

# Etravirine (TMC-125): The evidence for its place in the treatment of HIV-1 infection

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**Introduction:** Etravirine is a novel nonnucleoside reverse transcriptase inhibitor (NNRTI) specifically designed to suppress the replication of viruses resistant to the three currently approved NNRTIs efavirenz, nevirapine, and delavirdine.

**Aims:** To assess the evidence for the place of etravirine in the treatment of HIV-1 infection.

**Evidence review:** In combination with a ritonavir-boosted protease inhibitor etravirine has demonstrated high antiviral activity against strains exhibiting up to three NNRTI resistance mutations. The drug appears to be well tolerated, with only nausea and rash occurring significantly more frequently with etravirine compared with placebo. Of note, neuropsychologic side effects that frequently limit the use of efavirenz were not reported more frequently with etravirine.

**Place in therapy:** Given its high activity against most NNRTI-resistant strains and its very good tolerability, etravirine is of high value for pretreated patients with NNRTI resistance and protease inhibitor exposure. Efforts should be made to demonstrate activity in switching strategies (due to toxicity) and earlier lines of failure or in the setting of primary NNRTI resistance in order to explore the potential of the drug beyond salvage therapy.

**Keywords:** etravirine, HIV-1, evidence

## Core evidence place in therapy summary for etravirine treatment in HIV-1 infection

Outcome measure	Evidence	Implications
<b>Patient-oriented evidence</b>		
Improvement of survival	Some	Superior viral load reduction and CD4+ T-cell increase most likely results in survival benefit (generally accepted surrogate markers)
Absence of cutaneous allergic reactions	Limited	Rash also observed with etravirine, no direct comparison with other NNRTI
Absence of neuropsychiatric side effects	Clear	Frequency of neuropsychiatric side effects with etravirine same as with placebo
Few treatment discontinuations	Clear	Side effects infrequent and virologic failure less likely with etravirine
<b>Disease-oriented evidence</b>		
Superior viral load suppression	Clear	Etravirine use associated with improved virus suppression
Superior CD4+ T-cell reconstitution	Clear	Etravirine use associated with superior increase in CD4+ T-cell counts

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(Continued)		
Outcome measure	Evidence	Implications
<b>Economic evidence</b>		
Cost-effectiveness in salvage therapy	Limited	Benefit probable, but not enough evidence
Cost-effectiveness in early therapy	No evidence	More costly than efavirenz and nevirapine, more evidence required
<b>Abbreviation:</b> NNRTI, nonnucleoside reverse transcriptase inhibitor.		

## Scope, aims, and objectives

Etravirine was licensed by the FDA in January 2008 under the trade name Intelence™.<sup>1</sup> It is currently licensed in the US, Canada, and Switzerland, and in the European Union. It belongs to the chemical class of diarylpyrimidine compounds and acts as a nonnucleoside reverse transcriptase inhibitor (NNRTI), which inhibits the enzyme in a noncompetitive way. The aim of this article is to summarize current knowledge about the development of etravirine and to discuss its role in the treatment of HIV-1 infection.

## Methods

The medical literature and the meeting abstracts of major scientific conferences on infectious diseases since January 1, 2003 were reviewed with regard to contributions on etravirine (formerly TMC125 or R165335, manufactured by Tibotec, a division of Janssen Cilag). In view of the rapid advances in the field of HIV treatment, meeting abstracts and internet communications were also included. PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez>) was searched using the search term “etravirine or TMC125 or TMC-125.” In addition, homepages of major conferences on HIV infection and infectious diseases ([www.retroconference.org](http://www.retroconference.org); [www.iasociety.org/AbstractSearch.aspx](http://www.iasociety.org/AbstractSearch.aspx); HIV Drug Resistance Workshop 2008: <http://www.hivpresentation.com/index.cfm>; European AIDS Clinical Society: [http://www.eacs.eu/index\\_ns.htm](http://www.eacs.eu/index_ns.htm); Interscience Conference on Antimicrobial Agents and Chemotherapy: <http://www.icaac.org/>) were searched for abstracts including the search term. If primary scientific sources were unavailable, information compiled in company documents was added. Table 1 shows the results of the literature search and the records considered for this review.

