Canadian consensus guidelines for the optimal use of etravirine in the treatment of HIV-infected adults

Marianne Harris MD CCFP1, Jonathan B Angel MD2, Jean-Guy Baril MD3, Anita Rachlis MD MEd FRCPC4, Benoit Trottier MD5


BACKGROUND AND OBJECTIVES: A group of five Canadian physicians with significant experience in HIV management was convened. Their goal was to develop guidance specifically for Canadian HIV-treating physicians on the appropriate use of etravirine (TMC125, Intellence, Tibotec BVBA, Belgium) in adult HIV-infected patients.

METHODS: Evidence from the published literature, conference presentations and expert opinions of the group members were used to develop the recommendations. Feedback on the draft recommendations was obtained from this core group, and from seven other physicians across Canada with clinical HIV treatment expertise and experience in the use of etravirine, as well as two Canadian scientists with HIV expertise. The final recommendations represent the core group’s consensus agreement, taking all feedback into consideration.

RESULTS AND CONCLUSIONS: The recommendations were developed to guide physicians in the optimal use of etravirine. The issues considered included HIV disease status, antiretroviral treatment history, drug resistance profiles, predictors of response to etravirine, background antiretroviral regimen and drug-drug interactions.

Key Words: Etravirine; HIV; NNRTI; Recommendations; Resistance; TMC125; Treatment

The current standard of care for adults who require treatment for HIV infection is to start with a combination of active agents from the nucleoside reverse transcriptase inhibitor (NRTI), protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes of drugs (1,2). Recommended first-line combinations are either NNRTI-based (one NNRTI plus two NRTIs) or PI-based (one ritonavir-boosted PI plus two NRTIs). With this approach, most patients can achieve sustained virological suppression to less than 50 copies/mL and substantially increased CD4 cell counts.

The first-generation NNRTIs – efavirenz (EFV), nevirapine (NVP) and delavirdine – are potent and highly selective anti-HIV-1 agents (3). NNRTI-based regimens are widely used globally, (NVP) and delavirdine – are potent and highly selective anti-HIV-1 agents (3). NNRTI-based regimens are widely used globally, and EFV-based therapy is the preferred first-line therapy in the current HIV-treatment guidelines due to a higher pill burden and less antiviral efficacy than the other two agents (1,2). While both EFV and NVP are widely prescribed in Canada, their use has been hampered in some cases by toxicity and resistance issues. Treatment-limiting side effects may include rash (for both agents, but more frequently for NVP), hepatotoxicity (for both, but potentially more severe for NVP) and central nervous system toxicity (neuropsychiatric side effects for EFV: dizziness, insomnia, somnolence, impaired concentration and vivid dreams) (5-7). NVP should not be initiated in women with CD4 cell counts greater than 250/mm3 and men with CD4 cell counts greater than 400/mm3, due to a higher risk of serious hepatotoxicity in these populations (5). EFV should not be used in pregnant women, women who wish to become pregnant or women of child-bearing potential who are not using consistent and reliable contraception, due to teratogenicity (1,2,4,6). In addition, these first-generation NNRTIs have a low genetic barrier to the development of drug-resistant viruses; a single mutation confers high levels of drug resistance to both agents, limiting their use in treatment-experienced patients (8-10).

1AIDS Research Program, St Paul’s Hospital, Vancouver, British Columbia; 2Division of Infectious Diseases, Department of Medicine, Ottawa Hospital, University of Ottawa, Ottawa, Ontario; 3Cinique médicale du Quartier latin, Centre hospitalier de l’université de Montréal, Université de Montréal, Montreal, Quebec; 4Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario; 5Cinique médicale l’Actuel, Université de Montréal, Montreal, Quebec
Correspondence: Dr Marianne Harris, St Paul’s Hospital, B518 – 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6. Telephone 604-806-8771, fax 604-806-8412, e-mail mharris@cfenet.ubc.ca
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In treatment-experienced patients, two or preferably more active agents are generally needed to achieve the goal of a viral load less than 50 copies/mL (1,2). Due to previous exposure and failure with first-generation NNRTIs or acquisition of NNRTI-resistant strains, these NNRTIs are likely to be inactive in treatment-experienced patients.

To deal with these challenging issues, a number of agents are available. The agents that are current options for treatment-experienced patients with treatment failure and/or resistance to one or more classes of antiretroviral (ARV) therapies include the following (these options are not mutually exclusive):

- Newer boosted PIs, such as darunavir (Prezista, Tibotec BV/BA, Belgium)/ritonavir or tipranavir (Aptivus, Boehringer Ingelheim GmbH, Germany)/ritonavir, if not previously used, with other active or partially active agents (11,12).
- New agents from novel classes, such as enfuvirtide, a fusion inhibitor (Fuzeon, Hoffmann-La Roche Ltd, Switzerland); maraviroc, a CCR5 receptor antagonist (Celsentri, Pfizer Inc, USA); and raltegravir, an integrase inhibitor (Isentress, Merck & Co Inc, USA), with other active or partially active agents (13-17).

