SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

GUIDELINES FOR
ANTIRETROVIRAL THERAPY IN CHILDREN

As a result of the present high cost, antiretroviral therapy (ART) will be denied to the majority of HIV-infected children in sub-Saharan Africa. Access to ART is now a clear discriminator between the 'haves' and 'have nots'. While this situation is unacceptable, ART is becoming an increasing option in paediatric practice. Promoting affordable ART for children is a priority for clinicians, health administrators and the pharmaceutical industry.

The use of ART in children is a highly specialised field. Initial and ongoing management of HIV-infected children by a paediatrician experienced in this field is strongly recommended. If this is impossible, we recommend consultation with such a paediatrician before initiation of ART so that the child may benefit from the most optimal regimen. Certainly, when a clinician decides to change therapy, consultation with an experienced treater should occur in order to ensure maximum efficacy of the new regimen.

ART in children follows the same principles as in adults, but generally lags behind in terms of its application in paediatric HIV medicine. The reasons for this are complex and include a reluctance to use new medication in children before efficacy and safety have been confirmed in adults, the need to develop liquid formulations, and because dosage adjustments are necessary. As a result, there are fewer therapeutic options available for children.

VIRAL DYNAMICS: PERSPECTIVES IN CHILDREN

Viral loads in children are far higher in the first year of life than those found in adults and only decline to adult values by 2 - 3 years of age. By 2 months of age most HIV-infected infants have viral loads above 100 000 RNA copies/ml, ranging from undetectable to 10 million copies/ml of plasma. The mean viral load in the first year of life is 185 000 copies/ml. Generally, the higher the viral load, the more rapid the disease progression, although in children there is considerable variability. A median viral load of 330 000 copies/ml has been correlated with rapid progression and death in infants below 1 year of age.[1]

Viral load assays are of value in monitoring ART in order to assess the efficacy of the regimen. A combination of viral load assay and CD4+% is most predictive of mortality, as indicated in Table I.[2]

TABLE I. BASELINE CD4+% AND HIV COPY NUMBER: RISK OF DYING

HIV RNA (copies/ml)	Baseline CD4+%	Patients (*N*)	Deaths (%)
< 100 000	> 15	103	15
	< 15	24	63
>100 000	> 15	89	36
	< 15	36	81

Mean age 3.4 years, mean follow-up 5.1 years.[2]

GOALS OF THERAPY[3]

As in adults, the goals of paediatric ART are:

- Maximal and durable suppression of viral load.
- Restoration or preservation of immunological function (usually measured with CD4+ lymphocyte cell count).
- Improvement in clinical symptoms.
- Reduction in morbidity and mortality.

The overall objective of therapy is to enhance the quality and quantity of life and to promote physical, social and intellectual development of the child in the context of a functional family. A practical goal is to avoid hospitalisation by minimising the impact of intercurrent disease, thus keeping the child with his/her family. Finally, the wellbeing of a child impacts positively on the parents' wellbeing and a healthy parent is vital to the child.

Even in the absence of ARVs

- good supportive care
- aggressive treatment of intercurrent infections
- provision of nutritional support, and
- prevention of opportunistic infections

promote significant improvement in quality of life and survival.

IS THERE A ROLE FOR MONOTHERAPY?

ART guidelines do not recommend monotherapy because of lack of sustained benefit and the superior efficacy of combination therapy. These guidelines also do not recommend monotherapy. Nevertheless, because of the high cost of ARVs, monotherapy may be of benefit in selected situations where financial considerations preclude combination therapy. However, this is not optimal treatment and an expert in paediatric HIV therapy should be consulted in this regard.

COMBINATION THERAPY

As in adults, a combination of at least three drugs is considered optimal therapy.[3] The higher viral loads in children may make suppression of plasma HIV RNA to below the limits of detectability more difficult to achieve than in adults.

While triple therapy is the most common regimen, quadruple therapy in children under 1 year of age, with high viral loads, may have a role to play.

