Paediatric HIV Resistance

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health
Department:
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REPUBLIC OF SOUTH AFRICA

ANTIRETROVIRAL DRUG DOSING CHART FOR CHILDREN 2013

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

	Abacavir (ABC)		Lamivudine (3TC)		Efavirenz (EFV)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Stavudine (d4T)	Didanosine (ddI)	Nevirapine (NVP)	Zidovudine (AZT)	
Target Dose	8mg/kg TWICE daily **OR** ≥10kg: 16mg/kg ONCE daily		4mg/kg TWICE daily **OR** ≥10kg: 8mg/kg ONCE daily		By weight band **ONCE** daily	300/75mg/m²/dose LPV/rtv **TWICE** daily	ONLY as booster for LPV/rtv when on Rifampicin **TWICE** daily (0.75xLPV dose bd)	1mg/kg/dose **TWICE** daily	180-240mg/m²/dose **ONCE** daily	160-200 mg/m²/dose **TWICE** daily (after once daily lead-in x 2 wks)	180-240mg/m²/dose **TWICE** daily	**Target Dose**
Available Formulations	Sol 20mg/ml Tabs 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg		Sol. 10mg/ml Tabs 150mg (scored), 300mg, ABC/3TC 600/300mg		Caps 50,200mg Tabs 50,200, 600mg (not scored)	Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg	Sol. 80mg/ml	Sol. 1mg/ml Caps 15,20,30mg	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored), AZT/3TC 300/150mg	**Available Formulations**
Wt. (kg)	**Currently available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed**											**Wt. (kg)**
<3	**Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg**											**<3**
3-3.9	2ml bd		2ml bd		**Avoid using when <10kg or <3 years:** dosing not established	*1ml bd	1ml bd	6ml	Avoid	5ml bd	6ml bd	**3-3.9**
4-4.9												**4-4.9**
5-5.9	3ml bd		3ml bd			*1.5ml bd	1.5ml bd	**7.5mg bd:** open 15mg capsule into 5ml water: give 2.5ml	100mg od: (2x50mg tabs)			**5-5.9**
6-6.9									125mg od: (1x100mg + 1x25mg tabs)	8ml bd	9ml bd	**6-6.9**
7-7.9	4ml bd		4ml bd					**10mg bd:** open 20mg capsule into 5ml water: give 2.5ml				**7-7.9**
8-8.9											1 cap bd OR 12ml bd	**8-8.9**
9-9.9												**9-9.9**
10-10.9	Choose only one option: 6ml bd OR 2x60mg tabs bd	Choose only one option: 12ml od OR 4x60mg tabs od	Choose only one option: 6ml bd	12ml od	200mg nocte (1x200mg cap/tab)	2ml bd	1.5ml bd	**15mg bd:** open 15mg capsule into 5ml water	150mg od: (1x100mg + 1x50mg tabs)	10ml bd		**10-10.9**
11-13.9												**11-13.9**
14-16.9	8ml bd OR 2.5x60mg tabs bd	5x60mg tabs od OR 1x300mg tab od OR 15ml od	½ x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od	300mg nocte: (200mg cap/tab + 100mg cap/tab)	Choose one option: -2.5ml bd -100/25mg **paeds tabs:** 2 bd -200/50mg **adult tabs:** 1 bd	2ml bd	**20mg bd:** open 20mg capsule into 5ml water (if the child is unable to swallow a capsule)	175mg od: (1x100mg + 1x50mg + 1x25mg)	1 tab am ¾ tab pm OR 15ml bd	2 caps am 1 cap pm OR 15ml bd	**14-16.9**
17-19.9												**17-19.9**
20-22.9	10ml bd OR 3x60mg tabs bd	1x300mg tab + 1x60mg tab od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 30ml od		Choose one option: -3ml bd - 100/25mg **paeds tabs:** 2 bd - 200/50mg **adult tabs:** 1 bd	2.5ml bd		200mg od: (2x100mg tabs)		2 caps bd OR 20ml bd	**20-22.9**
23-24.9		1x300mg tab + 2x60mg tabs od										**23-24.9**
25-29.9	1x300mg tab bd	2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od OR 1xABC/3TC 600/300mg tab od	400mg nocte: (2x200mg caps/ tabs)	Choose one option: - 3.5ml bd - 100/25mg **paeds tabs:** 3 bd - #200/50mg **adult tabs:** 1 bd + 100/25mg **paeds tabs:** 1 bd	3ml bd	**30mg bd**	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd	**25-29.9**
30-34.9						Choose one option: - 4ml bd - 100/25mg **paeds tabs:** 3 bd - #200/50mg **adult tabs:** 1 bd + 100/25mg **paeds tabs:** 1 bd						**30-34.9**
35-39.9						Choose one option: - 5ml bd - 200/50mg **adult tabs:** 2 bd	4ml bd					**35-39.9**
>40					600mg tab nocte							**>40**

od = once a day
(usually at night)
bd = twice a day

* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.
# Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm

