Adolescent Guidelines

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Paediatricians View

Status of Adolescent Guidelines
WHO Consolidated Guidelines - 2013

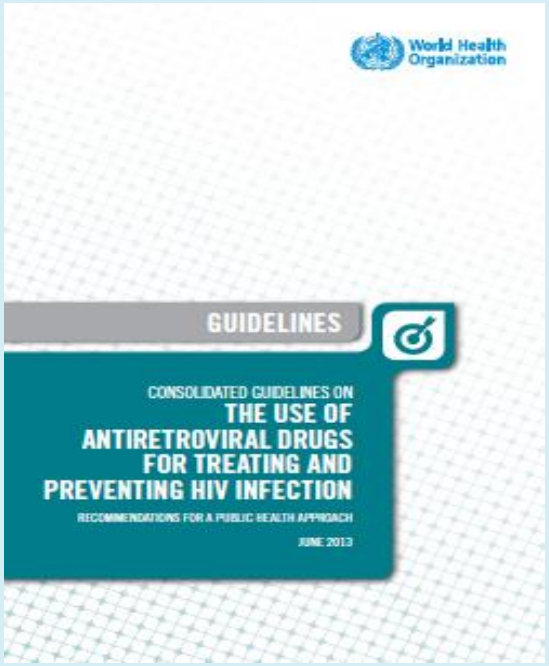


Table 4.2. Key recommendations and guidance for adolescents

Chapter	Topic	Chapter subsections
Chapter 5: HIV diagnosis and ARV drugs for HIV prevention	HIV testing and counselling in health facilities	Section 5.1.2
	Community-based HIV testing and counselling	Section 5.1.3
	HIV testing and counselling in specific populations: Adolescents	Section 5.1.4.4
Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment	General care for people living with HIV	Section 6.3
	Preparing people living with HIV for ART	Section 6.4
	What to expect in the first months of ART	Section 6.5
Chapter 7: Antiretroviral therapy	When to start ART in adults and adolescents	Section 7.1.1
	First-line ART for children three years and older (includes adolescents)	Section 7.2.4
	TB co-treatment in children with HIV	Section 7.2.5
	Monitoring response to ART and the diagnosis of treatment failure (includes adolescents)	Section 7.3
	Monitoring and substitutions for ARV drug toxicities (includes adolescents)	Section 7.4
	Key ARV drug interactions (includes adolescents)	Table 7.16
	Second-line ART for adults and adolescents	Section 7.5.1
	Second-line ART for children (includes adolescents)	Section 7.5.2
	Third-line ART (includes adolescents)	Section 7.6

Chapter	Topic	Chapter subsections
Chapter 8: Managing common coinfections and comorbidities	Prevention, screening and management of coinfections	Section 8.1
	Preventing and managing other comorbidities and chronic care for people living with HIV	Section 8.2
	Nutritional care and support among adolescents and adults living with HIV	Section 8.2.4.1
Chapter 9: Guidance on operations and service delivery	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Adherence to ART: Adolescents	Section 9.2.1
	Decentralization and Task shifting	Sections 9.4.3 and 9.5.2
Chapter 10: Guidance for programme managers	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Implementation considerations for key recommendations for programme managers: raising the CD4 threshold for initiating ART in adults and adolescents from 350 to 500 cells/mm³	Section 10.6; Box 10.2
Chapter 11: Monitoring and evaluation	Monitoring implications of new recommendations	Section 11.2
Annexes	Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children	Chapter 12
	Annex 2. Algorithm for the 2013 recommendations for adults and adolescents	
	Annex 3. Dosages of recommended ARV drugs for adults and adolescents	

Status of Adolescent Guidelines South Africa 2013

- Short version – ART Guidelines 2013 - In between adult and paediatric guidelines - inconsistencies / regimens poorly defined
- Full version of the guideline – not released – included into the STG – EDL – Paediatric Hospital Edition 2013
- Plan for a consolidated guideline for 2015 – including management of paed/adolescent/adults and pregnant patient in one guideline.

