

# ANNEX E: PRESCRIBING INFORMATION AND WEIGHT-BASED DOSING OF AVAILABLE ARV FORMULATIONS FOR INFANTS AND CHILDREN

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## Introduction

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**The availability of low-cost, high-quality, child-friendly ARV formulations, particularly FDC products, has had a significant impact on the scale-up of ART for children.**

**WHO strongly endorses the use of these products, and encourages the continued development of improved formulations appropriate for paediatric use.**

This Annex contains information on antiretroviral (ARV) drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing. Situations that are frequently encountered in resource-limited settings are taken into consideration, including the possible lack of refrigeration and the lack of liquid or formulations of ARVs for small children. For simplification, doses are provided in ranges based on children's weights. Although weight and height can both be measured, it may be impractical to expect providers in many settings to accurately calculate body surface area (BSA). When determining weight-band-based dosing for drugs that are usually dosed by BSA, careful consideration was given to the usual surface area for children of that weight in cohorts from developing countries.

WHO began the work of developing simplified guidance on ARVs for use in children as a result of recommendations made at a technical consultation in November 2004. Since then, the guidance has been regularly updated by the Paediatric ARV Working Group. Members of this working group are listed in Annex A.

The Paediatric ARV Working Group reviews current scientific data and uses pharmacokinetic modelling data to develop guidance to manufacturers on which ARV medicines are likely to be required.

The primary sources of information for the guidance are the package inserts from the innovator for each drug at the time of writing. This information is supplemented with data from other authoritative publications and expert consultation. Providers are advised to consider the most recent guidelines and product labelling as this information may have been updated.

Generic (multisource) ARV drugs are manufactured by several companies. These products include a number of important paediatric fixed-dose combination (FDC) tablets that contain doses of drugs appropriate for small children. Paediatric FDCs are preferable for implementation in resource-limited settings, and while most of them are of acceptable quality, providers should consult the WHO document *Access to HIV/AIDS drugs and diagnostics of acceptable quality* for guidance (<http://www.who.int/hiv/amds/selection/en/index.html>).

WHO operates a voluntary prequalification system that was set up in 2001. This service facilitates access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis (TB). Manufacturers (including manufacturers of generic products) who wish their medicines to be included in the prequalified products list are invited to apply. Each manufacturer must present extensive information on the product (or products) submitted to allow qualified assessment teams to evaluate quality, safety and efficacy. The manufacturer must open its manufacturing sites to an inspection team that assesses working procedures for compliance with WHO Good

Manufacturing Practices. Alternatively, the inspections carried out by stringent regulatory bodies are recognized and their work is not duplicated by WHO. A list of WHO-prequalified products is continuously updated and is available at <http://mednet3.who.int/prequal/>.

This Annex will be updated regularly as new data become available and readers are recommended to check the WHO website on paediatric HIV care (<http://www.who.int/hiv/topics/paediatric/en/index.html>).

## General principles

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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](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.

## **The need for new formulations and new research**

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Although a number of child-friendly formulations, particularly paediatric FDC tablets and paediatric single drugs in solid forms, are available, it is clear that additional formulations will be needed to facilitate the scale-up of treatment for infants and children, and to keep pace with new recommendations and guidance.

Additional research is necessary to better understand the best dosing formulations for children. Dispersible tablets are easier to dose in children, but require access to clean water, and have not been studied in breast milk, which is important for administration to infants. Breast milk dispersibility is especially important for formulations that will be used for infant prophylaxis to prevent mother-to-child transmission (MTCT) of HIV infection. One option for prevention of mother-to-child transmission (PMTCT) in the new WHO recommendations calls for long-term infant prophylaxis with NVP. In the first few weeks of life, this is best accomplished by using NVP liquid, but beyond 6 weeks, infant dosing would be made easier if there was a dispersible scored 20 mg NVP tablet.

Darunavir (DRV) will be an important drug for paediatric treatment in the future, especially as increasing numbers of children require third-line therapy. DRV is usually boosted with low-dose ritonavir (RTV). At present, although there are several capsule strengths of DRV available, including strengths that are suitable for paediatric dosing, no DRV/RTV co-formulation is available.

Once-daily FDCs containing tenofovir (TDF), efavirenz (EFV) and emtricitabine (FTC) or 3TC have become the mainstays of adult treatment. Currently, TDF is not approved for use in children less than 12 years, but a number of paediatric studies are in progress and a paediatric approval is expected. An FDC containing TDF 75 mg and 3TC 75 mg together with a scored adult tablet containing TDF 300 mg and 3TC 300 mg would align well with the harmonized schedule.

For countries that choose to use ABC as a first-line drug in children, it is critical to have access to a triple-drug FDC containing ABC, 3TC and NVP. This would complement the dual FDC of ABC/3TC.

A number of additional high-priority formulations have been identified by the Paediatric ARV Working Group and these are listed below.

**Urgently needed dosing strengths of drugs not yet available in child-friendly formulations**

Drug	Formulation (mg)	Comments
<b>DRUGS NEEDED FOR PMTCT</b>		
NVP	20 mg scored tablet	Used for infant prophylaxis from 6 weeks onwards
<b>DRUGS NEEDED FOR PAEDIATRIC ART</b>		
LPV/RTV	40/10 mg sprinkle	Heat-stable formulation that will be equivalent to 0.5 ml of liquid and used to treat infants and children who are unable to take the paediatric tablet
ABC/3TC	Scored adult 300/150 mg tablet	Used in children >25 kg
ABC/3TC/NVP	60/30/50 mg	Triple FDC to align with the dual FDC
RTV	50 mg heat-stable sprinkle or tablet	Useful for co-administration with unboosted PIs and for super boosting when PIs need to be dosed with rifampicin
TDF/3TC	75/75 mg tab	
	Scored 300/300 mg tab	
DRV/RTV	Unclear	Current labelling calls for different ratios of DRV to RTV for different age brackets. It is unclear what the correct ratio should be to produce a co-formulated FDC, but this is a priority formulation
Raltegravir	Unclear	Raltegravir is not yet approved for paediatric use but this is high-priority formulation

See updated guidance on required paediatric formulations at <http://www.who.int/hiv/topics/paediatric/technical/en/index>.

## Harmonized dosing schedules

Simplified table giving number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above												Strength of adult tab (mg)		Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening															
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg		20 – 24.9 kg		25 – 34.9 kg		am	pm	am	pm
<b>SINGLE DRUGS</b>																	
AZT	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	300	1	1	
ABC	60	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	300	1	1	
NVP	50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	200	1	1	
ddl	25	2 <sup>a</sup>	2 <sup>a</sup>	3	2	3	3	4	3	4	4	4	4	25	5	5	
<b>COMBINATIONS</b>																	
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	300/150	1	1	
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	300/150/200	1	1	
ABC/AZT/3TC	60/60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	300/300/150	1	1	
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	<sup>b</sup>			
d4T/3TC	6/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	30/150	1	1	
d4T/3TC/NVP	6/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	30/150/200	1	1	
LPV/r <sup>c</sup>	100/25	NR	NR	NR	NR	2	1	2	2	2	2	2	2	100/25	3	3	

<sup>a</sup> This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

<sup>b</sup> See ABC/3TC FDC dosing table.

<sup>c</sup> Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, fos-amprenavir (FPV), rifampicin.

## Simplified table giving ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of paediatric liquid (mg/ml) and adult tab/cap (mg)	Children 6 weeks of age and above												
		Number of tablets/capsules or ml by weight-band morning and evening												
		3 – 5.9 kg		6 – 9.9 kg		10 – 13.9 kg		14 – 19.9 kg		20 – 24.9 kg				
am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	
AZT	10 mg/ml; 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	0.5	0.5	1	1	0.5
ABC	20 mg/ml; 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	0.5	0.5	1	1	0.5
3TC	10 mg/ml; 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	0.5	0.5	1	1	0.5
d4T	1 mg/ml; 15 mg or 20 mg	6 ml	6 ml	9 ml	9 ml	1 (15 mg)	1 (15 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)	1 (20 mg)
NVP	10 mg/ml; 200 mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	1	0.5	0.5	1	1	0.5
ddl	10 mg/ml; 25 mg	3 ml <sup>a</sup>	3 ml <sup>a</sup>	5 ml	5 ml	6 ml	6 ml	4	4	3	3	4	4	4
LPV/r	80/20 mg/ml	1 or 1.5 ml <sup>b</sup>	1 or 1.5 ml <sup>b</sup>	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	3 ml	3 ml	3 ml

<sup>a</sup> This dose of ddl is only appropriate for children 3 months of age or older and weighing between 5 kg and 5.9 kg.

<sup>b</sup> LPV/r liquid: for 3 – 3.9 kg, use 1 ml a.m. and 1 ml p.m.; for 4 – 5.9 kg use 1.5 ml a.m. and 1.5 ml p.m. In addition, higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV or rifampicin.