However, each option has its own disadvantages, and the best use of new agents is a particular challenge to clinicians:

- Newer PIs: toxicities (including hepatotoxicity and dyslipidemia) for both darunavir/ritonavir (18) and tipranavir/ritonavir (19); drug interactions (20-21).
- Novel class agents: limited efficacy and safety data; unknown long-term toxicity; maraviroc efficacy limited to patients with viruses that use the CCR5 receptor (approximately 50% of treatment-experienced patients in most reports); enfuvirtide requires twice daily subcutaneous injection and is associated with significant injection site reactions that limit tolerability (22-26).

Alternatives that address the unmet need for an active agent with good safety and long-term tolerability, limited resistance, low pill burden and minimal drug interactions would be welcome additions to the available treatment options. Etravirine (TMC125, Intellence, Tibotec BV/BA, Belgium), a newly approved, second-generation NNRTI, differs from earlier agents in the NNRTI class in several significant ways (27).

Etravirine has been shown to be active against most viruses resistant to other NNRTIs, and has a favourable safety profile to date. It has a higher genetic barrier to resistance than first-generation NNRTIs, and can be combined with most other agents due to mostly minimal interactions. Therefore, although further study is needed to confirm its long-term benefits and toxicities, etravirine offers a viable treatment option as one component of a multidrug regimen for patients with drug-resistant HIV infection.

GUIDELINES: OBJECTIVE AND METHODS

The purpose of the guidelines is to provide guidance to Canadian health care providers on the appropriate use of etravirine in adults with HIV infection. It should be noted that the recommendations are not a substitute for the judgement of a physician experienced in treating these patients.

To develop the guidelines, a five-member group of Canadian infectious disease specialists and family physicians with significant experience in HIV management met in December 2007. Group members reviewed the relevant literature for their predetermined area of focus, and presented their findings to the group for discussion. Recommendations were based on expert opinion and scientific evidence. The strength of recommendations and quality of evidence were rated using the scheme utilized by the United States Department of Health and Human Services in their guidelines (Table 1) (1). The document was developed by reviews and comments on drafts by the original core group of five, as well as by nine additional physicians and scientists across Canada with HIV expertise and/or clinical experience with etravirine. The recommendations represent the core group’s consensus agreement, after considering comments from other physicians and scientists.

OVERVIEW OF ETRAVIRINE

Etravirine, also known as TMC125 (Intellence), is a diarylpyrimidine NNRTI that was selected during the identification of compounds active against NNRTI-resistant HIV-1 (28,29). Etravirine binds directly to the reverse transcriptase and interferes with the enzyme’s catalytic site (30). Its conformational flexibility allows it to fit into this site even in the presence of amino acid substitutions that confer resistance to first-generation NNRTIs (28,31). In vitro, etravirine is active against both wild-type HIV-1 and NNRTI-resistant HIV-1 mutants, with a higher genetic barrier to the development of resistance than other available NNRTIs (ie, more than one mutation in the HIV-1 genome is required to confer a clinically significant reduction in susceptibility to the drug [29,32]). Etravirine has been approved for use in Canada in combination with other ARV agents for the treatment of HIV-1 infection in treatment-experienced adults who have failed previous therapy and have HIV-1 strains resistant to multiple ARV agents, including NNRTIs.

Etravirine efficacy

Treatment-experienced patients: The efficacy of etravirine in treatment-experienced adults has been demonstrated in several trials, most notably the phase III DUET studies (33-36).

An early phase II proof of principle trial (TMC125-C207) was conducted as an open-label study in 16 HIV-infected men (31). Patients had to have experienced virological failure (defined as HIV-1 RNA greater than 2000 copies/mL) on an ARV regimen that included at least two NRTIs and one NNRTI. Most patients (81%) received NVP as the NNRTI in their failed regimen, and 19% received EFV. Patients had to have documented EFV-resistant HIV as a marker of NNRTI resistance at the time of trial entry. Study treatment consisted of etravirine 900 mg twice a day for seven days as a substitute for the

<table>
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<tr>
<th>TABLE 1 Rating scheme for recommendations</th>
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<tr>
<td>Strength of recommendation</td>
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<tr>
<td>A: Strong</td>
</tr>
<tr>
<td>B: Moderate</td>
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<tr>
<td>C: Optional</td>
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<tr>
<td>D: Should usually not be offered</td>
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<tr>
<td>E: Should never be offered</td>
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Modified from reference 1
of 0.89 log_{10} copies/mL was observed (P<0.001 versus baseline). At the end of treatment (day 7), a median decrease in viral load of –1.18 log_{10} copies/mL (P<0.001) in the 400 mg and 800 mg counts were greater by 37 cells/mm³ to 38 cells/mm³ in the etravirine groups at 48 weeks (39). Mean increases in CD4 cell counts were statistically significant. Similar trends were seen for virological responses among treatment groups were found in baseline viral loads or CD4 cell counts.