The rationale for combination therapy is to increase the likelihood of achieving undetectable plasma HIV RNA, thereby minimising the possibility of viral breakthrough and resistance. However, it is recognised that even partial viral suppression is usually accompanied by an improved clinical outcome.

ADHERENCE

Adherence to ART is vital for a successful outcome. The factors that impact on adherence are:

- Affordability of ART. Before initiating therapy, treaters should ascertain whether the parents/caregiver can afford a proposed regimen over a prolonged period of time.
- Motivation and commitment of caregiver/parent to the child's lifelong therapy. Adherence involves administering every dose of medication 1 - 3 times daily, every day of every year. Weekends away, schooling and other parental obligations need to be anticipated and planned for.
- Parental/caregiver understanding that poor adherence is the single most important factor associated with drug failure and resistance, and implies loss of future therapeutic options.

NOTE:

- *Good adherence should be emphasised at each visit. It is useful to compare ART with therapy for diabetes and hypertension, both of which may require lifelong therapy and where poor compliance is associated with disease progression.*
- *In addition, the treater should be aware that the doses might need to be modified at each visit as the child gains weight and grows.*

CLASSIFICATION OF HIV IN CHILDREN

The Centers for Diseases Control have utilised both clinical and immunological parameters for paediatric practice (Tables II and III).[4]

TABLE II. CLINICAL CATEGORIES FOR CHILDREN WITH HIV INFECTION

CATEGORY	CHARACTERISTICS
N	No signs or symptoms considered to be the result of HIV infection or only 1 condition listed in A
A (mild)	Two or more conditions listed below but none from B or C ■ Lymphadenopathy (≥ 0.5 cm at more than 2 sites; bilateral,1 site) ■ Hepatomegaly ■ Splenomegaly ■ Parotitis ■ Dermatitis ■ Recurrent or persistent upper respiratory tract infections, sinusitis, or otitis media
B (moderate)	Symptomatic conditions other than from A or C and attributed to HIV infection; including but not limited to: ■ Anaemia (< 8 g/l), neutropenia (< 1 000/mm^3), thrombocytopenia (< 100 000/mm^3) – persisting ≥ 30 days ■ Bacterial meningitis, pneumonia or sepsis (single episode) ■ Candidiasis, persisting > 2 months in children > 6 months of age ■ Cardiomyopathy ■ Cytomegalovirus (CMV) infection, onset < 1 month of age ■ Diarrhoea – recurrent or chronic ■ Hepatitis ■ Herpes simplex virus (HSV) stomatitis > 2 episodes within a year ■ HSV bronchitis, pneumonitis or oesophagitis with onset < 1 year of age ■ Herpes zoster (shingles) ≥ 2 episodes or > 1 dermatome ■ Leiomyosarcoma ■ Lymphoid interstitial pneumonitis (LIP) or pulmonary lymphoid hyperplasia complex ■ Nephropathy ■ Nocardiosis ■ Persistent fever (> 1 month) ■ Toxoplasmosis, onset < 1 month of age ■ Varicella, disseminated
C (severe)	Any condition listed below: ■ Serious bacterial infections, multiple or recurrent (at least 2 culture-confirmed episodes within a 3-year period) of: septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity ■ Candidiasis (oesophageal or pulmonary) ■ Coccidioidomycosis (disseminated) ■ Cryptococcosis (disseminated) ■ CMV disease with onset at age > 1 month (at site other than lymph nodes, spleen, liver) ■ Encephalopathy ■ HSV causing mucocutaneous ulcer persisting > 1 month, or bronchitis, oesophagitis, pneumonitis, oesophagitis in a child > 1 month ■ Histoplasmosis (disseminated) ■ Kaposi's sarcoma ■ Lymphoma: primary in brain, Burkitt's, immunoblastic, large cell, B cell or unknown ■ *Mycobacterium tuberculosis* (disseminated or extrapulmonary) ■ *Mycobacterium avium* complex or *Mycobacterium kansasii* (disseminated) ■ PCP ■ Progressive multifocal leukoencephalopathy ■ Salmonella septicaemia (recurrent) ■ Cerebral toxoplasmosis with onset > 1 month of age ■ Wasting syndrome in the absence of illness other than HIV that could explain the following: persistent weight loss > 10% of baseline, or downward crossing of at least 2 of the following percentiles on a weight-for-age chart (95th, 50th, 25th, 5th) in a child ≥ 1 year of age; or < 5th centile weight for height on 2 consecutive measurements ≥ 30 days apart plus (1) chronic diarrhoea (≥ 2 loose stools per day ≥ 30 days); or (2) documented fever ≥ 30 days intermittent or constant