Weight (kg)	3-4.9	5-9.9	10-13.9	14-29.9	≥30
Cotrimoxazole Dose	2.5ml od	5ml od	5ml od	10ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5ml od	2.5ml od	5ml od	5ml od	10ml or 1 tab od

	Choose only one option:		Choose only one option:	
10-10.9	6ml bd OR 2x60mg tabs bd	12ml od OR 4x60mg tabs od	6ml bd	12ml od
11-13.9				
14-16.9	8ml bd OR 2.5x60mg tabs bd	5x60mg tabs od OR 1x300mg tab od OR 15ml od	½ x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od
17-19.9				
20-22.9	10ml bd OR 3x60mg tabs bd	1x300mg tab + 1x60mg tab od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 30ml od
23-24.9		1x300mg tab + 2x60mg tabs od		
25-29.9	1x300mg tab bd	2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od OR 1xABC/3TC 600/300mg tab od
30-34.9				
35-39.9				
>40				

Preliminary evaluation of referrals for Antiretroviral Therapy (ART) Treatment Failure in a Public Access paediatric ART Program in KwaZulu Natal, South Africa.

- Evaluation of the first fifteen patients referred to the Paeds ID unit at King Edward VIII Hospital:
- In 33% (5) of children the viral load was less than 1000 copies/ml at the time of resistance test, however the average last VL at the referral hospital/clinic was 18 633 c/ml (range 3251-52275)
- The mean duration between the last viral load and resistance testing was 8.3 weeks (range 1-27 weeks)

- Of the children with a detectable viral load:
  - 27% (4) of children had no mutations with an average VL 43 507 c/ml (range 22 022 – 59 000)
  - 13% (2) of children had a single mutation (M184V), and
  - 27% (4) of children had multiple mutations (3 NRTI + NNRTI mutations and 1 NRTI + PI mutations).

Conclusions

- The average duration on therapy for the children with multiple mutations was 152 weeks compared to 140 weeks for all subjects.

- The majority (73%) of patients referred either suppressed an repeat testing or had no or a single mutation at the time of resistance testing, emphasising the need for intensive adherence counselling prior to performing resistance testing.

When should a HIV infected Child have an HIV resistance testing

- Infant vertically infected by a mother with treatment failure.

- Child failing a PI based regimen – despite adequate adherence.

- Child with a complicated NRTI history

What to do with a Resistance test result

- Must ensure that the patient is going to be compliant to the new regimen

- Must have an available third line regimen to put the patient on.

ANTIRETROVIRAL DRUG FORMULATIONS AVAILABLE IN SA

DRUG	FORMULATION	MANUFACTURER	RECOMMENDED FORMULATION	R	WR	UK
ATAZANAVIR CAPSULES	300MG	ASPEN		X		
ATAZANAVIR CAPSULES	200MG	ASPEN		X		
ATAZANAVIR (CAPSULES)	150MG	ACTIVO, BMS		X		
ATAZANAVIR (CAPSULES)	100MG	ACTIVO, BMS			X	
ATAZANAVIR	PAED FORMULATION?					X
DARUNAVIR	300MG	ASPEN		X		
DARUNAVIR	75, 150	ASPEN			X	
FOSAMPRENAVIR	700MG	GSK		X		
FOSAMPRENAVIR SUSPENSION	50MG/ML	GSK		X		
TENOFOVIR	300MG	ASPEN, CIPLA, NOVAGEN, SONKE		X		
TENOFOVIR TABLET	250, 200 ,150	CIPLA, NOVAGEN			X	
TENOFOVIR ORAL POWDER	40mg/scoop	ASPEN			X	
RALTEGRAVIR	400MG	MSD*		X		
RALTEGRAVIR	100MG	MSD	Application for chewable, scored tablet		X	
RALTEGRAVIR	25mg	MSD	Application for chewable tablet		X	
ETRAVIRINE	200, 100mg	PHARMACARE		X		
ETRAVIRINE	25MG				X	

