



TECHNICAL SUMMARY

30 November 2006

WHO RECOMMENDATIONS ON ARV MEDICINES FOR TREATING AND PREVENTING HIV INFECTIONS IN YOUNGER CHILDREN

All WHO fact sheets, press releases, features and other information on HIV/AIDS can be found on <http://www.who.int/hiv>

There is an urgent need for affordable, safe, quality ARV formulations appropriate for paediatric use, particularly solid fixed dose combination (FDC) formulations to facilitate programming planning, improve adherence and facilitate scale up of HIV care for children, in line with a public health approach.

WHO strongly encourages the development of child-friendly fixed dose combination (FDC) formulations (e.g. crushable, dispersible, granular, scored tablets or capsules) in doses that can be safely used to treat HIV infected paediatric patients, particularly infants and younger children.

In its 2006 Antiretroviral treatment (ART) guidelines for children, WHO has provided guidance on target dosing for all the currently recommended ARVs for children (these are contained in Annex E of the 2006 guidelines <http://www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf>).

Using a generic tool developed by WHO and working with an international group of paediatric ARV experts [referred to hereafter as the paediatric ARV working group (PAWG)], WHO has examined existing single and fixed dose ARV products, as well as future products with a view to determining 'ideal' and 'acceptable' formulations for the treatment and prevention of HIV infection in children.

The expert group followed the principles and dosing recommendations made in Annex E of the WHO 2006 Antiretroviral treatment (ART) guidelines for children, and uses the same weight bands. Addi-

tional principles used to examine both existing and ideal products and the summary findings are provided in the report of the PAWG meeting held in October 2006. (available at <http://www.who.int/hiv/events/paediatricmeetingreport.pdf>)

Key recommendations or findings were as follows:

Review of existing ARV products

Single ARV drugs

Smaller solid dosage forms do not currently exist and are urgently needed. Suggested priority products are identified, and listed in the next section. Greater access to enteric coated preparations of Didanosine (ddI) in 125mg and 200mg strengths is required.

Newly developed FDCs for children

Five new d4t containing FDC ARV tablet products, and one solution were identified and assessed (see table FDC 5, FDC 6, FDC 7, FDC 10, FDC 10S, FDC 12). The expert group felt that these products can be used to deliver ARVs to children according to WHO treatment recommendations, and analysed what dosing schedules would be required to achieve WHO intended delivered dose for each drug at each weight band.

The PAWG note that the weight bands and dosing schedule recommended by the manufacturers may be different to those developed by the PAWG which are derived from recent WHO treatment and dosing

guidelines. In particular, the working group felt that it was important to dose the FDCs to achieve a higher intended Nevirapine (NVP) dose in light of recent data

confirming that a minimum total daily dose of 320 mg/m² (160 - 200mg mg/m² per dose given twice daily) is preferred.

D4T FDC preparations examined

Fixed dose combination	Active Components	Strength in mg	Manufacturer
FDC 5	D4T/3TC/NVP	5:20:35	Ranbaxy Laboratories Ltd
FDC 6	D4T/3TC/NVP	6 :30:50	Cipla Ltd.
FDC 7	D4T/3TC/NVP	7:30:50	Thai Government Pharmaceutical Organization (GPO)
FDC 10	D4T/3TC/NVP	10:40:70	Emcure Pharmaceuticals & Ranbaxy Laboratories Ltd
FDC 10 suspension (FD10S)	D4T/3TC/NVP	10:40:70 per 5 mls reconstituted	Emcure Pharmaceuticals
FDC 12	D4T/3TC/NVP	12 :60 :100	Cipla Ltd.

The PAWG recognized that intended target dosing can be achieved using Annex E weight bands and the PAWG developed recommended tablet schedules for a range of these FDC products. The PAWG felt that there is no intrinsic advantage to one product over another in terms of intended dose, provided the appropriate WHO dosing schedule for that product is followed. It is important to note that using any ONE FDC product, intended dosing for all ARV components for all weight bands may not be achieved. For example some of the existing FDCs cannot be used for younger children, while others may be too impractical to recommend in older children.

The report and its annexes will include a recommended WHO intended dosing schedule (based on Annex E of the WHO 2006 Antiretroviral treatment (ART) guidelines for children and providing intended delivered dose) for each of the products identified. It is important to note that the working group did not examine any data, and cannot make any recommendations related to the quality of these ARV products.

Ideal ARV products for children

Single ARV products

For MTCT prevention:

Zidovudine (AZT) 12mg sachet granules, Nevirapine (NVP) 6mg sachet granules,

For ARV treatment:

NVP 55mg scored tablets, Abacavir (ABC) 60mg scored tablet, Efavirenz (EFV)100mg

and 600mg scored tablets, AZT 60mg scored tablet, Stavudine (d4T) 7mg scored tablet, Lamivudine (3TC) 30mg scored tablet, ritonavir 100mg heat stable tablet, emtricitabine (FTC) 35mg scored tablet).

ARV FDC products for children

The PAWG identified a range of solid ARV FDC products that, if available, would offer considerable advantages to agencies responsible for ARV procurement and distribution, as well as to prescribers, pharmacists, dispensers, parents/caregivers and children considerable advantages and support efforts towards universal access to ART for children.

A single weight based common dosing schedule suitable for all weights and ages of children could be then be used for all first line ARV products (see prototype tables at end of document). Changes in the numbers of tablets required for any FDC or FDC single tablet ARV combination would also always occur at the same weight.

The PAWG felt these products offer considerable theoretical and practical advantages, and call upon the pharmaceutical industry, international drug regulatory authorities and other international partners to take immediate steps to secure their development and availability globally for treatment programmes. Unfortunately none of the existing FDC products examined could be used in the same manner. Further details of the simplified standardized dosing can be found in the detailed meeting report.

D4T FDC preparations examined

Degree of Priority	Product	Strength (mg)
Urgent	AZT/3TC/NVP	60:30:55
	AZT/3TC	60:30
	D4T/3TC	7:30
	D4T/3TC/NVP	7:30:55
	Lopinavir/ritonavir(Lop/r)	90:22.5
High	ABC/3TC	60:30
	AZT/3TC/ABC	60:30:60
Important	EFV/FTC	100:35

Proposed simplified dosing table for ideal products identified Twice daily drugs

Drug	Strength of child tab (mgs)	Number of tablets by weight band						Strength of adult tab (mgs)	Number of tablets by weight band	
		3-4.9 kg	5-6.9 kgs	7-11.9 kgs	12-16.9 kgs	17-19.9 kgs	20-24.9 kgs		25-29.9 kgs	30-34.9 kgs
AZT	60		1	1.5	2	2.5	3	100	2	3
AZT/3TC	60/30		1	1.5	2	2.5	3	300/150	1	1
AZT/3TC/NVP	60/30/55		1	1.5	2	2.5	3	300/150/200	1	1
ABC/3TC	60:30		1	1.5	2	2.5	3	300/150	1	1
ABC	60		1	1.5	2	2.5	3	300	1	1
3TC	30		1	1.5	2	2.5	3	150	1	1
D4T	7		1	1.5	2	2.5	3	30	1	1
D4T/3TC/NVP	7/30/55		1	1.5	2	2.5	3	30/150/200	1	1
NVP	55		1	1.5	2	2.5	3	200	1	1

Once daily drugs

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		3-4.9 kg	5-6.9 kgs	7-11.9 kgs	12-16.9 kgs	17-19.9 kgs	20-24.9 kgs		25-29.9 kgs	30-34.9 kgs
FTC	35		1	1.5	2	2.5	3	100	2	3
EFV/FTC	100/35							600/200		