TABLE III. IMMUNOLOGICAL CATEGORIES FOR CHILDREN WITH HIV INFECTION

	AGE OF CHILD					
	< 12 MONTHS		1 - 5 YEARS		6 - 12 YEARS	
IMMUNOLOGICAL CATEGORY	CD4+/ML	CD4+ %	CD4+/ML	CD4+ %	CD4+/ML	CD4+ %
1. No immunosuppression	≥ 1 500	≥ 25	≥ 1 000	≥ 25	≥ 500	≥ 25
2. Moderate immunosuppression	750 - 1 499	15 - 24	500 - 999	15 - 24	200 - 499	15 - 24
3. Severe immunosuppression	< 750	< 15	< 500	< 15	< 200	< 15

INDICATIONS FOR STARTING ART

Highly active antiretroviral therapy (HAART) should be used whenever possible for the best clinical results and to prevent resistance.

There are two distinct clinical settings in infants:

- Where HIV infection has been confirmed in infants < 3 months of age by one qualitative followed by a quantitative PCR test. This strategy is especially worthwhile if HAART can be given to this infant.
- Where HIV is identified later either because of symptomatic disease in the infant or child, or because of a positive diagnosis in the mother.

INDICATIONS FOR ART IN CHILDREN

- Any symptoms of HIV infection (clinical categories A, B, or C).
- Any evidence of CD4+ suppression (immune categories 2 or 3).
- An infant < 12 months of age.
- Any asymptomatic children over 12 months of age with an HIV RNA level > 100 000 copies/ml.

In any child, it may be beneficial to wait until compliance can be assured and the family has been adequately counselled and are ready for the rigours of ART.

INITIATION OF THERAPY

FIRST 1 - 2 VISITS (including visits to hospitalised children)

Counselling and information – topics to be covered include:

- HIV prognosis
- Treatment
- Adherence issues
- Drug formulations
- Taste issues (including taste test where appropriate).

NEXT VISIT

Graphically illustrate the drugs, how and when to take them, preferably with actual drugs or samples.

1 - 2 WEEKS LATER

A phone call to the caregiver/parent is recommended to discuss tolerance and adherence issues.

ONE MONTH AFTER STARTING TREATMENT

A general examination should be conducted by the clinician and blood tests carried out to monitor drug toxicity.
Tolerance and adherence issues should be discussed.

THREE MONTHS AFTER STARTING TREATMENT

A general examination should be conducted by the clinician and blood tests carried out to monitor drug toxicity.

Bloods should be taken for HIV viral load and CD4+ count.

Adverse effects, tolerance and adherence issues should be discussed.

THREE-MONTHLY THEREAFTER

A general examination should be conducted and blood tests carried out to monitor drug toxicity, the HIV viral load and CD4+ count. If the patient's results remain stable, clinical examinations and blood tests can be carried out 6-monthly.

Discuss adverse effects, tolerance and adherence issues with caregiver.

MONITORING: SPECIAL CONSIDERATIONS FOR CHILDREN

VIRAL LOAD

- For children on triple therapy, viral suppression of < 10-fold (1 log) and dual NRTI therapy < 5-fold (0.7 log) are not regarded as adequate therapeutic results.
- In children who have responded with durable but not absolute viral suppression, a reproducible increase > 3-fold (0.5 log) in children ≥ 2 years and > 5-fold (0.7 log) in infants < 2 years may be considered as indications to change ARVs.
- A repeat test is recommended whenever a routine measurement yields an unexpected result.
- Additional non-routine testing may be indicated if the clinical condition changes.
- Two measurements one month apart should be performed before instituting changes.

