIV-1-infected patients treated for 7 days (28). Patients were randomized to receive 25, 50, 100 or 150 mg/day rilpivirine or placebo; 47 subjects were included in the study and 9 were randomized to each of the four rilpivirine groups and 11 subjects received placebo. Each group

receiving rilpivirine achieved significantly greater reductions in mean viral load compared to placebo. The mean reduction in viral load from baseline for all groups receiving rilpivirine was 1.199 $\log_{10}$ copies/ml of HIV-1 RNA compared to 0.002 $\log_{10}$ copies/ml of HIV-1 RNA on placebo ($p < 0.01$). A significantly greater proportion of subjects in each rilpivirine group achieved a mean reduction in viral load of > 1 $\log_{10}$ copies/ml of HIV-1 RNA. Twenty-five subjects receiving any dose of rilpivirine achieved this outcome compared with no subject on placebo ($p < 0.01$). The $CD4^+$ cell counts following treatment were not reported because the differences were highly variable and were deemed to be not clinically relevant by the authors.

A randomized, active-control, partially blinded phase IIb trial of rilpivirine is ongoing. The goal of this trial is to evaluate the safety and efficacy of rilpivirine in comparison to EFV. Treatment-naïve HIV-1-infected patients (n=368) were randomized to receive 25, 75 and 150 mg of rilpivirine or 600 mg of EFV. The rilpivirine and EFV arms demonstrated similar efficacy; approximately 80% of patients in each of the arms were able to achieve viral load of < 50 copies/ml at week 48 (29).

Safety

As rilpivirine is only in the early stages of clinical development, it is difficult to assess the safety and tolerability of this agent. The most frequent adverse events reported in the TMC278-C201 trial were gastrointestinal in nature (28). Nine of 36 subjects (25%) receiving rilpivirine experienced adverse gastrointestinal events (including nausea and abdominal pain) compared with 2 of 11 subjects (18%) receiving placebo. Although none of the subjects had any form of hepatitis at screening, grade 1 hepatic laboratory abnormalities emerged in a number of patients receiving rilpivirine. These abnormalities included increased alanine aminotransferase, increased hyperbilirubinemia and decreased lactate dehydrogenase. Four subjects (11%) receiving rilpivirine experienced skin and subcutaneous tissue disorders, compared to none on placebo. The occurrence of neuropsychiatric events was very low in both groups (1 in the rilpivirine group *versus* 2 in the placebo group).

In the ongoing phase IIb clinical trial comparing rilpivirine and EFV, the most common adverse events reported were nausea (35% in the rilpivirine groups *vs.* 29% in the EFV group) and headache (18% *vs.* 16%). Nervous system disorders were observed less frequently in the rilpivirine groups (28%) compared to the EFV group (48%). Psychiatric events were also less frequent in the rilpivirine groups (13%) compared to the EFV group (16%). The incidence of rash was lower in the rilpivirine groups (8%) than the EFV group (19%). Grade 3 or 4 adverse events were more common in the rilpivirine groups in comparison to the EFV group (25% *vs.* 16%), but a similar incidence of serious adverse events (10% *vs.* 9%) and grade 3 or 4 laboratory abnormalities (22% *vs.* 20%) was seen in the rilpivirine and EFV groups (29). Future clinical trials conducted in larger populations will reveal whether or not the adverse reactions observed in this preliminary study represent real limitations for this agent.

UK-453061

Pfizer's UK-453061 has performed well *in vitro*, demonstrating efficacy against both wild-type and clinically relevant mutant HIV-1 strains, including K103N, Y181C and G190A (30). Dosing studies were performed in healthy male adults and the drug was found to be rapidly absorbed and well tolerated (31). A randomized, double-blind, placebo-controlled, multicenter study was then conducted in NNRTI-naïve patients. The subjects in the intervention group received 7-day monotherapy with UK-453061 and had a mean viral load decrease of ≥ 1.7 $\log_{10}$ copies/ml of HIV-1 RNA from baseline values (32). This agent appears to be quite promising and will most likely progress into phase II/III clinical trials.

RDEA-806

Ardea's RDEA-806 has also shown promising activity against both wild-type and clinically relevant mutant HIV-1 strains (33). Additionally, RDEA-806 demonstrated prolonged suppression of viral breakthrough, suggesting that it has a high genetic barrier to resistance (34). A randomized, double-blind, placebo-controlled study was conducted in healthy male volunteers and RDEA-806 was well tolerated and demonstrated good pharmacokinetics that would probably allow for once-daily dosing. Positive results were recently reported from a phase IIa trial examining the efficacy of RDEA-806 as 7-day monotherapy in comparison to placebo in NNRTI-naïve patients.

