General principles

Details on individual drugs are available from the various manufacturers or the US treatment guidelines (http://www.aidsinfo.nih.gov) or the PENTA 2009 guidelines for the use of antiretroviral therapy (ART) in paediatric HIV-1 infection, which are published in the journal *HIV Medicine* (*HIV Med. 2009* Nov; 10 (10): 591 – 613). Common and important toxicities of ARV drugs are provided in the main text of this document.

The WHO dosing guidance provided here includes weight-based tables. The target dose for each ARV drug is shown in the introduction of the individual drug tables. However, in some cases, the dosing in a particular weight-band may be somewhat above or below that recommended by the manufacturer. Decisions about dosing were based upon the manufacturer's information, ARV drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight-band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing.

It is recommended that national treatment advisory panels and/or expert groups review and consider these principles and the prescribing information given in this Annex within the context of their current national policies, practice and drug regulatory requirements.

The principles that were followed in developing the WHO simplified tables include the following.

- Liquid formulations are difficult to use for a variety of reasons, including cost, difficulty of storage, need for accurate measurement, palatability and the nature of the excipient.
- Solid formulations and FDCs generally are preferred to liquid formulations.
- It is preferable to use one type of formulation when constructing a treatment regimen.
- Where solid formulations are not available or suitable, and liquid formulations are the only option:
  - Oral syringes or other standardized devices of various sizes should be made available to support accurate dosing.
  - Large volumes of liquid formulations should be avoided where possible.
  - In general, children should be switched to available solid formulations as soon as possible or as soon as they are tolerated.
- Many tablets, but not all, may be divided in half but generally not further for drug safety reasons. Scored tablets are more easily split, and most paediatric tablets and FDCs are manufactured with a score line. Where tablets are not scored, WHO recommends that tablet splitting is conducted in the dispensing pharmacy using appropriate tablet cutters.

- If paediatric solid formulations are not available, use solid formulations currently available for adults. However, some adult FDCs may contain ratios of ARVs that are not best suited for children and this can result in underdosing of individual components when tablets are halved. Underdosing should be avoided, particularly for those drugs that may lead to rapid emergence of resistance (e.g. non-nucleoside reverse transcriptase inhibitors [NNRTIs]).
- In order to deliver once-daily dosing of nevirapine (NVP) during the first two weeks of induction of a NVP-containing regimen, triple-drug FDCs should be combined with dual FDCs (that do not contain NVP). Alternatively, if dual FDCs are not available, the individual components of the regimen should be prescribed.
- Different morning and evening doses should be avoided where possible. Where tablets can be divided, the use of even quantities of tablets is recommended (e.g. where 3 tablets daily is recommended, the morning dose would be 1.5 tablets and the evening dose 1.5 tablets). When tablets cannot be divided and morning and evening doses have to be unequal, it is recommended that the larger of the two doses be taken in the morning (e.g. where 3 tablets daily is recommended, dose 2 tablets in the morning and 1 tablet in the evening).
- The doses in the tables are presented in weight-bands, accepting that some deviation from target dosing will occur.
- Children have to be weighed at each clinic visit so that appropriate dose changes can be made as children grow and gain weight.
- When capsules are opened or tablets dissolved or crushed and added to food or liquid, it is important that the dose be consumed immediately and that the entire volume/amount of food or liquid is consumed to ensure administration of the full dose.

Where manufacturers'dosing was provided in BSA, weight-based doses were determined by using BSA values estimated from median heights-for-weight from international growth charts. BSA estimates for each weight were derived from the mid-upper arm circumference/weight-for-height study database (MUAC/WFH), which includes data from over 560 nutritional anthropometry surveys. These weight-for-BSA estimates were structured into a dosing tool developed by WHO (http://www.who.int/hiv/paediatric/generictool/en/index.html). The Paediatric Working Group used this tool to assess various dosing schedules in terms of the intended dose delivered relative to the target dose at each weight for a variety of single drugs and FDCs. The tool demonstrates potential over- or underdosing for any given weight. Available evidence was reviewed, including published and unpublished data, to better understand the potential impact of off-target dosing (http://www.who.int/hiv/pub/paediatric/ARV_WG_meeting_report_may2008.pdf).

In general, the Working Group attempted to avoid dosing any drug or component of an FDC below 90% or above 125% of the target dose (or target range for products with an established dosing range). Exceptions to this rule may be justified based on available pharmacokinetic data, toxicity considerations, and thresholds for the development of HIV drug resistance. In particular, the Working Group accepted higher dosing for children less than 3 years of age for drugs with a known increase in metabolism or clearance in this population, such as NVP, lamivudine (3TC), stavudine (d4T), abacavir (ABC) and lopinavir/ritonavir (LPV/r). A primary objective of the Working Group was to create a single, simplified and harmonized dosing schedule wherein, for all drugs or combinations, changes

in the numbers of tablets/capsules and switches from one formulation to another occurred within the same weight-bands.

The first harmonized schedule was published in 2008 and, since then, has been expanded significantly to include a number of additional drugs and formulations.

WHO will continue to work to simplify prescribing, dispensing and dosing guidance, and to work with the pharmaceutical industry (originator and generic manufacturers) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate scaling up of paediatric ART. WHO will make available additional guidance on required formulations, dosing information and pharmacovigilance activities.