Simplified table giving number of tablets of child-friendly solid formulations for once-daily dosing

Drug	Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily				Strength of tab/cap (mg)	Number of tablets or capsules by weight-band once daily
		3 – 5.9 kg	6 – 9.9 kg	10 – 13.9 kg	14 – 19.9 kg		
		Once daily	Once daily	Once daily	Once daily	Once daily	Once daily
<b>SINGLE DRUGS</b>							
EFV <sup>a</sup>	200 mg	NR	NR	1	1.5	200	2
ddl <sup>b</sup>	125 mg or 200 mg EC	NR	NR	1 (125 mg)	1 (200 mg)	2 (125 mg)	2

<sup>a</sup> EFV is not recommended for children below 3 years and weighing less than 10 kg.

<sup>b</sup> ddl EC is not recommended for children weighing less than 10 kg; this dose is recommended only for those 10 kg and above.

NR = not recommended EC = enteric coated

## Drug formulations and dosages

### 1. Nucleoside reverse transcriptase inhibitors (NRTIs)

1.1. LAMIVUDINE (3TC)			
FORMULATIONS			
Tablets	Capsules	Liquid	FDC
150 mg	None	10 mg/ml	<b>Baby 30 mg 3TC</b> <b>Adult 150 mg 3TC</b> <ul style="list-style-type: none"> <li>• 3TC + d4T + NVP</li> <li>• 3TC + d4T</li> <li>• 3TC + AZT + NVP</li> <li>• 3TC + AZT + ABC</li> <li>• 3TC + AZT</li> <li>• 3TC + ABC</li> </ul> <b>Junior 60 mg 3TC</b> <ul style="list-style-type: none"> <li>• 3TC + d4T + NVP</li> <li>• 3TC + d4T</li> </ul>
DOSE AND FREQUENCY OF DOSING			
<p><b>Target doses</b></p> <ul style="list-style-type: none"> <li>• Age less than 30 days of life: 2 mg/kg/dose twice daily (this dose should be used for infant prophylaxis during the first 30 days of life)</li> <li>• Age more than 30 days of life: 4 mg/kg/dose twice daily</li> <li>• Weight more than 50 kg: 150 mg twice daily</li> </ul> <p>Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are available for children switching to once-daily dosing once viral suppression occurs on ART.</p> <p><b>Administration – adult tablets</b></p> <ul style="list-style-type: none"> <li>• Can be crushed and contents mixed with a small amount of water or food and taken immediately</li> </ul> <p><b>Storage</b></p> <ul style="list-style-type: none"> <li>• Store tablets/capsules at room temperature (25°C; range 15 – 30°C).</li> <li>• Store liquid at room temperature (25°C; range 15 – 30°C).</li> <li>• Use within one month of opening.</li> </ul>			
OTHER COMMENTS			
<p><b>General</b></p> <ul style="list-style-type: none"> <li>• Well tolerated</li> <li>• No food restrictions</li> <li>• Also active against hepatitis B</li> </ul>	<p><b>Pharmacokinetic data</b></p> <ul style="list-style-type: none"> <li>• Available for all ages</li> </ul>	<p><b>Major drug interactions</b></p> <ul style="list-style-type: none"> <li>• None</li> </ul>	

Ref: [http://us.gsk.com/products/assets/us\\_epivir.pdf](http://us.gsk.com/products/assets/us_epivir.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

## LAMIVUDINE

Recommended dosing based on weight-bands for children >6 weeks of age using liquid and adult tablets

Weight range (kg)		Target dose 4 mg/kg twice daily to a maximum of 150 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	3 ml	3 ml
4	4.9	10	mg/ml liquid	3 ml	3 ml
5	5.9	10	mg/ml liquid	3 ml	3 ml
6	6.9	10	mg/ml liquid	4 ml	4 ml
7	7.9	10	mg/ml liquid	4 ml	4 ml
8	8.9	10	mg/ml liquid	4 ml	4 ml
9	9.9	10	mg/ml liquid	4 ml	4 ml
10	10.9	10	mg/ml liquid	6 ml	6 ml
11	11.9	10	mg/ml liquid	6 ml	6 ml
12	13.9	10	mg/ml liquid	6 ml	6 ml
14	16.9	150	mg tablet	½	½
17	19.9	150	mg tablet	½	½
20	24.9	150	mg tablet	1	½
25	29.9	150	mg tablet	1	1
30	34.9	150	mg tablet	1	1

## 1.2 STAVUDINE (d4T)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	15 mg 20 mg 30 mg	1 mg/ml	<b>Baby 6 mg d4T</b> <b>Junior 12 mg d4T</b> <b>Adult 30 mg d4T</b> <ul style="list-style-type: none"><li>• d4T + 3TC + NVP</li><li>• d4T + 3TC</li></ul>

### DOSE AND FREQUENCY OF DOSING

#### Target doses

- Weight less than 30 kg 1 mg/kg/dose twice daily
- Weight more than 30 kg 30 mg/dose twice daily

Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available for children switching to once-daily dosing once viral suppression occurs on ART.

- Adults 30 mg/dose twice daily

#### Administration – capsules

- Can be opened and mixed with small amount of food or water and taken immediately (stable in solution for 24 hours if kept refrigerated)

#### Administration – liquid

- Liquid must be well shaken prior to each use.

#### Storage

- Store capsules at room temperature (25°C; range 15 – 30°C) in a tightly closed container.
- Store powder for solution at room temperature (25°C; range 15 – 30°C) in a tightly closed container (to protect from excessive moisture).
- After constitution, solution needs refrigeration (2 – 8°C) and must be stored in original container.
- Discard any unused solution after 30 days.

### OTHER COMMENTS

#### General

- Well tolerated in short term, but significant long-term toxicities
- No food restrictions

#### Pharmacokinetic data

- Available for all ages

#### Major drug interactions

- Do not use d4T with AZT due to an antagonistic effect.

Ref: [http://packageinserts.bms.com/pi/pi\\_zerit.pdf](http://packageinserts.bms.com/pi/pi_zerit.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**STAVUDINE**

**Recommended dosing based on weight-bands for children >6 weeks using liquid and capsules**

Weight range (kg)		Target dose 1 mg/kg twice daily up to 30 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	1	mg/ml liquid	6 ml	6 ml
4	4.9	1	mg/ml liquid	6 ml	6 ml
5	5.9	1	mg/ml liquid	6 ml	6 ml
6	6.9	1	mg/ml liquid	9 ml	9 ml
7	7.9	1	mg/ml liquid	9 ml	9 ml
8	8.9	1	mg/ml liquid	9 ml	9 ml
9	9.9	1	mg/ml liquid	9 ml	9 ml
10	10.9	15	mg capsule	1	1
11	11.9	15	mg capsule	1	1
12	13.9	15	mg capsule	1	1
14	16.9	20	mg capsule	1	1
17	19.9	20	mg capsule	1	1
20	24.9	20	mg capsule	1	1
25	29.9	30	mg capsule	1	1
30	34.9	30	mg capsule	1	1

### 1.3 ZIDOVUDINE (AZT OR ZDV)

#### FORMULATIONS

Tablets	Capsules	Liquid	FDC
60 mg 300 mg	100 mg 250 mg	10 mg/ml	<b>Baby 60 mg AZT</b> <b>Adult 300 mg AZT</b> <ul style="list-style-type: none"><li>• AZT + 3TC + NVP</li><li>• AZT + 3TC</li><li>• AZT + 3TC + ABC</li></ul>

#### DOSE AND FREQUENCY OF DOSING

- Maximum dose 300 mg twice daily

##### Target dose

- Liquid (oral dosing) 180 – 240 mg/m<sup>2</sup> per dose given twice daily (total daily dose 360 – 480 mg/m<sup>2</sup>)
- For children with suspected nervous system involvement, it may be beneficial to use a dose at the higher end of the range.

##### Maximum dose

- 300 mg twice daily

##### MTCT prevention dose

- Oral target dose 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 6 weeks of age, depending on national recommendations
- Intravenous target dose of 1.5 mg/kg infused over 30 minutes every 6 hours until oral dosing is possible
- For prophylaxis against MTCT, liquid (oral dosing) is preferred in infants since accurate dosing with paediatric tablets is not possible.

##### Administration – capsules

- Can be opened and dispersed in water or onto a small amount of food and immediately ingested

##### Administration – tablets

- 60 mg tablets are scored and can be split.
- 300 mg tablets are often not scored – may be cut in half with a tablet cutter in a pharmacy.
- Tablets may be crushed and combined with a small amount of food or water and immediately ingested.
- Some paediatric FDC formulations of this drug are dispersible.