## Disease overview

HIV-1 infection is still spreading on a worldwide level. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates 33.2 million people are living with

HIV infection worldwide,<sup>2</sup> the majority of whom are infected with HIV-1 and reside in subSaharan Africa and South-East Asia. Several countries of the former Soviet Union show rapidly increasing numbers of infected people, mainly in intravenous drug users. In those countries affected, HIV infection has serious consequences for both the individuals and the societies. Individually, it results in social marginalization, poverty, and inability to work and sustain the economic basis of living for those infected and their families. For societies, the loss of young adults in the midst of their productive years and the secondary costs due to healthcare and childhood poverty markedly reduce the economic development perspectives.

Despite long-standing prevention campaigns, HIV infection continues to spread in the US and Western Europe as well. Highly active antiretroviral therapy (HAART), which is widely available in developed countries, has massively improved morbidity and mortality in those infected.<sup>3,4</sup> It can control virus replication for many years in the individual. The associated burden of healthcare costs, especially for antiretroviral drugs, is increasingly being viewed as a challenge to healthcare systems.

**Table 1** Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	114	57
Records excluded	93	46
Records included	21	11
Additional studies identified	3	
Level 1 clinical evidence		
Level 2 clinical evidence	6	1
Level ≥ 3 clinical evidence	11	10
trials other than RCT		
Case studies	1	

**Notes:** For definition of levels of evidence, see *Core Evidence* website (<http://www.dovepress.com/core-evidence-journal>).

**Abbreviation:** RCT, randomized controlled trial.

Fortunately, the overall rate of resistance against antiretroviral drugs in treated patients appears not to increase,<sup>4–8</sup> probably due to more rational use and a wider spectrum of agents available to achieve optimal virus inhibition. However, transmission of resistant virus strains remains a problem in newly infected individuals,<sup>6,9</sup> resulting in suboptimal response.<sup>10,11</sup>

## Current therapy options

The choice of the antiretroviral regimen is highly individualized and based on considerations such as primary resistance, the probability of treatment interruptions or nonadherence, drug interactions with HIV and concomitant medication, as well as on patient desires. There is broad consensus on the aim of achieving and maintaining a viral load that is undetectable with the most sensitive standard assays once antiretroviral therapy has been initiated. Initial treatment should comprise two nucleoside/nucleotide reverse transcriptase inhibitors. The third drug should either be an NNRTI or a protease inhibitor. There is some indication of a better virologic response with the NNRTI efavirenz, but more resistance in case of failure, often associated with cross resistance within the drug class.<sup>12</sup> In later lines of therapy, individual tolerance and the resistance profile of the virus determine the choice of drugs. Therefore, beyond initial therapy, most drugs that retain antiviral activity, are tolerated sufficiently well, and have no unfavorable pharmacokinetic interactions are used as combination partners. In this setting, drugs are added rather than exchanged. Due to their low genetic hurdle to resistance, NNRTIs are not used frequently beyond first- or second-line therapy.

Most protease inhibitors, NNRTIs, and nucleoside/nucleotide reverse transcriptase inhibitors are licensed for all lines of therapy. The novel, less cross-resistant protease inhibitors tipranavir and darunavir, the fusion inhibitor enfuvirtide, the R5 coreceptor blocker maraviroc, and the integrase inhibitor raltegravir, however, are currently licensed for later lines only. Accordingly, clinical trial results mainly reflect their use in salvage therapy, with an ~50%–100% increase of virologic response rates over placebo when the respective compound is added to a background combination selected according to the patient's virus resistance genotype ("optimized background"). All NNRTIs except etravirine (ie, efavirenz, nevirapine, and delavirdine) are highly cross resistant and require only 1–2 mutations in viral reverse transcriptase in order to lose their activity almost completely (ie, they have a low "genetic hurdle").<sup>13,14</sup> The key NNRTI mutation K103N is rapidly selected for during failure of the most widely used NNRTI efavirenz, facilitated by reduced

adherence,<sup>15</sup> and confers cross resistance to nevirapine and delavirdine. It has little impact on viral replication capacity,<sup>16</sup> whereas protease inhibitor and nucleoside reverse transcriptase inhibitor mutations reduce it.<sup>17–21</sup> In the absence of therapy, this loss of viral "fitness" leads to counter-selection in favor of wild-type virus and to the virtual disappearance of resistance mutations in genotypic resistance analyses.<sup>22</sup> However, they remain present as minor variants probably indefinitely.<sup>23–25</sup>