Definitions

- Children (Law) - below the age of 18 years, unless, under the law applicable to the child, majority is attained earlier.

- Adolescents - aged 10–19 years.
  - Early Adolescents – ≥ 10 – < 14 years
  - Late Adolescents – ≥ 15 – 19 years

- Young people - aged 10–24 years.

- Legal Issues
  - Age of consent for HIV testing
  - Age of consent for medical treatment

    12 years
  - Age of consent for medical proceedures /operations

    18 years
  - Age of sexual consent

    16 years
- Health Care systems issues
  - Most Paediatric services – cut-off is 12 yrs
  - Most centers have no dedicated Adolescent wards

When to start ART

WHO 2013	SA Guideline 2013
CD4 count ≤ 500 cell/mm3 As a priority start individuals with severe disease (WHO stage 3 and 4 or CD4 ≤ 350 cell/mm3	CD4 count ≤ 350 cell/mm3* irrespective of clinical staging
Initiate regardless: Active TB disease HBV Co-infection with severe chronic liver disease Pregnant and breastfeeding women with HIV HIV-positive individual in sero-discordant partnership	Initiate regardless: All types of TB WHO stage 3 or 4 disease irrespective of CD4 count
	*To change to ≤ 500 cells/mm3 from 1 january 2013

Paediatric or Adult WHO Staging Criteria

- Paediatric WHO staging - <15yrs
- Adult WHO staging - > 15yrs

Adults and adolescents[a]	Children
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/or chronic thrombocytopaenia (<50 x 10^9/l)	Unexplained moderate malnutrition[b] not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) or chronic thrombocytopaenia (<50 x 10^9/l)

Adults and adolescents[a]	Children
Clinical stage 3	
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4[c]	
HIV wasting syndrome *Pneumocystis (jirovecii)* pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal *Salmonella*) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition[d] not responding to standard therapy *Pneumocystis (jirovecii)* pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Lymphoma (cerebral or B-cell non-Hodgkin) HIV-associated nephropathy or cardiomyopathy

What to start
WHO Guidelines 2013

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults **(Including pregnant and breastfeeding women and adults with TB and HBV coinfection)**	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)

What to start – SA Guidelines

	Age	Regimen
NON-PREGNANT	≥ 15 yrs and ≥ 40 kg	TDF / FTC / EFV (FDCtee)
	< 15 yrs or < 40 kg	ABC / 3TC / EFV
PREGNANT	≥ 12 yrs and ≥ 40 kgs	TDF / FTC / EFV (FDCtee)
	< 12 yrs or < 40 kgs	ABC / 3TC / EFV

Available TDF Formulations in SA

Table 2 **Dosing Recommendations for Pediatric Patients ≥2 Years of Age and Weighing ≥17 kg Using VIREAD Tablets**

Body Weight Kilogram (kg)	Tablets Once Daily
17 to <22	150 mg
22 to <28	200 mg
28 to <35	250 mg
≥35	300 mg

Viread Package insert

Estimating Glomerular Filtration rate in adolescent patients

Name	Formula
2009-Schwartz	eGFR = k * height/PCr k = 36.5
Schwartz-Lyon	eGFR = k * height/PCr k = 36.5 in males aged >13 years k = 32.5 in others

Height is expressed in cm. PCr = Plasma creatinine, expressed in µmol/L.
doi:10.1371/journal.pone.0053439.t002

De Souza VC, Rabilloud M, Cochat P, Selistre L, et al. (2012) Schwartz Formula: Is One k-Coefficient Adequate for All Children?. PLoS ONE 7(12): e53439. doi:10.1371/journal.pone.0053439
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0053439

Counahan-Barrat Formula

(Height (cm) x 40) / Serum Creatinine (umol/L)

Slightly over cautious - < 80 – refer for assessment

Issues of Bone Mineral Density

- As yet true effect remains unresolved – adolescence is associated with rapid bone deposition.
- Viread Study 352 (2yrs-12yrs) Total body BMD gain was less in the TDF arm compared to the AZT or D4T group.
- Viread Study 321 (12yrs-18yrs) Mean rate of BMD gain was less at 48wks in TDF arm compared to placebo arm.
- In both trials – skeletal growth unaffected but markers of bone turnover ⇧ .
- Effects were more prominent in pre-pubescent adolescents (tanner stage 1-2)

