CHAPTER 1:

Initiating Anti-Retroviral Therapy

Initiating Anti-Retroviral Therapy

Although the virological effects of starting antiretroviral treatment (ART) occur early after treatment initiation, the clinical benefits of treatment may take a few weeks before becoming evident. Consequently, starting lifelong ART should not be seen as an emergency measure. In general, it is opportunistic infections (OIs) and other HIV-related conditions that cause most of the morbidity and mortality seen in people living with HIV/AIDS (PLHA); these conditions should therefore be treated as a priority and stabilized before ART is begun. Furthermore, adequate time should be taken to prepare patients and/or their caregivers well enough to ensure a clear understanding of ART and the requirement of long-term, high-level adherence to ART. Finally, HIV disease is a chronic illness, the management of which requires that a lasting, effective partnership is developed between the patient, their family, community and health care workers, in order to ensure a successful treatment outcome.

1.1 DIAGNOSIS OF HIV INFECTION

1.1.1 Entry Points for HIV positive patients into Care

Counselling and testing services should be used in all health care settings to facilitate identification of HIV-positive adults and children as early in the disease process as possible. Ideally, **all** PLHAs should be in clinical care.

- *VCT services should refer HIV positive patients to HIV care clinics/CCC as soon after diagnosis as possible*
- *In- and out-patient services (OPD, TB, STI, FP, MCH, medical/paediatric wards): Diagnostic Counselling & Testing (DCT or provider initiated testing) should be carried out aggressively in these settings; the aim is for universal testing in these areas in high prevalence settings.*
- *PMCT services: all pregnant women should undergo HIV testing & their spouses encouraged to be tested. An HIV test should be repeated late in pregnancy in HIV negative women in discordant relationships or relationships where partner status is unknown.*
- *MCH-CWC/maternity: all exposed children should be identified using maternal records, maternal or infant antibody testing as early as possible & enrolled into care.*
- *Infant diagnostic testing or IDT (DNA PCR) is increasingly available and should be used at the earliest opportunity on exposed infants to identify those with HIV infection (see appendix 5)*
- *HIV Ab testing should routinely be offered to sick children in paediatric out- and in-patient services*. If <18 mo & the antibody test is positive, DNA PCR should be done*
- *All patients attending CCC with children under the age of 15 should be advised/encouraged to bring those children for HIV testing**
- *Community: all CBOs supporting orphans and vulnerable children should arrange to have children tested for HIV whose parents may have died of HIV infection.**

*HIV *testing of children should always be done in consultation with the parents or the caregivers.* ***The opportunity for testing of the parent or CG should not be missed.*** *CCC = Comprehensive Care Centre; MCH = maternal & child health; CWC = child welfare clinic; CBOs = Community-based organizations*

1.1.2 Laboratory Diagnosis of HIV Infection

Prior to ART initiation, patients **must have a confirmed HIV diagnosis**.

- Adults and children > 18 months: a confirmed positive HIV antibody (Ab) test (HIV ELISA/EIA) is definitive.

- Children less than 18 months:
  - Determine **HIV-exposure status of infants as early as possible** after birth, using maternal medical information (e.g. antenatal card) or HIV Ab testing of infants whose mother's status is unknown.
  - In **exposed** children < 18 months **a positive virological test**, such as **HIV DNA or RNA PCR** is required for confirmation of HIV infection. HIV Ab tests should not be used to confirm diagnosis because maternal HIV antibodies acquired passively from the mother during pregnancy may persist for up to 18 months, resulting in some false positive results. (*See framework for follow-up of HIV positive mother-infant pairs and algorithm for Infant Diagnostic Testing in appendices 4 and 5*).

Interpretation of Diagnostic Test Results in Children

In children > 18 months of age:

- Breastfeeding HIV-exposed children should be re-tested using standard EIA tests at least **6 weeks** after complete cessation of breast-feeding to exclude HIV infection

In children < 18 months of age

- Positive Ab test in the mother or the child confirms HIV **exposure**. If a **virological test is not available**, repeat the Ab test in the child after 18 months to confirm the diagnosis
- **Where a virological test is available**
  - o A negative DNA PCR excludes HIV infection; breastfeeding HIV PCR negative exposed children should be re-tested at least **6 weeks** after cessation of breastfeeding *(see IDT algorithm)*.
  - o A positive DNA PCR confirms HIV infection

Table 1: Summary of Laboratory Diagnosis of HIV Infection

Age	HIV diagnosis confirmed as follows:
Adults and children > 18 months	Positive HIV antibody tests (rapid or long EIA)
Children < 18 months	Positive HIV PCR* from age 6-8 weeks or as soon after, during routine child welfare clinic visits
Children < 18 months where PCR is not available	Positive antibody test after the child is > 18 months

* DNA or RNA PCR

1.1.3 Clinical Diagnosis of HIV Infection

In all patients a confirmed laboratory diagnosis of HIV infection is required before ART can be started. However in children under 18 months, clinical information can be used to support ART initiation where a child is severely unwell **and** a PCR test is not available, as summarized in the table below.

Table 2: Presumptive Diagnosis of Severe HIV Infection in Children < 18 Months

Presumptive severe HIV diagnosis in HIV antibody-positive children < 18 months old where virological confirmation of infection is not possible

Presumptive severe HIV diagnosis may be made in a child < 18 months who is symptomatic with 2 or more of the following:

- Oral candidiasis (thrush)
- Severe pneumonia requiring oxygen
- Severe wasting/malnutrition
- Severe sepsis requiring injectable antibiotics

Other factors that support the diagnosis of severe HIV infection in an HIV sero-positive infant are recent maternal death or advanced HIV disease in mother. CD 4 % < 25% or CD4 <1500cells/mm3 in child

1.2 PATIENT EVALUATION AND PREPARATION FOR ART

All newly diagnosed patients should undergo a thorough evaluation, which should include

- Medical assessment and preparation
- Psychosocial assessment and preparation, including education on HIV disease; adherence counselling and discussion of the overall treatment plan. *(See table 6)* The content of the preparation and education of **the child** depends on their age and their capacity to understand and participate, and should be updated as the child matures. For young children, the adult caregiver (CG) should be prepared and educated to enable them to support the child's treatment.

1.2.1 Medical Assessment and Preparation of Patients

The goal of the medical assessment of PLHA is to identify patients who need ART and ensure that they meet the medical criteria for starting therapy. The assessment involves a thorough history, screening for TB (pg 41) and treating/stabilizing any OIs, starting preventive therapy against OIs, addressing any pre-existing medical problems, WHO clinical staging and determining if and when ART is required.

WHO Clinical Staging (*see appendices 1 & 2)* in both adults and children is useful for

- Defining the degree of disease severity
- Determining HIV disease prognosis
- Determining when to start ART
- Monitoring patients clinically before and during ART.

Only patients with a confirmed laboratory diagnosis of HIV infection should be staged clinically.

Table 3: Summary of WHO Clinical Staging

Classification of HIV-associated clinical disease	WHO Clinical Stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

1.2.1.1 Chemoprophylaxis for Opportunistic Infections

Cotrimoxazole

- **ALL** HIV-infected adults, adolescents and children should be **started** on cotrimoxazole (CTX) as soon after the diagnosis of HIV infection as possible.
- All PLHA/CLHA should **remain** on CTX regardless of ARV treatment, clinical or immunological status.
- All **HIV-exposed** children should be started on CTX from the age of 4-6 weeks. CTX should only be discontinued when the child has been confirmed as HIV negative at least 6 weeks *after* complete cessation of breastfeeding

Table 4: Dose of Prophylactic Cotrimoxazole

Weight of Child (kg)	CTX suspension 240mg per 5ml	CTX tablets single strength 480mg (SS)	CTX double strength tablets 960mg (DS)
1 – 4	2.5 ml	¼ SS tab	--
5 – 8	5 ml	½ SS tab	¼ DS tab
9 – 16	10 ml	1 SS tab	½ DS tab
17 – 30	15 ml	2 SS tabs	1 DS tab
> 30	20 ml	2 SS tabs	1 DS tab
Adults: any weight.		2 SS tablets	1 DS tablet

Cotrimoxazole Desensitization (See Appendix 4)

- CTX is effective as a chemo-prophylactic agent against a broad range of organisms; for this reason all effort should be made to ensure that patients who can, start and continue to use CTX.
- A rash may occasionally develop, usually about 7-14 days following initiation of CTX. It is often a relatively mild maculopapular rash with or without itchiness. Infrequently, more severe rash may develop with severe exfoliation of the skin and Stevens-Johnson syndrome (SJS).

- Patients with mild to moderately severe rash should stop CTX and once recovered should undergo desensitization as shown in Appendix 3.
  - o Desensitization is effective in the majority of patients. The rapid regimen can be used in situations where treatment for PCP is needed.
- Patients with severe rash (oedema, vesiculation of the skin, mucosal involvement) should **NOT** be desensitized; CTX should be stopped and never be re-used.
- Dapsone is recommended for patients unable to use CTX; unfortunately dapsone is not as effective a chemo-prophylactic agent as CTX; it is effective against only PCP when used alone. (Ideally pyremethamine which is not easily available should be used in addition to provide prevention against toxoplasmosis).
  - **o Dose of Dapsone**
    - Available as 25mg and 100mg tabs
    - Children: 2mg/kg OD; maximum dose is 100 mg OD
    - Adults: 100mg OD
  - o Dapsone should be commenced in patients with WHO stage 4 disease and/or those with a CD4 < 200.
  - o Dapsone should be discontinued once the CD4 has been greater than the following values for at least 6 months.
    - 200 cells/mm^3 for adults and children > 5 years
    - Age-specific threshold for severe immunodeficiency for children < 5years *(See table 9)*.

Isoniazid Preventive Therapy (IPT)

This section applies only to centres that have been approved to provide IPT

Preventive therapy against TB is the use of anti-TB drugs(s) in individuals with latent *Mycobacterium tuberculosis* infection in order to prevent the progression to active disease. HIV is the most powerful risk factor for progression from latent infection to active disease. Use of IPT can reduce the number of HIV patients developing active TB. **ALL** newly registered patients should be screened for active TB (by asking about symptoms; physical examination and sputum examination; CXR may be done routinely if available as part of screening; CXR should be done in **all** symptomatic pts). IPT should only be used in pts **in whom active TB has been excluded, active pt follow up is possible *and* high level adherence can be attained.** IPT should also be used in HIV + children in whom TB has been excluded. **Patients treated for TB in the preceding 2 years are not suitable for IPT.**

Where IPT is **NOT** used routinely, it should still **be offered to *all* children under 5 years exposed to "open TB" in a close contact** in whom active TB has been excluded**.** *Consideration should also be given to IPT provision in all HIV infected children after exclusion of TB in approved centres, because of the proven benefits. Such childern should be monitored closely for symptoms and signs of TB disease while on IPT*

Patient Assessment for IPT

Assess Suitability for IPT

- Symptoms? (fever, weight loss, cough; failure to gain weight in children)[1]
- CXR abnormal?1
- Sputum (repeat x3) for AFB positive (in adults and older children with cough)?[2]
- Treated for TB in the preceding 2 years?

IF ANSWER TO ANY OF THE ABOVE IS "YES" THE PATIENT IS NOT SUITABLE FOR IPT.

If No to all answers pt is suitable for IPT.

Which patients could receive IPT if suitable as per above criteria?