The R5 coreceptor blocker, maraviroc, is only active in patients with no evidence of virus strains using the X4 coreceptor. It has demonstrated high activity in two parallel trials, in which it was added to an optimized background regimen (MOTIVATE-1 and -2).<sup>26</sup> In later lines of therapy, however, half of the patients carry viruses using either both the R5 and the X4 coreceptor or only X4,<sup>27</sup> rendering maraviroc inactive. Even in antiretroviral naïve patients, 18% exhibited X4 use.<sup>28</sup> Moreover, the drug failed to demonstrate equivalence to efavirenz (both in combination with zidovudine and lamivudine) in antiretroviral naïve patients (MERIT study),<sup>29</sup> probably due to emergence of X4-using variants undetected at baseline.<sup>30</sup> Maraviroc is also a substrate of CYP3A4. Therefore, dose adjustment is necessary when combined with inducers (eg, most NNRTIs) or inhibitors of CYP3A4 (eg, ritonavir).<sup>31</sup>

Raltegravir, the first licensed HIV integrase inhibitor, has demonstrated high antiviral activity when added to an optimized background regimen in patients with virologic failure and resistant virus.<sup>32–34</sup> In contrast to maraviroc, raltegravir showed equivalent virologic suppression when compared with efavirenz in previously untreated patients. It is mainly metabolized by UGT1A1;<sup>35</sup> despite minor interactions, dose adjustment is not considered necessary in combination with other antiretroviral drugs.<sup>36</sup>

## Unmet needs

Patients who develop extended antiretroviral drug resistance need as many virologically active agents as possible in order to compose a regimen with two or more active drugs. As outlined above for maraviroc, R5 inhibitors only represent an option in some patients. Moreover, in clinical routine, toxicity issues often prevent the use of some active drugs, so that the number of viable options for the individual may be substantially smaller than predicted by the resistance genotype. Therefore, there is a general need for many potentially active compounds to be available.

Development of novel compounds from within an existing class has the advantage of exploiting a well established treatment principle with less risk of unexpected toxicities than for compounds with novel modes of action. Accordingly, the

protease inhibitors tipranavir and darunavir were developed to target viruses resistant against earlier generations of protease inhibitors.

Due to broad cross resistance within the group of NNRTIs, a promising second-line NNRTI treatment option was lacking. Such an option is attractive because it should help to overcome the limitations of the low genetic hurdle and cross resistance of efavirenz, nevirapine, and delavirdine. Furthermore, should transmitted NNRTI resistance increase, novel, less cross-resistant compounds would be needed even in early lines of therapy.

## Clinical evidence with etravirine

Etravirine is a diarylpyrimidine compound that was specifically designed to bind to HIV-1 reverse transcriptase in a more flexible manner than efavirenz and nevirapine and to require more than one key NNRTI resistance mutation for resistance development<sup>37–39</sup> (ie, to possess a higher genetic hurdle to resistance).

A phase I/II 7-day monotherapy trial in 19 HIV-infected, antiretroviral-naïve subjects showed a  $-1.99 \log_{10}$  decline in HIV plasma viremia with etravirine as opposed to  $-0.06 \log_{10}$  in controls.<sup>40</sup> A similar open-label phase IIa trial in 16 individuals on a failing regimen containing efavirenz or nevirapine and with documented phenotypic NNRTI resistance yielded a median plasma HIV RNA reduction of  $-0.89 \log_{10}$ .<sup>41</sup> Study TMC125-C203 was a randomized, phase IIb, placebo-controlled, two-stage trial evaluating safety, tolerability, and preliminary efficacy of three twice-daily doses of etravirine<sup>42</sup> (400, 800, and 1200 mg twice daily of the phase II TF035 formulation). No evidence of relevant neuropsychiatric side effects was found, and virus load suppression was superior at week 24 in the etravirine arm in stage II of the trial.<sup>43</sup>

