KWAZULU-NATAL

STEP-BY-STEP GUIDE

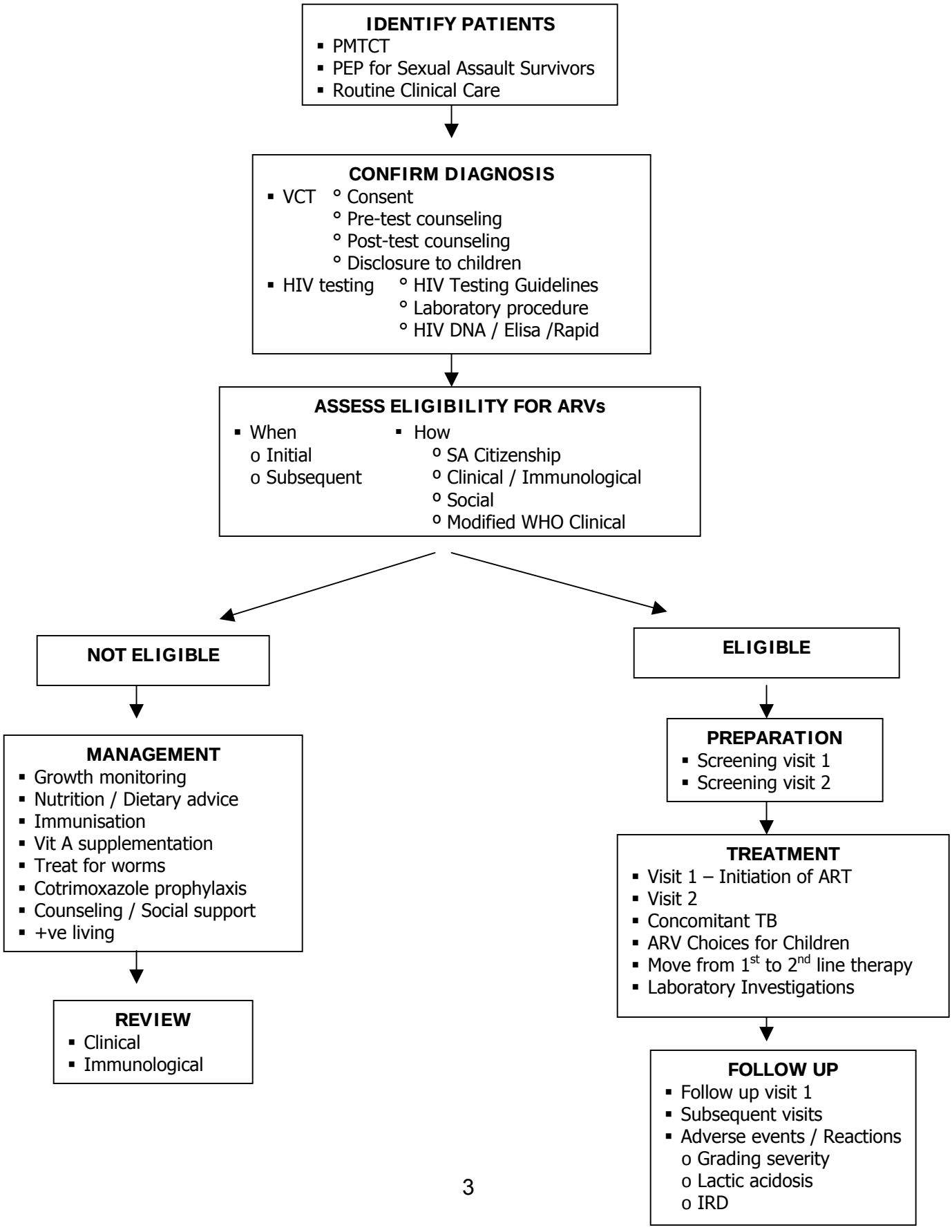
FOR

PAEDIATRIC ART PROGRAMME

TABLE OF CONTENTS

March 2005

PAEDIATRIC ART PROGRAMME



TREATMENT TIMELINE

Time	Activity
	Identify patients
	Confirm diagnosis
	Assess eligibility for ART programme
- 4 weeks	Screening 1
- 2 weeks	Screening 2
0 weeks	Treatment 1
2 weeks	Treatment 2
4 weeks	Follow up 1
8 weeks +	Subsequent Visits - 12 weeks - 3 monthly (x3) - 6 monthly

IDENTIFY PATIENTS

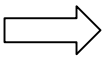
PMTCT PROGRAMME

Symptomatic children:

- HIV disease is suspected on the basis of their clinical status as detailed below.