- **All** children < 5 years exposed to "open" PTB in a close contact, with a negative TB screen should be given IPT regardless of HIV sero-status as a minimum standard of care
- **All** HIV positive children whom TB has been excluded (clinics encouraged to offer this based on available evidence)
- **All** HIV positive patients in whom TB has been excluded (universal use of IPT for PLHA)

[1] These patients should be investigated for active TB (they are TB suspects); [2] these patients should be treated for PTB

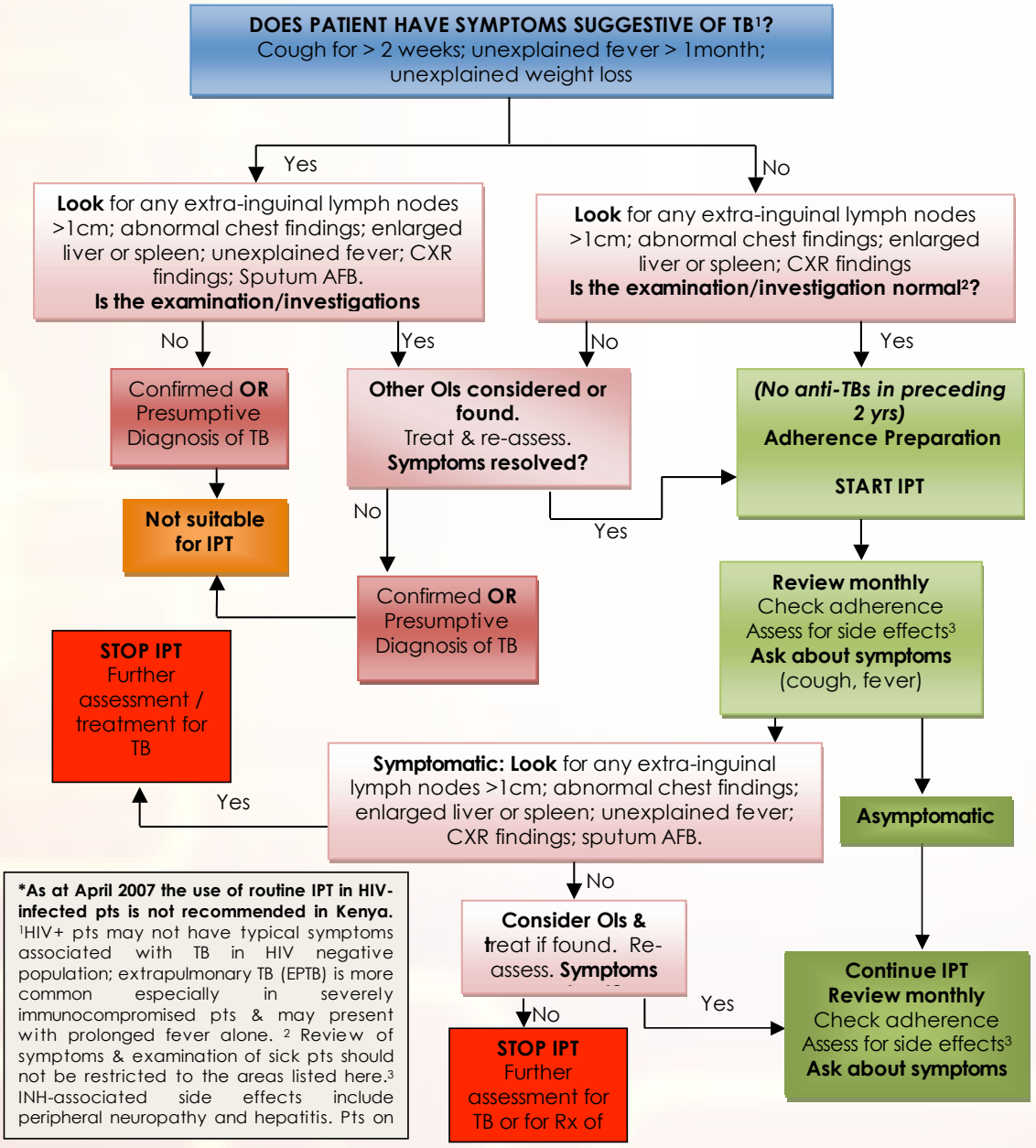
Dose of Isoniazid for IPT

Child: 10mg/kg/day (max 300mg OD) for 6 months

Adult/ Adolescent: INH 300 mg OD + Pyridoxine 50 mg OD for 6 months

ISONIAZID PREVENTIVE THERAPY (IPT) FOR PLHA AND CLHA

IPT should only be used in pts **in whom active TB has been excluded, active pt follow up is possible *and* high level adherence can be attained.** IPT should also be used in HIV + children in whom TB has been excluded. **Patients treated for TB in the preceding 2 years are not suitable for IPT.**



***As at April 2007 the use of routine IPT in HIV-infected pts is not recommended in Kenya.** [1]HIV+ pts may not have typical symptoms associated with TB in HIV negative population; extrapulmonary TB (EPTB) is more common especially in severely immunocompromised pts & may present with prolonged fever alone. [2] Review of symptoms & examination of sick pts should not be restricted to the areas listed here.[3] INH-associated side effects include peripheral neuropathy and hepatitis. Pts on

Table 5: Summary of Initial Medical Evaluation

History and Examination (See Table 13 for clinical assessment)

- Thorough history and physical examination to exclude opportunistic conditions and to allow correct determination of WHO staging should be carried out. The history should include:
  - Previous OIs such as TB, severe illness requiring hospitalization; history of TB in household contact of CLHA1
  - Drug history (previous use of ARV drugs including ARV drugs for PEP or PMCT interventions in women or children)
  - In women, pregnancy status and the risk of pregnancy, parity & reproductive plans
  - Screening for TB and STIs in adults & adolescents based on symptoms
- For children, use growth chart to assess growth, development & immunization status; determine breastfeeding status
- Full physical examination

Laboratory Evaluation

- Baseline blood tests that should be done; include FBC (Hb); LFTs (ALT); CD4 count; pregnancy test (adults & adolescents if EFV is to be used).
- Sputum for AFB and CXR in patients with symptoms suggestive of TB or those exposed to "open" PTB
- Where there is no access to the full complement of tests, the minimum tests in brackets should be carried out. ***Lack of laboratory tests should not be a barrier to initiation of ART in symptomatic patients who qualify for treatment.***
- Other desirable tests, which should be done at baseline if available, include Renal function tests –RFTs (Creatinine); bilirubin, amylase/lipase, serum lipids, cervical cytology, VDRL and hepatitis B & C serology (note that Hepatitis B vaccination is now part of EPI package)
- Viral load (VL) where available should be done at baseline; VL is **not** necessary for treatment initiation

Treatment and Prophylaxis of OIs

- Any OIs or conditions diagnosed during the clinical assessment should be treated as a priority
- ALL PLHA/CLHA1 should be started on CTX2 prophylaxis regardless of age, clinical, immunological or ARV treatment status.
- Start all PLHA on multivitamin supplements once a day
- In CLHA1, immunization status should be reviewed & updated if necessary. Immunization of CLHA is the same as for HIV negative children. BCG should **NOT** be given to children with severe symptoms of HIV disease (e.g. Stage 3 or 4).
- Fluconazole should be given to patients with cryptococcal meningitis (CM) from the time of completion of the consolidation phase of treatment until immune reconstitution has occurred. Careful follow-up of patients who have discontinued CM prophylaxis is needed; prophylaxis should be resumed promptly should CD4 count fall to < 100 cells/mm3 or should any WHO stage 4 conditions develop.

- In approved facilities, isoniazid preventive therapy (IPT) should be given to all HIV+ patients at enrolment, after careful exclusion of active TB.
- In approved facilities CLHA should be given IPT. Where IPT is not used routinely, CLHA < 5 years with a history of exposure to open TB in a close contact without symptoms suggestive of TB and a normal CXR should be given IPT as recommended by the NLTP guidelines.

1.2.2 Psychosocial Assessment and Preparation of Patients for ART

(see Table 6)

The goal of the psychosocial assessment and preparation of PLHA/CLHA is to

- Begin the process of empowering the patient/CG through education and support.
- Address the patient's/CG's concerns raised as a result of a diagnosis of HIV infection.
- Educate the patient/CG on HIV infection, disease progression and its management.
- Discuss with the patient/CG about disclosure and its benefits.
- Discuss and offer the patient/CG opportunity to join local support organizations.
- Identify (and support the patient in addressing) any factors in the patient's family and social circumstances that may impact negatively on patient's health and ART outcome.
- Provide adherence education and counselling, and develop mechanisms to ensure high-level adherence.
- **Ensure patient is ready, willing and able to start and continue with ART if clinically indicated.**

The initial psychosocial assessment and preparation often takes 2-3 sessions and should be started at the earliest opportunity. Always assess patients/CG's understanding and knowledge before giving further information. The specific issues to be addressed are summarized in Table 6 below.

1.2.2.1 Adherence

Adherence is central to the success of ART. Almost perfect adherence (rates exceeding 95%) is desirable in order to maximize the benefits of ART. This means the patient has to take the correct dose of drugs at the correct times while observing any dietary or fluid restrictions. Adherence protocols should be available in the CCC and all HCWs should be familiar with them to ensure consistency of adherence messages. Organized clinic records including diary, daily list of defaulters, tracker cards and community contacts should be maintained. The clinic should have a clearly defined and prioritized system of tracing defaulting patients. Community groups and patients' support groups should be enlisted to help with adherence education support and patient tracking.

Checklist to Maximize Adherence: ART Initiation

Patient/CG attended all scheduled preparation visits?	
Patient/CG prepared well before ART begins? Written info provided where useful? (see Table 6)	
Patient/CG given information on and understands the benefits of ART?	
Patient/CG able to demonstrate how they will take/give child their ARVs?	
Patient given information about predictable and common side effects of intended regimen?	
Patient/CG knows what to do should common mild or serious side effects occur?	
Patient advised and encouraged to identify a treatment supporter (TS), ideally a family member?	
Has patient disclosed diagnosis? (TS, family members at risk, sexual contacts?) For adolesents HIV status should be disclosed to them.	
Is the status of family/contacts at risk known and recorded?	
Patient informed of and attended group sessions for education and counselling?	
Patient locator information and contact details up to date?	
Adherence preparation information recorded?	
Next appointment given?	

Checklist to Maximize Adherence: Continuing Care

Check if patient/CG attended appointment (s) as planned?	
If not, why? Was medication missed? Were there financial reasons? Is the problem likely to recur? If so work with patient/CG towards a plan to reduce likelihood of missed medication.	
Have any new issues/concerns arisen about ARVs or other medication patient is on? If so discuss them	
Has patient experienced any new symptoms? If so could they be related to ARVs?	
Review issues raised at the last appointment; review progress and discuss.	
Perform assessment of adherence at each visit:	
Report on adherence from patient and/or TS/CG (has the patient missed any pills since last visit? If so how many? Why? Is problem likely to recur? How can this be avoided? Does patient have a TS? Has the TS been prepared to support ART? Perform pill count.	
Patient/CG able to demonstrate how they are taking/giving child their ARVs?	
Has patient disclosed diagnosis? (TS, family members at risk, sexual contacts? Status of family/contacts at risk? Fill family status and follow-up card). Continue disclosure process as necessary; offer support in disclosure	

Monitor social situation – any new issues? (especially important for children)	
Is the patient/CG a member of any patient support group? If not do they have the relevant information	
Patient/CG locator information and contact details up to date?	
Adherence follow up information recorded?	
Next appointment given?	
Continued support provided during clinic visit?	
Review biological markers (clinical progress, CD4 and VL if available) and relate to adherence assessment Any findings during the session requiring clinician or other referral?	