##### Storage

- Store capsules at room temperature (25°C; range 15 – 30°C) in a tightly closed container (to protect from moisture).
- Store tablets at room temperature (25°C; range 15 – 30°C).
- Liquid is stable at room temperature but needs storage in a glass jar and is light sensitive.

#### OTHER COMMENTS

##### General

- No food restrictions
- Use with caution in children with anaemia due to potential for bone marrow

##### Pharmacokinetic data

- Available for all ages

##### Major drug interactions

- Do not use with d4T or ribavirin.

Ref: [http://us.gsk.com/products/assets/us\\_retrovir.pdf](http://us.gsk.com/products/assets/us_retrovir.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**ZIDOVUDINE**

Recommended dosing based on weight-bands for children &gt;6 weeks using liquid and adult tablets

Weight range (kg)		Target dose 180 – 240 mg/m <sup>2</sup> twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	6 ml	6 ml
4	4.9	10	mg/ml liquid	6 ml	6 ml
5	5.9	10	mg/ml liquid	6 ml	6 ml
6	6.9	10	mg/ml liquid	9 ml	9 ml
7	7.9	10	mg/ml liquid	9 ml	9 ml
8	8.9	10	mg/ml liquid	9 ml	9 ml
9	9.9	10	mg/ml liquid	9 ml	9 ml
10	10.9	10	mg/ml liquid	12 ml	12 ml
11	11.9	10	mg/ml liquid	12 ml	12 ml
12	13.9	10	mg/ml liquid	12 ml	12 ml
14	16.9	300	mg tablet	½	½
17	19.9	300	mg tablet	½	½
20	24.9	300	mg tablet	1	½
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

**ZIDOVUDINE**

Recommended dosing based on weight-bands for children &gt;6 weeks using liquid and capsules

Weight range (kg)		Target dose 180 – 240 mg/m <sup>2</sup> twice daily		Dose (ml or capsules)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	6 ml	6 ml
4	4.9	10	mg/ml liquid	6 ml	6 ml
5	5.9	10	mg/ml liquid	6 ml	6 ml
6	6.9	10	mg/ml liquid	9 ml	9 ml
7	7.9	10	mg/ml liquid	9 ml	9 ml
8	8.9	100	mg capsule	1	1
9	9.9	100	mg capsule	1	1
10	10.9	100	mg capsule	1	1
11	11.9	100	mg capsule	1	1
12	13.9	100	mg capsule	1	1
14	16.9	100	mg capsule	2	1
17	19.9	100	mg capsule	2	1
20	24.9	100	mg capsule	2	2
25	29.9	100	mg capsule	2	2
30	34.9	100	mg capsule	3	3

**ZIDOVUDINE****Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets**

Weight range (kg)		Target dose 180 – 240 mg/m <sup>2</sup> twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60	mg tablet	1	1
4	4.9	60	mg tablet	1	1
5	5.9	60	mg tablet	1	1
6	6.9	60	mg tablet	1.5	1.5
7	7.9	60	mg tablet	1.5	1.5
8	8.9	60	mg tablet	1.5	1.5
9	9.9	60	mg tablet	1.5	1.5
10	10.9	60	mg tablet	2	2
11	11.9	60	mg tablet	2	2
12	13.9	60	mg tablet	2	2
14	16.9	60	mg tablet	2.5	2.5
17	19.9	60	mg tablet	2.5	2.5
20	24.9	60	mg tablet	3	3
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

## 1.4 ABACAVIR (ABC)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
60 mg 300 mg	None	20 mg/ml	<b>Baby 60 mg ABC</b> <ul style="list-style-type: none"><li>• ABC + AZT + 3TC</li><li>• ABC + 3TC</li></ul> <b>Adult 300 mg ABC</b> <ul style="list-style-type: none"><li>• ABC + AZT + 3TC</li><li>• ABC + 3TC</li></ul>

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- Age less than 16 years or weight less than 37.5 kg: 8 mg/kg/dose twice daily

Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are now available.

#### Maximum dose

- Age less than 16 years or weight less than 37.5 kg: 300 mg/dose twice daily

#### Administration – tablets

- 60 mg tablets are scored and can be split.
- Tablets may be crushed and mixed with a small amount water or food and ingested immediately.

#### Storage

- Store tablets at controlled room temperature of 20 – 25°C.
- Store liquid at controlled room temperature of 20 – 25°C.
- Liquid may be refrigerated but do not freeze.

### OTHER COMMENTS

#### General

- Parents/caregivers must be warned about potential hypersensitivity reaction.
- Screening for HLA-B\*5701 may identify those most likely to have hypersensitivity.
- ABC should be stopped permanently if hypersensitivity reaction occurs.
- No food restrictions

#### Pharmacokinetic data

- Available for children above the age of 3 months

#### Major drug interactions

- None reported.

Ref: [http://us.gsk.com/products/assets/us\\_ziagen.pdf](http://us.gsk.com/products/assets/us_ziagen.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**ABACAVIR****Recommended dosing based on weight-bands for children >6 weeks using liquid and adult tablets**

Weight range (kg)		Target dose <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	20	mg/ml liquid	3 ml	3 ml
4	4.9	20	mg/ml liquid	3 ml	3 ml
5	5.9	20	mg/ml liquid	3 ml	3 ml
6	6.9	20	mg/ml liquid	4 ml	4 ml
7	7.9	20	mg/ml liquid	4 ml	4 ml
8	8.9	20	mg/ml liquid	4 ml	4 ml
9	9.9	20	mg/ml liquid	4 ml	4 ml
10	10.9	20	mg/ml liquid	6 ml	6 ml
11	11.9	20	mg/ml liquid	6 ml	6 ml
12	13.9	20	mg/ml liquid	6 ml	6 ml
14	16.9	300	mg tablet	½	½
17	19.9	300	mg tablet	½	½
20	24.9	300	mg tablet	1	½
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets					
Weight range (kg)		Target dose <16 years or <37.5 kg: 8 mg/kg/dose given twice daily Maximum dose >16 years or ≥37.5 kg: 300 mg/dose given twice daily		Dose (tablet)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60	mg tablet	1	1
4	4.9	60	mg tablet	1	1
5	5.9	60	mg tablet	1	1
6	6.9	60	mg tablet	1.5	1.5
7	7.9	60	mg tablet	1.5	1.5
8	8.9	60	mg tablet	1.5	1.5
9	9.9	60	mg tablet	1.5	1.5
10	10.9	60	mg tablet	2	2
11	11.9	60	mg tablet	2	2
12	13.9	60	mg tablet	2	2
14	16.9	60	mg tablet	2.5	2.5
17	19.9	60	mg tablet	2.5	2.5
20	24.9	60	mg tablet	3	3
25	29.9	300	mg tablet	1	1
30	34.9	300	mg tablet	1	1

## 1.5 DIDANOSINE (ddl)

### FORMULATIONS

Chewable tablets (buffered)	Enteric-coated beadlets in capsules	Liquid	FDC
25 mg 50 mg 100 mg 200 mg	125 mg 200 mg 250 mg 400 mg	10 mg/ml	None

### DOSE AND DOSE FREQUENCY

#### Target dose

- Age less than 3 months: 50 mg/m<sup>2</sup>/dose twice daily
- Age 3 months to 13 years: 90 – 120 mg/m<sup>2</sup>/dose twice daily

#### Maximum dose

- Age 13 years or older, or weight more than 60 kg: 200 mg/dose twice daily or 400 mg once daily

#### Administration – chewable (buffered) tablets

- At least two tablets of appropriate strength must be used at any one time for adequate buffering (e.g. if the child's dose is 50 mg, administer two 25 mg tablets instead of one 50 mg tablet).
- ddl tablets should be chewed, crushed or dispersed in water or clear juice before they are taken.
- ddl tablets should not be swallowed whole.

#### Administration – enteric-coated beadlets in capsules (EC)

- EC capsules should be swallowed whole. If there is no other therapeutic option and the child is too small to swallow capsules, they should be opened and taken with a small quantity of food or liquid, not with a meal.
- The beadlets inside the capsule should not be crushed or chewed, and if the capsules are opened, the beadlets should be sprinkled on a soft food that does not require chewing.
- Opened capsules should be taken immediately after mixing.

#### Administration – liquid

- It is not easy to use and should be avoided if possible.
- Prior to dispensing, the pharmacist must constitute dry powder with purified water to an initial strength of 20 mg/ml and immediately mix the resulting solution with antacid to a final strength of 10 mg/ml.

#### Storage

- Keep liquid refrigerated (2 – 8°C).
- Liquid remains stable for 30 days (shake well before using).
- Discard any unused liquid after 30 days.

### OTHER COMMENTS

#### General

- ddl is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids.
- In children this effect may be less marked and ddl may not have to be administered on an empty stomach.

