Reviewer No. 2 checklist for:

6.4.2.2 Etravirine

In the WHO Essential Medicines List

(1) Have all important studies that you are aware of been included?
   Yes ☑ No ☑

Although the basic efficacy and safety data from the pivotal DUET-1 and DUET-2 trials was presented in the application, no mention was made of other studies or clinical experience with this agent, or of emerging safety data. There was also inadequate coverage of the issue of resistance to ETV. [a simple PubMed search yielded 297 citations].

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes ☑ No ☑

The two pivotal studies have provided adequate evidence of the efficacy of a combined ETV and boosted-darunavir (DRV/r) 3rd-line option.

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ☑ No ☑

Given the paucity of data from resource-constrained settings, in which the use of NNRTI-based 1st-line regimens is more prevalent, the concerns about ETV plus boosted-darunavir (DRV/r) use in patients requiring concomitant treatment for tuberculosis, and the lack of data in children, this cannot be considered evidence in meaningfully “diverse settings”.

(4) Are there adverse effects of concern?
   Yes ☑ No ☑

However, these are as expected for this patient group.

(5) Are there special requirements or training needed for safe/effective use?
   Yes ☑ No ☑

Appropriate use of 3rd-line or rescue regimens in resource-constrained settings will be hampered by lack of access to viral load measurements as well as genetic typing and interpretation of such results. As yet, no “public health” approach to third line options has been developed, although the clinical need has been identified.
(6) Is this product needed to meet the majority health needs of the population?

Yes ☐ No ✓

The 2010 WHO guidelines for adults are worth considering in detail:

“18.2. Evidence
A targeted literature review of relevant studies provides limited evidence to guide third-line strategies in resource-limited settings, with few studies of newer agents in these settings. Data from RCTs, predominantly in developed countries, are available for boosted darunavir (DRV/r), etravirine and raltegravir. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. There was no uncertainty among the panel concerning the need for third-line regimens. However, there was uncertainty about how making third-line regimens available would affect the provision of first-line and second-line ART. There was also uncertainty about what third-line drugs should be provided, as many studies are still in progress.

18.3. Summary of findings
The evidence is very limited, particularly in resource-limited settings. However, as access to monitoring improves and the scale-up of initial ART continues, demand for second-line and third-line regimens will increase. The criteria for diagnosing second-line failure are the same as those used for diagnosing first-line failure. In a pooled subgroup analysis, DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping was shown to be superior to the control group (bPI plus OBR, where the bPI was selected by the investigator) in highly treatment-experienced individuals. (180,181) These studies were conducted in high- middle income countries (Argentina, Brazil) and some well-resourced settings. In a further analysis, DRV/r was well tolerated in treatment-experienced, HBV- or HCV-coinfected patients, with no differences in liver-related adverse events between DRV/r and the control bPI group.(182) In developed country settings, DRV/r has been reported to be cost-effective compared to LPV/r.(183) In individuals with limited treatment options, raltegravir (RAL) plus OBR provided better viral suppression than OBR alone for at least 48 weeks.(184,185) Similarly, etravirine (ETV) plus OBR provided better viral suppression and improved immunological response than OBR alone.(186) In patients with multidrug-resistant virus who have few remaining treatment options, the combination of RAL, ETV, and DRV/r was well tolerated, and was associated with a rate of virological suppression similar to that expected in treatment-naive patients.(187)

18.4. Benefits and risks
Benefits
Therapy with newer agents is associated with a reduction in clinical progression and immunological deterioration. DRV/r has a higher genetic barrier to resistance compared to earlygeneration PIs and is active against multidrug-resistant HIV isolates. While high-level resistance to ETV following NVP or EFV failure appears uncommon, low-level resistance is common. (188–190)
Risks
There are few studies of newer agents in third-line regimens in resource-limited settings. Most studies have been conducted in well-resourced or high-income to middle-income countries, and have demonstrated benefit for non-critical outcomes (viral load suppression or immunological improvement). There is evidence from postmarketing reports of higher rates of hypersensitivity to ETV than previously reported. Etravirine and raltegravir are not approved for use in individuals less than 16 years of age. There are limited data on the use of newer drugs in pregnancy, including very limited pharmacokinetic and safety data.

18.5. Acceptability and feasibility
Physicians and PLHIV want a third-line regimen to be available. In studies conducted in well-resourced settings and in modelled cost-effectiveness analysis, DRV/r has been demonstrated to be cost-effective compared to other bPIs in heavily pretreated patients. The acquisition cost for ETV is one to two times higher than that of EFV and NVP. The acquisition cost of DRV and RAL has not been established in resource-limited settings but is expected to be high. The availability of these drugs in resource-limited settings now and in the near future is uncertain.”


The 2010 WHO guidelines for children only mention the ongoing research programme.

(7) **Is the proposed dosage form registered by a stringent regulatory authority?**

- Yes [✓]
- No [　]

(8) **What action do you propose for the Committee to take?**

Not to include etravirine on the EML at this stage.

(9) **Additional comment, if any.**

While there is undoubtedly a clinical need for 3rd-line or rescue regimens, in the absence of a suitable public health approach to the selection and use of such agents, particularly in resource-constrained settings, their inclusion in the WHO Model EML at this stage would seem premature.

**References**


