



WORLD HEALTH ORGANIZATION

**Preferred antiretroviral medicines for treating and preventing HIV infection in younger children.**

Report of the WHO Paediatric Antiretroviral Working Group

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## List of acronyms

3TC	Lamivudine
ABC	Abacavir
ARV	Antiretroviral
ART	Antiretroviral treatment
ATV	Atazanavir
AZT	Zidovudine
BD	Twice daily
BSA	Body surface area
CNS	Central nervous system
d4T	Stavudine
ddI	didanosine
EFV	Efavirenz
FDC	Fixed dose combination
FTC	Emtricitabine
HIV	Human immunodeficiency virus
PAWG	Paediatric antiretroviral working group
G8	Group of Eight (International forum for the governments of Canada, France, Germany, Italy, Japan, Russia, the United Kingdom and the United States)
GFTAM	Global Fund for TB AIDS and Malaria
FPV	fos-amprevavir
IDPF	International Drug Purchase Facility
IDV	Indinavir
LPV/r	Lopinavir/ritonavir
MTCT	mother-to-child transmission ( of HIV)
Nr	not recommended
NVP	Nevirapine
NFV	Nelfinavir
PI	Protease inhibitor
PK	Pharmacokinetics
RTV	Ritonavir
SQV	Saquinavir
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization
UN	United Nations
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNITAID	International facility for the purchase of drugs against HIV/AIDS, Malaria and Tuberculosis
UNICEF	The United Nations Children's Fund
ZDV	Zidovudine

# **Preferred ARV medicines for treating and preventing HIV infection in children.**

Report of the WHO Paediatric Antiretroviral Working Group

## **Introduction**

There is an urgent need for affordable, safe, quality ARV formulations appropriate for paediatric use, particularly solid fixed dose combination (FDC) formulations to facilitate programme planning, improve adherence and accelerate the pace of ART scale up using simplified standardized treatment approaches as outlined in the public health approach of WHO [1, 2]. Pharmaceutical industry and regulatory authorities are requesting guidance on the range and characteristics of the required ARV products, including on formulation strength for single ARV products and proportions of active pharmaceutical ingredients for fixed dose combination (FDC) ARV products. Recently a number of ARV FDC products for paediatric use have been developed. The WHO paediatric ARV working group (PAWG) initially constituted to develop dosing recommendations for the WHO guidelines has since met to prioritize single and fixed dose ARV formulations needed, and agree upon key research and pharmacovigilance activities that are urgently required. This is a summary report of the working group findings and recommendations to date.

## **Background:**

In 2006, there were an estimated 2.3 million children living with HIV infection largely acquired through mother to child transmission. HIV/AIDS now accounts for 3% of deaths in children younger than five years globally—and 6% in sub-Saharan Africa, where HIV has become one of the major killers of young children [3, 4]. While the majority of MTCT infections can be prevented, current global estimates suggest that by the end of 2005 only around 10% of women living with HIV are gained access to effective interventions to prevent new infections in their children. It is therefore necessary alongside efforts to scale up access to prevention services to provide optimal HIV care for those children infected where prevention efforts have failed. In the absence of HIV care, including antiretroviral treatment, the progression of HIV infection in children is particularly aggressive [5]. While enormous progress in treating adults living with HIV has been made since the launch of 3X5 and other global initiatives to increase access to HIV care and treatment, children are still not gaining access to the medicines including ARVs that can prolong their lives. WHO and UNAIDS estimated that by the end of 2006, 115 500 (103 000–128 000) children had access to treatment, representing a coverage rate of about 15%, with sub-Saharan Africa having the lowest treatment coverage for children of any region [4].

WHO, in collaboration with UNICEF, has recently committed to making paediatric medications a priority area of work, and has initiated a series of activities designed to assess and update the essential medicines list in regards to its applicability to the needs of children. Following the commitment by G8 members and, subsequently, heads of states and governments at the 2005 UN World Summit, the UNAIDS Secretariat and UN partners, including WHO, have undertaken to work towards universal access to HIV/AIDS prevention, treatment and care by 2010. WHO as a

UNAIDS cosponsor and the lead UN agency responsible for health, sees children's access to HIV prevention, treatment, care and support as a critical area of work.

There are many problems and obstacles not related to ARV products that have impeded progress in the scale-up of paediatric HIV treatment. But recent international efforts now provide significant momentum and opportunities to expand the access of children to safe effective HIV therapies. Industry, both originator and generic and regulatory authorities, including the prequalification programme are seeking guidance on the most needed HIV products to support universal paediatric access.

A WHO/UNICEF consultation on pediatric ARV formulations held in November 2004 recommended that guidance for dosing on pediatric ARVs should be simplified. In developing the 2006, WHO ART treatment recommendations a small working group therefore worked to develop an annex with recommended dosing based on weight bands for existing ARV products. However, the lack of a full range of ARV products designed specifically for treating children means that this guidance is incomplete.. Formulations, particularly FDC formulations in solid forms for treating smaller children (including those under 14 kg) were recognized to be urgently needed to allow scale up of treatment for younger infants and children. The limitations of liquid formulations (including storage difficulty, volumes required, palatability, excipient nature and cost) and the potential benefits of a small range of solid FDCs (improved adherence and easier programming) needs to guide recommendations for optimal products for children of all ages.