#### Pharmacokinetic data

- PK data are available for all ages. However, pharmacokinetic data in infants less than 2 weeks of age are variable.

#### Major drug interactions

- TDF and ribavirin are not recommended to be taken with ddl.

Ref: [http://packageinserts.bms.com/pi/pi\\_videx\\_ec.pdf](http://packageinserts.bms.com/pi/pi_videx_ec.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**DIDANOSINE****Recommended dosing based on weight-bands for children >3 months using liquid and chewable tablets**

Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m <sup>2</sup> /dose twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	NR	NR
4	4.9	10	mg/ml liquid	NR	NR
5	5.9	10	mg/ml liquid	3 ml	3 ml
6	6.9	10	mg/ml liquid	5 ml	5 ml
7	7.9	10	mg/ml liquid	5 ml	5 ml
8	8.9	10	mg/ml liquid	5 ml	5 ml
9	9.9	10	mg/ml liquid	5 ml	5 ml
10	10.9	10	mg/ml liquid	6 ml	6 ml
11	11.9	10	mg/ml liquid	6 ml	6 ml
12	13.9	10	mg/ml liquid	6 ml	6 ml
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Recommended dosing based on weight-bands for children >3 months using chewable tablets					
Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m <sup>2</sup> /dose twice daily		Dose (tablet)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	25	mg tablet	NR	NR
4	4.9	25	mg tablet	NR	NR
5	5.9	25	mg tablet	2	2
6	6.9	25	mg tablet	3	2
7	7.9	25	mg tablet	3	2
8	8.9	25	mg tablet	3	2
9	9.9	25	mg tablet	3	2
10	10.9	25	mg tablet	3	3
11	11.9	25	mg tablet	3	3
12	13.9	25	mg tablet	3	3
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Note: 25 mg chewable tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least two tablets.

NR not recommended

**DIDANOSINE****Recommended once-daily dosing based on weight-bands using enteric-coated capsules**

Weight range (kg)		Target dose 240–300 mg/m <sup>2</sup> /day		Dose (ml or tablets)
Bottom	Top	Formulation		a.m. or p.m.
3	3.9	NR		NR
4	4.9	NR		NR
5	5.9	NR		NR
6	6.9	NR		NR
7	7.9	NR		NR
8	8.9	NR		NR
9	9.9	NR		NR
10	10.9	125	mg EC capsule	1
11	11.9	125	mg EC capsule	1
12	13.9	125	mg EC capsule	1
14	16.9	200	mg EC capsule	1
17	19.9	200	mg EC capsule	1
20	24.9	125	mg EC capsule	2
25	29.9	125	mg EC capsule	2
30	34.9	125	mg EC capsule	2

NR not recommended

## 1.6 EMTRICITABINE (FTC)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	200 mg	10 mg/ml	None

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- Liquid 6 mg/kg
- Capsules 200 mg capsule once daily (weight more than 33 kg)

#### Storage

- Store capsules at 25°C (range 15 – 30°C).
- Liquid should be stored refrigerated (2 – 8°C).
- Liquid should be used within 3 months if not refrigerated.

### OTHER COMMENTS

#### Pharmacokinetic data

- Available for children aged 3 months to 18 years

#### Major drug interactions

- None reported

Ref: [http://www.gilead.com/pdf/emtriva\\_pi.pdf](http://www.gilead.com/pdf/emtriva_pi.pdf)  
<http://www.pediatrics.org/cgi/content/full/121/4/e827>

## 1.7 TENOFOVIR (TDF)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
300 mg	None	None	<b>Adult 300 mg TDF</b> <ul style="list-style-type: none"><li>• TDF + FTC + EFV</li><li>• TDF + FTC</li><li>• TDF + 3TC</li><li>• TDF + 3TC + EFV</li></ul>

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- 300 mg/day for children 12 years of age and more

#### Storage

- Store tablets at 25°C (range 15 – 30°C).

### OTHER COMMENTS

#### General

- TDF is the preferred ARV in children with hepatitis B aged more than 12 years.

#### Pharmacokinetic data

- Available for children 12 years of age and above

#### Major drug interactions

- None reported

Ref: [http://www.gilead.com/pdf/viread\\_pi.pdf](http://www.gilead.com/pdf/viread_pi.pdf)

## 2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

2.1 EFAVIRENZ (EFV)			
FORMULATIONS			
Tablets	Capsules	Liquid	FDC
200 mg 600 mg	50 mg 100 mg 200 mg	30 mg/ml	<b>Adult 600 mg EFV</b> • EFV + TDF + FTC • EFV + TDF + 3TC
DOSE AND FREQUENCY OF DOSING			
<p><b>Target dose</b></p> <ul style="list-style-type: none"> <li>• Liquid 19.5 mg/kg/day or</li> <li>• Capsule/tablet 15 mg/kg/day once daily</li> <li>• Weight more than 40 kg 600 mg once daily</li> </ul> <p><b>Administration – tablets</b></p> <ul style="list-style-type: none"> <li>• 200 mg tablet is double-scored and can be split.</li> </ul> <p><b>Administration – capsules</b></p> <ul style="list-style-type: none"> <li>• Capsules may be opened and added to a small amount of food or liquid; they have a very peppery taste but can be mixed with sweet foods to disguise the taste.</li> </ul> <p><b>Storage</b></p> <ul style="list-style-type: none"> <li>• Storage at 25°C (range 15 – 30°C)</li> </ul>			
OTHER COMMENTS			
<p><b>General</b></p> <ul style="list-style-type: none"> <li>• EFV can be given with food but if taken with food, especially high-fat meals, absorption is increased by an average of 50%.</li> </ul> <p><b>Pharmacokinetic data</b></p> <ul style="list-style-type: none"> <li>• Available for children more than 3 years of age</li> <li>• Insufficient data on dosing for children less than 3 years of age or weighing less than 10 kg</li> </ul> <p><b>Major drug interactions</b></p> <ul style="list-style-type: none"> <li>• It is not recommended to take amodiaquine with EFV.</li> </ul>			

Ref: [http://packageinserts.bms.com/pi/pi\\_sustiva.pdf](http://packageinserts.bms.com/pi/pi_sustiva.pdf)  
<http://www.medicines.org.uk/emc/medicine/10381>  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**EFAVIRENZ****Recommended maintenance dosing based on weight-bands**

Weight range (kg)		Target dose 15 mg/kg/day (capsule/tablet) Weight >40 kg: 600 mg once daily		Dose (tablets)
Bottom	Top	Formulation		Once daily
3	3.9	NR		NR
4	4.9	NR		NR
5	5.9	NR		NR
6	6.9	NR		NR
7	7.9	NR		NR
8	8.9	NR		NR
9	9.9	NR		NR
10	10.9	200	mg tablet	1
11	11.9	200	mg tablet	1
12	13.9	200	mg tablet	1
14	16.9	200	mg tablet	1.5
17	19.9	200	mg tablet	1.5
20	24.9	200	mg tablet	1.5
25	29.9	200	mg tablet	2
30	34.9	200	mg tablet	2

NR not recommended

## 2.2 NEVIRAPINE (NVP)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
50 mg 200 mg	None	10 mg/ml	<b>Baby 50 mg NVP</b> <b>Adult 200 mg NVP</b> <ul style="list-style-type: none"> <li>• NVP + d4T + 3TC</li> <li>• NVP + AZT + 3TC</li> </ul> <b>Junior 100 mg NVP</b> <ul style="list-style-type: none"> <li>• NVP + d4T + 3TC</li> </ul>

### DOSE AND DOSE FREQUENCY

#### Target dose – maintenance therapy

- 160 – 200 mg/m<sup>2</sup> to maximum dose of 200 mg twice daily

#### Target dose – prophylaxis

Aim for exposure of 100 ng/ml

- Birth to 6 weeks of age:
 

weight less than 2.5 kg	10 mg per day
weight more than 2.5 kg	15 mg per day
- Age 6 weeks to 6 months 20 mg per day
- Age 6 months to 9 months 30 mg per day
- Age 9 months to end of breastfeeding 40 mg per day

#### Special considerations for PMTCT in infants

- Give first dose as early as possible after delivery, preferably within first 6 hours.
- If infant weight is not available, administer 1 ml liquid and thereafter follow national MTCT dosing recommendations.

#### Special considerations on maintenance therapy

- Induction dose: during the first 14 days omit the evening dose of NVP. If the morning and evening doses are unequal, give the higher dose in the morning and omit the lower evening dose.
- Maintenance dose: target dose is 160–200 mg/m<sup>2</sup> given twice daily and adjusted for more aggressive dosing in the younger age group.
- If a mild rash occurs during the first 14 days of induction dosing, continue once-daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue the drug.