	In the prepubertal stage 1, there may be fine vellus hair that is no different from that found over the abdominal wall	
	In stage 2, there is growth of sparse straight hair, primarily at the base of the penis or along the labia.	
	In stage 3, hair increases in quantity and is darker and curlier.	
	Stage 4 is characterized by pubic hair that resembles adult pubic hair, although the escutcheon covers a smaller area than seen in adults	
	Finally, in stage 5, pubic hair has increased further in volume, spread onto the medial thighs, and taken on characteristic male or female configuration.	

Tanner stage and HIV infected Children

- Children with HIV infection have delays both in the age of onset of puberty and in their progression through the pubertal stages.
- The median delay in pubertal onset is 2 years for girls and 1 year for boys.
- Entry into the late pubertal stages is delayed by about 2.5 years in girls and 1.5 years in boys.
- Children with increased immune system dysfunction tend to have the most substantial delays in pubertal development.

EFV Dosage

- Appropriate dose for patient
- >40kg – 600mg
- < 40kg

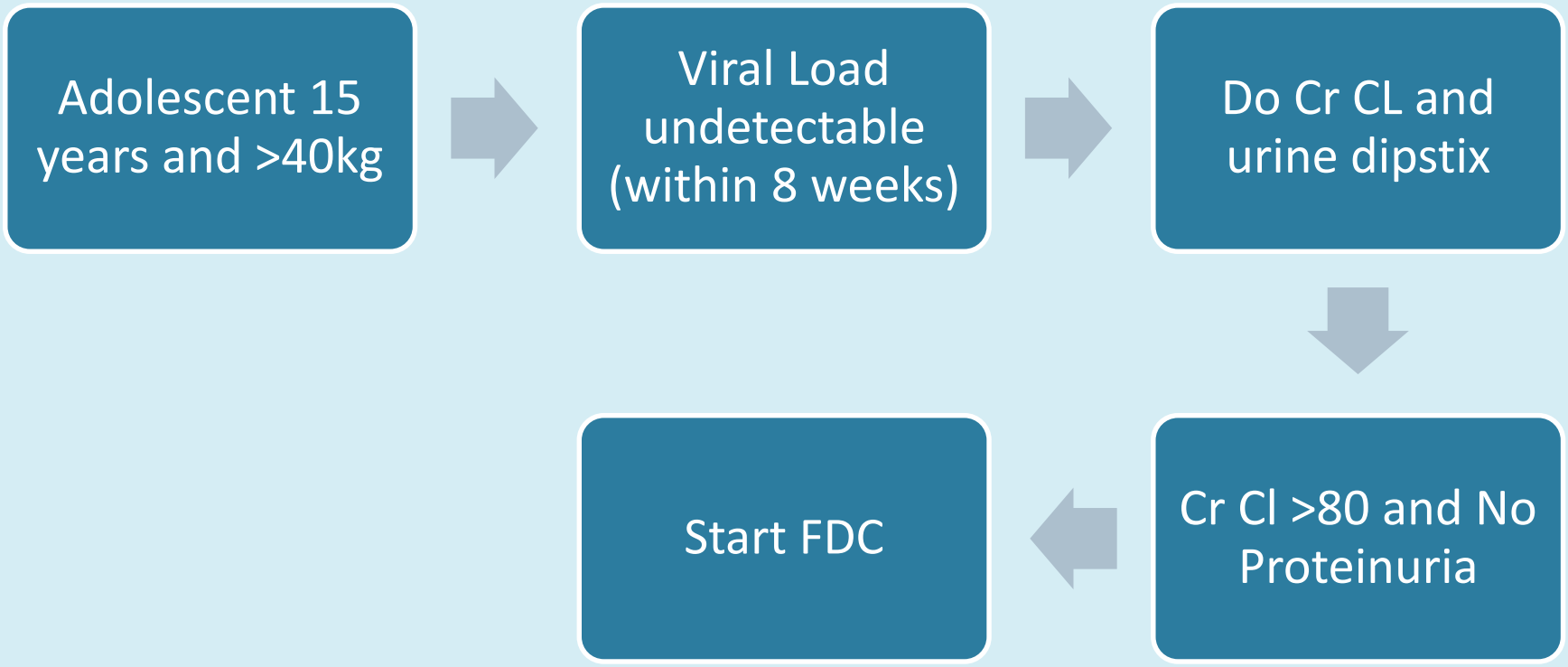
Weight range	Dosage
32.5 – 40 kg	400mg
25 – 32.5 kg	350mg
20 – 25 kg	300 mg