The market for paediatric ARV preparations is narrower than the market for adult formulations, and should be anticipated with increasing coverage of more effective PMTCT interventions to not expand further. A range of financing options, including the GFTAM and the UNITAID/IDPF offer opportunities to overcome some of the financial barriers to production and procurement of pediatric ARVs.

### **Objectives of the working group**

- To review the status of pediatric ARV products for younger children (safety, pharmacokinetics and toxicity).
- To develop criteria for prioritization of new pediatric ARV products for HIV infected children.
- To examine the results of analysis of intended dosing for actual and potential ARV FDC combinations.
- To develop a summary list of recommended priority products, including FDCs to guide manufacturers, regulatory authorities and the WHO in assessment and development of new pediatric ARV products.
- To develop a list of key research areas regarding pharmacokinetics, toxicity and dosing that need to be answered to further facilitate and support ARV FDC development and safely monitor their use in paediatric populations.

This report summarizes the recommendations and findings of the work undertaken by the working group throughout 2006-2007, and based on meetings held in October 2006 (Geneva) and July 2007 (London).

### **Paediatric ARV working group members**

The paediatric ARV working group was established in 2005 to work with the WHO HIV department in the development of the dosing recommendations contained in WHO antiretroviral treatment recommendations (ART). Representatives of the pharmaceutical industry (originator or generic) are not included. Participants include clinical care providers (paediatricians and clinical pharmacologists) providing ART to HIV infected children, technical advisers of partners implementing programme activities in resource limited countries and paediatric ART pharmacology researchers and pharmacists. WHO regional offices also nominate regional or country experts to attend face to face meetings, and additional experts have been invited to share emerging data or other specific expertise on an as required basis. Participants are listed in the annex.

## Working methods

The PAWG initially worked through a series of teleconferences. Face to face meetings have been held three times (February 2006; October 2006; and July 2007), initially involving only the core working group established from the WHO guidelines development group. In 2007 a web based working space was established to facilitate sharing of working documents. At the latter two meetings, the working group first prioritized the range of ARV products required, through a ranking exercise based on current WHO treatment recommendations. For the priority products identified they evaluated a range of dose strengths against criteria agreed in the development of the 2006 WHO treatment recommendations. The analysis was facilitated by use of a generic tool developed by WHO that allows the intended dose delivered to be assessed for any given single or combined product for any body weight (or if indicated based on body surface area [BSA]) (see <http://www.who.int/hiv/paediatric/generictool/en/index.html>). The tool demonstrates potential over- or under- dosing for any given weight. Available published and unpublished evidence was also reviewed (see WHYTE report). The group sought to identify a short list of combined triple, dual, and single ARV products for paediatric HIV treatment and prevention of MTCT in the infant. The PAWG also assessed existing FDC products.

Methods used to evaluate and characterize ideal ARV products:

- Used the previously determined 2006 WHO recommendations [1] (provided as Annex E of the treatment guidelines document), target doses and weight bands as a benchmark, and followed the underlying principles contained therein.
- Reviewed currently available published and unpublished data to assess dosing. (A detailed report is available separately (add link to WHYTE report)).
- Used a WHO generic tool to assess and evaluate the expected dose delivered of any product in relation to intended dose targets as set out in the above mentioned WHO recommendations.
- Attempted to ensure that for all formulations, changes in the numbers of pills and switches from one formulation to another, occurred at the same weight bands.
- Attempted to avoid dosing any single ARV component below 90% of intended delivered dose and not more than 25 % above intended dose (or intended dose range for products with an established dose range). For nevirapine, the group sought to avoid dosing below 100% of the minimum of the dose range (150mg/m<sup>2</sup>).
- Each individual drug considered was assessed for a range of tablet strengths using the same tool and principles.

- Sought to justify discrepancies of dose delivered and intended dose based on available pharmacokinetic data, consideration of toxicity, and threshold for development of HIV drug resistance.
- Accepted higher dosing for children under 3 years for drugs with known increased metabolism or clearance in the child (Nevirapine, Lamivudine, Stavudine, Abacavir, Lopinavir/ritonavir).

Further information on the WHO generic dosing tool can be found at:  
<http://www.who.int/hiv/paediatric/en/index.html>

## Findings and recommendations

### A. Criteria for prioritizing new pediatric ARV products

The following criteria for assessing potential ARV products for use in paediatric populations were followed:

- Maximum number of tablets at any one dose should be no more than three.
- Minimum dose is one half tablet of products that are scored
- Limit the number of dosing forms for each single ARV or FDC required for prevention and treatment of HIV in adults and children.
- Harmonize dosing schedules and weight-based dose switching points for all products wherever possible.
- Avoid using different doses in the morning and evening wherever possible.
- Recognize that younger children, particularly those under three years, behave differently with respect to pharmacokinetics and pharmacodynamics and that they may therefore need specific products or modified dosing recommendations.
- Require products suitable for the infant or child 14 kg or below.
- Require soluble or dispersible solid forms for optimal prevention and treatment in early childhood.
- Seek combinations that facilitate TB/HIV co-treatment for children

The actual or predicted cost of individual products was not considered.