Note: Viral loads can be temporarily raised for up to a month by intercurrent infections or vaccinations.

NOTE 1

The percentage of children on triple therapy that achieve and maintain a plasma viral load of below 400 copies/ml varies from approximately 25% to 75%.

Patients should be sequentially tested using the same method and the same laboratory.

NOTE 2

Therapeutic options for children are limited. Because ART is currently a lifelong commitment, it may be preferable not to switch ARVs until definite evidence of clinical failure has occurred. Such evidence includes:

- *failure to thrive*
- *reappearance of 'refractory' oral candidiasis*
- *other intercurrent disease such as cryptosporidial diarrhoea, and*
- *invasive bacterial sepsis or neuro-developmental deterioration.*

CD4+ LYMPHOCYTE COUNTS AND PERCENTAGES

The CD4+ count should be measured whenever the viral load is determined, except when the viral load is repeated to verify an unexpected result.

CD4+ lymphocyte counts are much higher in infancy than adulthood but the CD4+ percentage remains constant. CD4+ percentages may be easier to work with, but CD4+ counts should also be used and knowledge of normal values for age is a prerequisite. A CD4+ percentage below 15% should be viewed in the same light as a CD4+ count < 200/µl in adults. (Refer Table III.)

CD4+ counts are useful for monitoring response to ARVs.

CD4+ counts can be temporarily lowered due to intercurrent infections or vaccinations and can take up to a month to recover.

Although there is a strong association between CD4+ percentage and the risk of opportunistic diseases, *Pneumocystis carinii* pneumonia in the first year of life may occur despite 'normal' counts for age.

It is important that all HIV-infected or -exposed children under 1 year of age should receive cotrimoxazole prophylaxis from 6 weeks of age. This can be stopped at 1 year, or when the diagnosis of HIV has been reasonably excluded.

HEIGHT AND WEIGHT

The 'Road to Health' chart is a valuable tool for monitoring the wellbeing of children. Failure to maintain growth is suggestive of progressive HIV disease or superimposed infection such as tuberculosis.

RECOMMENDED ARV REGIMENS

CHILDREN UNDER 3 MONTHS OF AGE

Recent data suggest that these children, if treated aggres-sively, can achieve viral suppression and normal immunity in a high percentage of cases[5] (Table IV).

TABLE IV. RECOMMENDED ARV REGIMENS IN CHILDREN UNDER 3 MONTHS OF AGE

Category I (NRTI – thymidine base)	Stavudine (d4T)
	Zidovudine (ZDV)
Category II (NRTI – other)	Didanosine (ddI)
	Lamivudine (3TC)
Category III (NNRTI)	Nevirapine (NVP)
Category IV (PI)	Ritonavir (RTV)
	Nelfinavir (NFV)
Category V (NRTI – new)	Abacavir (ABC)*

SUGGESTED DRUG REGIMENS

- 2 NRTIs (one from category I and one from category II)
  plus
  1PI (one from category IV) + ABC*
- 2 NRTIs (one from category I and one from category II)
  plus
  NVP
  plus
  ABC*
- 2 NRTIs
  plus
  1 PI
  plus
  1 NNRTI (one each from categories I - IV)

** Currently abacavir can be used in South Africa with Medicines Control Council (MCC) approval on a named patient basis. Phone (012) 312-0279.*

A 4-drug regimen may be more effective than the standard 3-drug regimen because of extremely high viral loads in young infants but should only be contemplated if parental commitment is obtained. This regimen will have long-term financial impact, as costs will increase dramatically as the child grows. The efficacy of downscaling to a 3-drug regimen awaits further studies. If cost constraints make the above regimens impractical, refer to Table VI.