Table 6: Summary of Patient Counselling and Preparation for ART

PATIENT EDUCATION*
HIV Disease
HIV disease: HIV attacks the immune system & weakens the body's defences against infection. Opportunistic infections: OIs occur when body's defences are weak – most are treatable; treatment is best started early, so "you should go/child should be taken to a HCF early". CD4 counts or percent: This is a measure of the strength of the immune system or body's defences; inform patients/CG of CD4 results to encourage self-management Disclosure: discuss importance of disclosure to a family member/friend to provide ART & psychosocial support as well as enable testing of contacts. Disclosure to responsible school staff may be essential for children reliant on them for continued care Management plan: discuss treatment & follow up plan; ensure patient/CG understands, consents to & is ready to support its implementation Respond to any questions patient may have
ARV Drugs and ART
Goals & effects of ART: For the patient, the main goal is improved quality of life & longevity. ART allows immune system to recover, reducing incidence of OIs thus reducing illness and likelihood of death. **Duration of Treatment:** discuss reasons why, based on currently available ARV drugs, ART is lifelong. Emphasize to CGs the tremendous improvement in the quality of life of treated CLHA & excellent outcome of ART

ARV Drugs

- Are powerful lifesaving drugs & the patient's health depends on their taking them or in the case of the child, being given them every day at the right time as prescribed & agreed to by patient/CG. They do NOT cure HIV
- Do NOT prevent HIV transmission; sexually active patients must use condoms correctly & consistently
- May interact with other drugs which may result in their not working: patients should avoid alcohol, herbal drugs, self-treatment

ARV drug regimen: Discuss regimen chosen for the patient. Explain about fixed dose combination (FDC) & the constituent drugs. Demonstrate with actual ARVs how patient should take them. **For CLHA, it is essential that CG understands & demonstrates how to measure out & dispense the drugs.** Ensure patient/CG knows about food requirements of ARVs where necessary & how to disguise unpleasant taste of some of the ARVs, especially for children.
Side effects (Adverse Drug Reactions, ADRs) and what to do. Reassure CG/parent or older child that children tolerate treatment very well. For all patients, discuss predictable ADRs with reference to regimen chosen without alarming them. Advise patient/CG to come/bring patient to CCC for ADRs that warrant attention, e.g. rash, vomiting, abdominal pain, jaundice and painful feet. Provide support for "mild" ADRs.

Follow-up (FU): Inform patient/CG of need for FU to ensure medication is working & to monitor for ADRs. Advise patient/CG on the schedule of appointments including the next appointment. Advise patient/CG on importance of keeping appointments.

ADHERENCE PREPARATION

Importance of adherence: Link adherence to successful ART outcome. Explain that high-level adherence is essential to maintain drug levels in the blood for ART to work. Explain that missing doses even if only occasionally makes ART ineffective & can result in treatment failure with recurrence of OIs or death. (Ask: What will you do to ensure you do not miss your drugs?). Discuss importance of adherence to non-ART medication, e.g. CTX, anti-TB drugs, IPT.

Review patient's willingness to start ART and/or CG's willingness to commit to supporting a CLHA to start ART

- Has the patient/CG demonstrated ability to keep appointments, to adhere to other medications (e.g. CTX)?
- Has adult patient disclosed his/her HIV status? If not, encourage him/her to do so. Disclosure to at least 1 person who can be the treatment supporter is important; lack of disclosure should not be used to delay ART initiation.
- Does the patient want treatment & understand what this treatment is for?
- Is the patient/CG willing and able to come for the required clinic follow-up?

If patient is not ready or willing to start (even if ART is indicated medically) defer & continue preparation; review in 1 month. If a CG is not able to commit to the requirements of ART for a CLHA defer & review social situation.

Discuss arrangements of how patient/CG will come for appointments (do you live nearby? If not, how will you commute? Is this sustainable? Can you pay for transport?) Consider and discuss the option of a HCF nearer the patient's home if it offers ART.

Discuss direct & indirect cost of treatment & investigations if relevant. (Is patient/CG realistic about their ability to afford treatment including transportation to HCF?)

Review proposed adherence promotion strategies e.g. family, friend or CHW to remind them (treatment supporter or CG should be identified and be educated on ART); pill cues (e.g. put tablets next to toothbrush if you brush your teeth twice a day); pill diary; alarm clock/ watch/phone. Review home, work or school situation to ensure permits adherence. Address any barriers to adherence, including pill storage, safety from violence.

Community Links & Patient Support Groups. Advise patient on community support groups & facilitate contact.

Disclosure (adults and caregivers; involve caregiver when discussing disclosure with older child).

- Discuss the importance of disclosure especially to partners who may be at risk of continued exposure to HIV
- Disclosure to a treatment supporter (TS) may be crucial in ensuring adherence and in providing emotional support. For CLHA in (boarding) schools, disclosure to responsible school staff is often necessary to ensure child continues clinical care & ART
- Discuss, encourage, facilitate & record testing of exposed individuals in the family &/or among sexual contacts
- Fill family status card, update it & follow through with info on status of family members until all are tested & in care if needed.

Clinic Adherence Support Tools

- **Fill ART DIARY & REGISTERS;** fill and update **"Patient Locator Card"** – practical contact details for patient & identified TS, as well as community support organization they are attached to that can facilitate default tracing. Fill appointment card.
- Give appointment for commencing ART

CONTINUING COUNSELING AND SUPPORT

- Always leave time for patients to raise issues of concern to themselves that may require counselling and support
- Remember that it may take time for patients to be able to open up and freely discuss their problems

*Patient education is a continuous process. Children should be educated from as early as possible, in an age-appropriate way, according to their desire for & capacity to absorb the information. CG should be actively involved in the child's evolving education.

1.3 CLINICAL CRITERIA FOR COMMENCING ANTIRETROVIRAL DRUG THERAPY

1.3.1 When to Start ART in Adults and Adolescents

All patients being considered for ART **must** have a confirmed positive HIV result.

Table 7: When to Start ART in Adults and Adolescents

IF CD4 TESTING IS NOT AVAILABLE:
• **All patients with WHO stages III and IV disease** • **Patients with WHO stage II plus TLC < 1200/mm3**
IF CD4 TESTING IS AVAILABLE:
• WHO stage I or II HIV disease, start ART if CD4 count ≤ 250/mm3* • WHO stage III disease, start ART if CD4 < 350. • WHO stage IV disease, start ART irrespective of the CD4 cell count

***Asymptomatic/mildly symptomatic (WHO Stage 1 & 2) patients with CD4 <350** should be observed and CD4 count monitored every 6 months. ART should be initiated before CD4 count falls below 200 cells/mm^3, **i.e. when CD4 count is between 200 and 250 cells/mm^3.** In effect WHO Stage 1 & 2 patients should start ART if the initial or follow-up CD4 count is ≤ 250 cells/mm^3; this is because the clinical outcome of patients starting ART with a CD4 < 200 is worse than that of patients starting ART when CD4 is > 200.

1.3.2 What to Start With: First Line ARV Drug Regimen for Adults and Adolescents

Stavudine (D4T) or Zidovudine (AZT)
+
Lamivudine (3TC)
+
Nevirapine (NVP) or Efavirenz (EFV)

Table 8: First Line ARV Drug Dosages for Adults and Adolescents

DRUG	DOSAGE
Nevirapine	200 mg OD x 2weeks; then 200mg BD to continue
Efavirenz	600 mg at night
Stavudine	30mg BD for all patients regardless of weight
Zidovudine	300mg BD
Lamivudine	150mg BD

ARV Dosage for Adolesent:

- if no or early sexual development use peadiatric dosage guide
- if obvious sexual development use adult dosage guide

1.3.3 When to Start ART in Children

- **CD4 NOT Available: Clinical Criteria for Initiation of ART in Children**
  - **All** children with a lab-confirmed diagnosis of HIV infection **and** WHO stage 3 or 4 disease.
  - Where PCR is not available, children < 18 months with a presumptive diagnosis of severe HIV disease (see Table 2). *Confirmation of the diagnosis should be arranged as soon as possible.*
- **CD4 Available: Immunological Criteria for Initiation of ART in Children**
  - The CD4 percentage or absolute count at which treatment initiation is necessary varies according to the age of the child as shown in Table 9 below.
  - ART should be started when the **CD4 is ≤ the threshold value for each age** as shown in Table 9
  - In the absence of a CD4 test, the total lymphocyte count can be used as shown in the same table

Table 9: CD4 at Which Treatment Should be Initiated in Children

Immunological Marker	Age Specific Recommendation to Initiate ART		
	</= 18 months	18months -5 yrs	≥5years
CD4%	< 25%	<20%	< 15%
CD4 Absolute Count (cells/mm3)	< 1500	<750	< 200

Table 10: Criterea for ART Initiation in Children

Age	Clinical Stage	CD4%	CD4 Count
< 18 months	WHO 3 or 4*	< 25%	< 1500
18 months - 5 years	WHO 3 or 4	< 20%	< 500
> 5 years	WHO 3 or 4	< 15%	250

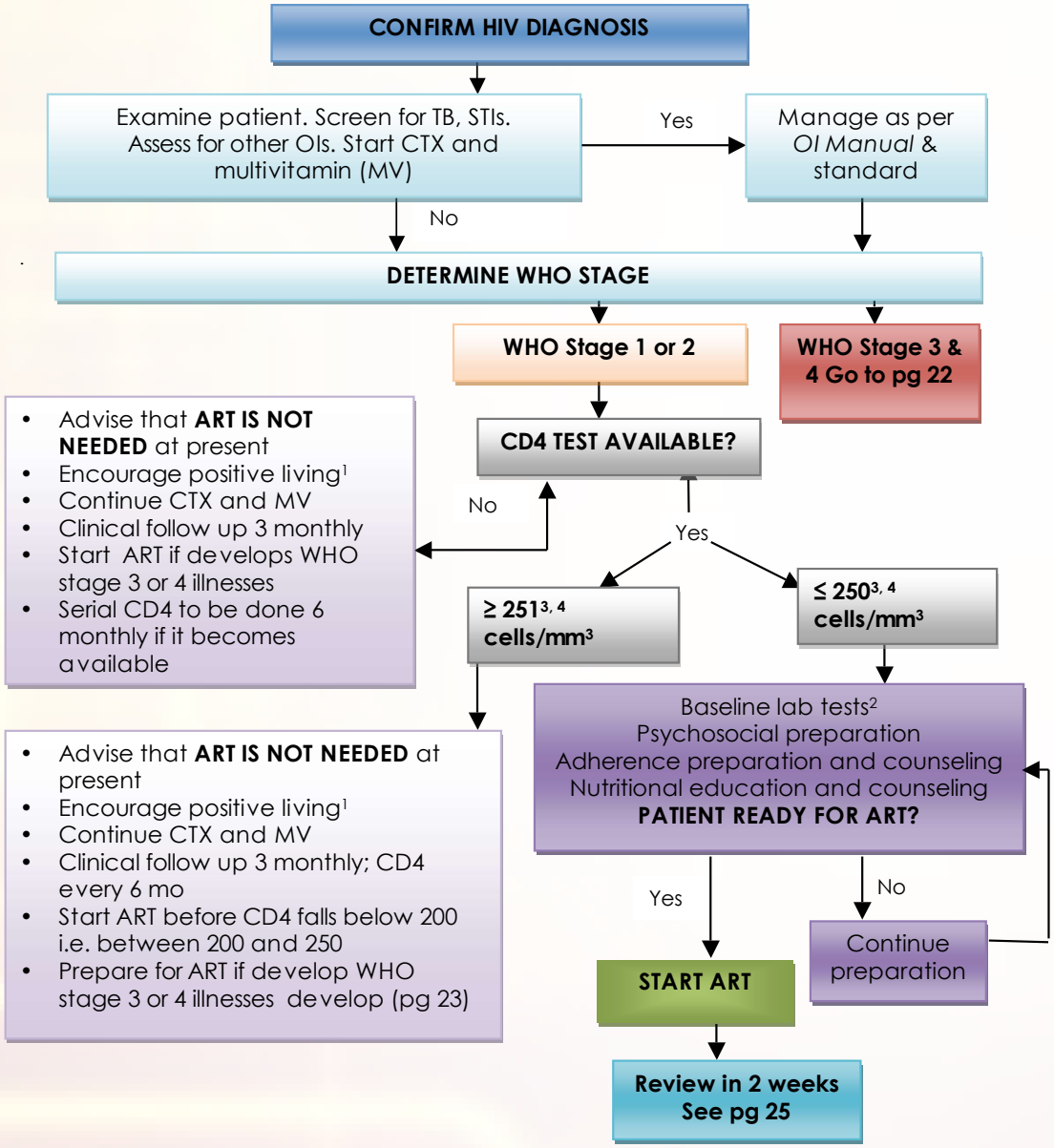
Child fulfilling any of the above criteria repuires ART
*Child < 18 months with presumptive stage 4 HIV diagnosis, preferable to have CD4 evidence of immunosuppression before ART initioation.