Evaluations continued for 48 weeks. At 24 weeks, the mean viral load decreased significantly in the etravirine groups versus the active control group by –1.04 log_{10} copies/mL (P=0.005) and –1.18 log_{10} copies/mL (P<0.001) in the 400 mg and 800 mg twice-a-day groups, respectively, versus –0.19 log_{10} copies/mL in the control group (37). The 48-week viral load changes from baseline were similar: –0.88 log_{10} copies/mL (P=0.018) and –1.01 log_{10} copies/mL (P=0.002) in the 400 mg and 800 mg twice-a-day groups, respectively, versus –0.14 log_{10} copies/mL in the active control group (38). The proportion of patients with viral load decreases of at least 1 log_{10} copies/mL from baseline were significantly greater at 24 weeks with etravirine than the control group (36.3% for the 400 mg group, P=0.005; 41.8% for the 800 mg group, P<0.001; versus 7.5% for the control group) (37). The proportions of patients with HIV-1 RNA less than 400 copies/mL were also significantly higher with either dose of etravirine versus the control group (30% for the 400 mg group, P=0.018; 38% for the 800 mg group, P=0.002; versus 7.5% for the control group). The same trend was seen for viral loads less than 50 copies/mL, but the differences from control were not statistically significant. Similar trends were seen for virological response data at 48 weeks (39). Mean increases in CD4 cell counts were greater by 37 cells/mm³ to 38 cells/mm³ in the etravirine groups than in the control group at 24 weeks, but these differences were not statistically significant (37). More patients discontinued therapy by week 24 in the control group (95% versus 26.3% and 24.1% in the 400 mg and 800 mg etravirine groups, respectively), primarily due to virological failure.

An exploratory phase II open-label, randomized, active controlled trial was conducted in 116 adults failing first-line NNRTI-based therapy (TMC125-C227) (40). These patients were PI naive, and were infected with HIV strains harbouring at least one NNRTI resistance-associated mutation. Patients were randomly assigned to receive either etravirine 800 mg twice a day plus two investigator-selected NRTIs (based on phenotypic resistance testing) or active investigator-selected control, which consisted of a PI (95% were ritonavir boosted) and two NRTIs. Baseline resistance to NRTIs and NNRTIs was greater than expected from a first-line failure population in both treatment groups. Many patients received the same NNRTIs they had used previously (35% to 37% received at least one, and 9% to 12% received more than one recycled NNRTI), possibly due to resource limitations in the countries included in the study. The viral load declined by 1.3 log_{10} copies/mL in eight weeks in the etravirine group, but this effect was not sustained, while the viral load continued to decline in the PI group. The lack of sustained response to etravirine was thought by the authors to be due to insufficient activity of the background regimen due to a high level of baseline NRTI resistance, but could also be due to reduced activity of etravirine due to extensive NNRTI resistance. Better responses were found in the etravirine arm of the study was discontinued after review of interim results by an independent safety monitoring board. This study reflected clinical practice at the time, as well as the resource availability where the study was conducted; limited treatment options were available, which was the likely reason for accumulation of resistance mutations.

The DUET studies were two double-blind, randomized phase III trials with identical designs conducted in a total of 1203 adults; a pooled analysis was prespecified (33-36). Patients had a minimum of one NNRTI resistance mutation in a previous genotype or at screening, three or more primary PI mutations at screening, three or more months of NRTI experience and a viral load greater than 1000 copies/mL. Patients who had fewer thymidine analogue mutations (TAMs) and M184V mutations. After adjustment for the level of NRTI and NNRTI resistance, virological response to etravirine was independent of the presence of signature NNRTI mutations, Y181C or K103N, at baseline. The etravirine arm of the study was discontinued after review of interim results by an independent safety monitoring board. This study reflected clinical practice at the time, as well as the resource availability where the study was conducted; limited treatment options were available, which was the likely reason for accumulation of resistance mutations.

The pooled DUET study results at 48 weeks are summarized in Table 2 (35,36). Overall, 61% of patients achieved undetectable viral loads (less than 50 copies/mL) in the etravirine group versus 40% in the placebo group (P<0.0001). The virological response (less than 50 copies/mL) was similar between patients with clade B HIV-1 virus (n=1115) and non-clade B HIV-1.
virus (n=74) at 24 weeks in both treatment groups (Tibotec BVBA, Belgium, unpublished data), although it should be noted that the number of patients with nonclade B HIV-1 virus was relatively small (6.2% of study patients) and, therefore, caution must be used in drawing conclusions from this comparison.