Asymptomatic children:

- HIV infection confirmed on routine HIV testing as part of the PMTCT programme.
    - HIV DNA PCR at 6 months
    - HIV DNA PCR at 9 months
    - Elisa test at 15 months



entry point to ART programme

SEXUAL ASSAULT POST EXPOSURE PROPHYLAXIS (PEP)

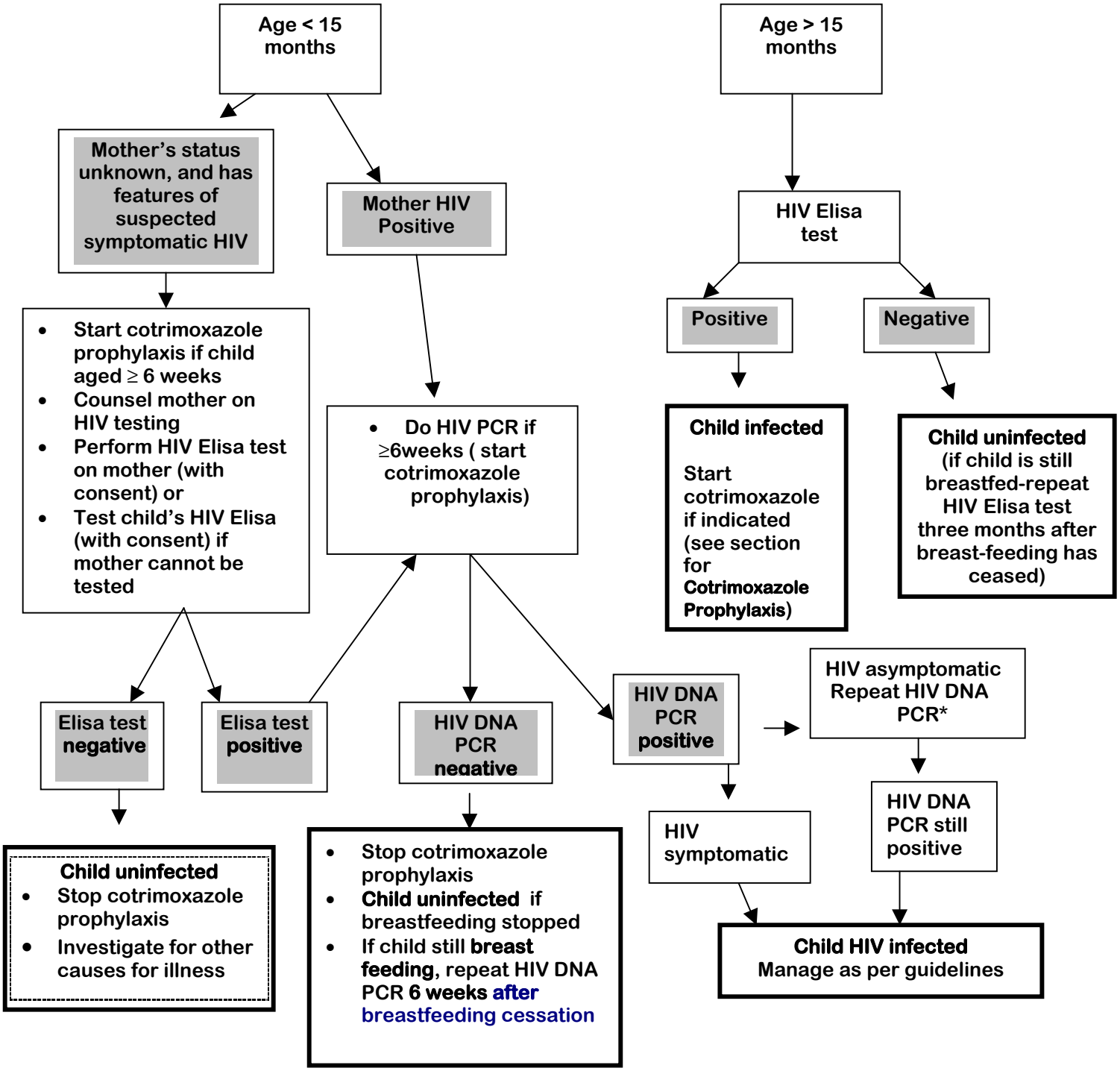
HIV+ status is identified during the PEP programme for survivors of sexual assault.

