### Stavudine (d4T) phase-out management: Guiding principles

1. It is recommended that in settings where d4T regimens are used as the preferred option for ART initiation, a phase-out plan towards using AZT- or TDF-based 1st-line regimens should be developed.

2. The d4T phase-out plan should be based on an assessment of the cost and feasibility of phasing out d4T use.

3. All countries continuing to use d4T as part of a preferred 1st-line regimen should undertake a risk assessment for continuing to use d4T at lower doses.

4. It is recommended that programs implement systems to monitor and manage toxicities for all ongoing use of d4T-containing regimens.

### Summary of evidence
- Some experts advocate for the complete removal of d4T (already a delisted option in the majority of ART guidelines form industrialized countries)
- Phasing out d4T is ongoing at global level but still the preferred 1st-line ARV in 56% of LMIC/LIC programs
- Most adverse events are related to mitochondrial toxicity and due to cumulative exposure (usually after 6 to 12 months of therapy)
- There are limited data on the toxicities of reduced doses (studies suggest that efficacy is maintained)
- Reduced dose d4T may be valid initial option in settings with limited N(t)RTI options, limited laboratory capabilities and/or as a backup option for treatment-limiting toxicity to AZT or TDF
- Option exists to initiate d4T-based ART and switch after 6 to 12 months before or immediately at detection of mitochondrial toxicities, but relative data is sparse.
- Close monitoring of its long-term toxicities is required
- Higher risk patients for lipoatrophy are those >35 years old, women with high BMI and/or pregnant
- Higher risk patients for lactic acidosis are women with high BMI and/or pregnant
- Higher risk patients for neuropathy are those receiving concomitant use of d4T and INH (seven-fold increase in the risk of peripheral neuropathy)

### Risks/Benefits

**Benefits**
- Phase-out of a drug associated with significant adverse events
- Reduction in stigma caused by lipoatrophy, disability caused by peripheral neuropathy and mortality due lactic acidosis
- Potential positive impact on adherence if disfiguring and unpleasant side-effects are avoided

**Risks**
- Current cheap, good and readily available generic FDCs for adults and children, well tolerated in the short-term, will need to be replaced
- Loss of a drug which is well tolerated in the short-term but has unacceptable complications in the long-term
- Potential for wasted stock of d4T FDCs
- Potential for reduced coverage due to increased cost of new regimens
- Uncertainty about the impact of AZT-induced anaemia and TFD renal toxicity as programs transition away from d4T to AZT or TDF

**Benefits outweigh risks**

**Values and acceptability**
- PLHIV place high value on avoiding d4T-related side-effects
- Physicians’ concerns about long term toxicities such as lipoatrophy, peripheral neuropathy and lactic acidosis
- Countries place high value on cheap and easily available regimens

**No uncertainty**

**Cost**
- Initial increased cost (TDF > AZT) which may be offset by reduced costs of d4T toxicity management in long term
- Prices of TDF and AZT combinations are significantly higher than d4T combinations but are progressively reducing (generic versions as dual and triple FDCs more available)
- Costs of lab monitoring and HCW training on AZT and TDF toxicity management

**Uncertainty about cost savings of d4T phase-out**

**Feasibility**
- Cost is a major limitation and moves away from easily available and affordable fixed-dose combinations
- TDF substitution may be more feasible if no renal monitoring is required
- Favours phased, planned replacement of d4T by AZT or TDF, with speed and completeness determined by health system structure, disease burden, ART coverage, lab capacity and funding
- Countries which have transitioned away from d4T suggest that it is feasible

**Uncertainty Yes**

**Gaps, research needs, comments**
- Further evaluation of safety and prevalence of major d4T toxicities at doses ≤30 mg BID in RLS is necessary
- Further evaluations of the cost of phase out d4T use
- Tools for risk assessment on continuing d4T use
- Tools for pharmacovigilance, detection and monitoring of major d4T toxicities

**Final comment**

**Strong recommendation**

In developing these recommendations, the panel placed high value on the disfiguring and unpleasant side effects of d4T and unacceptability to PLHIV over and above the cost and programmatic implications of moving to alternative safer, but more expensive drugs.