DOSAGES FOR CHILDREN UNDER 3 MONTHS OF AGE (TABLE V)

TABLE V. DOSAGE OF ARVS IN INFANTS UNDER 3 MONTHS OF AGE (SEE TABLE VII FOR STORAGE AND COMMENTS)

DRUG	FORMULATION	DOSAGE
NRTI		
Zidovudine (ZDV) Retrovir®	Susp 10 mg/ml	4 mg/kg/dose 8 hrly until 29 days, then 160 mg/m²/dose 8 hrly
Didanosine (ddI) Videx®	Susp 10 mg/ml Tabs 25mg	50 mg/m²/dose 12 hrly
Stavudine (D4T) Zerit®	Susp 1 mg/ml	< 29 days: 0.5 mg/kg/ dose 12 hrly > 30 days: 1 mg/kg/ dose 12 hrly
Abacavir (ABC) Ziagen®	Susp 20 mg/ml	8 mg/kg/dose 12 hrly
Lamivudine (3TC)®	Susp 10 mg/ml	< 1 month: 2 mg/kg/ dose 12 hrly > 1 month: 4 mg/kg/ dose 12 hrly
NNRTI		
Nevirapine Viramune®	Susp 10 mg/ml	5 mg/kg/day x 14 days then 120 mg/m²/dose 12 hrly x 14 days then 200 mg/m²/dose 12 hrly
PI		
Ritonavir (RTV) Norvir®	Susp 80 mg/ml	> 1 month 450mg/m²/ dose 12 hrly
Nelfinavir (NFV) Vira-cept®	Powder 50 mg/g Tabs 250 mg	55 - 65 mg/kg/dose 12 hrly

Once the infant reaches 3 months of age, follow the dosages in Table VII.

CHILDREN OVER 3 MONTHS OF AGE (TABLE VI)

TABLE VI. RECOMMENDED ARV REGIMENS IN CHILDREN OVER 3 MONTHS OF AGE

Category I (NRTI - thymidine base)	Stavudine (d4T)* Zidovudine (ZDV)*
Category II (NRTI - other)	Didanosine (ddI)* Lamivudine (3TC)*§ Abacavir (ABC)*†
Category III (NNRTI)§	Nevirapine (NVP)* efavirenz (EFV)*‡§
Category IV (PI)	Ritonavir (RTV)* Nelfinavir (NFV) Saquinavir (SQV) (soft gel) Indinavir (IDV)

*Available in paediatric formulations.
†Currently abacavir can be used in South Africa with Medicines Control Council (MCC) approval on a named patient basis. Phone (012) 312-0279.
‡Efavirenz (EFV) is only available in capsule form. There are no data for children under 3 years of age.
§Require single mutation for development of resistance and therefore some experts only use them in regimens with a good chance of attaining undetectable viral loads.

PREFERRED REGIMENS

- 2 NRTIs (1 each from categories I and II) + 1 PI
- 2 NRTIs + EFV or NVP (1 each from categories I, II and III)

Note: EFV and NVP develop resistance rapidly if undetectable viral loads are not achieved; they should only be used for viral loads < 150 000 copies/ml.

ALTERNATIVE REGIMEN

- 1 NRTI + EFV or NVP + 1 PI (1 each from categories I + II + III + IV)

Note: although very potent, this regimen leaves few alternatives available for future use and should only be considered in special circumstances.

- ABC + ZDV + 3TC – for children with low viral loads.

DUAL NRTI: REGIMEN WHERE THERE ARE COST CONSTRAINTS (MORE AFFORDABLE, BUT SUBOPTIMAL)

d4T + ddI
ZDV + ddI
ZDV + 3TC*
d4T + 3TC*

*Some experts only use 3TC where there is a good chance of attaining undetectable plasma HIV RNA.

ADDITIONAL PRACTICE POINTS

HYDROXYUREA IN CHILDREN

There are few data for hydroxyurea (HU) in children. HU should only be used with ddI alone or together with d4T. When combined with these drugs, HU can reduce the viral load more than the nucleosides alone. Resistance mutations to HU do not occur, and in addition it may produce beneficial immunological effects. These unique properties make HU a potentially important and affordable adjunct to currently available therapies.