Table 11: First Line Antiretroviral Treatment Regimens in Children

CHILD'S CHARACTERISTICS	RECOMMENDED REGIMEN
A. Child previously NOT exposed to Nevirapine for PMCT HIV transmission	
Age < 3 yrs and weight < 10kg	Zidovudine (AZT)1 + Lamivudine (3TC) + Nevirapine (NVP)2
Age > 3 yrs and weight > 10kg	AZT1 +3TC + Efavirenz (EFV) or NVP2
B. Child exposed to single dose NVP (failed prophylaxis)	
All ages	AZT1 + 3TC + (LPV/r)3

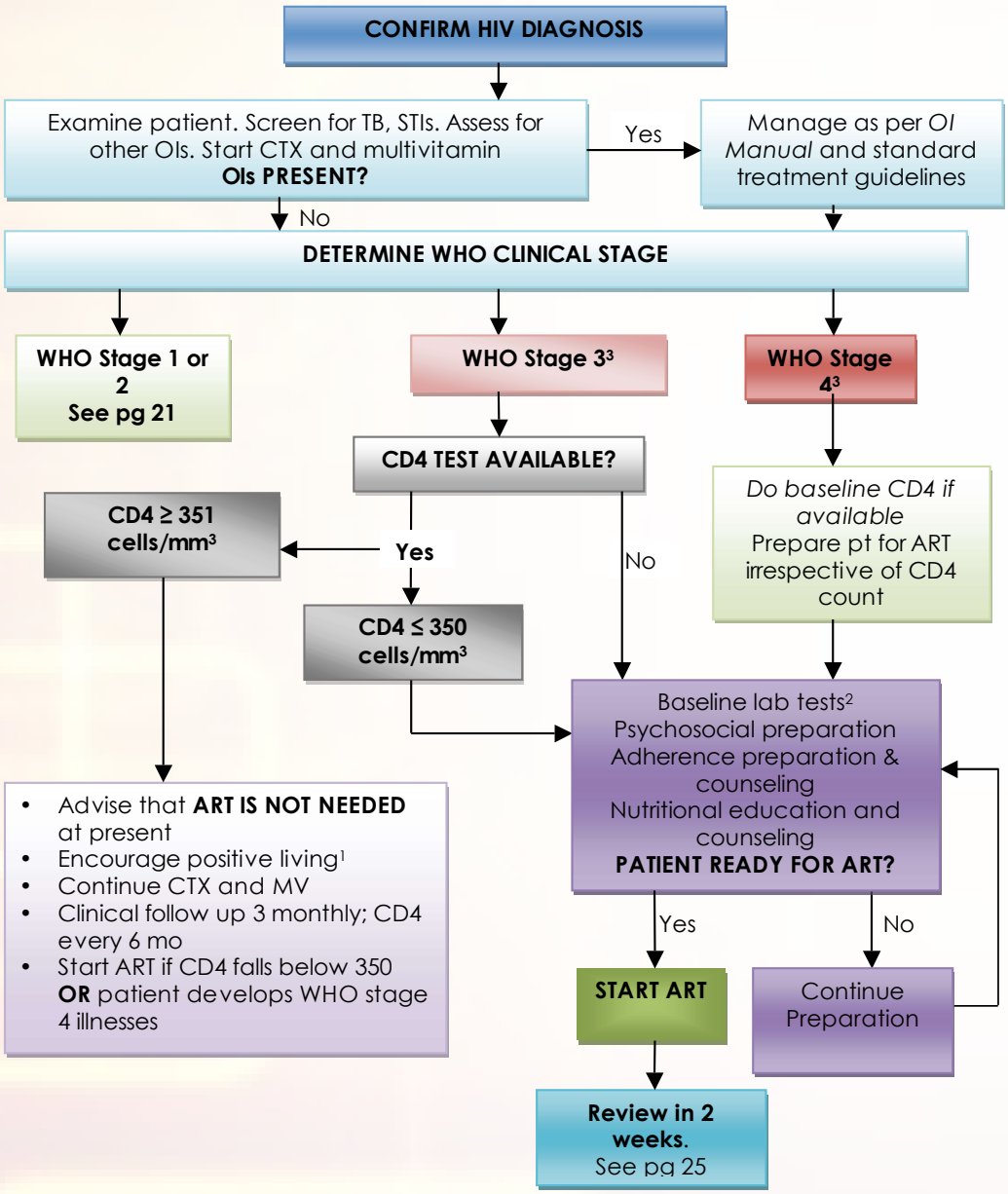
[1]In cases of severe anaemia (Hb < 8 g/dl), **give *D4T* in place of *AZT***. Where available "junior FDCs" suitable for children should be used (see appendix 8). [2]Start NVP at half dose for 14 days then step it up to full dose from day 15. [3]Nelfinavir or other heat stable PI/r may be used instead of LPV/r in cases where refrigeration is not available or ambient temperatures prohibit its use. All pharmacies stocking ARV drugs should have a refrigerator. LPV/r syrup can be kept at a maximum temperature of 25° C for up to 1 month and can therefore be dispensed to patients without refrigerators; in these circumstances patients should store the medicine in a cool dry place.

WHEN TO START ART: WHO STAGES 1 & 2



1Basic hygiene, clean (boiled or treated for drinking) water, nutritional education, Insecticide treated nets (ITNs), exercise, safer sex, OI prevention & treatment
2Baseline lab tests: Hb (FBC), ALT (LFT), pregnancy test (if needed) at a minimum. 3The cut-off of 250 is used to accommodate the statement in Table 7 that "in asymptomatic/mildly symptomatic pts ART should be started before CD4 falls below 200 e.g. 200-250" Patients who start ART if CD4 <200 have a higher mortality than those starting when the CD4 >200. 4 In CLHA with WHO stage 1 & 2 disease ART should be started if the CD4 is below the age based cut-offs in Table 9.

WHEN TO START ART: WHO STAGES 3 & 4



1Basic hygiene, clean (boiled or treated for drinking) water, nutritional education, Insecticide treated nets (ITNs), exercise, safer sex, OI prevention & treatment
2Baseline lab tests: Hb (FBC), ALT (LFT), pregnancy test. 3In CLHA start ART in all pts with WHO stage 3 or 4 disease regardless of the CD4 percentage or count

2 Baseline lab tests: Hb (FBC), ALT (LFT), Creatinine, sputum AAFB2, pregnancy test
*if available

1.4 FOLLOW-UP OF PATIENTS ON ART

The purpose of the follow-up of patients on ART is to

- Determine response to ART
- Detect drug side effects
- Screen for, prevent and treat TB, and other OIs
- For children monitor growth, review nutritional status and offer appropriate immunization
- Provide reproductive health services including provision of contraception, prevention and treatment of STIs, prevention of onward HIV infection (prevention among positives)
- Assess and support adherence and provide on-going psychosocial support
- Dispense medication.

Follow-up is based on clinical, laboratory, adherence and psychosocial assessment as summarized below. The schedule of clinical follow up should be at 2 weeks after initiation of ART, and then on a monthly basis until patient is stabilized; adherent, stable patients with a good understanding of ART, its goals and demand for high-level adherence can be reviewed every 2-3 months.

Table 12: Summary of Follow-up of Patients Starting ART

1. CLINICAL MONITORING (Time 0, 2,4,8,12,16 weeks etc. Can be at 2-3 month intervals in stable patients)
Ask patient caregiver or older child:
How have you been? What problems have you developed? Have you had any of the following? If yes, ask for how long • Fever? Night sweats? • Cough? Sputum production? Sputum for AFB if available. CXR if symptomatic (fever, cough >2 weeks, weight loss) • Poor appetite? Mouth sores? Pain on swallowing? Nausea or vomiting? Diarrhoea? • New skin rash? • Headache? • Fatigue? • Tingling, burning, numb or painful feet/legs? • Any other pain? If yes, where? • Problems sleeping at night? • For adolescent & adults: are you sexually active? Regular partner(s)? Is partner's HIV status known? Condoms used consistently & correctly? Do you have genitourinary symptoms? (Discharge, ulcers, pain passing urine? Treat syndromically if symptomatic) • For women: when was the LMP? If sexually active is contraception used? Desired? If needed offer options according to whether or not on ART (see Table 15 below.) • Have you been treated for a medical problem recently? If yes, ask for & record diagnosis & treatment received.

- Which medications are you taking and how often?
- Family members at risk tested? If so on ART/care? If not encourage/ facilitate disclosure and testing
- For infants & younger children: ask caregiver, is the child's immunization up to date? If not facilitate.

Examine the patient:

- Plot the patient's weight and note the trend. For children measure height as well and note trend
- Measure temperature, blood pressure, respiratory rate; look for signs associated with anticipated drug side effects (e.g. pallor, rash, etc); look for oral lesions, thrush; further assessment based on presenting symptoms
- If new infection/OI record in trend sheet
- If new treatment is prescribed explain to patient what it is & why it is necessary, & record in trend sheet.

2. LABORATORY TESTS

- As per schedule Table 14, based on patient treatment and as per clinical problems
- Record lab results including CD4 (VL if available) in a trend sheet and note the trend

3. ASSESS AND STRENGTHEN ADHERENCE (refer to adherence checklist)

- ***Involve treatment supporter or child in discussions. For younger children advice/ discuss with the caregiver***
- Have you/the child had any problems taking your/their medication? If so what?
- How are you taking/giving the child your/their medications? Can you demonstrate?
- Are you/the child taking any other drugs (traditional or herbal remedies, anti-TBs, illicit drugs etc)?
- Perform pill count and record; if missed pills discuss, identify reasons why; help patient/ CG work out strategy to improve adherence. Note adherence history.
- Relate adherence to biological markers (CD4, weight, VL if possible)
- HCW should determine if there is an adherence problem; if so how will this be addressed? Who needs to be involved? Is there a need for more intensive adherence support?
- Confirm next appointment date

4. PSYCHOSOCIAL ASSESSMENT

- How are things at home? At work/school?
- Have you/the child been feeling sad or unhappy or have you/child lost interest in your normal activities recently?
- Have you been feeling scared or frightened recently?