#### Administration – tablets

- Some manufacturers make 200 mg tablets that are scored and can be divided into two equal parts. Other preparations may not be scored and where possible should be divided with a pill cutter. Broken tablets can be crushed and combined with a small amount of water or food and taken immediately.
- 50 mg tablets are scored and can be split.

#### Administration – liquid

- Use an oral dosing syringe or dosing cup.
- Shake well before use.

#### Storage

- Store liquid at 25°C (range 15 – 30°C).
- Bottle of liquid should be used within 6 months of opening.

## NEVIRAPINE (NVP)

### OTHER COMMENTS

#### General

- Parents must be warned about a potential severe, life-threatening rash during the 14-day lead-in period. The once-daily induction dose is used to reduce the frequency of rash.
- NVP should be permanently discontinued and not restarted in children who develop severe rash.
- Can be given without regard to food

#### Pharmacokinetic data

- Available from birth

#### Major drug interactions

- Avoid NVP if rifampicin is co-administered; also interacts with ketoconazole.

Ref: [http://bidocs.boehringer-ingenheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt & folderPath =/Prescribing\\_+ Information/Pls/Viramune/Viramune.pdf](http://bidocs.boehringer-ingenheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt & folderPath =/Prescribing_+ Information/Pls/Viramune/Viramune.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

## NEVIRAPINE

Recommended maintenance dose based on weight-bands for children >6 weeks using liquid and adult tablets

Weight range (kg)		Target dose 160 – 200 mg/m <sup>2</sup> to max 200 mg twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	5 ml	5 ml
4	4.9	10	mg/ml liquid	5 ml	5 ml
5	5.9	10	mg/ml liquid	5 ml	5 ml
6	6.9	10	mg/ml liquid	8 ml	8 ml
7	7.9	10	mg/ml liquid	8 ml	8 ml
8	8.9	10	mg/ml liquid	8 ml	8 ml
9	9.9	10	mg/ml liquid	8 ml	8 ml
10	10.9	10	mg/ml liquid	10 ml	10 ml
11	11.9	10	mg/ml liquid	10 ml	10 ml
12	13.9	10	mg/ml liquid	10 ml	10 ml
14	16.9	200	mg tablet	1	½
17	19.9	200	mg tablet	1	½
20	24.9	200	mg tablet	1	½
25	29.9	200	mg tablet	1	1
30	34.9	200	mg tablet	1	1

## NEVIRAPINE

Recommended maintenance dose based on weight-bands for children >6 weeks using paediatric and adult tablets

Weight range (kg)		Target dose 160 – 200 mg/m <sup>2</sup> to max 200 mg twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	50	mg tablet	1	1
4	4.9	50	mg tablet	1	1
5	5.9	50	mg tablet	1	1
6	6.9	50	mg tablet	1.5	1.5
7	7.9	50	mg tablet	1.5	1.5
8	8.9	50	mg tablet	1.5	1.5
9	9.9	50	mg tablet	1.5	1.5
10	10.9	50	mg tablet	2	2
11	11.9	50	mg tablet	2	2
12	13.9	50	mg tablet	2	2
14	16.9	50	mg tablet	2.5	2.5
17	19.9	50	mg tablet	2.5	2.5
20	24.9	50	mg tablet	3	3
25	29.9	200	mg tablet	1	1
30	34.9	200	mg tablet	1	1

## 2.3 ETRAVIRINE (ETV)

### FORMULATIONS

Tablets	Capsules	Liquid	FDC
25 mg 100 mg	None	None	None

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- 5.2 mg/kg twice daily from 6 years of age to a maximum adult dose of 200 mg twice daily

#### Administration – tablets

- Tablets are scored.
- Tablets are dispersible in water.

#### Storage

- Store tablets at 25°C (range 15 – 30°C) in a tightly closed container (to protect from moisture).

### OTHER COMMENTS

#### General

- Well-tolerated and no flavour
- Safety and effectiveness not yet well established in younger children

#### Major drug interactions

- Rifampicin and rifabutin

Ref: [http://www.intelence-info.com/intelence/assets/pdf/INTELENCE\\_PI.pdf](http://www.intelence-info.com/intelence/assets/pdf/INTELENCE_PI.pdf) (100 mg tablets)

Konigs et al., *Pharmacokinetics and dose selection of etravirine in HIV-infected children between 6 and 17 years, inclusive*. Conference on retroviruses and Opportunistic Infections, Montreal, Canada February 2009

### 3. Protease inhibitors (PIs)

3.1 SAQUINAVIR (SQV) HGC			
FORMULATIONS			
Tablets	Hard gel capsules	Liquid	FDC
500 mg	200 mg	None	None
DOSE AND FREQUENCY OF DOSING			
<b>Target dose – hard gel capsules (HGCs)</b> <ul style="list-style-type: none"><li>• Studies have reported using 33 mg/kg three times a day.</li></ul>			
<b>Administration – tablets</b> <ul style="list-style-type: none"><li>• Usually taken with RTV</li><li>• Should be taken with food as absorption is improved; it is suggested that it be taken within two hours after a meal.</li></ul>			
<b>Storage</b> <ul style="list-style-type: none"><li>• Store capsules at room temperature (25°C; range 15 – 30°C) in a tightly closed container (to protect from moisture).</li><li>• SQV HGCs do not need refrigeration.</li></ul>			
OTHER COMMENTS			
<b>General</b> <ul style="list-style-type: none"><li>• Not licensed for use in children less than 16 years of age or less than 25 kg in weight</li><li>• Safety and effectiveness not yet well established in younger children</li></ul>			
<b>Major drug interactions</b> <ul style="list-style-type: none"><li>• None reported</li></ul>			

Ref: <http://www.gene.com/gene/products/information/invirase/pdf/pi.pdf>  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

### 3.2 LOPINAVIR/RITONAVIR (LPV/r) (CO-FORMULATION)

#### FORMULATIONS

Co-formulated heat-stable tablets	Capsules	Liquid	FDC
<b>Paediatric</b> LPV 100 mg/RTV 25 mg <b>Adult</b> LPV 200 mg/RTV 50 mg	None	LPV 80 mg/ml + RTV 20 mg/ml	None

#### DOSE AND FREQUENCY OF DOSING

##### LPV target dose

- 230 – 350 mg/m<sup>2</sup> twice daily

##### Maximum dose

- LPV 400 mg + RTV 100 mg twice daily

##### Administration – tablets

- Must be administered intact and cannot be split or crushed

##### Administration – liquid

- Must be well shaken

##### Storage

- Liquid should be refrigerated.
- Can be stored at room temperature (up to 25°C) for two months (at >25°C the drug degrades more rapidly).
- For tablets, exposure to high humidity is not recommended for more than 2 weeks.

#### OTHER COMMENTS

##### General

- Higher doses of LPV/r may be required when co-administered with enzyme-inducing drugs such as NVP, EFV, FPV, rifampicin.
- No food restrictions although bioavailability is reportedly increased when administered with food
- Should be taken with food
- In non-fasting state, absolute bioavailability of LPV/r liquid is decreased by 22% compared with LPV/r tablet.
- Low volume but bitter taste
- Once-daily dosing is not approved for infants or children.
- LPV/r liquid has a high alcohol content.

##### Pharmacokinetic data

- Available for 14 days and older

##### Major drug interactions

- Not recommended to be taken with rifampicin, omeprazole or simvastatin

Ref: <http://www.rxabbott.com/pdf/kaletatabpi.pdf>  
[http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_\\_ApprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label__ApprovalHistory)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**LOPINAVIR/RITONAVIR****Recommended dosing based on weight-bands for children >6 weeks using liquid**

Weight range (kg)		Target dose 230 – 350 mg/m <sup>2</sup> twice daily		Dose (ml)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	80 mg LPV/20 mg RTV	ml liquid	1 ml	1 ml
4	4.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
5	5.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
6	6.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
7	7.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
8	8.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
9	9.9	80 mg LPV/20 mg RTV	ml liquid	1.5 ml	1.5 ml
10	10.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
11	11.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
12	13.9	80 mg LPV/20 mg RTV	ml liquid	2 ml	2 ml
14	16.9	80 mg LPV/20 mg RTV	ml liquid	2.5 ml	2.5 ml
17	19.9	80 mg LPV/20 mg RTV	ml liquid	2.5 ml	2.5 ml
20	24.9	80 mg LPV/20 mg RTV	ml liquid	3 ml	3 ml
25	29.9	80 mg LPV/20 mg RTV	ml liquid	3.5 ml	3.5 ml
30	34.9	80 mg LPV/20 mg RTV	ml liquid	4 ml	4 ml

**LOPINAVIR/RITONAVIR**
**Recommended dosing based on weight-bands for children >6 weeks using paediatric tablets**

Weight range (kg)		Target dose 230 – 350 mg/m <sup>2</sup> twice daily		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	100 mg LPV/25 mg RTV	tablet	NR	NR
4	4.9	100 mg LPV/25 mg RTV	tablet	NR	NR
5	5.9	100 mg LPV/25 mg RTV	tablet	NR	NR
6	6.9	100 mg LPV/25 mg RTV	tablet	NR	NR
7	7.9	100 mg LPV/25 mg RTV	tablet	NR	NR
8	8.9	100 mg LPV/25 mg RTV	tablet	NR	NR
9	9.9	100 mg LPV/25 mg RTV	tablet	NR	NR
10	10.9	100 mg LPV/25 mg RTV	tablet	2	1
11	11.9	100 mg LPV/25 mg RTV	tablet	2	1
12	13.9	100 mg LPV/25 mg RTV	tablet	2	1
14	16.9	100 mg LPV/25 mg RTV	tablet	2	2
17	19.9	100 mg LPV/25 mg RTV	tablet	2	2
20	24.9	100 mg LPV/25 mg RTV	tablet	2	2
25	29.9	100 mg LPV/25 mg RTV	tablet	3	3
30	34.9	100 mg LPV/25 mg RTV	tablet	3	3

Note: Children 14 – 24.9 kg can be dosed with adult tabs (200 mg LPV/50 mg RTV), 1 tab am and 1 tab pm.