In addition to the virological and immunological benefits of etravirine, the DUET studies also examined and were able to demonstrate clinical benefit at 24 weeks. In the overall population, the incidence of the new Centers for Disease Control and Prevention (CDC) category C (AIDS-defining) illnesses or death was lower in etravirine-treated patients (n=599) versus controls (n=604) at 24 weeks (3.7% versus 6.8%), but the difference was not statistically significant. In the subgroup of patients reusing or not using enfuvirtide, the incidence of new CDC category C (AIDS-defining) illnesses or death was significantly lower in etravirine-treated patients (n=446) versus controls (n=444) at 24 weeks (3.8% versus 8.3%, respectively; P=0.0051), largely due to a significant difference in new AIDS-defining illness (3.1% versus 7.2%, P=0.0067) (42). The majority of these category C illnesses in each DUET study were serious conditions such as Pneumocystis jiroveci pneumonia, cytomegalovirus, Mycobacterium avium complex (MAC) and Kaposi’s sarcoma (Tibotec BVBA, Belgium, unpublished data).

Health-related quality of life was also improved after 24 weeks of etravirine treatment in the DUET studies (43). ARV-naive patients: Limited, short-term data are available for the use of etravirine in a small number of ARV-naive patients. A randomized, double-blind, placebo-controlled, proof of principle trial in 19 ARV-naive men compared treatment with etravirine monotherapy versus placebo for seven days (TMC125-C208) (44). Patients had a mean viral load of 4.4 log_{10} copies/mL at screening. They were randomly assigned (2:1) to receive either etravirine 900 mg twice a day or matched placebo monotherapy. After seven days of treatment, a significantly greater decrease in mean viral load from baseline was seen in the etravirine group versus the placebo group (1.99 log_{10} copies/mL versus 0.06 log_{10} copies/mL; P=0.001). All patients in the etravirine group had decreases of 1 log_{10} copies/mL or more, compared with none in the placebo group. Two patients in the etravirine group achieved viral loads of less than 50 copies/mL, compared with none in the placebo group.

Due to considerations of regimen simplicity, particularly in ARV-naive patients, a once-daily etravirine dosing regimen is under consideration. Pharmacokinetic studies in HIV-1-negative healthy volunteers indicate that once-daily dosing provided etravirine exposures similar to twice-daily dosing (45). Therefore, once-daily etravirine appears to be a promising possibility, but further research is needed.

Pediatric patients: No data are currently available for the efficacy of etravirine in children and adolescents up to 18 years of age. In a small pharmacokinetic study (46), 16 healthy children six to 17 years of age received a dose of 4 mg/kg twice a day, which was found to be comparable in exposure with 200 mg twice a day (new formulation) in adults. Exposure was not found to be associated with age. Etravirine was safe and well tolerated, with no immediate or short-term exposure-associated safety issues in these children.

Based on the small amount of data available, no recommend-

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**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Etravirine plus background (n=599)</th>
<th>Placebo plus background (n=604)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load &lt;50 copies/mL, % of patients</td>
<td>61</td>
<td>40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean viral load reduction from baseline, log_{10} copies/mL</td>
<td>−2.25</td>
<td>−1.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD4 cell count increase, cells/µL</td>
<td>+98</td>
<td>+73</td>
<td>0.0006</td>
</tr>
<tr>
<td>Response by ENF use*, %</td>
<td>82</td>
<td>61</td>
<td>0.0116</td>
</tr>
<tr>
<td>Reusing or not using ENF</td>
<td>57</td>
<td>33</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Phenotypic susceptibility score (PSS) = number of active background antiretrovirals (ARVs). Darunavir (DRV) considered sensitive if fold change (FC) below the stated value. *Response = viral load less than 50 copies/mL; †DRV is considered fully active if FC is less than 10 and partially active if FC less than 40. ENF Efavirenz
overall, grade 3 rash 3.3% versus 1.1%, respectively) (48). Most rashes were mild to moderate in severity, and macular or maculopapular in nature. No rashes with mucosal involvement were reported with etravirine. The rash was generally self-limiting, resolving within one to two weeks with continued therapy (median duration 11 days). The risk of rash with etravirine was not increased compared with placebo in patients with a history of NNRTI-related rash. In DUET-1, rash (any type) was reported in seven of 19 (36.8%) etravirine-treated patients with a history of NNRTI-associated rash compared with 59 of 285 (20.7%) etravirine-treated patients without a history of NNRTI-associated rash. A similar fold difference was found in the placebo group: six of 36 (16.7%) versus 27 of 272 (9.9%) patients, respectively. In DUET-2, rash (any type) was reported in three of 27 (11.1%) etravirine-treated patients with a history of NNRTI-associated rash compared with 46 of 268 (17.2%) etravirine-treated patients without a history of NNRTI-associated rash. Again, a similar fold difference was found in the placebo group: four of 46 (8.7%) versus 29 of 250 (11.6%) patients, respectively. No association between severe rash and hepatotoxicity was found (Tibotec BVBA, Belgium, unpublished data). Cases of Stevens-Johnson syndrome and erythema multiforme were rare (less than 0.1% for both, in the population of all clinical trial patients); toxic epidermal necrolysis was not reported (49). No association was observed between the incidence of rash and the CD4 cell count at the initiation of etravirine therapy (48).