CLINICAL SERVICES

Identification of 1 or more signs suspicious of HIV (see IMCI guidelines) during routine clinic, OPD or hospital visits.

CONFIRM DIAGNOSIS

HIV TESTING GUIDELINES



HIV BLOOD SAMPLE REQUIREMENTS

Test	Sample	Transport	Time Frame
CD4	EDTA without gel	Room temperature	72 hours
HIV DNA PCR	EDTA without gel	On ice	48 hours
HIV Viral Load	EDTA with gel	Process within 6 hrs then store at 4° C	Same day

ASSESS ELIGIBILTY FOR ART

Patients must be South African citizens and satisfy clinical / immunological and social criteria before being accepted for treatment.

SOUTH AFRICAN CITIZENSHIP

A South African Birth Registration number or ID number is required for eligibility for the ART programme.

CLINICAL/ IMMUNOLOGICAL CRITERIA

- Recurrent hospitalisations (> 2 admissions per year) for HIV complications OR a prolonged hospitalisation for HIV (> 4 weeks)

  OR

- The patient satisfies the modified WHO Stage II/III disease (see below)

  OR

- For relatively asymptomatic patients, one can consider CD4 percentage
  - <20% in a child < 18 months of age
  - <15% in a child > 18 months of age.

SOCIAL CRITERIA

These criteria are extremely important for the success of the program and need to be adhered to – the principle is that adherence to treatment must be at least probable.
The following are required:

- One identifiable caregiver
- Demonstrated reliability in the adult caregiver
- Supportive social environment

MODIFIED WHO CLINICAL STAGING

The South African National Paediatric HIV Consensus Team have modified the original WHO Clinical Staging Guidelines for practical reasons. These will be updated to conform to the WHO modifications when they appear.

Stage I

- Asymptomatic
- Persistent generalized lymphadenopathy
- Hepatosplenomegaly

Stage II

- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infection
- Lineal gingival erythema (LGE)
- Extensive Human Papilloma virus infection (>5% of body area)
- Molluscum infection (>5% of body area)
- Recurrent oral ulcerations (2 or more episodes in 6 months)
- Parotid enlargement
- Chronic or recurrent upper respiratory tract infection (otitis media, sinusitis: 2 or more episodes in any 6-month period)

Stage III

- Unexplained low weight for age / low height for age / low weight for height
- Unexplained persistent fever (intermittent or constant for longer than 1 month)
- Herpes zoster (2 or more dermatomes)
- Persistent or recurrent oral candidiasis (outside neonatal period)
- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Tuberculous lymphadenopathy (axillary, cervical or inguinal)
- Severe recurrent presumed bacterial pneumonia (2 or more episodes in 6 months)
- Acute necrotizing ulcerative gingivitis/periodontitis
- Lymphoid Interstitial Pneumonitis (LIP)
- Unexplained anaemia (<8gm/dl) neutropenia (<1000/mm3) or thrombocytopenia (<30,000/mm3 for > 1 month)
- HIV related cardiomyopathy
- HIV related nephropathy

Stage IV

- Unexplained severe wasting or severe malnutrition not responding to nutritional rehabilitation and treatment of underlying disease
- Age <18 months with symptomatic disease including a combination of 2 or more of the following: any failure to thrive, oral thrush, sepsis, severe pneumonia requiring oxygen (i.e. cough or difficult breathing with chest indrawing or a danger sign or stridor), bone or joint infection
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infection (2 or more episodes within one year e.g. empyema), pyomyositis, bone or joint infection, meningitis, but excluding pneumonia
- Chronic orolabial or cutaneous Herpes simplex infection (>1 month duration)
- Kaposi's sarcoma
- Oesophageal, bronchial or pulmonary candida
- CMV retinitis
- Cryptococcal meningitis
- Any endemic mycosis or mycobacterial disease
- Cryptosporidiosis or isosporiasis or other diarrhoea for >1 month
- Cytomegalovirus infection (onset at age >1month of organ other than liver, spleen or lymph nodes)
- Cerebral or B cell non-Hodgkin's Lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- HIV Encephalopathy
- Acquired rectovaginal fistula
- Chronic lung disease including bronchiectasis

SCREENING VISIT 1

1. Complete history and clinical evaluation, including weight and height.

2. Update growth chart.

3. Calculate surface area:

Body surface area $BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$ m^2

4. Nutritional assessment by dietician.

5. Ensure that TB adequately excluded.

6. Name the caregiver/s responsible for medication and make sure that this person is present during all discussion regarding antiretroviral therapy.