When to simplify

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	• Reduced risk of d4T-related toxicity • May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen)	• Aligned with adult regimens
LPV/r	No need to change, but **consider** substituting NVP or EFV for LPV/r if there is sustained virological response on LPV/r	• May improve adherence as a result of better palatability and use of fixed-dose combinations in more manageable formulations (once-daily scored tablets) • Reduced risk of metabolic alterations	• Aligned with adult regimens • Preserve PI for second-line ART • No cold-chain requirement • Reduced drug cost
AZT	No need to change but **may consider** changing to ABC or TDF	• May improve adherence as a result of once-daily dosing (if on EFV) • May reduce the risk of exacerbating anaemia	• Aligned with adult regimens
ABC	No need to change, but **can consider** changing to TDF, especially for adolescents weighing more than 35 kg	• Fixed-dose combinations can be used (if also on EFV)	• Aligned with adult regimens
NVP	No need to change, but **may consider** changing to EFV particularly from age 3 years	• May improve adherence as a result of once-daily dosing (if combined with ABC or TDF)	• Aligned with adult regimens

Transition from Paediatric ART regimens to Adolescent/Adult Regimens

Adolescents with an undetectable Viral load (< 50 copies/ml) and no side-effects on ABC + 3TC + EFV, can remain on the same regimen until the patient becomes eligible for the Fixed Drug Combination (FDC) – (TDF + FTC + EFV) at 15 years and > 40kg.