Children 25 – 34.9 kg can be dosed with adult tabs (200 mg LPV/50 mg RTV), 2 tabs am and 1 tab pm.

### 3.3 RITONAVIR (RTV)

#### FORMULATIONS

Co-formulated tablets	Heat-stable tablets	Liquid	FDC
<b>Paediatric</b> 100 mg LPV + 25 mg RTV <b>Adult</b> 200 mg LPV + 50 mg RTV	100 mg	80 mg/ml	None

#### DOSE AND FREQUENCY OF DOSING

##### Target dose

- RTV is used to boost other protease inhibitors.

##### Administration – tablets

- Must be administered intact and cannot be split or crushed

##### Administration – liquid

- Liquid may be taken alone or mixed with milk or food but should not be mixed with water or other fluids.
- Liquid is unpalatable and excipient contains 43% alcohol.

##### Storage

- Store tablets at 20 – 25°C (range 15 – 30°C). Exposure of tablets to high humidity outside tight container for longer than 2 weeks is not recommended.
- Store liquid at room temperature (20 – 25°C). Do not refrigerate. Shake well before each use. Use within 30 days of dispensing. Avoid exposure to excessive heat. Keep cap tightly closed.
- Liquid should be protected from light.

#### OTHER COMMENTS

##### General

- Adverse event profile seen during clinical trials and post-marketing surveys similar to that for adults
- Should be taken with food

##### Pharmacokinetic data

- Available for infants and children

##### Major drug interactions

- None reported

Ref: <http://www.rxabbott.com/pdf/kaletratapi.pdf>  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

### 3.4 DARUNAVIR (DRV)

#### FORMULATIONS

Film-coated tablets	Capsules	Liquid	FDC
75 mg 150 mg 300 mg 400 mg 600 mg	None	None	None

#### DOSE AND FREQUENCY OF DOSING

**Target dose**

- 10 – 20 mg/kg twice daily

**Maximum dose**

- 600 mg DRV with 100 mg RTV twice daily

**Administration – tablets**

- Once-daily dosing should not be used in paediatric patients.
- Should be taken with food

**Storage**

- Store at temperature of 25°C (range 15 – 30°C).

#### OTHER COMMENTS

**General**

- RTV increases metabolism and absorption, and should be given with every dose of DRV.
- The preferred ratio of DRV to RTV is 8:1. Adding more RTV does not lead to further boosting of DRV levels.
- Parents/carers should be warned about potential skin rash.
- Rarely, DRV has been observed to cause liver problems.

**Pharmacokinetic data**

- Available for children aged 6 years or more

**Major drug interactions**

- None reported

Ref: [http://www.prezista.com/prezista/documents/us\\_package\\_insert.pdf](http://www.prezista.com/prezista/documents/us_package_insert.pdf)

### 3.5 ATAZANAVIR (ATV)

#### FORMULATIONS

Tablets	Capsules	Liquid	FDC
None	100 mg 150 mg 200 mg 300 mg	None	None

#### DOSE AND FREQUENCY OF DOSING

##### Target dose ATV/RTV

###### Treatment-naïve

- Weight 15 kg to less than 25 kg: 150 mg ATV/80 mg RTV
- Weight 25 kg to less than 32 kg: 200 mg ATV/100 mg RTV
- Weight 32 kg to less than 39 kg: 250 mg ATV/100 mg RTV

###### Treatment-experienced

- Weight 25 kg to less than 32 kg: 200 mg ATV/100 mg RTV
- Weight 32 kg to less than 39 kg: 250 mg ATV/100 mg RTV

##### Maximum dose

- ATV 300 mg/RTV 100 mg once daily

##### Administration

- Should be taken with food

##### Storage

- Store capsules at 25°C (range 15 – 30°C).

#### OTHER COMMENTS

##### General

- To be used in combination with RTV in paediatric patients
- Recommended for patients aged 6 to <18 years of age
- Not to be used in patients less than 3 months of age due to risk of kernicterus. There are insufficient data for patients less than 6 years of age.
- Dosage is based on body weight (8.5 mg/kg for weights 15 kg to less than 20 kg, and 7 mg/kg for weight 20 kg or more)

##### Pharmacokinetic data

- Available for children aged 3 months to 21 years

##### Major drug interactions

- None reported

Ref: [http://packageinserts.bms.com/pi/pi\\_revataz.pdf](http://packageinserts.bms.com/pi/pi_revataz.pdf)

#### **4. Fixed-dose combinations (FDCs)**

Antiretroviral therapy generally requires the use of three or more drugs. This often requires taking a large number of tablets/capsules each day. Fixed-dose combinations (FDCs) of ARV drugs allow for once- or twice-daily dosing, leading to improved adherence, which may result in greater efficacy and may assist in reducing the development of viral resistance. FDCs are cheaper than individual drugs and may help to alleviate programmatic concerns of logistics regarding drug supply and delivery. WHO encourages the use of FDCs when formulations of assured quality and proven bioequivalence are available and offer operational advantages. Not all available FDCs have been evaluated for prequalification by WHO. Further details and a list of current prequalified drugs are available at: <http://mednet3.who.int/prequal/>.

Countries that have not included FDCs in their national formularies are encouraged to do so.

## 4.1 ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC)

### FORMULATION

#### FDC tablets

AZT 60 mg + 3TC 30 mg  
AZT 300 mg + 3TC 150 mg

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- AZT 180 – 240 mg/m<sup>2</sup> twice daily
- 3TC 4 mg/kg twice daily

#### Maximum dose

- 1 adult tablet/dose twice daily

#### Administration

- Paediatric tablet is scored and can be split.
- Can be crushed and contents mixed with a small amount of water or food and taken immediately

#### Storage

- Store tablets between 2°C and 30°C

### OTHER COMMENTS

#### General

- See comments under individual drug components.
- No food restrictions
- AZT/3TC FDC can be used for lead-in dosing when initiating AZT + 3TC + NVP therapy.

#### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://us.gsk.com/products/assets/us\\_combivir.pdf](http://us.gsk.com/products/assets/us_combivir.pdf)  
[http://www.cipladoc.com/therapeutic/pdf\\_cipla/duovir.pdf](http://www.cipladoc.com/therapeutic/pdf_cipla/duovir.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**AZT PLUS 3TC**

**Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/30	tablet	1	1
4	4.9	60/30	tablet	1	1
5	5.9	60/30	tablet	1	1
6	6.9	60/30	tablet	1.5	1.5
7	7.9	60/30	tablet	1.5	1.5
8	8.9	60/30	tablet	1.5	1.5
9	9.9	60/30	tablet	1.5	1.5
10	10.9	60/30	tablet	2	2
11	11.9	60/30	tablet	2	2
12	13.9	60/30	tablet	2	2
14	16.9	60/30	tablet	2.5	2.5
17	19.9	60/30	tablet	2.5	2.5
20	24.9	60/30	tablet	3	3
25	29.9	300/150	tablet	1	1
30	34.9	300/150	tablet	1	1

## 4.2 ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC) PLUS NEVIRAPINE (NVP)

### FORMULATION

#### FDC tablets

AZT 60 mg + 3TC 30 mg + NVP 50 mg  
AZT 300 mg + 3TC 150 mg + NVP 200 mg

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- AZT 180 – 240 mg/m<sup>2</sup> twice daily
- 3TC 4 mg/kg twice daily
- NVP 160 – 200 mg/m<sup>2</sup>

#### Maximum dose

- 1 adult tablet/dose twice daily

#### Administration

- Paediatric tablet is dispersible and may be split.
- Can be dispersed into a small volume of water or crushed and mixed into a small amount of food and taken immediately

#### Storage

- Store tablets between 2°C and 30°C.