7. Treatment literacy to provide wellness counselling (group sessions).

8. Take blood for staging CD4 level.
   (EDTA tube without gel; to lab at room temperature within 72 hours)

NB. If adherence by the family is questionable, they should be brought back for adherence counselling/assessment until such time as the team feels that treatment can be commenced.

SCREENING VISIT 2

1. History and clinical evaluation, including weight and height.
2. Update growth chart.
3. Check that nutritional assessment done by dietician.
4. Confirm name of the caregiver/s responsible for medication.
5. Treatment literacy in a group session.

NB. If adherence by the family is questionable, they should be brought back for adherence counselling/assessment until such time as the team feels that treatment can be commenced.

ANTIRETROVIRAL CHOICES FOR CHILDREN

	6 months up to 3 years	**>3years and >10 kg**
1st Line	Stavudine (d4T) Lamivudine (3TC) Kaletra®	Stavudine (d4T) Lamivudine (3TC) Efavirenz (Stocrin®)
2nd Line	Zidovudine (AZT) Didanosine (ddI) Nevirapine/ Efavirenz	Zidovudine (AZT) Didanosine (ddI) Kaletra®
For children on TB treatment	Stavudine (d4T) Lamivudine (3TC) Ritonavir	Stavudine (d4T) Lamivudine (3TC) Efavirenz (Stocrin®)

TREATMENT VISIT 1

1. History and clinical evaluation, including weight and height.
2. Update growth chart.
3. Calculate surface area:

Body surface area $BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$ m^2

4. Nutritional assessment by dietician.
5. Check staging CD4 result (taken at first screening visit).
6. Identify the correct drug regimen.
7. Take blood for baseline investigations (see Laboratory Investigations Table).
8. Review the importance of adherence and devices to assist adherence.
9. Explain possible side effects of ARVs
10. Prescribe medication for 1 month.
11. Issue pillboxes, syringes and diary cards.
12. Make a treatment plan with the parent or guardian
13. Arrange adherence phone call in 1 week (if possible).
14. Arrange follow up visit after 2 weeks.

TREATMENT VISIT 2

1. Adherence assessment (3 day recall).

2. Reconcile returned empty containers with volume of medication prescribed since the last visit.

3. Explain exact drug schedule for the child to the guardian, using the diary card.

4. Adjust drug schedule if needed (e.g. nevirapine).

5. Issue pillboxes, syringes and diary cards where needed.

6. Arrange follow up visit after 2 weeks.

LABORATORY INVESTIGATIONS

Time	D4T/3TC/ Kaletra	d4T/3TC/ Efavirenz	AZT/ddI/ NVP	AZT/ddI/ Efavirenz	AZT/ddI/ Kaletra	D4T/3TC/ Ritonavir
-4 weeks (staging)	CD4	CD4	CD4	CD4	CD4	CD4
0 weeks (baseline)	Viral Load FBC ALT TG/Cholesterol (fasting) Glucose (fasting)	Viral Load FBC ALT	Viral Load FBC ALT	Viral Load FBC ALT	Viral Load FBC ALT TG/Cholesterol (fasting) Glucose (fasting)	Viral Load FBC TG/Cholesterol (fasting) Glucose (fasting)
2 weeks			ALT			
1 month			FBC ALT	FBC	FBC	
2 months			FBC ALT	FBC	FBC	
3 months			FBC	FBC	FBC	
6 months **(and 6 monthly)**	CD4 Viral Load FBC ALT TG/Cholesterol (fasting) Glucose (fasting)	CD4 Viral Load FBC ALT	CD4 Viral Load FBC ALT	CD4 Viral Load FBC ALT	CD4 Viral Load FBC ALT TG/Cholesterol (fasting) Glucose (fasting)	CD4 Viral Load FBC TG/Cholesterol (fasting) Glucose (fasting)

