Dear 18th Expert Committee for Essential Medicines,

Thank you very much for reviewing our applications for the drugs recommended in third-line antiretroviral therapy by 2010 WHO ART guidelines (raltegravir, etravirine, and darunavir). Thanks also to Reviewer 2 for their constructive review of our application on etravirine (ETR). We found his/her comments very helpful and have responded to each of them (please see in red text after each reviewer's comments below).

In general terms, we would like to say there was no uncertainty among the ART guidelines review committee on the need to have third-line ART regimens available (the uncertainty was in fact on the best choice of regimen and how to make it available in an equitable manner). Regarding the decision-making process adopted in WHO ART guidelines review, it is important to say that one of the major reasons for inclusion of third-line recommendations was the recent cohort data showing high mortality rates among HIV-infected patients failing to second-line therapy\(^1\). This was the most critical outcome considered in these guidelines, which used the GRADE\(^2\) methodology for quality evidence review. Benefits in important but less critical outcomes as virologic suppression and immunological improvement were also shown. Therefore, despite limited experience with raltegravir, etravirine, and darunavir in resource-limited settings (RLS) the WHO ART guidelines committee put a high value on this mortality risk and on balancing the need to develop policies for third-line therapy in RLS while expanding access to first- and second-line therapy, as part of a "sequential" treatment strategy (see 1st recommendation on page 58 of the ART guidelines). There are also some analyses showing that third-line is cost-effective in highly experienced patients in industrialized settings. Of course there are cost and operational challenges in RLS, and that's why their use was made in conditional recommendations in 2010 WHO ART guidelines.

We also have used a targeted literature review of relevant RCT studies using combinations of boosted DRV, ETR and RAL with or without different optimized background therapy (POWER study for DRV, DUET studies for ETR, and BENCMRK studies for RAL). Despite to be few and predominantly done in industrialized-settings, they support the use of these agents together in third-line (see 2nd recommendation at page 58). However there were no head-to-head comparisons among these three drugs in order to identify the best drug combination(s) and that is the main reason why no specific preferred combination(s) was suggested in our guidelines. However, as observed with second-line regimens, there are concerns about the resistance risk if these third-line drugs are used as "functional monotherapy" (i.e. using only one new antiretroviral instead of two or three new drugs). Therefore, raltegravir, etravirine, and darunavir should be combined in the third-line regimen (using 2 or all of these 3 drugs), with or without optimized background therapy (i.e. one or more of the antiretrovirals used in previous regimens).

However, long term safety is an important point to be considered, and limited data on pregnancy and children/adolescents is also a concern. This is why these new drugs are recommended in third-line combinations rather than first- or second-line therapy.

Finally, WHO is engaged on continuity of post marketing vigilance with these and also other new drugs. However, recent published data have also shown that these drugs have a better toxicity profile when compared with other drugs in the same class, such as ETR versus EFV in terms of occurrence of CNS side effects\(^3\), and DRV when compared with LPV in terms of GI tolerance and dyslipidemias. Expanding use of these drugs into second-line will therefore be considered in future guideline reviews, particularly with supportive long term safety data and better formulations (FDCs).

Yours sincerely,
WHO Antiretroviral Treatment and Care Unit (ATC)
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 X

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,1,2,3,4,5,6 or of emerging safety data.7,8,9,10 There was also inadequate coverage of the issue of resistance to ETV.11,12,13,14,15 [a simple PubMed search yielded 297 citations].

ATC: Thank you very much indeed for providing the references. In response to the efficacy data, WHO uses the GRADE2 framework for recommendations. The GRADE framework recommends to use RCTs (or observational data with a comparator when RCTs are not available) to rank the quality of evidence and to attribute an effect to an intervention rather than to chance alone. Therefore, for third line regimens, the guidelines committee focused on a study population of people with multi-drug resistant HIV. The intervention was one of the new ARVs (RAL, ETR, or DRV) and the comparator was placebo or no drug. The main outcome of interest was mortality, although viral suppression and immunological criteria were also prioritised by the guidelines committee. The DUET studies were presented because they compared ETR to no drug in combination with an optimised background regimen. References 1-6 either did not compare ETR to placebo/no drug (text are quoted directly from abstract) or did not feature a study population with multi drug resistant HIV.

References

ATC: “Virological, immunological and clinical outcomes were compared according to the inclusion or not of NRTIs in the regimen, after 48 weeks of follow-up.” [intervention is NRTIs]


ATC: “We evaluated the effectiveness of rescue regimens containing etravirine and the factors associated with treatment response.” [no comparator].