### OTHER COMMENTS

#### General

- See comments under individual drug components.
- No food restrictions

#### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://www.cipladoc.com/therapeutic/pdf\\_cipla/duovir\\_n.pdf](http://www.cipladoc.com/therapeutic/pdf_cipla/duovir_n.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**AZT PLUS 3TC PLUS NVP**

**Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/30/50	tablet	1	1
4	4.9	60/30/50	tablet	1	1
5	5.9	60/30/50	tablet	1	1
6	6.9	60/30/50	tablet	1.5	1.5
7	7.9	60/30/50	tablet	1.5	1.5
8	8.9	60/30/50	tablet	1.5	1.5
9	9.9	60/30/50	tablet	1.5	1.5
10	10.9	60/30/50	tablet	2	2
11	11.9	60/30/50	tablet	2	2
12	13.9	60/30/50	tablet	2	2
14	16.9	60/30/50	tablet	2.5	2.5
17	19.9	60/30/50	tablet	2.5	2.5
20	24.9	60/30/50	tablet	3	3
25	29.9	300/150/200	tablet	1	1
30	34.9	300/150/200	tablet	1	1

### 4.3 STAVUDINE (D4T) PLUS LAMIVUDINE (3TC)

#### FORMULATION

##### FDC tablets

d4T 6 mg + 3TC 30 mg  
d4T 12 mg + 3TC 60 mg  
d4T 30 mg + 3TC 150 mg

#### DOSE AND FREQUENCY OF DOSING

##### Target dose

- d4T 1 mg/kg twice daily
- 3TC 4 mg/kg twice daily

##### Administration

- Paediatric tablet is dispersible and crushable, can be split.

##### Storage

- Store tablets between 2°C and 30°C.

#### OTHER COMMENTS

##### General

- See comments under individual drug components.
- d4T and 3TC can be used in the evening for lead-in dosing for d4T + 3TC + NVP.

##### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://www.cipladoc.com/therapeutic/pdf\\_cipla/lamivir\\_s\\_baby\\_junior.pdf](http://www.cipladoc.com/therapeutic/pdf_cipla/lamivir_s_baby_junior.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**D4T PLUS 3TC****Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	6/30	mg tablet	1	1
4	4.9	6/30	mg tablet	1	1
5	5.9	6/30	mg tablet	1	1
6	6.9	6/30	mg tablet	1.5	1.5
7	7.9	6/30	mg tablet	1.5	1.5
8	8.9	6/30	mg tablet	1.5	1.5
9	9.9	6/30	mg tablet	1.5	1.5
10	10.9	6/30	mg tablet	2	2
11	11.9	6/30	mg tablet	2	2
12	13.9	6/30	mg tablet	2	2
14	16.9	6/30	mg tablet	2.5	2.5
17	19.9	6/30	mg tablet	2.5	2.5
20	24.9	6/30	mg tablet	3	3
25	29.9	30/150	mg tablet	1	1
30	34.9	30/150	mg tablet	1	1

#### 4.4 STAVUDINE (D4T) PLUS LAMIVUDINE (3TC) PLUS NEVIRAPINE (NVP)

##### FORMULATION

###### FDC tablets

d4T 6 mg + 3TC 30 mg + NVP 50 mg

d4T 12 mg + 3TC 60 mg + NVP 100 mg

d4T 30 mg + 3TC 150 mg + NVP 200 mg

##### DOSE AND FREQUENCY OF DOSING

###### Target dose

- d4T 1 mg/kg twice daily
- 3TC 4 mg/kg twice daily
- NVP 160 – 200 mg/m<sup>2</sup> to a maximum dose of 200 mg twice daily

###### Maximum dose

- One 30 mg d4T-based tablet twice daily

###### Administration

- Paediatric tablet is dispersible and crushable, can be split.
- If unable to swallow, disperse 1 tablet in 2 teaspoons of water.

###### Storage

- Store tablets below 25°C.

##### OTHER COMMENTS

###### General

- See comments under individual drug components.
- A lead-in dose of NVP, at half of the normal daily dosage, is used for 2 weeks to decrease the likelihood of developing rash.
- For lead-in dosing, d4T + 3TC + NVP can be used in the morning and d4T + 3TC in the evening.
- If the child experiences a rash in the lead-in period, then remain on half the dosage until the rash resolves. Wait no longer than 28 days for the rash to resolve, then seek an alternative regimen.

###### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://www.cipladoc.com/therapeutic/pdf\\_cipla/triomune\\_baby\\_junior.pdf](http://www.cipladoc.com/therapeutic/pdf_cipla/triomune_baby_junior.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**D4T PLUS 3TC PLUS NVP**

**Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	6/30/50	tablet	1	1
4	4.9	6/30/50	tablet	1	1
5	5.9	6/30/50	tablet	1	1
6	6.9	6/30/50	tablet	1.5	1.5
7	7.9	6/30/50	tablet	1.5	1.5
8	8.9	6/30/50	tablet	1.5	1.5
9	9.9	6/30/50	tablet	1.5	1.5
10	10.9	6/30/50	tablet	2	2
11	11.9	6/30/50	tablet	2	2
12	13.9	6/30/50	tablet	2	2
14	16.9	6/30/50	tablet	2.5	2.5
17	19.9	6/30/50	tablet	2.5	2.5
20	24.9	6/30/50	tablet	3	3
25	29.9	30/150/200	tablet	1	1
30	34.9	30/150/200	tablet	1	1

#### 4.5 ABACVIR (ABC) PLUS ZIDOVUDINE (AZT) PLUS LAMIVUDINE (3TC)

##### FORMULATION

##### FDC tablets

##### Paediatric

ABC 60 mg + AZT 60 mg + 3TC 30 mg

##### Adult

ABC 300 mg + AZT 300 mg + 3TC 150 mg

##### DOSE AND FREQUENCY OF DOSING

##### Target dose

- ABC 8 mg/kg twice daily
- AZT 180 – 240 mg/m<sup>2</sup> twice daily
- 3TC 4 mg/kg twice daily

##### Maximum dose

- 1 adult tablet/dose twice daily

##### Administration

- Paediatric tablet is crushable and can be split.

##### Storage

- Store tablets between 2°C and 30°C.

##### OTHER COMMENTS

##### General

- See comments under individual drug components.
- Parents/carers must be warned about potential hypersensitivity reaction.
- ABC should be stopped permanently if hypersensitivity reaction occurs.

##### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://us.gsk.com/products/assets/us\\_trizivir.pdf](http://us.gsk.com/products/assets/us_trizivir.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**ABC PLUS AZT PLUS 3TC**

**Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/60/30	tablet	1	1
4	4.9	60/60/30	tablet	1	1
5	5.9	60/60/30	tablet	1	1
6	6.9	60/60/30	tablet	1.5	1.5
7	7.9	60/60/30	tablet	1.5	1.5
8	8.9	60/60/30	tablet	1.5	1.5
9	9.9	60/60/30	tablet	1.5	1.5
10	10.9	60/60/30	tablet	2	2
11	11.9	60/60/30	tablet	2	2
12	13.9	60/60/30	tablet	2	2
14	16.9	60/60/30	tablet	2.5	2.5
17	19.9	60/60/30	tablet	2.5	2.5
20	24.9	60/60/30	tablet	3	3
25	29.9	300/300/150	tablet	1	1
30	34.9	300/300/150	tablet	1	1

## 4.6 ABACVIR (ABC) PLUS LAMIVUDINE (3TC)

### FORMULATION

#### FDC tablets

#### Paediatric

ABC 60 mg + 3TC 30 mg

#### Adult

ABC 600 mg + 3TC 300 mg

### DOSE AND FREQUENCY OF DOSING

#### Target dose

- Lamivudine: 4 mg/kg twice daily
- Abacavir: 8 mg/kg twice daily

#### Administration

- Paediatric tablet is scored and can be split.
- Can be crushed and contents mixed with a small amount of water or food and taken immediately

#### Storage

- Store tablets between 2°C and 30°C.