Other adverse events associated with first-generation NNRTIs, including hepatic abnormalities, nervous system and psychiatric effects, and other laboratory abnormalities, have been examined in detail in etravirine trials. Hepatic abnormalities, including indicative laboratory abnormalities such as changes in alanine aminotransferase and aspartate aminotransferase levels, occurred at similar or lower incidences in etravirine versus placebo groups (35-37,47). The incidence of hepatic adverse events in the etravirine arms remained fairly consistent throughout the treatment period in the DUET studies (pooled 48 week analysis) (Tibotec BVBA, Belgium, unpublished data). In hepatitis B and C coinfected patients in the DUET studies, the incidence of grades 3 and 4 alanine aminotransferase and aspartate aminotransferase elevations, hepatic adverse events and discontinuations due to hepatic adverse events were similar between the etravirine and placebo groups (50). Hepatitis B and C coinfection and mild to moderate hepatic insufficiency (Child-Pugh stages A and B [51]) did not substantially alter etravirine pharmacokinetics and, therefore, no dose adjustments are recommended for these patients (Tibotec BVBA, Belgium, unpublished data; [52]).

Nervous system disorders (including headache, somnolence and dizziness) in etravirine arms generally occurred at similar or lower frequencies than in placebo arms in clinical trials, including the DUET studies (35,36,53). The one exception to these results was found in a study (37) of patients with NNRTI- and PI-resistant HIV (TMC125-C223), which reported more nervous system disorders in the etravirine arms than the active control arm (33.8% to 40.5% versus 20.0%, respectively). Psychiatric disorders (including insomnia, anxiety and depression) also occurred at similar or lower rates in etravirine versus placebo arms in clinical trials, including the DUET studies (35,36,53), except again in the TMC125-C223 trial, in which their incidence in the etravirine arms was higher than in the placebo arm (10.1% to 11.3% versus 2.5%, respectively) (37). The differing data reported in the TMC125-223 study may be related to longer treatment durations with etravirine (34 to 35 weeks in the etravirine arms versus 18 weeks in the placebo arm), due to the higher rate of early discontinuation largely due to virological failure, in the placebo arm (95% versus 24% to 26% in the etravirine arms). Overall, nervous system and psychiatric disorders were mild in severity and did not lead to etravirine discontinuation (54). No increased risk of psychiatric disorder events was seen in patients with a history of these disorders.

Overall, the profile of laboratory abnormalities was found to be similar in etravirine and placebo arms in clinical trials (35,36). No consistent or clinically relevant trends in vital signs, electrocardiogram or laboratory data were noted (48). One study (37) (TMC125-C223) reported more grade 3 or 4 pancreatic amylase levels in etravirine-treated patients versus placebo (8.2% versus 0%, respectively). However, no consistent, clinically relevant or dose-associated increases in mean amylase levels were found. Three patients in the etravirine arm of the C223 study had clinical pancreatitis, all of whom had other risk factors (didanosine with and/or without tenofovir, or previous pancreatitis). In all trials combined, the incidence of pancreatitis in patients treated with etravirine was less than 1% (49). The slightly increased incidence rates of grade 3 or 4 abnormalities of triglyceride and total cholesterol levels with etravirine versus placebo in the DUET studies were not considered to be clinically significant (35,36).

Based on long-term animal studies to date at exposures equivalent to those observed in humans at the recommended clinical dose, etravirine does not appear to have teratogenic or postpartum effects (Tibotec BVBA, Belgium, unpublished data). The drug has been assigned a pregnancy category B, meaning that animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies of etravirine in pregnant women.

Patients more likely to benefit from etravirine therapy

Patients in the DUET studies exhibited a virological response (defined as a viral load less than 50 copies/mL) to etravirine that was superior to placebo irrespective of baseline viral loads or CD4 cell counts (55). However, better responses were achieved in patients with higher baseline CD4 cell counts and lower baseline viral loads in both treatment groups. At 24 weeks, the proportion of patients with viral loads less than 50 copies/mL were 76% and 62% in the etravirine and placebo groups, respectively, in patients with baseline viral loads less than 30,000 copies/mL, and were 44% and 26%, respectively, in patients with baseline viral loads of 100,000 copies/mL or greater. The proportions of patients with viral loads less than 50 copies/mL at 24 weeks were 39% and 23% in the etravirine and placebo groups, respectively, in patients with baseline CD4 counts less than 50/mm3, and were 73% and 55%, respectively, in patients with baseline CD4 counts 200/mm3 or greater.