- Have you been worried about drinking too much alcohol or taking drugs recently (e.g. cannabis, miraa)?
- What usual physical activities are you/child doing?
- What else do you want to talk about?
- If patient is sad or has lost interest, assess for depression.
- Assess disclosure to sexual contact(s) and family members who may be affected; support as appropriate

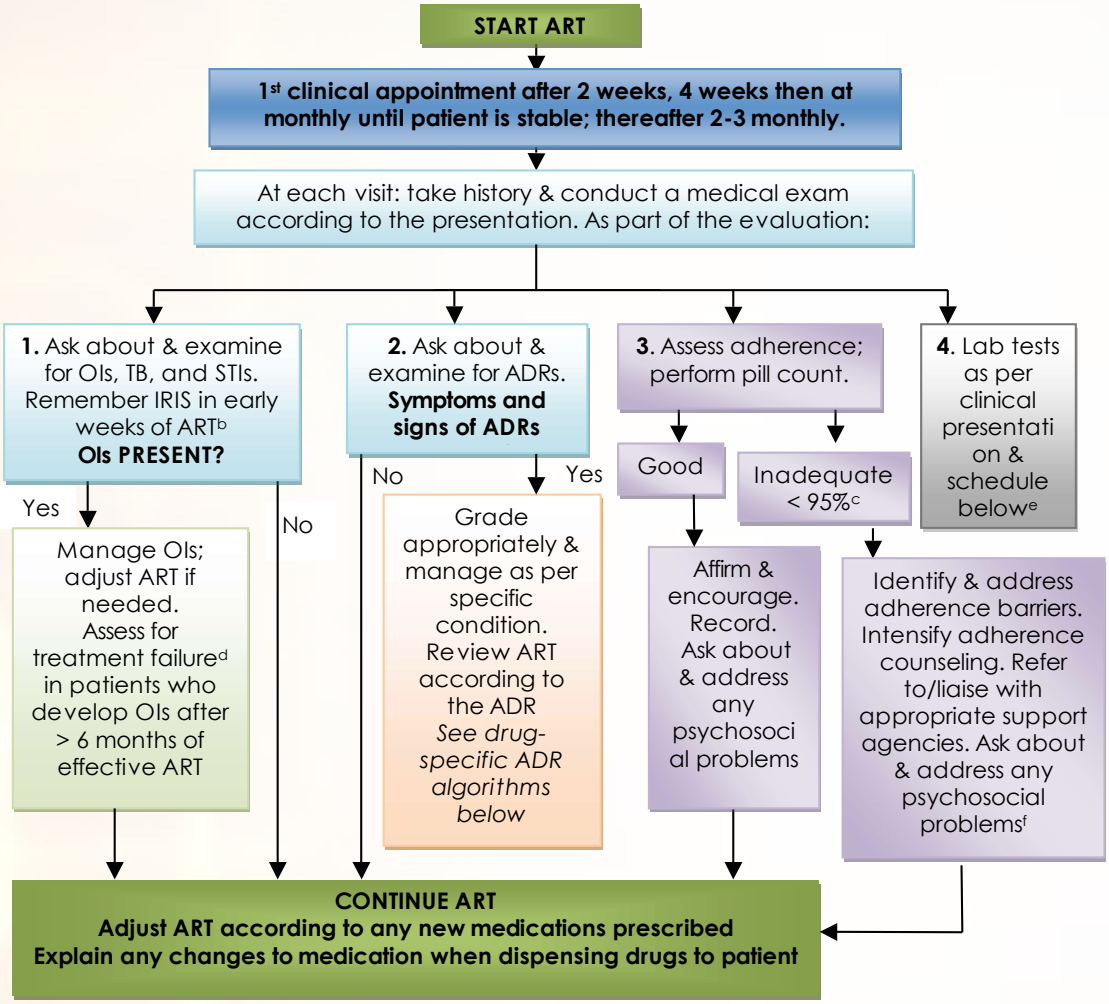
5. DISPENSE MEDICATION

- ***Involve treatment supporter/CG in discussions***
- Do a pill count to assess adherence and reconcile prescription
- Explain any changes to prescription
- Demonstrate & ensure patient understands how and when drugs are to be taken; ask CG to demonstrate
- Explain any food or fluid requirements; demonstrate ways of disguising foul taste of some medicines
- Instruct patient/CG how drugs are to be stored
- Advise patient to avoid herbal or self-medication
- Emphasize next appointment date

Table 13: Summary of Schedule of Laboratory Tests for Patients on ART

	Week		Month								
Appointment	**0**	**2**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**STABLE**
Wt, Ht1,	+	+	+	+	+	+	+	+	+	+	Every visit
Clinical											
Evaluation,											
ADRs											
Adherence	+	+	+	+	+	+	+	+	+	+	Every Visit
check											
Check ART	+	+	+	+	+	+	+	+	+	+	Every Visit
doses with											
weight											
FBC	+		+[2]		+[2]		+			+	Every 6mo
LFTs (ALT)	+	+[8]	+[3,8]	+[8]	+[3,8]		+			+	Every 6mo
Creatinine4	+				+		+			+	Every 6mo
Pregnancy											
Test5 (PT)											PRN
Urinalysis	+				+		+			+	Every 6mo
Fasting Lipid											
Profile &											
Glucose6	+						+			+	Annually
CD4 count/ %	+						+			+	Every 6mo
Viral Load7	+						+			+	Every 6mo

[1]Height should be measured in children regularly to monitor growth and at initial assessment in adults, for BMI calculation
[2]Schedule when AZT is used
[3]Schedule when NVP is used
[4]All pts should have creatinine done if available. NRTI doses may need adjustment if renal function (RF) abnormal. TDF should be avoided if RF abnormal (See Table 21).
[5]PT should be done at baseline if EFV is to be used; thereafter PRN
[6]Schedule if PIs used
[7]Where resources allow. Baseline VL NOT necessary for ART initiation
[8]Schedule in pregnant women: ALT should be done at baseline, 2, 4 weeks then monthly until woman delivers; especially important in women with CD4 >250 at ART initiation on NVP-based regimen.



a Stable patients are those with no clinical conditions requiring on-going treatment, who have been on ART for some months (e.g. 6 months), understand the requirements of ART and are adherent. bSee OI Manual. cE.g. > 3 missed pills/month if on a triple FDC like triomune. dSee pgs 27-28. eAssess & manage lab abnormalities appropriately. fWhere adherence is deemed to be extremely poor & not correctable in the short term, the clinical team may decide to discontinue ART while contributing issues are resolved. In patient record adherence > 95% is termed "satisfactory" and that <95% "unsatisfactory" ADRs = adverse drug reactions.

CHAPTER 2:

Treatment Failure And Second Line Treatment Regimens In Adults

2.1 Introduction

Treatment failure (TF) should be suspected if there is a clinical or immunological deterioration. Where TF is suspected a thorough review of the patient's clinical notes, CD4 history and adherence history must be carried out to define the trends over time. Viral load tests if available can be very helpful especially where the clinical or immunological indicators are not conclusive. A thorough adherence review is mandatory and should include assessment of social and financial circumstances where necessary, to ensure future treatment success. HCWs and patients should aim to get the maximum longevity out of the first line treatment. If well tolerated and taken correctly the 1st line regimen can last several years while still effective.

Table 14: Definition of Treatment Failure (TF)

	CLINICAL	IMMUNOLOGICAL1	VIROLOGICAL
ADULTS	After 6 months of effective ART the following should trigger assessment for/ indicate TF2: o Recurrence of prior opportunistic conditions o Onset of new WHO Stage 3 & 4 conditions	o Fall of > 50% of CD4 from peak value o Return of CD4 to ≤ pre-ARV treatment level	o Failure to reduce VL to undetectable levels after 24 weeks of effective ART o A sustained increase in VL after a period of full suppression
CHILDREN	The following clinical conditions should trigger an assessment for TF after at least 6 months of effective ART include: o New or recurrence of WHO Stage 3 or 4 disease o Lack of or decline in growth response over a 6-month period, after treating for excluding other causes, e.g. malnutrition, TB o Failure to meet neuro-developmental milestones	o Return in CD4 cell percentage or count to pre-therapy baseline or below threshold levels for age o > 50% fall from peak level on ART of CD4 cell percentage or absolute count o New progressive age related severe immunodeficiency o Development of severe Immunodeficiency after initial immune recovery o Rapid rate of decline to below threshold of age related severe immunodeficiency o For these with servere Immunodeficiency (CD4 < 15%) if decline continues do not wait!	o Persistently elevated VL despite effective ART o Progressive increase in VL after starting effective ART o Repeated VL detection in children with earlier undetectable levels

1CD4 preferably done in the absence of concurrent infection 2Treatment Failure

2.2 Principles &criteria for Changing to Second Line ART Regimen

- Do not rush into 2nd line treatment.
- Discuss failing patients in a multi-disciplinary team meeting to get input on all aspects of their care.
- Ascertain if poor adherence is the cause of failure of 1st line ART; address adherence issues before introducing 2nd line. If adherence can't be improved upon, attempt directly observed therapy with a family member, CHW or a friend
- In patients with weight loss, consider TB as a possible cause.
- PTB in patients on ART does not necessarily indicate TF; look for other clinical, immunological (and virological) evidence
- Development of the Immune Reconstitution Inflammatory Syndrome (IRIS), which may occur in the first 6 months of treatment, should not be considered as treatment failure.
- When initiating second-line treatment review ART history including previous preventive therapy for MCT
- The new regimen should include as many active new drugs as possible; change entire regimen where possible
- Review all other medications for drug interactions with new ARV drugs
- Do not discontinue ART regimen until the new regimen becomes available2

2Once TF is diagnosed, the failing regimen should not be stopped until the new 2nd line drugs become available; if failing ART is stopped, a rapid rise in VL & fall in CD4 occurs increasing the likelihood of severe OIs & death. Continuation of a failing ART allows further resistant mutations to develop; this may compromise future treatment options. To reduce the likelihood of further resistant mutations developing while still maintaining the CD4 count, 3TC can be continued on its own, pending the availability of a 2nd line regimen.

Table 15: Second Line ARV Drug Treatment after Standard 1st Line in Adults and Adolescents

STANDARD 1ST LINE REGIMEN	2ND LINE REGIMEN
D4T or AZT + 3TC + NVP or EFV	TDF or DDI + ABC + LPV/r

1. LPV/r is sited here since it is the only PI/r presently available in the public sector. This may change in the future as other PI/r FDCs become available.
2. Patients on ABC-containing 2nd line treatment who develop hypersensitivity to ABC can be treated with TDF/AZT/PI/r OR ddI/3TC/PI/r.
3. Nelfinavir or other heat stable PI/r can be used instead of LPV/r in cases where refrigeration is not available for the LPV/r soft gel formulation. (Heat stable LPV/r is likely to be available from mid 2007)
4. TDF should ideally not be used in children and young adolescents; unless no other options exist. TDF is not recommended in pregnancy.

Table 16: Alternative Options in Patients on Other Initial Regimens

ALTERNATIVE FIRST LINE	SUBSEQUENT SECOND LINE
AZT/3TC/EFV or NVP	ddI/ABC[2]/ LPV/r[1];TDF[3]/ABC[2]/ LPV/r[1];
ddI/d4T/EFV or NVP	TDF/3TC/ LPV/r[1] or ABC/3TC/ LPV/r[1]
TDF[2]/3TC/EFV or NVP	AZT/TDF/ LPV/r[1]; 3TC/AZT/ LPV/r[1]
TDF[2]/FTC/NVP or EFV	AZT/TDF/ LPV/r[1]; 3TC/AZT/ LPV/r[1]
ABC/3TC/AZT	NNRTI/ LPV/r[1]/TDF or NNRTI/ LPV/r[1]ddI
d4T/ddI/ IDV[4]	TDF/3TC/ LPV/r[1] or ABC/3TC/ LPV/r[1]
AZT/3TC/IDV[4]	TDF/ABC/ LPV/r[1] ddI/ABC/ LPV/r[1]

[1] See 1 and 3 under table 16 above. [2]See 2 above. [3] See 4 above

Table 17: Second Line ARV Drug Treatment after Standard 1st Line in Children

Second-line Treatment Regimen after Standard 1st Line Treatment
Didanosine (DDI) + Abacavir + LPV/r