FOLLOW UP VISIT 1

1. History and clinical evaluation, including weight and height.

2. Update growth chart.

3. Adherence assessment (3 day recall).

4. Reconcile returned empty containers with volume of medication prescribed since the last visit.

5. Look for signs of toxicity or adverse reactions (see Adverse Events/Reactions Table).

6. Review exact drug schedule for the child with the parent/guardian.

7. Adjust drug schedule if needed.

8. Do laboratory investigations as required (see Laboratory Investigations Table).

9. Issue medication for 4 weeks.

10. Issue pill boxes, syringes and diary cards where needed.

11. Arrange follow up visit in 4 weeks.

SUBSEQUENT VISITS

1. History and clinical evaluation, including weight and height.

2. Update growth chart.

3. Calculate surface area every 6 months:

Body surface area $BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$ m^2

4. Adherence assessment (3 day recall).

5. Reconcile returned empty containers with volume of medication prescribed since the last visit.

6. Look for signs of toxicity or adverse reactions (see Adverse Events/Reactions Table).

7. Review exact drug schedule for the child with the parent/guardian.

8. Adjust drug schedule if needed.

9. Do laboratory investigations as required (see Laboratory Investigations Table).

10. Issue medication for 4 weeks.

11. Issue pill boxes, syringes and diary cards where needed.

12. Arrange follow up visits:
    a. < 12 weeks — monthly
    b. >12 weeks — 3 monthly for clinical assessment (NB monthly to pharmacy for treatment)
    c. Sick children — according to clinical status

MOVE FROM FIRST TO SECOND LINE THERAPY

Consider a move to second-line therapy under the conditions listed in the table below.
For practical purposes it is primarily the clinical features that are of importance.

Clinical	Immunological	Virological
Growth failure Loss of neurodevelopmental milestones New evidence of WHO stage III disease Recurrence of prior opportunistic infections	Confirmed return of CD4 % to baseline More than 50% decline in CD4 %	Rebound of viral load to baseline

ADVERSE EVENTS / REACTIONS

Grading the Severity of Paediatric Adverse Reactions(PACTG)

Laboratory Test Abnormalities				
Item	**Grade 1 Toxicity**	**Grade 2 Toxicity**	**Grade 3 Toxicity**	**Grade 4 Toxicity**
Haemoglobin 3 mo. Up to 2 yrs	9.0 - 9.9 g/dL	7.0 – 8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Haemoglobin 2 years and over.	10 -10.9 g/dL	7.0 – 9.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Absolute Neutrophil Count	0.75 - 1.2 $x10^9$/L	0.4-0.749 $x10^9$/L	0.25-0.399 x 10^9/L	<0.25 x 10^9/L
ALT (SGPT)	1.1-4.9 x upper normal limit	5.0-9.9 x upper normal limit	10.0-15.0 x upper normal limit	>15 x upper normal limit
Triglycerides	-	1.54 - 8.46 mmol/L	8.47 - 13.55 mmol/L	>13.56 mmol//L
Cholesterol	-	4.43 - 12.92 mmol/L	12.93 - 19.4 mmol/L	>19.4 mmol/L

Clinical Adverse Events				
Item	**Grade 1 Toxicity**	**Grade 2 Toxicity**	**Grade 3 Toxicity**	**Grade 4 Toxicity**
Peripheral neuropathy	Diagnosis of peripheral neuropathy is difficult in children. Screen motor function against milestones and refer to specialist if peripheral neuropathy is suspected.			
Skin Rash / Dermatitis*	-	Diffuse maculo-papular rash OR dry desquamation	Vesiculation OR ulcers	Exfoliative dermatitis OR Stevens-Johnson syndrome OR erythema multiforme OR moist desquamation

ACTION ON GRADING

Grades 1 and 2:

- Child remains on therapy.
- Repeat the test.
- Reassess clinically within 2 weeks.

Grade 3:

- Test should be repeated within 1 week.
- If still Grade 3, stop ALL antiretroviral drugs and seek expert medical advice.

Grade 4:

- Stop all drugs immediately and seek specialist advice.
- If the patient restarts therapy after the event has resolved, and the same grade 4 event recurs, appropriate changes or withdrawal of antiretroviral therapy may need to be made.
- Decisions should be made on an individual basis, and discussed with experts as required.

d4T (Stavudine; Zerit®)

Formulation:
Syrup - 1 mg/ml (Requires refrigeration)
Capsules - 20 mg, 30 mg & 40 mg

Dose:
1 mg/kg/dose

Frequency:
12 hourly

Comments:
Can administer with food.
Do not combine with AZT.
Combination with ddI has ↑ rate of toxicity.
Dissolve 20 mg capsule in 20 ml water gives a concentration of 1 mg/ml.