**ATC:** “This multicenter, open-label, Phase IIIb, 48-week pilot study assessed safety, tolerability, and effectiveness of the PI darunavir (DRV), boosted with ritonavir (DRV/r), and the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (ETR), when substituted for ENF/PI (±NNRTI)-based therapy” [no comparator].


**ATC:** “We investigated the effect of replacing EFV with etravirine (ETR) on patient preference, sleep, anxiety and lipid levels.” [This study was available January 2011, after the application was submitted. Moreover, the study population did not have multidrug resistant HIV].


**ATC:** “The Phase III, nonrandomized, open-label EAP investigated etravirine 200 mg twice daily plus a background regimen (BR) in patients who had failed multiple antiretroviral regimens.” [no comparator].


**ATC:** “HIV RNA suppression rates after 24 weeks of treatment with etravirine, darunavir/ritonavir and raltegravir in the etravirine early access programme” [no comparator].


ATC: WHO collaborated with Tibotec to provide the most recent safety data on ETR to the Essential Medicines committee. The manufacturer provided all safety data at the time of the application on pages 4-5 of the application. Moreover, as is the case with efficacy outcomes, comparison with placebo/no drug is typically used when attributing the risk of an adverse event to a drug rather than to chance alone. Therefore, safety data from the DUET RCTs were presented on page 17 of the application.


ATC: WHO and partners had identified mortality, viral suppression, and treatment-limiting adverse events as critical outcomes when deciding on agents to use for third line. While resistance mutations are very important this was the last outcome used, and was treated as an ‘important’ rather than ‘critical’ outcome during the guidelines formation. This is because drug resistance is highly patient specific and depends on the strain of HIV the patient was infected with and their adherence to previous regimens. Given that third line data were from industrialised settings where antiretroviral therapy regimens are highly heterogeneous across practitioners it would be very hard to (1) ensure the study population of an RCT has the same resistance profile at study baseline and (2) objectively compare the resistance mutations accrued with different regimens during the study.

(2) Is there adequate evidence of efficacy for the proposed use?
Yes X 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 X

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”.

ATC: Lack of safety and PK data in different populations, while important, should not preclude availability of a lifesaving intervention in resource-limited settings, particularly in highly experienced individuals with absence of options. Indeed, observational data has shown high rates of mortality after second-line failure.

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

However, these are as expected for this patient group.

ATC: Indeed, there is a need to be vigilant of toxicity with all antiretrovirals.

(5) Are there special requirements or training needed for safe/effective use?
Yes X 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.

ATC: The public health approach to ART recommends use of clinical and immunological markers of failure when viral labs are not available. These criteria for failure, admittedly not ideal, can be used for identifying first-, second-, and third-line ART failure. A few countries are using third-line regimens as part of their ART national policies. Moreover, at this stage the public health approach is to ensure availability to third line regimens containing a combination of ETR, RAL, and/or DRV/r.

(6) Is this product needed to meet the majority health needs of the population?
Yes No X

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, predominately 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 (PI plus OBR, where the PI 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 PI 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 early generation 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.(191) 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.(192) 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 PIs 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.

ATC: The use of these drugs has been recommended by WHO to attend the needs of HIV-infected patients failing second-line and in need of third line regimens, with impact on mortality in this population.

(7) Is the proposed dosage form registered by a stringent regulatory authority?
Yes X No
ATC: Yes we agree that ETR is registered by stringent regulatory authorities (FDA and EMEA) since end of 2008.

(8) What action do you propose for the Committee to take?
Not to include etravirine on the EML at this stage.

ATC: We disagree, as there is a need for HIV programmes to commence the process of identifying suitable third-line agents. At this point WHO has identified DRV, RAL, and ETR to suit this purpose. Considering the high rates of mortality among people continuing failing second-line regimens, WHO strongly feels that ensuring availability of an effective third line regimen (featuring a combination of ETR, RAL, and DRV/r) will save lives.

(9) Additional comment, if any.
While there is undoubtedly a clinical need for third-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.

ATC: The 2010 guidelines currently recommend RAL, ETR, and/or DRV/r for third-line regimens, and some countries have already started to introduce third-line therapy in their national portfolios. This recommendation was the driving force behind submitting applications for these three ARVs to the Essential Medicines Committee. We do hope the Committee reviews these comments and the applications in detail. Inclusion of these drugs in EML can enhance the adaptation of national EML and facilitate the procurement and price negotiations. Please do not hesitate to contact HIV Department (ATC and AMDS teams) with any questions or concerns.

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