

## Third-line regimens

### Recommendations

1. It is recommended that National programs should develop policies for third-line therapy that address funding, sustainability and the provision of equitable access to ART. (Conditional recommendation, low quality of evidence)
2. Third line regimens should include ideally two new drugs with predicted activity such as boosted DRV, raltegravir and etravirine. (Conditional recommendation, low quality of evidence)
3. If patients are on a failing regimen without further therapeutic options, a tolerated regimen should be continued. (Conditional recommendation, very low quality of evidence)

### Domains and considerations

#### Quality of evidence

The quality of evidence was not based on a systematic but a targeted literature review for relevant studies. Indirectness was noted among these trials. With the optimized background regimen based on genotypic or phenotypic testing and study populations which were generally not in low- and middle-income countries. Strong recommendations not possible until more information is available on the role of etravirine, darunavir and raltegravir in 3<sup>rd</sup>-line in the context of a RLS.

Data from RCTs in developed and developing country settings are available for boosted darunavir (DRV/r), etravirine (ETR) and raltegravir (RAL). Taken together, these data support the success of these newer agents in ART experienced patients. DRV/r has been demonstrated to be non-inferior and well tolerated compared to LPV/r.

**DRV/r** (TITAN Power 1-2-3)

**RAL** (BENCHMARK 1-2, EASIER)

**ETR** (Duet 1, 2, TMC-125 C223, Cohen, Montaner)

**Combination of all three** (TRIO)

**Uncertainty about the current quality of evidence but many studies are ongoing**

#### Risks/Benefits

##### Benefits

- Avoid death and disease progression in patients failing second-line therapy
- Third-line/salvage studies conducted in developed/high-middle income countries showed benefit using non-critical outcomes (viral load suppression)

##### Risks

- Information about long-term safety is limited
- Potential drug-drug interactions with TB, malaria, hepatitis and opioid substitution therapy (OST) drugs
- New evidence on higher rates of hypersensitivity to etravirine than previously reported (recent warning informing about etravirine hypersensitivity risk published in Aug 09)
- Raltegravir is not approved for use in individuals <16 years old
- Limited data on use of these drugs in pregnancy
- Limited resources diverted from scale-up of ART coverage

- Equity of access may be compromised

**Benefits outweigh risks**

**Values and acceptability**

- Physicians and PLHIV want to have a 3<sup>rd</sup>-line regimens available but the panel also valued maintaining access to 1<sup>st</sup>-line ART

**No uncertainty**

**Cost**

- Expensive and costly to national programmes
- In studies conducted in developed countries and in modeled cost-effectiveness analyses, DRV/r has been demonstrated to be cost effective compared other boosted PIs in heavily pretreated patients
- The acquisition cost for etravirine is 1 to 2 times that of EFV and NVP
- The acquisition cost of DRV and raltegravir is not well established in RLS but is expected to be high
- Provision of 3<sup>rd</sup>-line will be costly and it is unclear if price reductions are likely

**No uncertainty**

**Feasibility**

- Availability of these drugs in RLS now and in the near future is uncertain
- Availability of generic formulations and FDCs in the near future is uncertain

**Uncertainty Yes**

**Gaps, research needs, comments**

- More information on critical patient outcomes on patients on 2<sup>nd</sup>-line ART
- Current and near-future licensing and availability of these new drugs in RLS
- Coming availability of generics and FDCs (UNITAID and patent pool initiative)
- Ongoing studies with once daily dosing for DRV/r and raltegravir
- Pilot studies on 3<sup>rd</sup>-line implementation and pharmacovigilance studies on monitoring long-term adverse events and other potential drug-drug interactions in RLS are necessary
- Toxicity monitoring of patients on 2<sup>nd</sup>-line and 3<sup>rd</sup>-line regimens
- "Green Light Committee" assesses suspected MDR TB cases and establishes mechanisms for countries to access the needed drugs. Could a GLC for 3<sup>rd</sup>-line ART be an option?
- GLC might be able to attract separate funding and negotiate lower prices for 3<sup>rd</sup>-line drugs than if countries do this independently and could be a mechanism to avoid countries having to balance the need to scale up vs. the need to fund 3<sup>rd</sup>-line regimens

**Final comment**

**Conditional recommendation**

In developing these recommendations, the panel placed high value on balancing the need to develop policies for 3<sup>rd</sup>-line therapy while maintaining increased access to 1<sup>st</sup>-line therapy. It was recognized that countries are financially constrained.