The PAWG also agreed on key principles to consider when prioritizing which new ARV drug formulations for children are required:

- Paediatric FDCs do not need to be restricted to the same ratios or combinations as used in adult FDC ARV products.
- Paediatric solid FDCs are expected to improve prescribing, adherence, supply, procurement, distribution, storage and dispensing.
- Products should ensure ARV drugs at the intended dosing recommended in 2006 WHO ART treatment guidelines for children (these are provided in Annex E of the treatment guidelines).
- Recommended priority products should include second line ARV agents.
- Solid, scored, palatable, easily crushable, granular or dispersible forms that allow for easy oral administration are preferred.
- Systematic efforts to ensure pharmacovigilance activities to detect, assess, and prevent both early and late adverse effects, must be undertaken as products are developed and used.

- Producers of new products should indicate willingness to submit for national registration in high burden countries (a list of highest burden countries is attached in the annex A).
- Products should have a long shelf life of not less than 24 months (except for protease inhibitors [PI] where this may not be possible), stability at high temperature and humidity, and be easy to store, transport and dispense.

## B. Specific considerations relating to pharmacokinetics, toxicity, and safety of paediatric antiretrovirals to guide development of new products.

Table 1 below provides a summary of the key factors that guided the working group in their considerations. A detailed review is also available at <http://www.who.int/hiv/paediatric/en/index.html>

**Table 1. Specific ARVs and pharmacokinetic, safety or other data to be considered in developing recommendations on new ARV products for children.**

Drug	Considerations	Target Dosing Range	References (* denotes key reference)
Zidovudine (AZT or ZDV)	Twice daily dosing (BD) is acceptable and preferred.  Dosing at the upper end of the range is recommended for CNS HIV disease Dosing at lower end maybe preferred in settings where anaemia is prevalent	180-240mg/m <sup>2</sup> per dose  Twice daily	[6-9]
Lamivudine (3TC)	Clearance <sup>i</sup> in children <3 years old is increased, and minimal observed toxicity allows for higher dosing in younger children (up to 5mg/kg BD). PK data on once daily dosing suggests acceptable troughs and overall troughs similar to BD dosing. Once daily dosing not recommended for children under 3 years.	4mg/kg per dose Twice daily	[7, 10-15]
Abacavir (ABC)	Clearance in children <3 years old is increased, and it should therefore be used twice daily in this age-group; once daily dosing not recommended for initiation of ART or in children	8-10 mg/kg per dose - twice daily	[10*, 11*, 16-19]

<sup>i</sup> Clearance here refers to the rate at which a drug and or its metabolites are removed from the body.

Drug	Considerations	Target Dosing Range	References (* denotes key reference)
Didanosine (ddI)	<p>&lt;3 years but can be used in children &gt;3 years.</p> <p>Because of potential for hypersensitivity, a substitution option should be available</p> <p>Enteric coated dosing forms are recommended rather than the buffered form. Needs to be given 1 hour before or 2 hours after food. Once daily dosing accepted over 6 years</p>	<p>≤ 3 months 50mg/m<sup>2</sup> per dose</p> <p>&gt; 3 months 120 mg/m<sup>2</sup> per dose</p> <p>Twice daily.</p>	[20-26]
Stavudine (d4T)	<p>Needed as a priority product despite well recognized longer term toxicities (lipodystrophy in children and adults), as it is initially well tolerated, is safer to use in anaemia than AZT, and has lower laboratory monitoring requirements.</p> <p>Avoid over-dosing wherever possible (noting recent revision to adult dosing recommendations to reduce), and especially for extended periods to minimize toxicity.</p>	1 mg/kg per dose twice daily	[7, 27-34]
Emtricitabine (FTC)	<p>Safety and efficacy established for use in children over 3 months of age, using once daily dosing.</p>	<p>6mg/kg for liquid forms</p> <p>4.8-6 mg/kg for solid forms</p> <p>Once daily</p>	[35-38]
Tenofovir (TDF)	<p>Have limited safety and toxicity data, and the dosing and safety continue to be studied in children.</p>	<p>300 mg once daily which approximates 8 mg/kg in adults</p> <p>Once daily</p>	[39-42]
Nevirapine (NVP)	<p>Can be used in adolescents?</p> <p>A BSA based dose range of 150-200mg/m<sup>2</sup> for nevirapine is used to generate weight band dosing. Products and dosing schedules were sought that avoid dosing below minimum of 150mg/m<sup>2</sup> wherever possible due to low barrier to development of HIV drug resistance[43, 44]</p> <p>A reduced dose is recommended for</p>	<p>150-200mg/m<sup>2</sup> per dose</p> <p>Twice daily</p>	[25, 45-59]