Note: DDI should be taken on an empty stomach

Table 18: Dosages of Second Line Drugs in Adults and Adolescents*

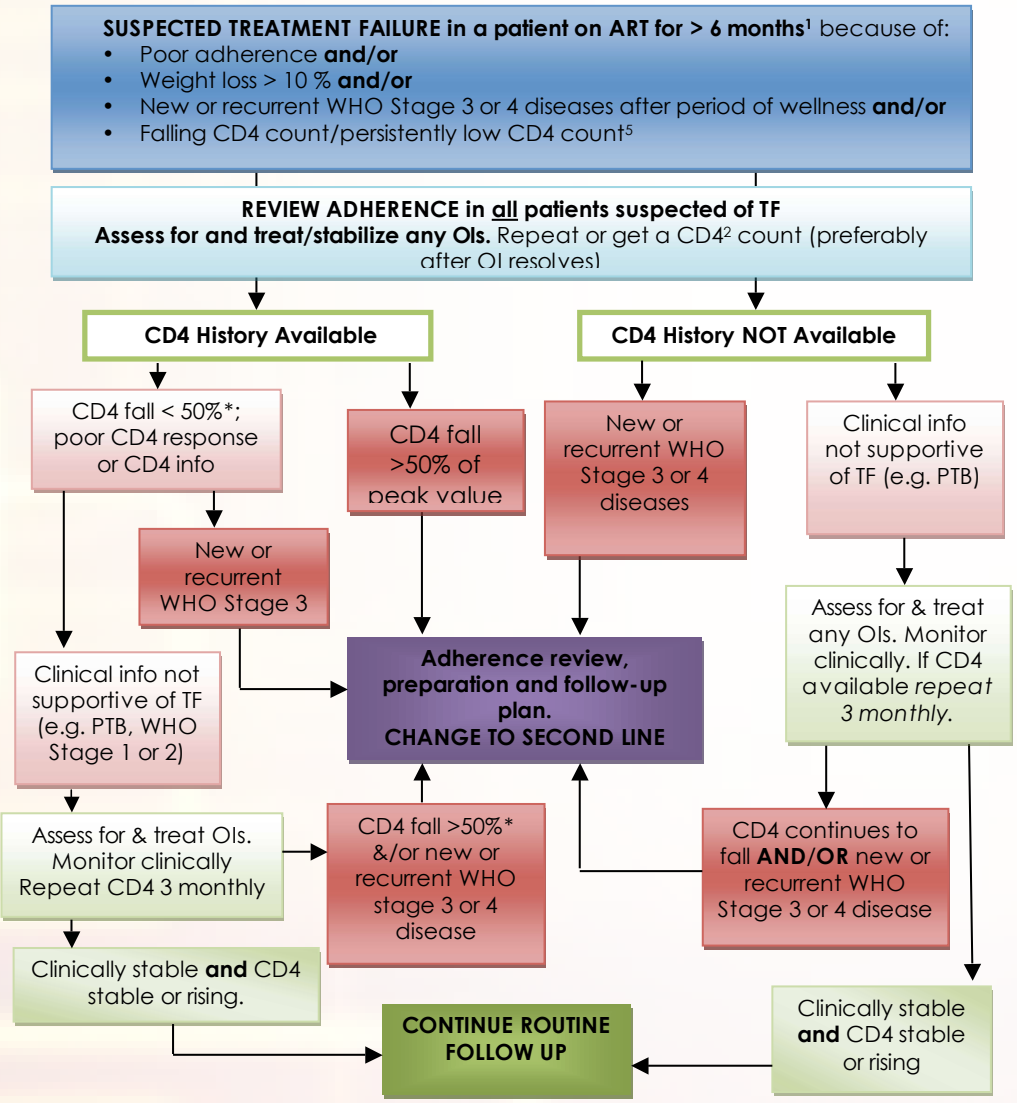
Generic name	Form	Dosing Recommendation	Food Effect
Didanosine	Enteric coated capsules (EC): 125, 200, 250 or 400 mg. Buffered tabs (BT): 25, 50, 100, 150, 200 mg	**Weight >60 kg:** 400 mg OD (BT or EC capsules) or 200 mg BD (BT). **Weight < 60 kg:** 250 mg OD (BT or EC capsule) or 125 mg BD (BT)	Take ½ -1 hour before or 2 hours after meal. Levels decrease 55%;
Abacavir (ABC)	300mg tablets	300mg BD	Take without regard to meals. Alcohol increases ABC levels by 41%; avoid
Tenofovir Disoproxil Fumarate (TDF)	300mg tablets	300mg OD	Take without regard to meals.

Lopinavir / Ritonavir	SGC: Each capsule contains LPV 133.3 mg + RTV 33.3 mg HS: Each tab contains LPV/r 200/50 for adults and 100/50 for children	(LPV 400 mg + RTV 100 mg) 3 capsules BD Adults: 2 tabs BD	Moderate fat meal increases AUC of capsules by 48%. Take with food. No food requirements
Nelfinavir	250 mg tablets or 625 mg tablets	1250 mg BD or 750 mg TID	Essential to take with fatty meal or snack. Levels increase 2 – 3x.

*For CLHA see the chart in Appendix 6 for correct dosing of 2nd line treatment.

CHANGING TO SECOND LINE TREATMENT BASED ON CLINICAL AND IMMUNOLOGICAL INDICATORS

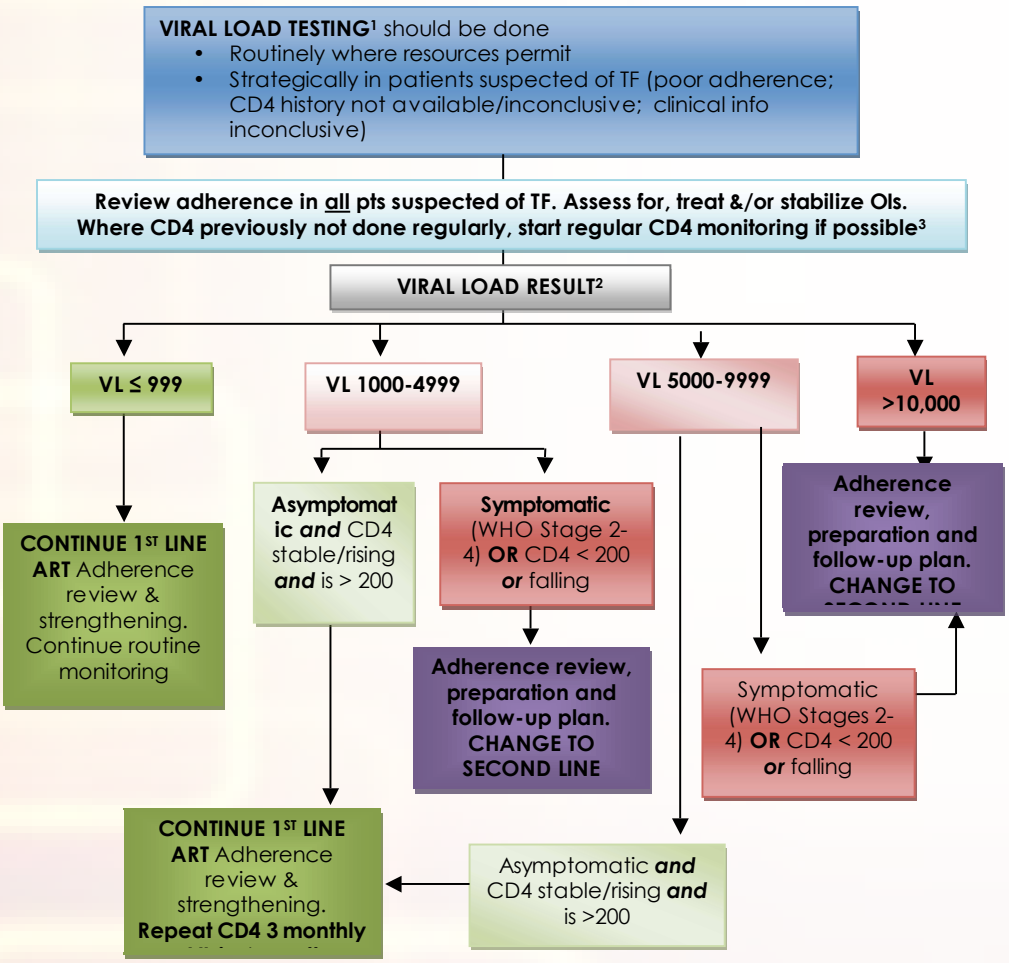
To facilitate timely diagnosis of treatment failure (TF), summary information for each patient on ART (including key longitudinal data such as weight, CD4 count and OIs) should be readily accessible to HCWs at each clinic visit. Pts suspected of TF should be discussed by a multidisciplinary team to ensure that all aspects of care are assessed and optimized.



1OIs in the first 6 months are unlikely to be an indication of ART failure in adherent pts; consider IRIS. 2Many pts may not have had regular CD4 counts done when ART was first initiated; CD4 tests increasingly accessible &, where possible, should be done in all pts on ART 6 monthly. 3Do NOT stop current ARVs until new drugs are available. 4If pt needs anti-TB as well as 2nd line treatment, discuss with senior clinician and see pg 43. 5CD4 rise on effective ART averages 100-150/year; poor CD4 response can occur in pts who are otherwise clinically well. Without viral load it can be difficult to determine if they are failing ART. * CD4 fall > 50% of peak value attained on ARV treatment.

CHANGING TO SECOND LINE TREATMENT BASED ON VIRAL LOAD TESTING: RECOMMENDATION FOR A RESOURCE-LIMITED SETTING

Plasma human immunodeficiency viral RNA measurement (Viral Load, VL) is the most useful tool for assessing response to treatment. Unfortunately it is still only minimally available. Where resources allow, all patients on ART should have a VL done at baseline and then every 6 months. If access is limited, it may be used strategically to support diagnosis of treatment failure (TF) in patients with inconclusive clinical or immunological indicators suggestive of TF. Ideally VL results should be confirmed prior to changing treatment



CHAPTER 3:

Adverse Drug Reactions And Co-morbidity In Patients On Art

3.1 ADVERSE DRUG REACTIONS (ADRs)

3.1.1 Introduction

- Side effects or ADRs are the commonest reason for which patients change their ARV drug treatment. Other potential reasons for treatment change include co-morbidity, pregnancy, drug stock outs.
- ADRs are also a common cause of non-adherence to ART.
- Mild side effects like headache, nausea, and fatigue are common with ARV drugs. Patients should be informed that minor side effects are common with ART, especially at the initiation of ART, but are generally transient and tend to resolve within weeks. While symptomatic treatment may be necessary, discontinuation of ART is rarely needed.
- Potentially severe ADRs while less common can be disabling or life-threatening. Some may occur early after ART initiation, e.g. NVP-associated rash and hepatotoxicity. Others occur later, after several months on ART, e.g. metabolic complications like lipodystrophy and lactic acidosis. ALL potentially severe ADRs should be recorded in patient notes and in the ART register, and reported as required.

3.1.2 Principles of Managing ARV Drug Toxicity

- Educate patient/CG on predictable ADRs related to the ART regimen used and what the patient/CG needs to do should the ADR(s) occur. Do NOT alarm the patient/CG.
- Establish that the adverse event is likely to be due to ARV drug(s); consider other medication or other disease process.
- Assess the severity of the ADR; manage the toxicity accordingly.
- Where alternative drugs are available and treatment substitution is deemed necessary, change of ARV drug should be prompt; this is important because some of the ARV-related ADRs respond poorly to treatment substitution and may not be fully reversible, e.g. lipodystrophy, peripheral neuropathy.
- In the setting of good therapeutic response, the development of a clearly definable toxicity permits single-drug substitutions without compromising the overall regimen, e.g. d4T/TDF to replace AZT in patients with AZT-related anaemia.
- Sometimes the entire ART regimen needs to be discontinued; e.g. life-threatening lactic acidosis necessitates ART discontinuation. After patient recovery, ART can be resumed using a regimen that contains drugs unlikely to cause the particular ADR.
- For patients who have been on ART for many months, always consider and assess the patient's treatment response prior to changing ARV drug. If treatment failure is likely or suspected, single-drug substitution is not appropriate.
- Treatment should be stopped if severe or life-threatening reactions occur. Manage the medical event prior to reintroducing ARV drugs using an appropriately modified regimen.