HU should be used with caution in individuals whose pre-treatment absolute neutrophil count is < 1 000/ml, as neutropenia could be aggravated. Severe pancreatitis has been reported in adults on combination NRTI therapy that has included HU. It is good clinical practice to monitor full blood count and amylase twice monthly for the first month of HU therapy and monthly thereafter. There are no data for HU in children under 2 years of age. HU should definitely not be used in children under 2 until more data are available.

NUCLEOSIDE ANALOGUES

Resistance to nucleoside analogues is slow to develop, with the exception of 3TC. Resistance to 3TC arises within weeks when the drug is used in a regimen that fails to suppress viral replication fully. For this reason many experts recommend the use of 3TC only in three-drug combinations. 3TC resistance may, however, sensitise HIV to the antiviral activity of ZDV, but the durability of this effect is uncertain.

All nucleoside analogues have been associated with lactic acidosis, a rare but potentially life-threatening metabolic complication of treatment. The pathogenesis is believed to involve drug-induced mitochondrial damage.

TABLE VII. DOSAGE AND FREQUENCY OF ARVS IN CHILDREN

DRUG	FORMULATIONS	DOSAGE (PER DOSE)	FREQUENCY	STORAGE	COMMENTS
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)					
Zidovudine (ZDV) Retrovir®	Susp: 10 mg/ml Caps: 100 mg, 250 mg	90 - 180 mg/m²	3	Room temperature	
Didanosine (ddI) Videx®	Susp: 10 mg/ml Tabs: 25 mg, 50 mg, 100 mg, 150 mg	90 - 120 mg/m²	2 Can give total daily dosage X 1 daily in older children	Refrigerate suspension	Half hr pre-meals or 1 hour after meals. Use single daily dose if necessary for compliance
Stavudine (d4T) Zerit®	Susp: 1 mg/ml Caps: 15 mg, 20 mg, 30 mg, 40 mg	1 mg/kg	2	Refrigerate suspension	Capsules stable in water suspension for 24 hours
Abacavir Ziagen®	Susp: 20 mg/ml Tabs: 300 mg	8 mg/kg	2	Room temperature	Use requires MCC approval BEWARE HYPER-SENSITIVITY REACTION
Lamivudine (3TC)®	Susp: 10 mg/ml Tabs: 150 mg	4 mg/kg 2 mg/kg for neonates (up to 1 month old)	2	Room temperature	
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)					
Nevirapine Viramune®	Susp: 10 mg/ml Tabs: 200 mg	120 - 200 mg/m² start at 120 mg/m² daily for 14 days and increase to bid dosage if no rash or severe side-effect	2	Room temperature	Skin rash usually occurs in 1st 6 weeks; do not increase dosage until rash resolves BEWARE LIVER TOXICITY
Efavirenz Stocrin®	Caps: 50, 100 and 200 mg (suspension available from manufacturer)	13 - < 15 kg: 200 mg; 15 - < 20 kg: 250 mg 20 - < 25 kg: 300 mg 25 - < 32.5 kg: 350 mg 32.5 - < 40 kg: 400 mg > 40 kg: 600 mg	1	Room temperature	No data < 3 yrs and < 13 kg. Give at night to avoid CNS side-effects
PROTEASE INHIBITORS					
Ritonavir Norvir®	Susp: 80 mg/ml	Start at 250 mg/m²/dose and increase by 50 mg/m² every 2 - 3 days up to 400 mg/m² If < 2 years of age 450 mg/m²	2		Take with food. Bitter; coat mouth with peanut butter or chocolate milk. Take 2 hours apart from Didanosine
Nelfinavir Vira-cept®	Susp: 50 mg/1 gram spoon and 200 mg per teaspoon Tabs: 250 mg	Paediatric: 55 mg/kg (adolescent: 750 mg tds) Some experts use 35-45 mg/kg/dose tds > 2 yrs of age. 45-55 mg/kg/dose tds < 2 yrs of age	2		Give 2 hr pre or 1 hr post ddI. Best with light meal. Do not use with rifampicin. Powder is 5% active drug and the rest is carrier powder. Most experts prefer to crush the tablets and suspend in milk or water or sprinkle on pudding
RIBONUCLEOTIDE REDUCTASE INHIBITOR					
Hydroxy-urea Hydrea®	Caps: 500 mg	30 mg/kg Not to be used in children < 2 yrs	1	Stored at room temperature. Suspend contents of capsule in 5 ml water and give prescribed amount	Few data in children, but likely to be beneficial, especially if PI or NNRTI cannot be used. Best to use with ddI and/or d4T. Monitor FBC. Withdrawn from ARV studies because of a few reports of fatal pancreatitis