Drug	Considerations	Target Dosing Range	References (* denotes key reference)
Efavirenz (EFV)	<p>the first two weeks when initiating nevirapine treatment regimens.(ref)</p> <p>Due to developmental changes in nevirapine metabolism, young children require a higher nevirapine dose relative to the NRTI components than delivered in current adult FDC combinations.</p> <p>Because of potential for severe toxicity, a substitution option should be available.</p> <p>Dosing has not been established for children under 3 years. Approved dosing is already provided based on weight bands, and the dosing provided approximates this. Syrup and solid forms are not bioequivalent, with the syrup being over 30% less bioavailable.</p> <p>Evening dosing is preferred</p>	<p>15 -18.75/kg solid form or 19.5 mg/kg syrup Once daily</p>	[31, 60-71]
Lopinavir/ritonavir ( LPV)/r)	<p>Clearance in children &lt;3 years old is increased.</p> <p>Heat-stable paediatric formulation is recently approved .</p> <p>Actual exposure depends on metabolism and inter patient variability, which is considerable. Pharmacokinetic data suggests higher clearance if given with NNRTI hence WHO target dosing is above approved dose.</p> <p>Lopinavir/ritonavir is currently the preferred PI.</p>	<p>&lt; 6 months &lt; 15 kg 12/3 mg/kg ≥ 15 kg 10/2.5 mg/kg Twice daily</p>	[62, 72-78]
Ritonavir (RTV)	<p>Needed to use as pharmacological booster in treatment of children with a PI and for children receiving rifampicin-based anti tuberculosis therapy.</p>	<p>As a booster for Lopinavir: Ritonavir target doses are : 7–15 kg: 3 mg/kg 15–40 kg: 2.5 mg/kg Twice daily Ritonavir dose and dosing frequency (once or twice daily) varies with the PI</p>	[79-83]

Drug	Considerations	Target Dosing Range	References (* denotes key reference)
		which it is combined with.	
Nelfinavir (NFV)	Even with very high doses infants have lower blood levels (Penta 7) Needs to be taken with a fatty meal. Not a priority product	<10 kg: dose listed is targeted to achieve a dose of ~75 mg/kg/dose twice daily  >10 kg to 19.9 kg: dose listed is targeted to achieve a dose of ~60 mg/kg/dose twice daily	[79, 80, 82, 84-92]
Saquinavir (SQV)	Bioavailability is very poor and manufacturing of appropriate paediatric dosing forms have so far not been successful.	Only above 25 kg, 50mg/kg Twice daily	[85, 86, 93, 94]
Indinavir (IDV)	Limited information about use in children and not considered further due to concerns regarding toxicity.	50 mg/kg, three times daily. When boosted with RTV, can be dosed twice daily without food restrictions.	
Atazanavir (ATV)	Limited information available about use in children	NA	[95]
fos-amprevavir (FPV)	Manufacturers recently have an FDA-approved suspension	<i>Therapy naive &lt; 6 years;</i> 30 mg/g twice daily, not to exceed the adult dose of 1,400 mg twice daily or 18 mg/kg plus ritonavir 3 mg/kg administered twice daily <i>Therapy experienced &gt; 6 years;</i> 18 mg/kg plus ritonavir 3 mg/kg administered twice daily	[96-98]

### C. Considerations for fixed dose combination in children

The working group emphasized the benefits that fixed dose combinations are expected to provide for children, while recognizing the potential associated risks. Based on available published evidence, early data from studies in progress and population based PK modeling, the working group recommends that the ratio for fixed dose combinations for use in younger children requires more nevirapine relative to the NRTI component than an adult FDC. Similar revised ratios are also necessary for other combination

ARV products. The working group felt that solid fixed dose combinations at dose strengths for the youngest children are the most urgently required FDC. Adult FDC combinations have been demonstrated to be bioequivalent to adult single drug combinations[99, 100], and bioequivalence data is also available for some of the existing paediatric FDC products.

#### D. Recommended Priority ARV Products identified

A list of priority ARV products was identified and ranked according to how urgent the participants felt need for development based on the criteria above (table 2 ). For each of these, a range of possible dosing strengths was assessed using the WHO generic tool.

**Table 2. Dosing strengths assessed for ARV products**

Priority	Product	Dosing strengths Reviewed (mg)
<b>Priority ARV Products for infant MTCT prevention</b>		
Urgent	Zidovudine	12 mg sachet granules 4 mg sachet granules
	Nevirapine	6 mg sachet granules 2 mg sachet granules
<b>Priority ARV Products required for treatment</b>		
Urgent	Zidovudine/Lamivudine/Nevirapine	60/30/50mg tablet 60/30/60mg tablet 150/75/100mg tablet
	Zidovudine/Lamivudine	60/30mg tablet 150/75mg tablet
	Stavudine/Lamivudine	6/30mg tablet 15/75mg tablet
	Stavudine/Lamivudine/Nevirapine	6/30/50mg tablet 5:20:35mg tablet 7:30:50mg tablet 12:60:100mg tablet 10:40:70 mg tablet
	Nevirapine	50mg tablet 100mg tablet
	Lopinavir/ritonavir	100/25mg tablet 90/22.5mg tablet
	Abacavir	60mg tablet 120mg tablet 150mg tablet
	High	Efavirenz
Abacavir/Lamivudine		60/30mg tablet 150/75mg tablet
Zidovudine		60mg tablet 100mg tablet
Zidovudine/Lamivudine/Abacavir		60/30/60mg tablet 150/75/150mg tablet