Conclusions

The development of a safe, second-generation NNRTI with a high barrier to genetic resistance and activity against HIV-1 strains carrying NNRTI-associated resistance mutations has the potential to greatly improve the treatment of HIV-infected patients. Etravirine has fulfilled some of these criteria, but it is not entirely unaffected by NNRTI resistance mutations. Although its activity against strains carrying common mutations, such as K103N and Y181C, should not be understated, its reduced efficacy against HIV-1 strains carrying multiple NNRTI-associated mutations is a major limitation to its clinical use. Patients experiencing virological failure while receiving a first-line EFV- or NVP-based regimen should be switched to a new regimen immediately to reduce the number of NNRTI-associated resistance mutations that are acquired; this practice will allow later treatments that utilize etravirine to be more effective. An additional limitation of etravirine is that it is expected to produce resistance to EFV and NVP. In order to determine whether or not it will be an effective adjunct, thorough genotypic analysis should be performed.

The TMC125-C223 and the DUET trials have shown the benefits of adding etravirine to a second-line PI-based regimen. Although the current guidelines do not recommend triple-class HAART regimens, they may be amended in the coming years to recognize the advantages of adding etravirine, or other emerging drugs, to traditional HAART regimens. Etravirine will most likely be used in salvage therapies and as an adjunct to second-line PI-based regimens for NNRTI-experienced patients.

The development of UK-453061 and rilpivirine is currently at a similar stage. These drugs appear to be well tolerated and have demonstrated the ability to significantly reduce the viral loads of treatment-naïve HIV-positive patients. More studies on UK-453061 and rilpivirine will reveal whether or not these drugs have the potential to succeed where etravirine has failed. Additionally, RDEA-806 has shown potential in *in vitro* studies and appears to be well tolerated in healthy adults. The results from the first preliminary study in treatment-naïve HIV-infected patients should be available soon, and will indicate if this drug is as effective *in vivo* as it has been in the laboratory. Although all of these drugs undoubtedly hold promise, the development of second-generation NNRTIs has proven to be a difficult process, as one may surmise from the list of drugs whose development has been discontinued. It has proven quite difficult to make the leap from good *in vitro* results to effective clinical treatments in this field.

References

1. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adult and Adolescents; Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Available from: http://www.aidsinfo.nih.gov/contentfiles/AdultandAdolescentsGL.pdf

2. Shafer, R.W., Smeaton, L.M., Robbins, G.K. et al. *AIDS Clinical Trials Group 384 Team: Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection*. N Engl J Med 2003, 49(24): 2304-15.

3. MacArthur, R.D., Novak, R.M., Pen, G. et al. *Long-term clinical and immunologic outcomes are similar in HIV-infected persons randomised to NNRTI vs. PI vs. NNRT+PI-based antiretroviral regimens as initial therapy: Results of NNRTI + the CPCRA 058 FIRST Study*. 16th Int AIDS Conf (Aug 13-18, Toronto) 2006, Abst TUAB0102.

4. U.S. Food and Drug Administration. *FDA approves new HIV drug after priority review.* Available from: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01783.html

5. Hui, D.Y. *Effects of HIV protease inhibitor therapy on lipid metabolism*. Prog Lipid Res 2003, 42(2): 81-92.

6. Staszewski, S., Morales-Ramirez, J., Tashima, K.T. et al. *Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults, Study 006 Team*. N Engl J Med 1999, 341(25): 1865-73.

7. Vanni, T., Morejón, K.M., Santana, R.C. et al. *Comparison of the effectiveness of initial combined antiretroviral therapy with nelfinavir or efavirenz at a university-based outpatient service in Brazil.* Braz J Med Biol Res 2007, 40(7): 963-9.

8. Matthews, G.V., Sabin, C.A., Mandalia, S. et al. *Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naïve patients: A cohort study*. AIDS 2002, 16(1): 53-61.

9. Ridler, S.A., Haubrich, R., DiRienzo, G. et al. *A prospective, randomised, phase III trial of NRTI-, PI-, and NNRTI-sparing regimens for initial treatment of HIV-1 infection*. 16th Int AIDS Conf (Aug 13-18, Toronto) 2006, Abst THLB0204.

10. Bacheler, L., Jeffrey, S., Hanna, G. et al. *Genotypic correlates of phenotypic resistance to efavirenz in virus isolates from patients failing nonnucleoside reverse transcriptase inhibitor therapy*. J Virol 2001, 75(11): 4999-5008.

11. Delaugerre, C., Rohban, R., Simon, A. et al. *Resistance profile and cross-resistance of HIV-1 among patients failing a non-nucleoside reverse transcriptase inhibitor-containing regimen*. J Med Virol 2001, 65(3): 445-8.

12. Bacheler, L.T., Anton, E.D., Kudish, P. et al. *Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy*. Antimicrob Agents Chemother 2000, 44(9): 2475-84.

13. Johnson, J.A., Li, J.F., Morris, L. et al. *Emergence of drug-resistance HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated*. J Infect Dis 2005, 192(1): 16-23.

14. Leith, J., Piliero, P., Storfer, S., Mayers, D., Hinzmann, R. *Appropriate use of nevirapine for long-term therapy.* J Infect Dis 2005, 192(3): 545-6.