3.1.2 Discontinuation of ARV therapy

Once patients are on current ART regimens, treatment should continue indefinitely. Occasionally it may be necessary to discontinue treatment, for instance in cases of

- Extremely poor adherence
- Serious drug toxicities (ADRs)
- Severe co-morbidity that precludes oral therapy, presents untenable drug interactions or pill burdens that patient cannot tolerate.

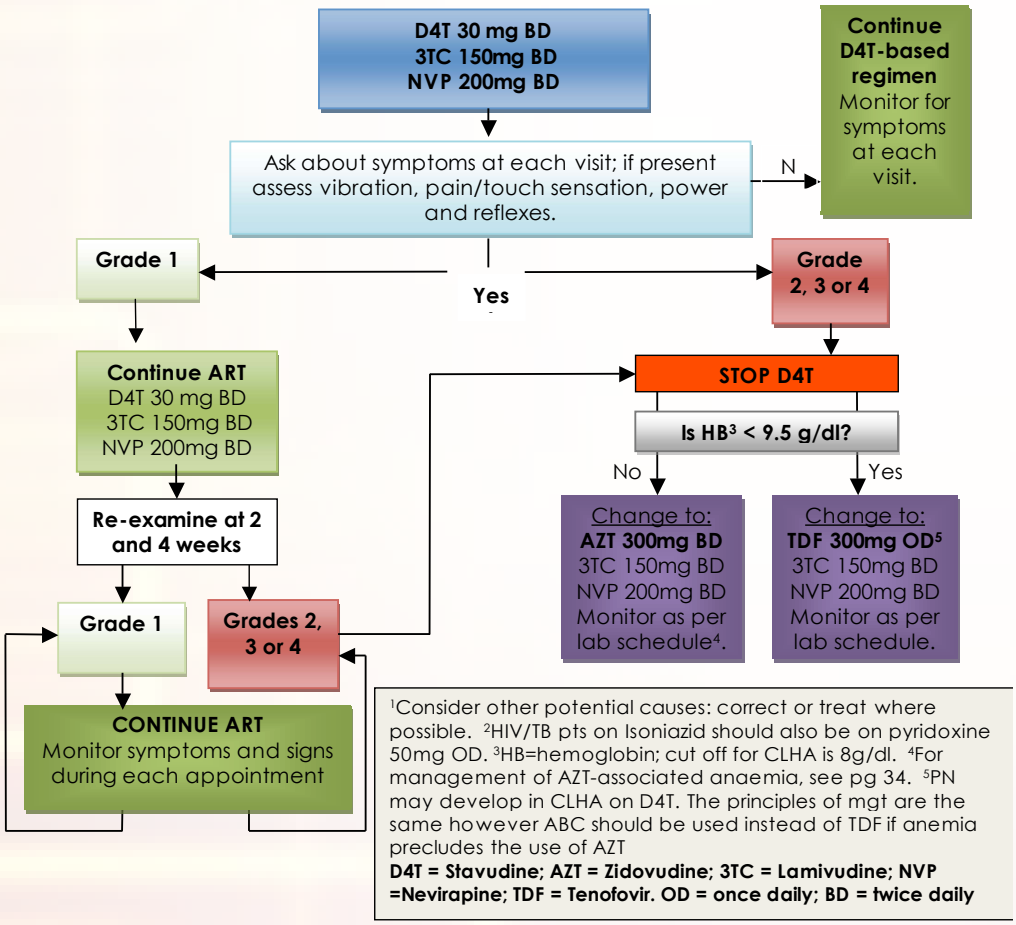
Discontinuation should only be considered after exploring all potentially corrective measures, including intensive counselling, additional CG education and family support for non-adherence.

Stopping NNRTIs

Stop the NNRTI and continue the NRTI backbone (e.g. 3TC + d4T) for a period of 2 weeks after stopping the NNRTI in patients likely to use a NNRTI in the future. This is necessary to avoid NNRTI drug resistance which may develop if NNRTIs are discontinued at the same time as the NRTI backbone. This is explained by the difference in half life (t ½) of the drugs: NNRTIs have very long t ½ while many of the NRTIs have a comparatively shorter t ½. Prolonged exposure to functional monotherapy with an NNRTI can rapidly lead to NNRTI resistance.

STAVUDINE-ASSOCIATED PERIPHERAL NEUROPATHY

Before starting ART, all patients should be assessed for pre-existing symptoms and/or signs of peripheral neuropathy (PN – pain, tingling, numbness, and weakness); D4T should be avoided in pts with pre-existing PN. Patients on ART should be asked specifically about symptoms of PN at each visit and advised to return early if symptoms worsen. D4T-associated nerve damage may be permanent, thus the need for aggressive management. Other causes1 of PN should always be considered in symptomatic patients, including other drugs2, malnutrition, alcohol, diabetes mellitus and vitamin B12 deficiency.



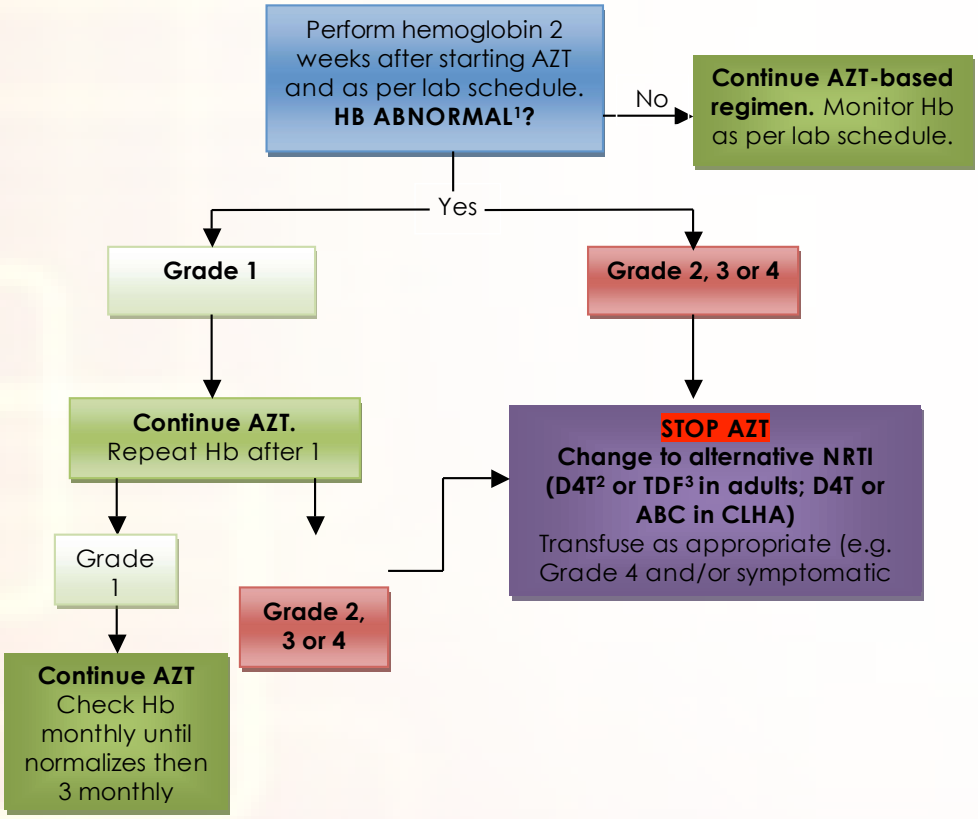
[1]Consider other potential causes: correct or treat where possible. [2]HIV/TB pts on Isoniazid should also be on pyridoxine 50mg OD. [3]HB=hemoglobin; cut off for CLHA is 8g/dl. [4]For management of AZT-associated anaemia, see pg 34. [5]PN may develop in CLHA on D4T. The principles of mgt are the same however ABC should be used instead of TDF if anemia precludes the use of AZT

D4T = Stavudine; AZT = Zidovudine; 3TC = Lamivudine; NVP =Nevirapine; TDF = Tenofovir. OD = once daily; BD = twice daily

	Grade 1	Grade 2	Grade 3	Grade 4
Symptoms	**Asymptomatic/mild.** No/little impact on social or functional activities	**Moderate:** Some interference social or functional activities	**Severe:** Continuous pain; difficulty walking.	**Incapacitating:** Severe pain. Cannot walk
Motor	Asymptomatic. Minimal weakness on exam. Normal walking	Symptomatic. Cannot walk on tiptoes or do full knee bends. Walks independently	Severe symptoms. Cannot rise from chair; needs assistance walking	Incapacitating symptoms. Bed or wheel chair bound. Severe motor weakness.
Sensory	Asymptomatic/mild burning, tingling. ± sensory changes on exam.	Symptomatic: pain, burning, tingling. Sensory alteration on exam	Severe sensory symptoms; sensory alteration on exam	Disabling sensory symptoms. Sensory alteration on exam

ZIDOVUDINE-ASSOCIATED HEMATOLOGICAL TOXICITY

AZT-associated bone marrow toxicity often affects the red cells causing anaemia, but can also result in neutropenia. Most patients with AZT-associated anaemia present within the first 3 months after starting ART. All patients starting ART including AZT should be assessed for anaemia, the cause investigated and corrected if found; remember that HIV per se can cause anaemia. In adults and adolescents do not start AZT if the baseline Hb < 9.5 g/dl and/or absolute neutrophil count < 750/mm3; in children do not start AZT if Hb < 8 g/dl.



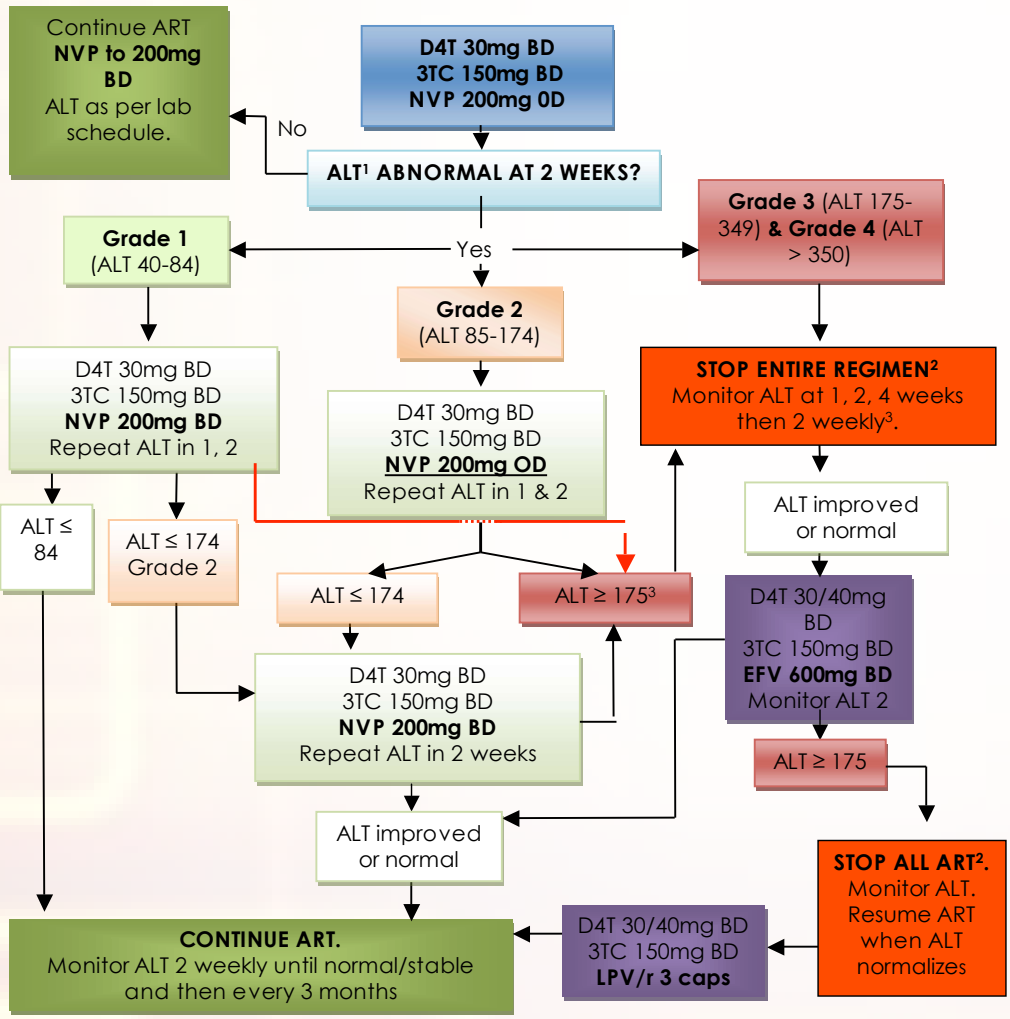
Haematological Index	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin (g/dl)	8.5 – 9.4	7.5 – 8.4	6.5 - 7.4	≤ 6.4
Neutrophils (cells/mm³)	1000 – 1300	750 – 999	749 - 500	≤ 500

[1]If Hb abnormal at any time in a pt on AZT, exclude other causes (see OI Manual); if deemed to be AZT-related manage as per the algorithm. [2]D4T should not be used in pts with a history of peripheral neuropathy. In pregnant women who need AZT as part of PMCT replace AZT with d4T if HB < 9.5 g/dl.