Third line Drugs in Children

Etravirine in Paediatrics

- Not FDA approved for use in children <6yrs and < 16 kg

- In ongoing phase II trial (PIANO) in treatment experienced children, 6 to 17 years
- Phase I and II IMPAACT P1090, treatment-naive/treatment-experienced, 2 months to 6 years, started

Etravirine Paediatric Doses
Dispersible tablets: 25mg (scored), 100mg

Age or Weight Band	Dose	Tablets
> 6 – 17 years	5.2 mg/kg bd	
16 to < 20kg	100mg bd	4 tablets 25mg bd or 1 tablet 100mg bd
20 to < 25kg	125mg bd	5 tablets 25 mg bd or 1 tablet 100mg + 1 tablet 25 mg bd
25 to < 30kg	150mg bd	6 tablets 25 mg bd or 1 tablet 100mg + 2 tablets 25 mg bd
≥30kg	200mg bd	8 tablets 25 mg bd or 2 tablets 100mg bd

Darunavir and Paediatrics

- **Daurinavir** currently indicated for the treatment of paediatric patients **≥ 3 years of age** when co-administered with ritonavir (licensed Dec 2008 FDA, awaiting EMEA registration, not MCC approved in SA)
- Ages < 3 years: Potential issues with seizures and death – in a rat model .
- Must be co-administered with ritonavir

FDA approved Dosages for Darunavir (with RTV) in paediatrics

Recommended dose for paediatric patients (aged 6 to < 18 years)

- ≥ 20 kg to < 30 kg: 375 mg DRV + 50 mg RTV bd
- ≥ 30 kg to < 40 kg: 450 mg DRV + 60 mg RTV bd
- ≥ 40 kg: 600 mg DRV + 100 mg RTV bd

- *Where possible give RTV 100mg capsule (even if 'overdosing')*
- *Child needs to be able to swallow tablets*
- *Should be taken twice daily and with food*
- *Do not use once-daily dosing in children <12 years of age or in any patient <18 years of age who is treatment experienced.*
- *Once-daily dosing (DRV 800 mg + RTV 100 mg) may be used in treatment naive paediatric patients 12–18 years of age and body weight >4 0 kg*

Dossier for the oral suspension (100mg DRV/ml) for treatment experienced children weighing ≥ 10kg has been submitted for approval.

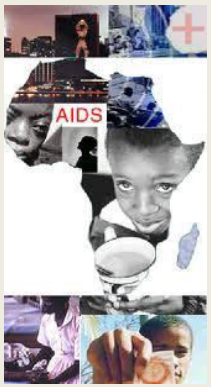
DRV suspension (100mg DRV/ml)

Recommended dosages

(to be taken within 30 minutes of a meal)

Weight (kg)	DRV dose bd (mg)	DRV dose bd (ml)	RTV dose bd (mg)	RTV dose bd (ml)
10 – 10.9	250	2.6	33	0.4
11 – 11.9	275	2.8	36	0.4
12 – 12.9	300	3.0	38	0.5
13 – 13.9	325	3.2	43	0.5
14 – 14.9	350	3.6	46	0.6
> 15 – 29.9	375	3.8	50	0.6

Raltegravir – paediatric studies



IMPAACT P1066

- Investigating RAL in de-escalating age bands
- Children < 2 years are now being enrolled in study to determine dose of granule formulation.

IMPAACT P1097:

- PK and safety study for neonates

After reviewing PK and safety data from both trials, Merck is planning a study of infants born to HIV-positive mothers from immediately after birth until HIV status confirmed.

Raltegravir Dosing Information:

Chewable Tablets (25mg, 100mg) and 400mg Tablets

Recommended dose by weight (2 – 12 yrs): 6 mg/kg BD

Weight Range in kilograms	Dose in mg BD	Chewable tablets per dose
7 - 9.9	50	2 x 25 mg
10 -13.9	75	3 x 25 mg
14 -19.9	100	100 mg
20 - 27.9	150	100 mg + 2 x 25 mg
28 - 39.9	200	2 x 100 mg
> 40	300	3 x 100 mg
> 12 YEARS	400	N/A

Current Recommendation for Raltegravir and Rifampin

- Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (eg, rifampicin) due to reduced plasma concentrations of raltegravir
- In updated US label, the recommended dosage of ISENTRESS is 800 mg twice daily during co-administration with rifampin
- In EU label:
  - Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered

Raltegravir

- Raltegravir is a potent integrase inhibitor with demonstrated efficacy in both first-line and salvage treatment
- Safety and tolerability has been consistently good
- Low-barrier to resistance, and should be used with at least two active antiretroviral therapy agents
- Should be used with caution in combination with Rifampicin
  - Rifampicin is an inducer of uridine dehydrogenase (UGT1A1) and may cause decreased levels of RAL

- Etravirine: >6yrs / > 16kg (swallow a tab)
- Daurinavir: >3yrs / >12kg (swallow a tab)
- Raltegravir: >2yrs / 14 kg (swallow a tab)

(DRV oral solution and Raltegravir granules – not licenced in SA only recently registered with the FDA)

TREATMENT OPTIONS FOR THIRD LINE TREATMENT FAILURE IN YOUNG CHILDREN ARE LIMITED

Referral Pathway for children with HIV Virological Treatment Failure in Kwa-Zulu Natal

- General Measures for treatment failure:

- All treatment centres should develop systems to identify patients with detectable viral loads as soon as possible.

- Any patient with a detectable viral load should receive enhanced adherence counselling.

- Counselling should ideally be conducted by staff with which the caregiver/patient has developed a trusting relationship.

- Assess for common causes of poor adherence in children:
  - Inappropriate formulation – esp Kaletra syrup in an older child or alluvia (200/50mg tablet) in child who cannot swallow the adult tablet.
  - Inappropriate dose – check that the appropriate dose has been prescribed and dispensed.
  - Inappropriate administration – crushing of film coated tablets, incorrect volumes given.
  - Change in caregiver or change in the health of the caregiver.
  - Unstable home environment.
  - Non-disclosure of status of the child.
  - Treatment fatigue.
  - Do-not believe that the medication is working.

- Counselling should be conducted in a non-threatening manner, focusing on addressing the possible reasons and potential solutions for poor adherence, rather than apportioning blame.

- Use objective criteria to assess adherence eg adherence to appointment dates, pill counts.

- Refer the caregiver/patient to appropriate support services eg social worker, psychologist where appropriate.

Treatment Failure on Efavirenz (or NVP) Regimen

- All patients should be referred for intensified adherence as outlined above.
- Address and rectify potential reasons for poor adherence.
- Monthly follow-ups focusing on reinforcing adherence, accessing adherence to visit dates
- Repeat HIV Viral load after 3 months of intensified adherence
- If still has HIV Viral load >1000 copies/ml – discuss with clinician experienced with Paediatric ART or refer to mother hospital for assessment.
- Change to second-line ART when all measures have been put in place to ensure optimal adherence.

Treatment Failure on Lopinavir/rtv Regimen

- All patients should be referred for intensified adherence as outlined above.
- Address and rectify potential reasons for poor adherence.
- Monthly follow-ups focusing on reinforcing adherence, accessing adherence to visit dates.
- Repeat HIV Viral load after 3 months of intensified adherence at the ART site.
  - If viral load decreases to <10 000 copies/ml – continue to support adherence to medication
  - If viral load remains >10 000 copies/ml – refer to mother hospital for assessment and evaluation

- Referral for Genotype testing:
  - Area 1: Edendale Hospital- ARV Clinic: Dr Spicer/Dr Krishna
  - Area 2/3: King Edward VIII Hospital – Paeds ID Clinic: Dr Archary/Dr Lawler/Dr Pillay

Request for Genotype Testing

KZN Branch National Health Laboratory Services	**Laboratory Barcode**

Surname		Name	
Age	M Y	Gender	M F
DOB	d d m m y y y y	SA ID	
Hospital		Ward/Clinic	

WHO Stage at Start of Treatment		Any New WHO Stage Defining Diagnosis?	Date and Diagnosis

Date	**Viral load**	**CD-4**	**CD-4%**	Reason for Detectable VL (i.e. Non-adherence, treatment break, virological failure)	Weight (Kg)
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					
d d m m y y					

ARV	**Start Date**	**Stop Date**	Reasons for changing/Toxicities
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	
	d d m m y y	d d m m y y	

TB Treatment			**Start Date**	**Stop Date**	Reasons for changing/Toxicities
REG 1	**REG 2**	**MDR**			
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	
			d d m m y y	d d m m y y	