	Stavudine	6mg tablet 15mg tablet
	Didanosine	125 ec 200 ec
	Lamivudine	30mg tablet 75mg tablet 150 mg tablet
<b>Important</b>	Efavirenz/Emtricitabine	100/35mg tablet
	Emtricitabine	35mg tablet
	Ritonavir	25mg tablet 100mg tablet
	Fosamprenavir	not yet determined
	Darunavir	not yet determined

### **Proposed ideal formulations and harmonized simplified dosing**

Both the outputs from the generic tool as well as clinical pharmacokinetic data if available were used to evaluate the different dosing strengths for the priority ARV products identified. The working group set out to simplify dosing by creating a single harmonized common dosing schedule suitable for all weights and ages of children, for use with all first line ideal ARV products. Implementation of this harmonized dosing would allow changes in the numbers of tablets required for any FDC or single ARV formulation at the same weight band. The working group felt that such a combined dosing schedule would offer considerable theoretical and practical advantages and support scale up. An *ideal* dosing strength that could be used according to such a unified, simplified and harmonized dosing schedule for all ARV agents was therefore sought and is provided in table 4 . A final list of ideal dosing strengths identified by the working group are given in table 3 and details of the simplified dosing for each product are provided in Annexes. This final list of ideal dosing strengths differs from the list provided in an earlier version of this draft document. Specifically, the ideal dosing strength of nevirapine – both in single ARV and FDC formulations has been revised based on early PK data and population based PK modeling of intended target dose and area under the curve (AUC). In addition, the d4T dosing strength has been revised to reflect findings of population pharmacokinetic modeling and recent revisions that reduced dosing recommendations for adults in order to reduce toxicity to d4T (see <http://www.who.int/hiv/treatment/en/index.html>).

The working group recognizes that further revision to these product profiles may be required as new data becomes available and that additional products will be necessary in the future as ART treatment recommendations evolve.

**Table 3. Ideal dosing strengths for priority ARV product. All tablets should be scored wherever possible**

Priority	Product	Ideal Dosing strengths
<b>Priority ARV Products for infant MTCT prevention</b>		
<b>Urgent</b>	Zidovudine	12 mg sachet granules
	Nevirapine	6 mg sachet granules
<b>Priority ARV Products required for treatment</b>		
<b>Urgent</b>	Zidovudine/Lamivudine/Nevirapine	60/30/50mg tablet*
	Zidovudine/Lamivudine	60/30mg tablet
	Stavudine/Lamivudine	6/30mg tablet*
	Stavudine/Lamivudine/Nevirapine	6/30/50mg tablet*
	Nevirapine	50mg tablet*
	Lopinavir/ritonavir	100/25mg tablet*
	Abacavir	60mg tablet
<b>High</b>	Efavirenz	100mg tablet
	Abacavir/Lamivudine	60/30mg tablet
	Zidovudine	60mg tablet
	Zidovudine/Lamivudine/Abacavir	60/30/60mg tablet
	Stavudine	6mg tablet*
<b>Important</b>	Didanosine	No new products identified
	Lamivudine	30mg tablet
	Efavirenz/Emtricitabine	100/35mg tablet
	Emtricitabine	35mg tablet
	Ritonavir	25mg tablet
	Fosamprenavir	Not yet determined

\* denotes a change from initial recommendations made in the first draft of the working group's report.

**Table 4: Simplified harmonized dosing schedule for ideal ARV products used in first line regimens**

Drug	Strength of child tab (mg)	Number of tablets by weight band (twice daily)									Strength of adult tab (mg)	Number of tablets by weight band (twice daily)	
		<i>Children less than 6 months of age<sup>#</sup></i>		Children 6 months of age and above								25-29.9 kg	30-34.9 kg
		3-3.9 kg	4-4.9 kg	3-3.9 kg	4-4.9 kg	5-5.9 kg	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg			
AZT	60	0.5	0.75	1	1	1	1.5	2	2.5	3	300	1	1
AZT/3TC	60/30	0.5	0.75	1	1	1	1.5	2	2.5	3	300/150	1	1
AZT/3TC/NVP	60/30/50	0.5	0.75	1	1	1	1.5	2	2.5	3	300/150/200	1	1
ABC	60	0.5	0.75	0.5	0.75	1	1.5	2	2.5	3	300	1	1
ABC/3TC	60/30	0.5	0.75	0.5	0.75	1	1.5	2	2.5	3	300/150	1	1
ABC/AZT/3TC	60/60/30	0.5	0.75	0.5	0.75	1	1.5	2	2.5	3	300/300/150	1	1
3TC	30	0.5	0.75	1	1	1	1.5	2	2.5	3	150	1	1
d4T	6	0.5	0.75	1	1	1	1.5	2	2.5	3	30	1	1
d4T/3TC	6/30	0.5	0.75	1	1	1	1.5	2	2.5	3	30/150	1	1
d4T/3TC/NVP	6/30/50	0.5	0.75	1	1	1	1.5	2	2.5	3	30/150/200	1	1
NVP	50	0.5	0.75	1	1	1	1.5	2	2.5	3	200	1	1

0.75 BD is delivered as 1 tablet AM and 0.5 tablets PM

<sup>#</sup>Doses for infants under 6 months are lower in view of altered absorption, distribution, metabolism, excretion, and pharmacologic effects of drugs in neonates and infants.