Side effects:
Common
- Headache
- GIT disturbance
- Skin rash

Rarer
- Pancreatitis
- Peripheral neuropathy
- ↑ Liver enzymes
- Lactic acidosis

Dosage per weight:

Weight (kg)	Volume/dose
4	4 ml
5	5 ml
6	6 ml
7	7 ml
8	8 ml
9	9 ml
10	10 ml
11	11 ml
12	12 ml
13	13 ml
14	14 ml
15	15 ml
16	16 ml
17	17 ml
18	18 ml
19	19 ml
20	20 ml
21	21 ml
22	22 ml
23	23 ml
24	24 ml
25	25 ml
26	26 ml
27	27 ml
28	28 ml
29	29 ml
30	30 ml
31	30 ml
32	30 ml
34	30 ml
35	30 ml
36	30 ml
37	30 ml
>37	1 tablet

3TC (Lamivudine; 3TC®)

Formulation:
Syrup - 10 mg/ml
Tablets - 150 mg

Dose:
4 mg/kg/dose

Frequency:
12 hourly

Comments:
Can be administered with food

Side effects:
Common
- Headache
- Fatigue
- Nausea & diarrhoea
- Skin rash
- Abdominal pain

Rarer
- Pancreatitis
- Peripheral neuropathy
- ↓ WCC
- ↑ Liver enzymes
- Lactic acidosis

Dosage per weight:

Weight (kg)	Volume/dose
4	1.5 ml
5	2.0 ml
6	2.5 ml
7	3.0 ml
8	3.0 ml
9	3.5 ml
10	4.0 ml
11	4.5 ml
12	5.0 ml
13	5.0 ml
14	5.5 ml
15	6.0 ml
16	6.5 ml
17	7.0 ml
18	7.0 ml
19	7.5 ml
20	8.0 ml
21	8.5 ml
22	9.0 ml
23	9.0 ml
24	9.5 ml
25	10.0 ml
26	10.5 ml
27	11.0 ml
28	11.0 ml
29	11.5 ml
30	12.0 ml
31	12.5 ml
32	13.0 ml
34	13.5 ml
35	14.0 ml
36	14.5 ml
37	15.0 ml
>37	1 tablet (150mg)

ddI (Didanosine; Videx®)

Formulation:
Suspension - 10 mg/ml (Requires refrigeration)
Tablets - 25 mg, 50 mg, 100 mg & 150 mg
(Buffered)

Dose:
90 - 120 mg/m^2/dose

Frequency:
12 hourly

Comments:
Do not administer with food - give 1 hour before or 2 hours after meals.
Suspension must be mixed with antacid.

Complications:
Common
- Abdominal pain
- Diarrhoea
- Nausea & vomiting

Rarer
- Pancreatitis
- Peripheral neuropathy
- Lactic acidosis

Dosage / surface area (m^2):

SA (m^2)	Volume/dose
0.30	25 mg
0.35	25 mg
0.40	25 mg
0.45	25 mg
0.50	50 mg
0.55	50 mg
0.60	50 mg
0.65	50 mg
0.70	50 mg
0.75	75 mg
0.80	75 mg
0.85	75 mg
0.90	75 mg
0.95	75 mg
1.00	75 mg
1.05	100 mg
1.10	100 mg

AZT (Zidovudine; Retrovir®)

Formulation:
Syrup - 10 mg/ml
Capsule - 100 mg
Tablets - 300 mg

Dose:
180 mg/m^2/dose

Frequency:
12 hourly

Comments:
Better tolerated with food.
Do not give with d4T.

Complications:
Common

Headache
Anaemia
↓ granulocytes

Rarer

Myopathy
Lactic acidosis

Dosage / surface area (m^2):

SA (m^2)	Volume/dose
0.30	5.5 ml
0.35	6.0 ml
0.40	7.0 ml
0.45	8.0 ml
0.50	9.0 ml
0.55	10.0 ml
0.60	11.0 ml
0.65	12.0 ml
0.70	13.0 ml
0.75	13.5 ml
0.80	14.5 ml
0.85	15.0 ml
0.90	16.0 ml
0.95	17.0 ml
1.00	18.0 ml
1.05	19.0 ml
1.10	20.0 ml

Nevirapine (Viramune®)

Formulation:
Syrup - 10 mg/ml
Tablets - 150 mg

Dose:
120 - 200 mg/m^2/dose

Frequency:
Daily for 14 days
THEN
12 hourly

Comments:
Can administer with food
Skin rash occurs within first 6 weeks - do not increase dose until rash resolves.
Stop treatment if LFTs ↑.