While etravirine is active and reduces viral load, even in the absence of other fully active agents, treatment response is enhanced with increasing numbers of other active ARV agents in the regimen. In the TMC125-C223 study (56), the mean decrease in viral load was substantially improved with etravirine compared with active control treatment by the addi-
tion of at least one, or two or more active ARVs: the mean viral load changes were $-0.59 \log_{10}$ copies/mL versus $+0.05 \log_{10}$ copies/mL for 800 mg etravirine versus active control with no active ARVs in the optimized background regimen; $-1.10 \log_{10}$ copies/mL versus $-0.18 \log_{10}$ copies/mL with one active ARV; and $-1.49 \log_{10}$ copies/mL versus $-0.49 \log_{10}$ copies/mL with two or more active ARVs. Similarly, in the pooled 48-week results for the DUET studies, the proportion of patients with viral loads less than 50 copies/mL was greater in the etravirine group versus the placebo group, and increased with the number of active agents in the background regimen – the proportions were 46% versus 6% with etravirine versus placebo, with no active ARV in the optimized background regimen; 63% versus 32% with one active ARV and 78% versus 67% with two or more active ARVs (35,36).

This finding of a better response with increased numbers of active ARVs included in the background regimen is not unique to etravirine; similar results have been found for other agents, including enfuvirtide (13,14), darunavir (11), maraviroc (57) and raltegravir (58,59). Trials of these agents confirm that the addition of a new drug to two or more fully active agents provides additional benefit.

Trials have also examined the relationship between the use of enfuvirtide in the background regimen and response (or factors related to response) to etravirine. In enfuvirtide-naive patients, viral loads less than 50 copies/mL were achieved in more enfuvirtide-treated patients who also received enfuvirtide than placebo-treated patients who also received enfuvirtide (35-37). This effect in the DUET studies was statistically significant at 48 weeks (less than 50 copies/mL in 71% versus 59% of placebo-treated patients; P=0.0116) (35,36). Because the use of enfuvirtide was a prespecified stratification variable, the DUET studies allowed for assessment of etravirine activity in the absence of enfuvirtide. As shown in Table 2, significantly more etravirine-treated patients reusing or not using enfuvirtide had viral loads less than 50 copies/mL at week 48 than placebo-treated patients reusing or not using enfuvirtide (57% versus 33% in the placebo group; P<0.0001) (35,36).

Less resistance to darunavir at baseline was associated with improved response in both treatment groups in the DUET studies, and response rates at 24 weeks remained higher for the baseline darunavir resistance (expressed as fold change [FC] in concentration of drug required to inhibit viral replication by 50% [IC50]) FC greater than 40, response rates were 44% and 2% in the etravirine and placebo groups, respectively. In patients with baseline darunavir resistance FC less than 10, response rates were 71% and 56% in the etravirine and placebo groups, respectively. These differences in response rate between treatment groups were less pronounced in the darunavir FC less than 10 subgroup when other active ARVs were included in the background, but the differences remained when up to two active ARVs were present in the background for the darunavir FC between 10 and 40 and FC greater than 40 subgroups.

It is difficult to know how to translate these darunavir FC findings into recommendations for clinical practice. Current clinical cutoffs, defined as baseline darunavir FC levels associated with 20% and 80% loss of wild-type virus response to darunavir/ritonavir, are 10 and 106.9 (60). That means that a partial response to darunavir can be expected for a wide range of mutational patterns and, therefore, it is difficult to predict the potential contribution of etravirine in a multidrug regimen that includes darunavir/ritonavir.

### Etravirine resistance

In vitro, etravirine has a high barrier to the development of resistance (29). Clinically, etravirine has been shown to be active against many HIV variants with mutations associated with first-generation NNRTIs and in the three-class resistance setting (37,40,55).

Based on data (61) from the DUET studies in patients not using enfuvirtide de novo, 13 baseline reverse transcriptase mutations were found to be associated with decreased virological response to etravirine (ie, the etravirine resistance-associated mutations [RAMs]): V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S. The most commonly observed etravirine treatment-emergent mutations in DUET patients were G190A and Y181C (62). An increased number of baseline etravirine RAMs was associated with decreased virological response to etravirine, whereas NNRTI RAMs that were not etravirine RAMs did not have an impact on response (61). Notably, the signature first-generation NNRTI RAM K103N was not identified as an etravirine RAM. Unlike first-generation NNRTIs, no single mutation had a significant impact on virological response to etravirine: three or more etravirine RAMs appear to be required for significant impact.