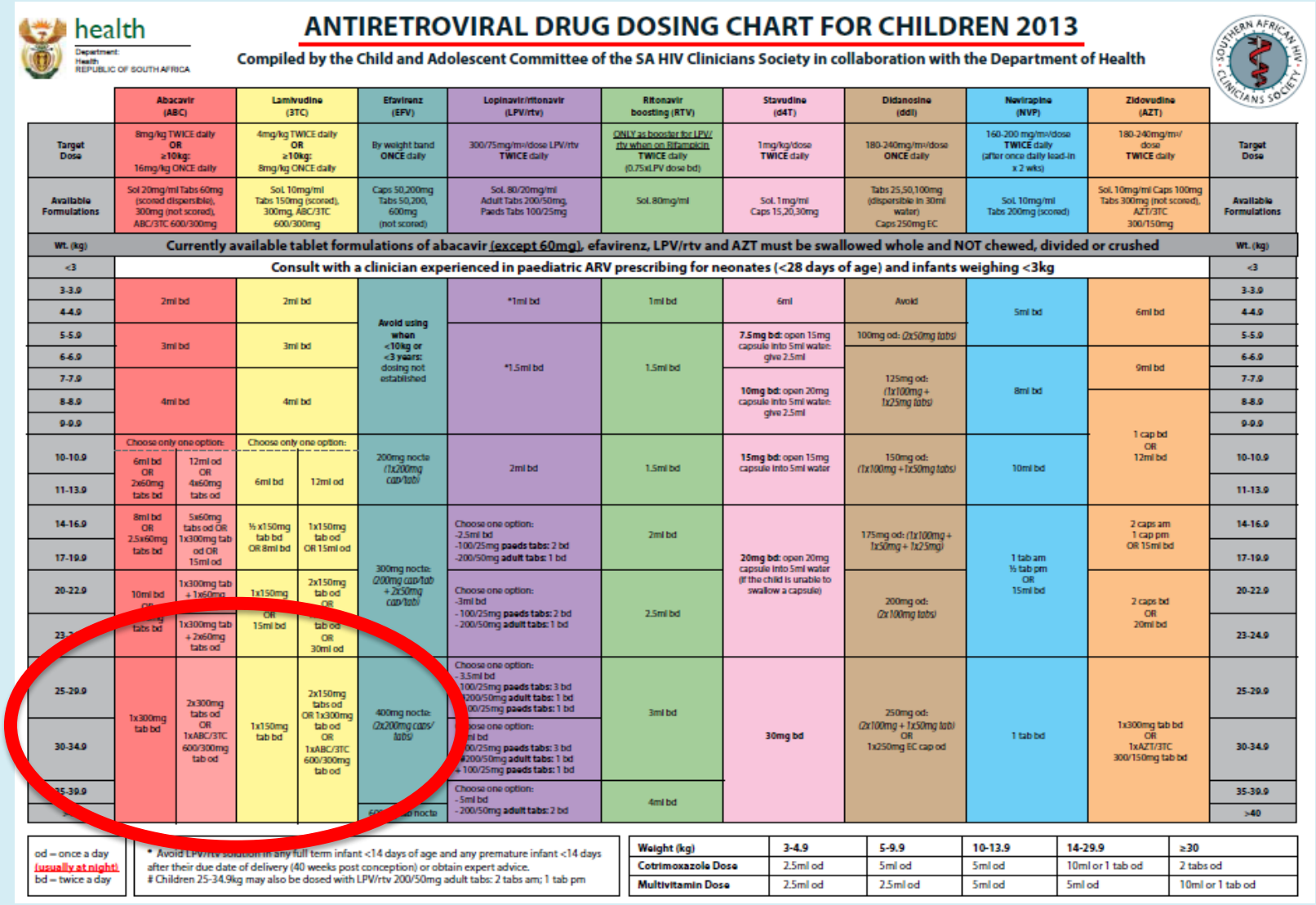

Adolescent 15 years and >40kg
Viral Load undetectable (within 8 weeks)
Do Cr CL and urine dipstix
Cr Cl >80 and No Proteinuria
Start FDC

What doses to use?

- > 40kg – $FDC_{(TEE)}$ 1 tablet daily

- < 40 kg

Paediatric or Adult treatment formulas



health
Department: Health
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 / 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 + 2x50mg 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 ½ 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 1x300mg tab + 1x60mg tabs bd / 1x300mg tab + 2x60mg tabs od	1x150mg OR 15ml bd	2x150mg tab od OR 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										23-24.9
25-29.9	1x300mg tab bd / 2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	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				ml bd 00/25mg **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			600 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

- > 25 kg – 40 kg

- ABC/3TC (600mg/300mg) 1 tablet daily
- EFV – 400mg daily (2 x 200mg tablets)

When to switch

Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome[b] occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm^3 **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm^3 or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure *(182)*. The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ARV regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

When to Transition to Adult Services

- Transition should be based on the maturity, developmental readiness and responsibility of the young person rather than chronological age.

- The aims of transition include increasing resilience and reducing risk taking behaviour including non-adherence, substance abuse and risky sexual behavior for young people, whilst offering an opportunity to increase autonomy, knowledge and life skills, linkages within the community and promote retention in treatment and care.

Summary of Treatment Guidelines

- Managed Transition from Paediatric – Adolescent – Adult treatment service.
- Becoming simpler with harmonizing of the treatment guidelines across the age ranges.
- Not to forget that adolescents have unique needs related to maintaining adherence, mental health and SRH needs

Key Populations – Are we doing enough?

- 4 Technical Brief for key populations:
  - HIV and young transgendered people
  - HIV and young men who have sex with men
  - HIV and young people who sex sex
  - HIV and young people who inject drugs

http://www.who.int/hiv/pub/guidelines/briefs_ykp_2014.pdf