Paediatric Section

Has Mother ever had SD NVP?	No		Yes		Date of SD Nevirapine		
Was Mother on PMTCT?	No		Yes		Gestation when started ARV's:		
Was Mother on HAART?	No		Yes		Date Started		
Viral Suppression at Delivery?	No		Yes		Viral load	Date	
NVP given to Baby?	No		Yes		NVP duration Weeks	6 Week PCR?	Result

Adult Section

Previous Mono or Dual ARV Therapy?	No		Yes		Dates and Regimen	
Female Px: Previous SD NVP	No		Yes		Date	
Female Px: Previous PMTCT Regimen?	No		Yes		Dates and Regimen	
Female Px: Currently Pregnant	No		Yes		Gestation	

General Section

Previous TB treatment	No		Yes		Dates and Regimen			
Current TB Treatment	No		Yes		Dates and Regimen			
HAART Interruption	No		Yes		Dates and Reason			
Serious Side Effects	No		Yes		Dates and Diagnosis			
OI in last 6 months	No		Yes		Dates and Diagnosis			
Last dose of HAART	Date and Time							
HBV sAg	Not tested		Negative		Positive		Date first Positive	

Recent Blood Results

HB	g/dl	Date	Creatinine	µmol/L	Date	Calc.GFR		Date	ALT	U/L	Date

Follow up Section

Mutations found	Wildtype		NRTI		NNRTI		PI	
Resistant ARVs			*	*	*	*	*	
Susceptible ARVs								
Regimen Change	Date	New HAART regimen						
Follow up 1	Date	Side Effects, Adherence, Other Issues						
Follow up 2	Date	Side Effects, Adherence, Other Issues						
Follow up 3	Date	Side Effects, Adherence, Other Issues						

*H= High-Level Resistance, I= Intermediate Level Resistance, L= Low-Level Resistance

Current medications (Anti-epileptic, Steroids, Warfarin, Statins)	Yes	No	list	
Traditional remedies/immune boosters	Yes	No	list	
Partner on ARV's	Yes	No		
Significant diarrhea or vomiting causing malabsorption	Yes	No		
Patient estimate of adherence in last 3 months	>90% doses taken	<90%	<50%	
Alcohol consumption	None	Average	Heavy (>3 drinks most days of week)	

SAMPLES WILL NOT BE PROCESSED IF ANY INFORMATION IS MISSING.

	Name	**Surname**	**Date**	**Signature**	**Cell/Tel Number**
Clinician					

Motivation for Third line regimen

REQUEST FOR THIRD LINE ANTIRETROVIRAL THERAPY

PATIENT DETAILS

Patient First Name			
Patient Surname			
Identity number		Patient number	
Date of Birth	Day/month/year		
Age			
Weight		**Height (children)**	
Gender	M/F		

FACILITY DETAILS

Facility Name	
Authorised Prescriber	
Contact Number	
Email Address	
Date	
Signature of Authorised Prescriber	
Date on which ART was initially started	

Past medication history:

Medication	Dose	Route	Interval	Duration	Discontinuation	
					Date mm/yy	Reason
			24 hourly	< 6 Mo 1-5 y > 5y	/	
			24 hourly	< 6 Mo 1-5 y > 5y	/	
			24 hourly	< 6 Mo 1-5 y > 5y	/	
			24 hourly	< 6 Mo 1-5 y > 5y	/	
			24 hourly	< 6 Mo 1-5 y > 5y	/	

Reason for discontinuation codes: SE = Side effect, AL = Allergy, FC = Formulary change, NC = Non adherent

Children: PMTCT history

Was child breastfed?

Did child receive nevirapine at birth and during breastfeeding?

CD 4 count				**Viral load**	
		Children			
Last 3 CD 4 counts results:		CD4%		*Last 3 VL results:*	
Date:		Date:		Date:	
Date:		Date:		Date:	
Date:		Date:		Date:	

Laboratory Resistance test attached: y/n	Results of Viral Resistance Test
Most recent available tests: ALT CrCl Neutrophil count	
Concomitant medication and indication Children: Is child able to swallow a tablet? y/n	
For office use only:	
Date received:	
Recommendation: Date:	

Submit completed forms to:

The Secretariat: Third Line ARV Peer Review Committee (PRC)

jamalk@health.gov.za

- Completed motivation form and genotype should be sent to: jamalk@health.gov.za
- A recommendation will be communicated directly to the site.
- Recommended regimen will be sent directly to the referring hospital.

Summary

- Third line options in children are limited.

- All efforts should be made to ensure durability of available regimens.