Body surface area (m^2) = $\sqrt{\text{height (cm)} \times \text{weight (kg)}} \div 60$

TABLE VIII. SIDE-EFFECTS OF ARVS IN CHILDREN		
CLASS	DRUG	SIDE-EFFECT
NRTI	ZDV (Retrovir®)	Anaemia, granulocytopenia Myopathy
	ddI (Videx®)	Common: abdominal pain, nausea and vomiting Uncommon: pancreatitis, peripheral neuropathy
	Stavudine (Zerit®)	Common: headache, rash, gastrointestinal Uncommon: pancreatitis and peripheral neuropathy
	Abacavir (Ziagen®)	Hypersensitivity reaction (with or without rash) – may be fatal in adults and children
	Lamivudine (3TC®)	Common: headache, fatigue and abdominal pain Uncommon: pancreatitis and peripheral neuropathy
NNRTI	Nevirapine (Viramune®)	Skin rash, sedative effect and diarrhoea. LIVER TOXICITY
	Efavirenz (Stocrin®)	Skin rash CNS – sleep disturbance, confusion, abnormal thinking Teratogenic in primates
PI	Ritonavir (Norvir®)	Nausea, vomiting, diarrhoea Hypercholesterolaemia and hypertriglyceridaemia
	Nelfinavir (Vira-cept®)	Diarrhoea Can exacerbate chronic liver disease Hypercholesterolaemia and hypertriglyceridaemia
Ribo-nucleotide Reductase Inhibitor	Hydroxyurea (Hydrea®)	Granulocytopaenia, anaemia Withdrawn from ARV studies because of reports of fatal pancreatitis in patients on combination therapy Side-effects more common in patients with advanced disease

DRUG INTERACTIONS OF NOTE

There are multiple opportunities for serious drug interactions. Treaters are advised to scrutinise package information and seek advice if uncertain.

- Efavirenz causes reduced levels of clarithromycin, but not azithromycin.
- Ritonavir should not be given with rifampicin, rifabutin, cisapride, midazolam and numerous other drugs.
- Rifampicin reduces levels of ritonavir, indinavir and nelfinavir (protease inhibitors) and NNRTIs (efavirenz and nevirapine) and should not be used together with any of these drugs.

The following drugs are metabolised by cytochrome P450 (CYP3A4), hence there is the possibility of multiple interactions:

Protease inhibitors (PI)
- Saquinavir
- Ritonavir
- Nelfinavir
- Indinavir

NNRTIs
- Nevirapine
- Efavirenz

Note: However, NVP+IDV decrease individual drug levels.

CHANGING THERAPY

- In case of toxicity or intolerance, a simple substitution can be made.
- When failure is due to viral resistance, at least two drugs should be changed.
- Consult an experienced treater.

SPECIFIC ISSUES FOR ADOLESCENTS

- Adult guidelines are appropriate for post-pubertal adolescents (Tanner stage V).
- For adolescents in early puberty (Tanner stage I and II; use paediatric guidelines).
- For intermediate puberty, monitor closely and choose either adult or paediatric guidelines.
- Non-compliance is problematical and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.

TABLE IX. TANNER STAGING FOR BOYS			
STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Pre-adolescent	Pre-adolescent
2	Scanty, long, slight pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult, less than adult	Larger, glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult	Adult

TABLE X. TANNER STAGING FOR GIRLS		
STAGE	PUBIC HAIR	BREAST
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border labia	Breast and papilla elevated as small mound; areola diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but less than adult	Areola and papilla form 2° mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature; nipple projects, areola part of general breast contour

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RECOMMENDED READING

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