### OTHER COMMENTS

#### General

- See comments under individual drug components.
- No food restrictions

#### Pharmacokinetic data

- Available for adolescents and adults

Ref: [http://us.gsk.com/products/assets/us\\_ziagen.pdf](http://us.gsk.com/products/assets/us_ziagen.pdf)  
<http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html>

**ABC PLUS 3TC**

**Recommended dosing based on weight-bands**

Weight range (kg)		Target dose as for individual components		Dose (tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	60/30	tablet	1	1
4	4.9	60/30	tablet	1	1
5	5.9	60/30	tablet	1	1
6	6.9	60/30	tablet	1.5	1.5
7	7.9	60/30	tablet	1.5	1.5
8	8.9	60/30	tablet	1.5	1.5
9	9.9	60/30	tablet	1.5	1.5
10	10.9	60/30	tablet	2	2
11	11.9	60/30	tablet	2	2
12	13.9	60/30	tablet	2	2
14	16.9	60/30	tablet	2.5	2.5
17	19.9	60/30	tablet	2.5	2.5
20	24.9	60/30	tablet	3	3
25	29.9	600/300 <sup>i</sup>	tablet	½	½
30	34.9	600/300 <sup>i</sup>	tablet	½	½

<sup>i</sup> Currently, there is no experience in using the 600/300 tablet to provide 300/150 twice-daily dosing. Consider halving the 600/300 tablet and giving one half tablet twice daily, or give one tablet daily. Adult ABC/3TC FDC tablets are not scored; a tablet cutter would be required to divide these tablets.

## ANNEX F: SERIOUS, ACUTE AND CHRONIC TOXICITIES CAUSED BY ARV DRUGS

### Clinical presentation, laboratory abnormalities and implications for ART management.

These toxicities may require therapy modification. Alternative explanations for toxicity should be excluded before concluding that it is caused by the ARV drug.

This table describes management of the ART regimen but does not indicate detailed clinical toxicity management.

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities <sup>a</sup>	Implications for ARV drug treatment
<b>Acute serious adverse reactions</b>		
<b>Acute, symptomatic hepatitis (NNRTI class, particularly NVP, more rarely EFV; NRTIs or PI class)</b>		
<ul style="list-style-type: none"> <li>• Jaundice</li> <li>• Liver enlargement</li> <li>• Gastrointestinal symptoms</li> <li>• Fatigue, anorexia</li> <li>• May have hypersensitivity component (rash, fever, systemic symptoms), usually occurs within 6–8 weeks</li> <li>• May have accompanying lactic acidosis (<i>see below</i>) if secondary to NRTI drug</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated transaminases</li> <li>• Elevated bilirubin</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs until symptoms resolve</li> <li>• If possible, monitor transaminases, bilirubin</li> <li>• If receiving NVP, it should NOT be readministered to the patient in future</li> <li>• Once symptoms resolve, either:               <ul style="list-style-type: none"> <li>– restart ART with substitution to alternative ARV (if on NVP regimen, this is required); or</li> <li>– restart same ART regimen with close observation; if symptoms recur, substitute an alternative ARV<sup>b</sup></li> </ul> </li> </ul>
<b>Acute pancreatitis (NRTI class, particularly d4T, ddI; more rarely 3TC)</b>		
<ul style="list-style-type: none"> <li>• Severe nausea and vomiting</li> <li>• Severe abdominal pain</li> <li>• May have accompanying lactic acidosis (<i>see below</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated pancreatic amylase</li> <li>• Elevated lipase</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs until symptoms resolve</li> <li>• If possible, monitor serum pancreatic amylase, lipase</li> <li>• Once symptoms resolve, restart ART with substitution of an alternative NRTI, preferably one without pancreatic toxicity<sup>b</sup></li> </ul>

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities <sup>a</sup>	Implications for ARV drug treatment
<b>Hypersensitivity reaction (ABC or NVP)</b>		
<ul style="list-style-type: none"> <li>• <b>ABC:</b> Combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild) may or may not occur; progressive worsening of symptoms soon after receiving ABC dose, usually occurs within 6–8 weeks</li> <li>• <b>NVP:</b> Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash usually occurs within 6–8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Elevated transaminases</li> <li>• Elevated eosinophil count</li> </ul>	<ul style="list-style-type: none"> <li>• Immediately discontinue all ARVs until symptoms resolve</li> <li>• NVP or ABC should NOT be readministered to the patient in future</li> <li>• Once symptoms resolve, restart ART with substitution of an alternative ARV for ABC or NVP<sup>b</sup></li> </ul>
<b>Lactic acidosis (NRTI class, particularly d4T)</b>		
<ul style="list-style-type: none"> <li>• Generalized fatigue and weakness</li> <li>• Gastrointestinal features (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss)</li> <li>• May have hepatitis or pancreatitis (see above)</li> <li>• Respiratory features (tachypnoea and dyspnoea)</li> <li>• Neurological symptoms (including motor weakness)</li> </ul> <p>Can occur at any time on ART</p>	<ul style="list-style-type: none"> <li>• Increased anion gap</li> <li>• Lactic acidosis</li> <li>• Elevated aminotransferase</li> <li>• Elevated creatine phosphokinase (CPK)</li> <li>• Elevated lactate dehydrogenase (LDH)</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs until symptoms resolve</li> <li>• Symptoms associated with lactic acidosis may continue or worsen despite discontinuation of ART</li> <li>• Once symptoms resolve, restart ART with substitution of an alternative NRTI with lower mitochondrial toxicity risk (e.g. ABC or AZT<sup>b</sup>)</li> </ul>

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities <sup>a</sup>	Implications for ARV drug treatment
<b>Severe rash/Stevens – Johnson syndrome (NNRTI class, particularly NVP, less common EFV)</b>		
<ul style="list-style-type: none"> <li>Rash usually occurs during first 6–8 weeks of treatment</li> <li><i>Mild-to-moderate rash</i>: erythematous, maculopapular, confluent, most often on the body and arms, with no systemic symptoms</li> <li><i>Severe rash</i>: extensive rash with moist desquamation, angioedema, or serum sickness-like reaction; or rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis</li> <li>Life-threatening Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN)</li> </ul>	<ul style="list-style-type: none"> <li>Elevated transaminases</li> </ul>	<ul style="list-style-type: none"> <li>If mild or moderate rash, ART can continue without interruption staying at induction dose until rash settles but with close observation, and only increase to maintenance dose once tolerated</li> <li>For severe or life-threatening rash, discontinue all ARVs until symptoms resolve</li> <li>NVP should NOT be readministered to the patient in the future</li> <li>Once symptoms resolve, restart ART with substitution of an alternative ARV for NVP (note: most experts would not change to another NNRTI drug if patient had severe or life-threatening Stevens – Johnson syndrome with NVP)<sup>b</sup></li> </ul>
<b>Severe life-threatening anaemia (AZT)</b>		
<ul style="list-style-type: none"> <li>Severe pallor, tachycardia</li> <li>Significant fatigue</li> <li>Congestive heart failure</li> </ul>	<ul style="list-style-type: none"> <li>Low haemoglobin</li> </ul>	<ul style="list-style-type: none"> <li>refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI<sup>b</sup></li> </ul>
<b>Severe neutropenia (AZT)</b>		
<ul style="list-style-type: none"> <li>Sepsis/infection</li> </ul>	<ul style="list-style-type: none"> <li>Low neutrophil count</li> </ul>	<ul style="list-style-type: none"> <li>If refractory to symptomatic treatment (e.g. transfusion), discontinue AZT only and substitute an alternative NRTI<sup>b</sup></li> </ul>

Possible clinical manifestations (most common ARV drug or drugs associated with the toxicity)	Possible laboratory abnormalities <sup>a</sup>	Implications for ARV drug treatment
<b>Chronic late serious adverse reactions</b>		
<b>Lipodystrophy/metabolic syndrome (d4T; PIs)</b>		
<ul style="list-style-type: none"> <li>• Fat accumulation and/or fat loss in distinct regions of the body:               <ul style="list-style-type: none"> <li>– increased fat around the abdomen, buffalo hump, breast hypertrophy</li> <li>– fat loss from limbs, buttocks and face occurs to a variable extent</li> </ul> </li> <li>• Insulin resistance, including diabetes mellitus</li> <li>• Potential risk for later coronary artery disease</li> </ul>	<ul style="list-style-type: none"> <li>• Hyper-triglyceridaemia</li> <li>• Hyper-cholesterolaemia;</li> <li>• Low high-density lipoprotein (HDL) levels</li> <li>• Hyperglycaemia</li> </ul>	<ul style="list-style-type: none"> <li>• Substitution of ABC or AZT for d4T may prevent progression of lipoatrophy</li> <li>• Substitution of an NNRTI for a PI may decrease serum lipid abnormalities</li> </ul>
<b>Severe peripheral neuropathy (d4T, ddl; more rarely 3TC)</b>		
<ul style="list-style-type: none"> <li>• Pain, tingling, numbness of hands or feet; inability to walk</li> <li>• Distal sensory loss</li> <li>• Mild muscle weakness and areflexia may occur</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• Stop suspected NRTI only and substitute a different NRTI that is not associated with neurotoxicity<sup>b</sup></li> <li>• Symptoms may take several weeks to resolve</li> </ul>

<sup>a</sup> All laboratory abnormalities may not be observed.

<sup>b</sup> See Table 7 (Section 9) for recommended ARV drug substitutions.