The TMC125-C223 trial investigated two doses of etravirine (400 and 800 mg twice daily) versus placebo, combined with an optimized background regimen in 199 patients with genotypic NNRTI resistance and at least three primary protease inhibitor resistance-associated mutations. Viral load reductions were  $-1.04$  and  $-0.18 \log_{10}$  in the etravirine arms compared with  $-0.19 \log_{10}$  in the comparator arm.<sup>44</sup>

The phase IIb study, TMC125-C227, investigated the antiviral activity of etravirine in 116 treatment-experienced, protease inhibitor-naïve HIV-1 infected patients with genotypic evidence of NNRTI resistance at screening or in prior resistance analyses. The study was a randomized, exploratory, active-controlled, open-label comparison of etravirine ( $n = 59$ ) and a protease inhibitor chosen by the investigator ( $n = 57$ ). It was conducted in South Africa, South

America, Asia, and Europe and used a different formulation of etravirine for which, however, exposure was comparable to the phase III formulation that is currently approved.<sup>45</sup> The suppression rate of HIV plasma viremia to  $<50$  copies/mL at week 12 was superior in the control arm (52%) compared with the etravirine arm (22%). This is explained by a higher number of mutations conferring resistance to NNRTI and to the nucleoside analogue backbone of the regimen.<sup>46</sup> Pretreatment definitely reduced the overall genetic hurdle to resistance against an NNRTI-based regimen in the study participants, so that fewer mutational steps had to be taken for the virus with etravirine. The hypothesis may be raised, however, that the evolutionary cost for the virus in terms of replicative fitness when acquiring new NNRTI mutations could be less than for protease inhibitor resistance mutations. This could contribute to a more rapid development of resistance on etravirine than expected. Etravirine, therefore, is unlikely to be sufficiently active in patients who have been left on a failing NNRTI-based regimen for longer and should be combined with other active compounds.

Etravirine was licensed based on the analyses of 24-week data from two randomized, double-blind, placebo-controlled, phase III trials (TMC125-C206 and TMC125-C216), generally referred to as DUET-1 and DUET-2.<sup>47,48</sup> Both trials were designed identically and results are presented here as a pooled analysis. A total of 1203 treatment-experienced patients were randomly assigned to receive etravirine ( $n = 599$ ) or placebo ( $n = 604$ ) in combination with a background regimen (BR) comprising the novel protease inhibitor darunavir, pharmacologically boosted with ritonavir 100 mg twice daily. Two additional investigator-selected agents had to be given, with or without enfuvirtide. Patients were eligible if their HIV plasma viral load was greater than 5000 copies/mL while on a stable antiretroviral regimen for at least 8 weeks. In addition, patients had  $\geq 1$  NNRTI resistance-associated mutations at screening or documented in a prior genotypic analysis, and  $\geq 3$  of the primary protease inhibitor resistance-associated mutations D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, or L90M. Randomization was stratified according to the intended use of enfuvirtide in the BR, previous use of darunavir/ritonavir, and screening viral load. Virologic response was defined as an undetectable viral load ( $<50$  HIV-1 RNA copies/mL) at week 24.

In the pooled analysis, demographics and baseline characteristics, as well as *de novo* or previous use of enfuvirtide were balanced between the etravirine and the placebo groups.

Virologic response was significantly superior in the etravirine arm compared with placebo (59.8% versus 40.2%).

Plasma viremia was reduced by a mean of  $-2.37 \log_{10}$  from baseline in the etravirine arm as opposed to  $-1.68 \log_{10}$  in the controls. Accordingly, CD4 count increased by a mean of 81 cells/mm<sup>3</sup> in the etravirine arm in contrast to 64 cells/mm<sup>3</sup> in the placebo arm. Among patients reusing or not using enfuvirtide in the background regimen, 56.7% achieved  $<50$  copies of HIV RNA per mL with etravirine, compared with 32.7% in the controls. The response rate was somewhat higher and the difference less pronounced when enfuvirtide was used for the first time in conjunction with etravirine (68.3% versus 61.3%).