## **E. Existing paediatric FDC Products**

Generic suppliers have recently begun manufacture of a number of paediatric FDCs. All of these contain combinations of d4T, 3TC and NVP in a variety of different ratios. Five FDC tablet products, and one FDC solution (table 5) were identified and assessed using the same criteria that were applied to the selection of ideal dosing strengths for priority ARV products. Of note, these FDCs were developed prior to the 2006 revision of the WHO paediatric ART guidelines and the working group noted that in some cases, the manufacturers' recommended dosing schedules would not achieve or consistently provide the WHO target intended doses. In particular the working group was concerned that any FDC must be dosed to achieve adequate NVP exposure in light of data confirming that a minimum total daily dose of 300 mg/m<sup>2</sup> (160 - 200mg mg/m<sup>2</sup> per dose given twice daily ) is preferred [52].

Of the solid FDC products assessed, only one (FDC 6) met the specification of the ideal dosing strength recommended by the PAWG. The ratio of components in the other solid forms was felt by the group to be unsuitable for dosing the smaller, younger child.

A FDC solution should be more versatile for dosing and could be used to deliver target intended dose for all components including for smaller children, However, the existing FDC 10s currently available is not in a ratio considered appropriate for the very young infant or child. It is also supplied as a powder and needs to be reconstituted with clean water before administration. Once reconstituted, the solution has to be refrigerated at 4°C. These are considerable impediments to the use of such a product and the PAWG did not consider FDC 10s to be a useful alternative to the solid FDC form.

**Table 5: Currently manufactured paediatric d4T containing FDC products**

Fixed dose combination <sup>ii</sup>	Active Components	Strength in mg
FDC 5	d4T/3TC/NVP	5:20:35
FDC 6	d4T/3TC/NVP	6 :30:50
FDC 7	d4T/3TC/NVP	7:30:50
FDC 10	d4T/3TC/NVP	10:40:70
FDC 10s	d4T/3TC/NVP suspension	10:40:70 per 5 ml reconstituted
FDC 12	d4T/3TC/NVP	12 :60 :100

## F. Recommended research Priorities

1. Paediatric specific pharmacokinetic data are urgently needed for the following antiretroviral drugs when co-administered with rifampicin or rifabutin:
  - a. Efavirenz
  - b. Nevirapine
  - c. Lopinavir/ritonavir
2. Additional pharmacology data are required for the following individual antiretroviral therapy agents in the following paediatric populations:
  - a. To establish dosing of efavirenz for children less than 3 years of age and <10kgs
  - b. Pharmacokinetic data for efavirenz and nevirapine in different genetic populations of children
  - c. Pharmacokinetic data for nevirapine in young children, particularly those under 6 months of age
  - d.
  - e. Initiating nevirapine-containing antiretroviral therapy regimens without a lead-in phase in children
  - f. Once daily dosing for lamivudine for children younger than 3 years
  - g. Once daily dosing of abacavir for children initiating ART
  - h. Dosing and medium and long term toxicity for Tenofovir and Atazanavir<sup>iii</sup> in children
  - i. Pharmacokinetic and toxicity data for efavirenz in children under 3 years.
3. Impact of nutritional status on the pharmacokinetics, pharmacodynamics, adverse events and efficacy in children with moderate to severe malnutrition for all antiretroviral drugs, especially nevirapine, stavudine, zidovudine and lopinavir/r
4. Establish pharmacovigilance systems and protocols to monitor:
  - a. Long term safety of all antiretroviral medicines in paediatric populations

<sup>ii</sup> These are simple numerical names given to FDC products given by the working group members, and the number denotes the milligrams of d4T contained, the s denotes solution. A range on manufacturers produce these products.

<sup>iii</sup> No suitable formulation available currently.

- b. Safety of zidovudine-containing antiretroviral therapy regimens in populations with high prevalence of malaria and/or anaemia
- c. Hepatotoxicity of nevirapine in populations with high prevalence of viral hepatitis
- d. Rates of abacavir hypersensitivity reactions in paediatric population in low income countries

(See [http://www.who.int/medicines/publications/PhV\\_for\\_antiretrovirals.pdf](http://www.who.int/medicines/publications/PhV_for_antiretrovirals.pdf))

5. Investigation of innovative drug formulations to improve:
  - a. Heat stability of formulations, particularly of lopinavir/ritonavir
  - b. Bioavailability
  - c. Acceptability
  - d. Long term adherence

## **G. Review of the dosing tool**

The group reviewed the assumptions and format of the WHO dosing tools outputs. The dosing tool as originally developed uses an estimated body surface area derived from WHO standard growth curves with BSA estimated using the Mostellar formula<sup>1</sup>. The values used were compared to BSA estimated from against the Mid Upper Arm Circumference/ Weight for height study database (MUAC/WFH) study database, which includes data from over 560 nutritional anthropometry surveys. The original values for estimated BSA derived from the Mostellar “WHO” formula was found to underestimate BSA in the middle weight range, and the group agreed that the dosage tool may be improved by adoption of a quadratic model presented at the meeting. All the final simple dosing recommendations are now presented based on the revised estimations of BSA. There is also a need for further research into the effect of body-shape on BSA estimators. A simple look up table was derived and will now be used for the dosing tool (table 6).