Analysis of 226,491 plasma samples submitted to Virco Lab Inc (USA) between January 1999 and June 2007 (excluding clinical trial samples) found that the coexistence of three or more etravirine-associated mutations occurred infrequently, even in patients with resistance to first-generation NNRTIs (63). Among isolates from patients with NNRTI resistance, 40% contained no etravirine RAMs and only 7.3% had three or more etravirine RAMs. As in the DUET studies, the etravirine RAMs that occurred most frequently were Y181C (27.6%) and G190A (21.1%). The combination of three etravirine RAMs that occurred most frequently was K101E + Y181C + G190A (34%) – the same combination that was most common in the DUET patient isolates (39% overall in the DUET studies, and notably, at a higher rate of 57% among responders). The number of NNRTI-resistant samples with etravirine RAMs declined over time (70% in 1999 to 54% in 2007), and the prevalence of some etravirine RAMs changed (eg, Y181C decreased from 44.9% to 20.7%). However, the ratio between samples with one, two, or three or more RAMs remained fairly constant (approximately 5:2:1).

Another study (64) included 1586 samples submitted for clinical resistance testing from 1998 to 2006 in Spain. All samples had first-generation NNRTI resistance. Etravirine RAMs with the greatest impact on virological response (based on the DUET studies), specifically V179F, G190S, Y181V, V106I and V179D, occurred at the lowest frequency (0.12% to 1.0%) of all the etravirine RAMs. A total of 8.2% of samples had three etravirine RAMs, and 1.14% had four or more etravirine RAMs. Overall, high-level etravirine resistance was rare in these patients with first-generation NNRTI resistance. Low to intermediate etravirine resistance was more common.

A retrospective study (65) of 1470 genotypes of viral isolates from NNRTI-experienced patients in Madrid, Spain, also found a low prevalence of etravirine RAMs, with Y181C and
Unboosted protease inhibitors

<table>
<thead>
<tr>
<th>HIV antiviral</th>
<th>Effect on antiretroviral AUC</th>
<th>Effect on etravirine AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir 400 mg qd*</td>
<td>↓ 17%†</td>
<td>↑ 50%</td>
</tr>
<tr>
<td>Indinavir 800 mg bid*</td>
<td>↓ 51%</td>
<td>↑ 46%</td>
</tr>
<tr>
<td>Ritonavir 600 mg bid*</td>
<td>NA</td>
<td>↓ 46%</td>
</tr>
<tr>
<td>Saquinavir 1200 mg single dose</td>
<td>↓ 52%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Boosted protease inhibitors

<table>
<thead>
<tr>
<th>HIV antiviral</th>
<th>Effect on antiretroviral AUC</th>
<th>Effect on etravirine AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir 300 mg/rtv 100 mg qd*</td>
<td>↓ 14%†</td>
<td>↑ 30%</td>
</tr>
<tr>
<td>Darunavir 600 mg/rtv 100 mg bid</td>
<td>1%</td>
<td>↑ 37%</td>
</tr>
<tr>
<td>Fosamprenavir 700 mg/rtv 100 mg bid*</td>
<td>↓ 69% amprrenavir</td>
<td>↑ 32% versus historical controls without PI/rtv</td>
</tr>
</tbody>
</table>

NRTIs

<table>
<thead>
<tr>
<th>HIV antiviral</th>
<th>Effect on antiretroviral AUC</th>
<th>Effect on etravirine AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir 400 mg/rtv 100 mg bid</td>
<td>↓ 20%</td>
<td>↑ 17%</td>
</tr>
<tr>
<td>Tipranavir 500 mg/rtv 200 mg bid*</td>
<td>↓ 18%</td>
<td>↑ 76%</td>
</tr>
</tbody>
</table>

CCR5 inhibitors

<table>
<thead>
<tr>
<th>HIV antiviral</th>
<th>Effect on antiretroviral AUC</th>
<th>Effect on etravirine AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc 300 mg bid†</td>
<td>↓ 53%</td>
<td>↑ 6%</td>
</tr>
<tr>
<td>Maraviroc 150 mg bid + DRV/rtv (600 mg/100 mg bid)</td>
<td>↑ 68%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Integrase inhibitors

<table>
<thead>
<tr>
<th>HIV antiviral</th>
<th>Effect on antiretroviral AUC</th>
<th>Effect on etravirine AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir 125 mg/rtv 100 mg qd</td>
<td>↑ 5%</td>
<td>↑ 1%</td>
</tr>
<tr>
<td>Raltegravir 400 mg bid</td>
<td>↓ 10%</td>
<td>↑ 10%</td>
</tr>
</tbody>
</table>