In addition to these clinical trials, a recently published case report supports the view that etravirine has high antiviral activity also when combined with raltegravir, a compound that was not available in the trials described above.<sup>49</sup>

Several analyses of NNRTI resistance patterns in clinical routine samples demonstrate that currently resistance to etravirine, as predicted by interpretation algorithms, is rare.<sup>50-55</sup>

In the DUET trials, etravirine exhibited the expected toxicity pattern. Of those events occurring at a rate of  $>10\%$ , only nausea (13.9% versus 11.1% with placebo) and rash (16.9% versus 9.3%) were significantly more frequent with etravirine. Severe reactions such as Stevens-Johnson syndrome, hypersensitivity reactions, and erythema multiforme occurred in fewer than 0.1% of patients. The rash resembled that observed during efavirenz treatment and led to discontinuation in only 2% of all patients in phase III studies. Other, less frequent, adverse events were widely distributed and probably represent the toxicity of the background combination as well. Of note, neuropsychologic side effects that frequently limit the use of efavirenz were not reported more frequently with etravirine.

Regarding quality of life, functional status, adherence, or symptom relief, there is as yet no published information from the etravirine trials.

As a consequence of the unmet needs described above, the features of the ideal product in the setting of NNRTI failure can be described as follows.

1. Lack of cross resistance within the NNRTI drug class.
2. No pharmacokinetic interactions with other antiretroviral drugs (especially ritonavir-boosted protease inhibitors), concomitant medication (eg, anticonvulsants, lipid-lowering drugs, and antigastric agents), and lifestyle or illicit drugs (eg, methadone, PDE-5 inhibitors).
3. Different profile of side effects (especially no neuropsychologic impairment, few allergic reactions).
4. Convenient pill count and dosing intervals (“one pill once a day”), comparable to efavirenz.
5. Lack of teratogenicity.

To what extent does etravirine fulfil these criteria?

1. It is highly active against resistant variants carrying key mutations such as K103N. However, accumulation of several NNRTI resistance mutations results in increasing degrees of cross resistance.<sup>56</sup> The drug should therefore be considered earlier during NNRTI failure and not be withheld until patients have failed for longer. Although it is not licensed for this indication, the drug might be useful in the setting of transmitted NNRTI resistance.
2. It is mainly metabolized via CYP3A4. This results in numerous interactions, especially with protease inhibitors and the R5 coreceptor blocker, maraviroc, that have to be considered when composing a regimen. The same applies to concomitant medication that is metabolized via the same pathway. Moreover, in an aging patient population, more interaction with concomitant medication has to be expected. Some interactions are unexpected<sup>57</sup> and preclude the use in some combinations. The lack of pH dependence of absorption<sup>58</sup> and the absence of QTc prolongation,<sup>59</sup> however, are positive features.
3. The rate of neuropsychologic side effects appears to be very low if at all different from placebo. Rash was observed with etravirine also.
4. Despite pharmacokinetic properties that would probably allow for once-daily dosing, this has not been pursued in clinical trials, mainly due to difficulties in formulation. The pill count is relatively high in comparison with the other NNRTIs, although it is comparable with ritonavir-boosted protease inhibitors.
5. Etravirine does not appear to be teratogenic in animal models,<sup>1</sup> but there are no reported observations during pregnancy.

Several aspects regarding the optimal position of etravirine in antiretroviral therapy remain to be investigated.

1. Use as a stand-alone third agent. The DUET trials have demonstrated high activity in combination with ritonavir-boosted darunavir, which was a novel compound when the studies started. Many study participants had low baseline resistance to darunavir, so that the results do not only reflect the effect of etravirine. Accordingly, in the TMC125-C223 trial, etravirine was used in conjunction with a ritonavir-boosted protease inhibitor. In the TMC125-C227 trial, in which it was applied as a stand-alone third agent, it showed little activity. This, however, may have been a problem of patient selection. It remains to be shown if – in a setting of less extensive baseline resistance or even wild-type virus – the drug could be used as a substitute for efavirenz or nevirapine,

eg, in subjects with transmitted NNRTI resistance or in case of intolerance.

2. Extent of pharmacokinetic interactions. Gender and ethnic differences in metabolism as well as interactions with concomitant medication have to be explored in further studies in order to provide physicians with proper dose recommendations.
3. Potential for once-daily dosing. Several antiretroviral compounds can be given once daily. For etravirine, however, the high pill burden of the current formulation represents an obstacle to this strategy.