Table 6. Revised look up table for BSA (Ref):

<b>Weight (Kg)</b>	<b>BSA Quadratic weight kg/m<sup>2</sup></b>
3	0.22
4	0.26
5	0.30
6	0.34
7	0.38
8	0.42
9	0.46
10	0.49
11	0.53
12	0.56
14	0.63
17	0.72
20	0.81
25	0.93
30	1.04
35	1.12

#### **H. Future plans for the paediatric ARV working group**

1. The group will review and approve final simple dosing tables for all priority products.
2. WHO HIV department should consider developing new terms of reference for PAWG.
3. The working group should then consider new drugs and drug classes in development.
4. WHO HIV department should maintain and keep up to date simple dosing recommendations for all existing and ideal products and use the working group to review these.
5. WHO HIV Department should consolidate and maintain the shared working space and paediatric ARV library.
6. WHO HIV department should commission and review summary data from population pharmacokinetic modeling outputs for nevirapine, 3TC and d4T.

#### **Conclusions**

1. Recommended priority products for ARV drug development were identified, and multiple dosage strengths were assessed for each product.
2. For each priority product an *ideal* dosage strength and dosing schedule was established.
3. For all first line priority products, the dosing schedule was harmonized to a single weight based schedule to be used for all first line ARV products and in children of all weights and ages.
4. The PAWG felt these products offer considerable theoretical and practical advantages, and recommend that the pharmaceutical industry, international drug regulatory authorities and other international partners take immediate steps to secure their development and availability for treatment programmes.

5. A detailed review of evidence and characteristics for each ARV drug and combination FDC product should be completed and made available in the public domain
6. Emerging pharmacokinetic data and new drug classes should be evaluated by the working group.

### **Immediate next steps**

1. Recommended priority products identified should be communicated to pharmaceutical industry by WHO and partners .
2. WHO HIV department should complete the additional work suggested by the group.
3. WHO HIV department in collaboration with the WHO cluster on Medicines Policy and Standards, Technical Cooperation for Essential Drugs and Traditional Medicine, that includes the WHO prequalification programme should review the recommendations and assess any implications for the 7<sup>th</sup> expression of interest or for the model essential medicines list.
4. The results of the analysis using the tool and the findings of analysis undertaken by working group should be published and made available on the WHO web site for public use.

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## **Annex A.**

### **List of regions with greatest burden of children living with HIV**

(Source: 2006 Report on the global AIDS epidemic, UNAIDS/WHO, May 2006. estimates)

<b>Region</b>	<b>Children living with HIV ( 0–14 years ) 2005</b>
Sub-Saharan Africa	2 000 000
South and South-East Asia	170 000
North America	11 000
North Africa and Middle East	31 000
Latin America	32 000
Eastern Europe and Central Asia	6900
East Asia	6400
Caribbean	22 000
Western and Central Europe	4000
Oceania	3000
<b>Global (total)</b>	<b>2 300 000</b>

### **Countries with greatest number of children in need of ART**

(Source Scaling up priority HIV/AIDS interventions in the health sector. Progress Report, April 2007-

[http://www.who.int/hiv/mediacentre/universal\\_access\\_progress\\_report\\_en.pdf](http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf)

<b>Country</b>	<b>Estimated number of children in need of ART</b>
South Africa	86,000
Nigeria	98,000
Mozambique	34,000
Ethiopia	12,000-61,000
India	17,000-94,000
DRC	45,000
Zimbabwe	45,000
Kenya	44,000
Uganda	42,000
Tanzania	41,000
Zambia	41,000
Malawi	23,000
Cote D' Ivoire	17,000
Cameroon	14,000
Angola	14,000
Rwanda	6,900
Lesotho	6,000
Swaziland	5,300
Namibia	4,900
Haiti	2,800

## Annex B

### Description of the WHO Generic tool for assessing paediatric dosing

The tool is an Excel based spreadsheet that allows for manipulation of the intended delivered dose given for any product (ARV in this case) for a range of weight bands to examine whether the intended dose is above or below the target dose recommended. Where dosing is only provided in body surface area then an estimation of the body weight is made from the body surface area (BSA)<sup>iv</sup> The BSA is estimated and based on the international standard height for any given weight and calculated using the Mostellar formula<sup>v</sup>. It can be adapted for single, dual or triple combinations. The generic tool, although not completed, can be used to assess existing or potential products and to work out dosing schedules for any particular single or combination product. This report contains some worked example spreadsheets.