*Coadministration not recommended by manufacturer; †Although coadministration of etravirine only reduces atazanavir exposure (area under the plasma concentration versus time curve [AUC]) 14% to 17% (with or without ritonavir [rtv]), atazanavir C_{max} was reduced 47% without rtv and 38% with rtv, explaining the manufacturer’s recommendation not to coadminister these agents; ‡Manufacturer advises that alterations in dose or regimen may be needed; bid Twice a day; DRV Darunavir; NA Not available; NRTI Nucleoside reverse transcriptase inhibitor; PI Protease inhibitor; qd Once a day; tid Three times a day

G190A being the most prevalent. Only 4.6% of isolates had three or more etravirine RAMs. Patients with previous NVP exposure (n=983) had a mean number of etravirine RAMs that was significantly higher than those with previous EFV exposure (n=960) (0.66 versus 0.43; P<0.001). Up to 25.4% of patients exposure (n=983) had a mean number of etravirine RAMs that G190A being the most prevalent. Only 4.6% of isolates had three or more etravirine RAMs. Patients with previous NVP exposure (n=983) had a mean number of etravirine RAMs that was significantly higher than those with previous EFV exposure (n=960) (0.66 versus 0.43; P<0.001). Up to 25.4% of patients exposure (n=983) had a mean number of etravirine RAMs that G190A being the most prevalent. Only 4.6% of isolates had three or more etravirine RAMs. Patients with previous NVP exposure (n=983) had a mean number of etravirine RAMs that was significantly higher than those with previous EFV exposure (n=960) (0.66 versus 0.43; P<0.001). Up to 25.4% of patients exposure (n=983) had a mean number of etravirine RAMs that...
In terms of investigational ARV agents, no clinically relevant pharmacokinetic drug-drug interaction has been found between ritonavir-boosted elvitegravir (an integrase inhibitor) and etravirine in healthy volunteers (78). Interactions between etravirine and the CCR5 receptor antagonist, vicriviroc, have not been assessed to date.

Other agents commonly used in the treatment of patients with HIV infection have varying interactions with etravirine (Table 4). The manufacturer (Pfizer Inc, USA) recommends that dose adjustments of sildenafil be considered when sildenafil is coadministered with etravirine, due to potentially significant decreases in exposure to sildenafil when coadministered with etravirine. No dose adjustment is recommended for atorvastatin, azithromycin, clarithromycin, methadone, omeprazole, ranitidine, rifabutin or oral contraceptives (49). However, the manufacturer advises that alternatives to clarithromycin should be considered for the treatment of MAC, because clarithromycin exposure is decreased by etravirine, and although concentrations of its active metabolite, 14-hydroxy-clarithromycin, are increased, the latter reduces activity against MAC. It should be noted that not all potentially interacting drugs have been formally tested with etravirine to date.

Etravirine in HIV-infected pregnant women
HIV-infected pregnant women who can no longer benefit from first-generation NNRTIs due to resistance or other reasons require treatment alternatives. Etravirine might be an option in these patients. However, no data are yet available regarding the safety of etravirine in treatment of HIV infection in pregnant women and prevention of mother-to-child transmission in utero; thus, etravirine use cannot be recommended in these patients.

RECOMMENDATIONS
- In three-class experienced patients with drug-resistant HIV and persistent viremia, etravirine should be used with other active agents from at least two additional classes, preferably including the PI darunavir/ritonavir (A1). Ritonavir-boosted lopinavir and/or saquinavir may be considered as alternative PIs in this setting (BIII). If active boosted PIs and NRTIs are not available as options, active agents from other classes, including raltegravir and other new agents, can be used (CIII).
- Resistance testing is recommended for all patients before treatment (AII). Etravirine is more likely to be efficacious in patients with two or fewer etravirine RAMs (AII).
- Drug interactions should be taken into account when deciding on agent and dose selection for therapy concomitant with etravirine (AII). The manufacturer’s dosing recommendations in the package insert or product monograph, or an expert pharmacist should be consulted (AIII).
- Current data are insufficient to recommend how to address pharmacokinetic issues when switching from NVP or EFV to etravirine. If such a switch is contemplated, a clinical pharmacologist should be consulted (BIII).
- Etravirine should not be used in PI-naïve, first-line NNRTI failures without a boosted PI (DII). Etravirine could be considered in this situation with the concomitant use of a boosted PI (CIII), when it is necessary to use etravirine to design a regimen with three active agents.

Conclusions
Etravirine is a second-generation NNRTI that helps fill an unmet therapeutic need for selected patients with drug-resistant HIV infection. Etravirine is from a known drug class, and has a good short-term safety profile. Longer-term safety has yet to be demonstrated. Etravirine also offers a higher genetic barrier to resistance than first-generation NNRTIs, is active against most virus resistant to first-generation NNRTIs and offers antiviral, immunological and clinical benefits. Etravirine provides a new option for treatment-experienced patients with resistance to other NNRTIs. These guidelines are intended to assist the treating physician in the optimal use of etravirine.

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