## Economic evidence

The following calculations are subject to price changes, and prices may vary in different countries. They are only meant to assess the order of magnitude of economic implications. Etravirine is currently sold at a price that results in an approximate yearly cost of \$US9500 (<http://www.healthpricer.com> and <http://www.pharmacychecker.com>, accessed for update 15.7.2009). This compares favorably with the annual cost of other drugs licensed for use in later lines of therapy: \$US11900 for darunavir 600 mg qd plus \$US1,350 for ritonavir boosting; \$US11590 for raltegravir; \$US12070 for maraviroc 150/300 mg twice daily; \$US12370 for tipranavir plus \$US2700 for ritonavir boosting; and approximately \$US29360 for enfuvirtide. It is, however, more expensive than the other compounds of the class: \$US7700 for delavirdine; \$US4360 for nevirapine; and \$US6910 for efavirenz.

Treatment with efavirenz and nevirapine was shown to be cost effective or cost saving in all lines of therapy in comparison with protease inhibitor-based regimens.<sup>60</sup> There are, as yet, no published cost-effectiveness studies using etravirine data. Given a lower price than protease inhibitors and enfuvirtide, however, there is no indication that it could be less cost effective than enfuvirtide<sup>61</sup> in later lines of therapy.

## Resource utilization

Etravirine is currently placed in later lines of therapy for patients with NNRTI resistance and protease inhibitor pretreatment. Primary virologic failure rates are decreasing,<sup>62</sup> as is the risk and prevalence of triple-class resistance.<sup>63,64</sup> Triple-class failure occurs slowly<sup>65</sup> and is lower among patients who initiated a modern HAART regimen as opposed to those initiated on suboptimal regimens.<sup>66</sup> This currently limits the use of etravirine to a relatively small percentage of patients. Furthermore, the overall prevalence of high-level antiretroviral drug resistance is decreasing, probably due to improved therapeutic options with the

novel compounds (tipranavir, darunavir, maraviroc, and raltegravir). Therefore, only a small fraction of all patients receiving antiretroviral treatment still have uncontrolled replication of NNRTI-resistant viruses at present and would be candidates for etravirine therapy. There are currently no data to support the use of etravirine as a replacement for other active compounds in a suppressive regimen, such as enfuvirtide, maraviroc, and raltegravir, which are more expensive. Replacement would be attractive for patients experiencing injection-site reactions to enfuvirtide and could help to reduce the overall cost of therapy. However, switch trials are needed in order to assess if etravirine is sufficiently active when given without a ritonavir-boosted protease inhibitor.

Assuming that these results were favorable, etravirine could also represent an option for subjects with primary, transmitted NNRTI resistance, especially since it is not always detected by standard sequencing techniques. This would affect ~5%–10% of newly infected individuals and lead to a broader use of the compound.

## Patient group/population

Antiretroviral-experienced adult patients with evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretroviral agents are likely to benefit most from etravirine, as long as the number of NNRTI resistance mutations is limited. An analysis of a large Italian resistance database (ARCA) suggests that exposure to nevirapine is associated with a higher risk of etravirine-associated resistance mutations than efavirenz.<sup>55</sup> Therefore, etravirine appears to be used most effectively in subjects failing on efavirenz rather than nevirapine. Although the K103N mutation alone does not confer resistance to the drug, the presence of Y181V, G190S, V179D/F/T, or three or more 2007 IAS-USA-defined NNRTI amino acid changes is associated with a markedly decreased response.

Of note, no benefit was shown in the TMC125-C227 trial, when etravirine was used only in combination with nucleoside/nucleotide reverse transcriptase inhibitors in patients who failed an NNRTI-based regimen. Therefore, use in the absence of other active “flanking” agents should be avoided where possible.

In the absence of any unexpected severe toxicity, improved virologic suppression will likely translate into improved immune reconstitution and clinical stability.

## Dosage, administration, and formulation

Etravirine (Intelence) is available as 100 mg tablets, and is taken as two tablets twice daily following a meal.