Dosage / surface area (m^2):

SA (m^2)	Volume/dose
0.30	3.6 ml
0.35	4.2 ml
0.40	4.8 ml
0.45	5.4 ml
0.50	6.0 ml
0.55	6.6 ml
0.60	7.2 ml
0.65	7.8 ml
0.70	8.4 ml
0.75	9.0 ml
0.80	9.6 ml
0.85	10.2 ml
0.90	10.8 ml
0.95	11.4 ml
1.00	12.0 ml
1.05	12.6 ml
1.10	13.2 ml

Side effects:

Common

Skin rash (including Stevens Johnson & Toxic Epidermal Necrolysis)
Sedation
Diarrhoea

Rarer

Liver toxicity (↑ liver enzymes, RUQ pain etc)
Hypersensitivity reaction (rash, fever, oral sores, conjunctivitis & facial oedema)

Efavirenz (Stocrin®)

Formulation:
Capsule - 50 mg & 200 mg

Dose:

10 - 14.9 kg	200 mg
15 - 19.9 kg	250 mg
20 - 24.9 kg	300 mg
22 - 32.4 kg	350 mg
32.5 - 39.9 kg	400 mg
> 40 kg	600 mg

Frequency:
Daily

Comments:
Not suitable for children < 3 years of age.
Give at night to avoid CNS side-effects.
Preferably take on empty stomach.

Side effects:
Common
Skin rash
CNS – drowsiness, insomnia, abnormal dreams
confusion, poor concentration, hallucinations
amnesia

Rarer
↑ Liver enzymes

Lopinavir/Ritonavir (Kaletra®)

Formulation:
Syrup - 80mg LPV & 20mg RTV / ml
(Needs to be kept < 25°C)
Capsule - 133mg LPV / 33mg RTV

Dose:
230 mg LPV/m^2/dose

Frequency:
12 hourly

Comments:
Administer with food (high fat meal increases absorption)
In regimen with ddI give Kaletra 1 hour after or 2 hours before ddI

Side effects:
Common
Diarrhoea
Nausea & vomiting

Rarer
↑ Cholesterol
↑ Triglycerides
Diabetes & hyperglycaemia

Dosage / surface area (m^2):

SA (m^2)	Volume/dose
0.30	0.9 ml
0.35	1.0 ml
0.40	1.2 ml
0.45	1.3 ml
0.50	1.4 ml
0.55	1.6 ml
0.60	1.7 ml
0.65	1.9 ml
0.70	2.0 ml
0.75	2.2 ml
0.80	2.3 ml
0.85	2.4 ml
0.90	2.6 ml
0.95	2.7 ml
1.00	2.9 ml
1.05	3.0 ml
1.10	3.2 ml

Ritonavir (Norvir®)

Formulation:

Syrup - 80mg / ml (At room temperature for 30 days only - otherwise refrigerate)

Capsule - 100mg

Dose:

400 mg/m^2/dose

Start at $^2/_3$ dose for 2 days, then $^3/_4$ dose for 2 days, then full dose, to minimise nausea

Frequency:

12 hourly

Comments:

Administration with food increases absorption

If in regimen with ddI should be 2 hours between taking each drug

Poorly tolerated due to extremely unpleasant taste

To increase tolerance - mix with milk/yoghurt
- dull taste buds with ice
- give peanut butter before
- give strong-tasting foods immediately after dose

Dosage / surface area (m^2):

SA (m^2)	Volume/dose
0.30	1.5 ml
0.35	1.5 ml
0.40	2.0 ml
0.45	2.0 ml
0.50	2.5 ml
0.55	2.5 ml
0.60	3.0 ml
0.65	3.0 ml
0.70	3.5 ml
0.75	3.5 ml
0.80	4.0 ml
0.85	4.0 ml
0.90	4.5 ml
0.95	4.5 ml
1.00	5.0 ml
1.05	5.0 ml
1.10	5.5 ml

Side effects:

Common

Nausea & vomiting
Diarrhoea
Headache
Abdominal pain
Anorexia

Rarer

Circumoral paraethesia
↑ Liver enzymes
Pancreatitis
↑ Triglycerides and Cholesterol
Diabetes & hyperglycaemia