The excel file for each product contains 3 major areas.

#### *Sheet one:*

Main data. This is where the data on the actual active ingredients are completed and can be manipulated depending on proportion or strength of API for different FDC products.

#### *Sheet 2:*

This sheet contains the doses selected examined by weight band and calculates the dose delivered based on the amount of formulation (ml/caps/tablets) selected for each weight. The amount intended to be delivered can be manipulated.

The formula using estimation of the Surface area (m<sup>2</sup>) for each weight generates a list of the maximum and minimum intended dose delivered and allows visualization of the dose delivered at the lowest weight/estimated surface area and the dose delivered at the Top weight/SA dose or estimated surface area.

Where this is over the maximum of the target range it is shaded red, where it is below the minimum of the target range it is shaded yellow.

BSA ranges are estimated using a quadratic equation derived from analysis of BSA from the MUAC WFH data base .

#### Sheet 3:

This provide a visual picture of how much each selected dose can be expected to deliver at compared to the recommended range for the target dose. This enables any over or under dosing to be easily visualized.

#### Sheet 4:

Where included this provides a simple summary table of the recommended dose by weight.

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<sup>iv</sup> These are based on estimated BSA derived from the MUAC WFH data base.

<sup>v</sup> Mosteller RD, *Simplified Calculation of Body Surface Area*, N Engl J Med, 1987;Oct 22;317(17):1098

## Annex C

List of PAWG members attending or contributing and Conflict of interest statements for those attending the October and July meeting.

Elaine Abrams, Edmund Caparelli, Rafealla DeLhomme, Diana Clarke, Siobhan Crowley, Shaffiq Essajee, Lisa Frigati, Carlo Giaquinto, Di Gibb, Charlie Gilks, Sue Hill, Pierre Humblet, Alice Zoungrana Kaboré, Addeodata Kekitiinwa, George Kizerbo, Helen Moller, Mark Mirochnick, Eloan Pinhiero, Lynne Mofenson, Harry Moultrie, Tony Nunn, Jorge A. Pinto, Paul Weidle, Lulu Oguda, Chewe Luo, Dr Nour El Hoda, Rakesh Lodha, Po-Lin Chan, Brian Eley, Atieno Ojoo.

WHO also wishes to acknowledge the comments and contributions by other global experts who were unable to attend all the meetings but have reviewed draft recommendations and participated in teleconferences to finalize recommendations: Tammy Myers, Gabriel Anabwani, Mark Kline, Ric Marlink, Thanyawee Puthanakit, Cathy Wilfert, Felipe Garcia, David Burger, Chewe Luo, Robert Gass, Emilia Rivendiera.

### CONFLICT OF INTEREST

Received from any organization in past five years:

Names	Type interest	Name of commercial entity
<i>D. Burger</i>	A fee for speaking	Roche, BMS, Gilead
<i>M. Mirochnick</i>	Funds for research	Doris Duke Charitable Foundation
<i>S. Essajee</i>		Roche, BMS, Gilead, Abbott, GSK, Merck
<i>D. Burger</i>		
<i>D. Burger</i>	Drugs or consumables for research	<i>Cipla</i>
<i>D. Burger</i>	Fees for consulting	Roche, BMS, GSK, Merck

Names	Type of interest	Name of commercial entity	Belongs to you or partner or unit	Current interest ( or year ceased)
<i>Edmund Capparelli</i>	Support of research - Kaletra protein binding in pregnancy	Abbott	Self	On going
	Consulting - re NRTI pharmacology	Glaxo-Smith Kline	Self	2003

	Consulting - PK study design and population PK analysis	Pfizer	Self	2005
	Membership DSMB - Nelfinavir PK in pregnancy	Pfizer	Self	On going
	Consulting - PK analysis for tipranavir and nevirapine	Baehringer-Igelhin	Self	2006
<i>Mark Mirochnick</i>	Research support	GlaxoSmithKline	Self	2006
<i>Rafaella L'Homme</i>	Pilot bioequivalence trial pedimmune baby and junior	Cipla	Partner	Result accepted for publication already
<i>Rafaella L'Homme</i>	CHAPASI PI sub-study Pedimine baby and junior	Cipla	Partner	2006
<i>A. Kekitinwa</i>	Substudy of Arrow PK scored ABC/3TC in Mulago	GSK	No	Not yet started
<i>D. Gibb</i>	CHAPASI trial, Zambia (PK)	Cipla	MRC, UK sponsored trial, EDCTP funded 2006 -2007	
	GSK Sub-study in Arrow Trial (PK scored 3TC, ABC, Combivir) PENTA 15 in trial (on going)	GSK providing drugs and contributes to PK Sub-study ... GSK providing drugs	MRC, UK sponsoring trial; MRC and DFID funded PENTA sponsoring	Planned 2008 ongoing
<i>Harry Moultrie</i>	Research - PACTG1020 <sup>a</sup> - Atazanavir			2006
	Research - TIBOTEC TMC114	TIBOTEC		2006
	Research PACTG 1060			2006
	Research NEVEREST	BMS		
	Research - TB-PK study			2006

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