Ingestion in the fasted state results in a 50% reduction in systemic exposure [area under the curve (AUC)].<sup>1</sup> The AUC is minimally reduced by ranitidine (14%), and increased by 41% by omeprazole,<sup>58</sup> which appears clinically irrelevant. Etravirine is a substrate of CYP 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4, but an inhibitor of 2C9 and 2C19. Therefore, a careful evaluation of drug interactions with protease inhibitors, maraviroc [dose adjustment necessary,<sup>67</sup> and concomitant therapy is required. Etravirine should not be coadministered with tipranavir/ritonavir [etravirine exposure reduced],<sup>68</sup> fosamprenavir/ritonavir [fosamprenavir exposure increased],<sup>69</sup> and atazanavir/ritonavir [atazanavir exposure decreased],<sup>70</sup> as well as with unboosted protease inhibitors and other NNRTIs. No dose adjustment is required for either compound in combinations with lopinavir/ritonavir.<sup>71</sup> For darunavir/ritonavir, no impact on darunavir levels but a decrease in etravirine AUC by 37% was observed in healthy volunteers.<sup>72</sup> Given the high antiviral activity of this combination in the DUET studies, however, no dose adjustment is recommended.

For possibly interacting concomitant medication such as antiarrhythmics and warfarin, dose adjustment and/or discontinuation should be considered. Due to its long terminal half-life of 41 ( $\pm$ 20) hours, treatment interruption or permanent discontinuation should probably be handled in the same way as with efavirenz, ie, continuation of the other drugs for some days after discontinuation of the NNRTI. Etravirine appears to have the potential for once-daily dosing, providing that the number of pills can be reduced in a future formulation. However, as the drug is being developed for later lines of therapy in which many other components are also dosed twice daily, this matter does not appear as a limitation to its use.

Etravirine has no clinically relevant effect on the pharmacokinetics of methadone.<sup>73</sup>

## Place in therapy

Etravirine has its place in therapy in patients with virus resistant to NNRTI and other antiretroviral agents carrying limited numbers of the aforementioned NNRTI resistance-associated amino acid changes. This has already been implemented in the current Department of Health and Human Services (DHHS) and European AIDS Clinical Society (EACS) guidelines for antiretroviral therapy in adults.<sup>74–76</sup> The drug is very valuable in increasing the number of drug options available to construct a well-tolerated and fully suppressive regimen and to contribute to clinical stability or improvement.

A limitation to its use is the fact that the favorable data leading to licensure were obtained only in combinations with ritonavir-boosted protease inhibitors. Although the label allows for other combinations, these data are still lacking and should be provided by further studies. It also has to be kept in mind that, due to unfavorable pharmacokinetic interactions, the drug can not be combined freely with all ritonavir-boosted protease inhibitors (see above), which might preclude its optimal use in some patients. Nevertheless, the lack of pharmacokinetic interaction with methadone makes it uncomplicated in patients on methadone substitution.

There are currently only limited pediatric data. Exposure of children 6–17 years of age to 4 mg/kg of bodyweight twice daily resulted in exposure similar to that of adults using 200 mg twice daily,<sup>77</sup> but studies on antiviral efficacy are lacking. Furthermore, there is as yet no experience during pregnancy. Because of lack of reproductive toxicity in animal models at an exposure similar to therapeutic levels in humans, etravirine was labelled Pregnancy Category B.<sup>1</sup> Although its use during pregnancy cannot be encouraged, pregnancies will likely occur in women receiving etravirine. These events should be recorded and evaluated in the registry supported by the manufacturer.

It is unclear if etravirine can actually replace fully active compounds in a salvage treatment regimen rather than being added as another active component. This strategy should be investigated in clinical trials.

If the galenic preparation can be improved further and the pill burden reduced, the long half-life would probably allow for once-daily dosing. This would make the drug more attractive for first-line therapy, but it could also be valuable for later lines. This use, however, is not supported by data so far and cannot be recommended at the present time.

In conclusion, etravirine is a valuable novel tool in the armamentarium of antiretroviral drugs. It could be valuable for earlier lines of failure, without a ritonavir-boosted protease inhibitor, and for primary NNRTI resistance, provided clinical trials show favorable results. Efforts should be made to further explore the potential of this drug.

## Disclosure

The author has served as an investigator, speaker and advisor for Tibotec (Janssen Cilag), Merck, Sharp & Dohme, Roche, Bristol-Myers Squibb, Pfizer, GlaxoSmithKline, Gilead, and Boehringer Ingelheim.

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