15. Temiz, N.A., Bahar, I. *Inhibitor binding alters the directions of domain motions in HIV-1 reverse transcriptase*. Proteins 2002, 49(1): 61-70.

16. De Bethune, M.P., Hertogs, K., Azijn, H. et al. *R165335-TMC125, a third generation non nucleoside reverse transcriptase inhibitor (NNRTI), inhibits 98% of more than 2000 recombinant HIV clinical isolates at 100 nM.* 40th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Toronto) 2000, Abst F-1841.

17. Andries, K., Azijn, H., Thielemans, T. et al. *TMC1225, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1*. Antimicrob Agents Chemother 2004, 48(12): 4680-6.

18. Das, K., Clark, A.D., Lewi, P.J. et al. *Roles of conformational and positional adaptability in structure-based design of TMC125-R165335 (etravirine) and related non-nucleoside reverse transcriptase inhibitors that are highly potent and effective against wild-type and drug-resistant HIV-1 variants*. J Med Chem 2004, 47(10): 2550-60.

19. *FDA approves INTELENCE(TM) (etravirine) for HIV combination therapy*. Johnson & Johnson Press Release, January 18, 2008.

20. Gazzard, B., Pozniak, A., Rosenbaum, W. et al. *An open-label assessment of TMC125 – A new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance*. AIDS 2003, 17(18): F49-54.

21. Gruzdev, B., Rakhmanova, A., Doubovskaya, E. et al. *A randomised, double-blind, placebo-controlled trial of TMC125 as 7-*

day monotherapy in antiretroviral naïve, HIV-1 infected subjects. AIDS 2003, 17(17): 2487-94.

22. Madruga, J., Cahn, P., Grinsztejn, B. et al. *Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-Week results from a randomised, double-blind, placebo-controlled trial*. Lancet 2007, 370(9581): 29-38.

23. Lazzarin, A., Campbell, T., Clotet, B. et al. *Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-Week results from a randomised, double-blind, placebo-controlled trial*. Lancet 2007, 370(9581): 39-48.

24. Nadler, J.P., Berger, D.S., Blick, G. et al. *Efficacy and safety of etravirine (TMC125) in patients with highly resistant HIV-1: Primary 24-week analysis*. AIDS 2007, 21(6): F1-10.

25. Woodfall, B., Vingerhoets, J., Peeters, M. et al. *Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 plus two NRTIs in study TMC125-C227*. 8th Int Congr Drug Ther HIV Infect (Nov 12-16, Glasgow) 2006, Abst PL5.6.

26. Guillemont, J., Pasquier, E., Palandjian, P. et al. *Synthesis of novel diarylpyrimidine analogues and their antiviral activity against human immunodeficiency virus type 1.* J Med Chem 2005, 48(6): 2072-9.

27. Janssen, P.A., Lewi, P.J., Arnold, E. et al. *In search of a novel anti-HIV drug: Multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile (R278474, rilpivirine)*. J Med Chem 2005, 48(6): 1901-9.

28. Goebel, F., Yakovlev, A., Pozniak, A.L. et al. *Short-term antiviral activity of TMC278 - a novel NNRTI - in treatment-naive HIV-1-infected subjects*. AIDS 2006, 20(13): 1721-6.

29. Pozniak, A., Morales-Ramirez, J., Mohapi, L. et al. *48-Week primary analysis of trial TMC278-C204: TMC278 demonstrates potent and sustained efficacy in ART-naive patients*. 14th Conf Retroviruses Opportunistic Infect (CROI) (Feb 25-28, Los Angeles) 2007, Abst 144LB. Available from: http://www.retroconference.org/2007/Abstracts/30659.htm

30. Corbau, R., Allan, G., Burt, C. et al. *UK-453,061: A non-nucleoside reverse transcriptase inhibitor for the treatment of drug-resistant HIV infections*. 47th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Chicago) 2007, Abst F1-945.

31. Davis, J., Jenkins, T., Asken, E., Stafford, H., Hackman, F., Weissgerber, G. *Safety, toleration and pharmacokinetics of single and multiple oral doses of UK 453,061, a novel NNRTi, in healthy male subjects*. 4th IAS Conf HIV Pathog Treat Prev (July 22-25, Sydney) 2007, Abst WEPEA 109.

32. Fätkenheuer, G., Staszewski, S., Plettenburg, A. et al. *Short-term monotherapy with UK-453,061, a novel NNRTI, reduces viral load in HIV infected patients*. 4th IAS Conf HIV Pathog Treat Prev (July 22-25, Sydney) 2007, Abst WESS202.

33. De La Rosa, M., Kim, H.W., Gunic, E. et al. *Tri-substituted triazoles as potent non-nucleoside inhibitors of the HIV-1 reverse transcriptase*. Bioorg Med Chem Lett 2006, 16(17): 4444-9.

34. Hamatake, R., Zhang, Z., Xu, W., Bellows, D., Raney, A., Giradet, J.L., Quart, B. *RDEA806, a potent NNRTI with a high genetic barrier to resistance*. 47th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 17-20, Chicago) 2007, Abst 1662.