AZT=Zidovudine; TDF=Tenofovir disoproxil fumerate; D4T= Stavudine; Hb=haemoglobin

NEVIRAPINE-ASSOCIATED HEPATOTOXICITY: MANAGEMENT OF PATIENTS PRESENTING EARLY AFTER ART INITIATION

NVP is the most common cause of ARV-associated liver toxicity. Early NVP hepatotoxicity is more likely in women especially if pre-treatment CD4 > 250 cells/mm3; where NVP is used in such pts, careful clinical and lab monitoring is essential7. Initiate NVP as per guidelines to reduce risk of toxicity. All patients starting NVP should be monitored as per lab schedule in Table 14. Pts with a baseline ALT ≥ 175 IU/L (Grade 3+) should not be started on NVP unless the abnormality resolves. Pts with abnormal LFTs should have a viral hepatitis screen if possible (see ART Guidelines for management of co-infected pts).

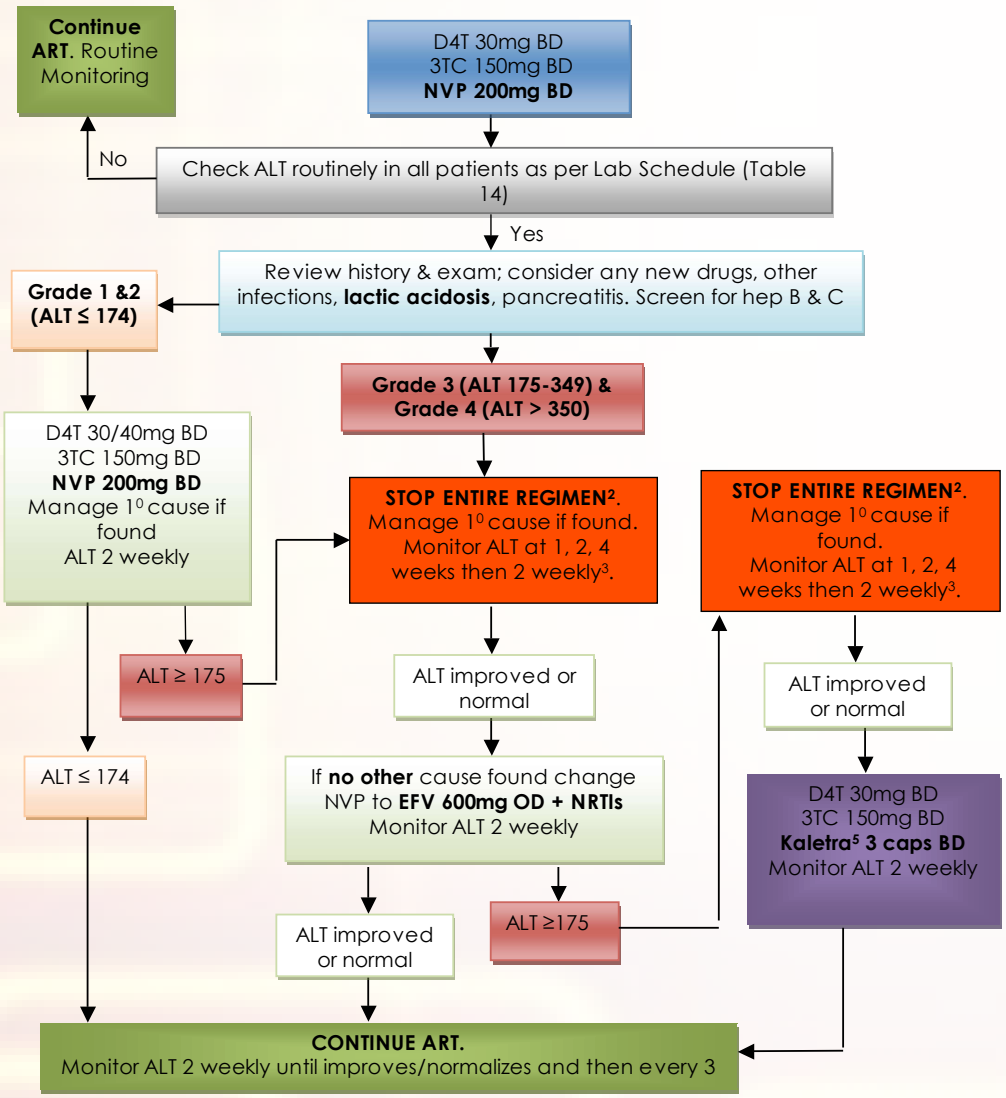


Normal ALT	Grade 1	Grade 2	Grade 3	Grade 4
< 35 (1xULN)[6]	40-84 (1.25-2.5xULN)	85-174 (2.65.0xULN)	175-349 (5.1-10xULN)	> 350 (>10xULN)

[1] ALT (alanine aminotransferase) or SGPT in international units/litre (IU/l); [2] Severely ill patients should be admitted, LFTs monitored & supportive care provided; [3] ART should be resumed as soon as LFTs improve & pt stabilizes; where LFTs fail to improve, consider other causes including other drugs; [4] PIs less likely causes of hepatotoxicity than NNRTIs.[5]Other PI/r may be used instead where available. [6]ULN = upper limit of normal.[7]Other risk factors for NVP toxicity include pre-existing liver disease (hepatitis, cirrhosis, alcoholism), use of other hepatotoxic drugs (anti-TBs) **D4T - Stavudine; 3TC – Lamivudine; NVP – Nevirapine; EFV – Efavirenz; LPV/r = Kaletra. OD – once daily; BD – twice daily**

NEVIRAPINE-ASSOCIATED HEPATOTOXICITY: MANAGEMENT OF ABNORMAL LFTs OCCURING AFTER THE FIRST 2 WEEKS

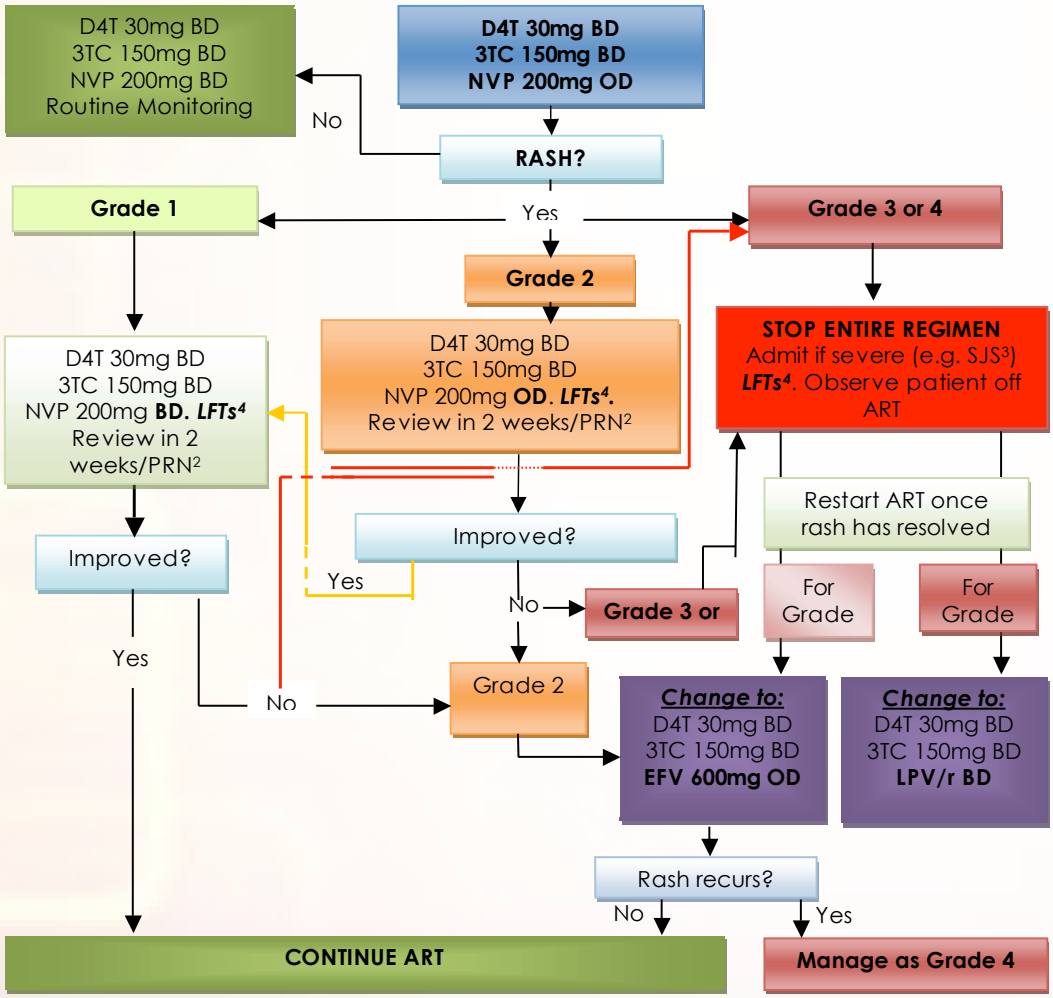
Early NVP-associated hepatotoxicity is a hypersensitivity type of reaction with most patients presenting within the first 12 weeks and rarely > 18 weeks after starting ART. Apart from all ARV drugs, 1other causes of hepatitis, including other drugs, should always be considered in pts presenting with abnormal LFTs and/or symptomatic liver disease several months after ART initiation.



For hepatotoxicity grading see pg **27.** [1] ALT (alanine aminotransferase; SGPT) in international units/liter (IU/l); [2] Admit severely ill patient, and exclude other causes; do full LFTs & provide supportive care; [3] Frequent LFTs required in severe toxicity; [4] Where LFTs fail to improve despite ART discontinuation, consider other causes of hepatitis; [5] PIs although less likely causes of hepatotoxicity than NNRTIs may also cause hepatotoxicity. (If **other cause identified** manage specifically; it may be possible to continue with **NVP+NRTIs)**

NEVIRAPINE-ASSOCIATED RASH

A mild rash is very common when starting NVP as part of ART1. To reduce the likelihood of NVP-associated toxicity, start NVP 200 mg OD for the first 2 weeks before escalating the dose to 200mg BD in patients who tolerate the treatment. Patients who develop any rash should be advised to attend the clinic immediately for assessment.

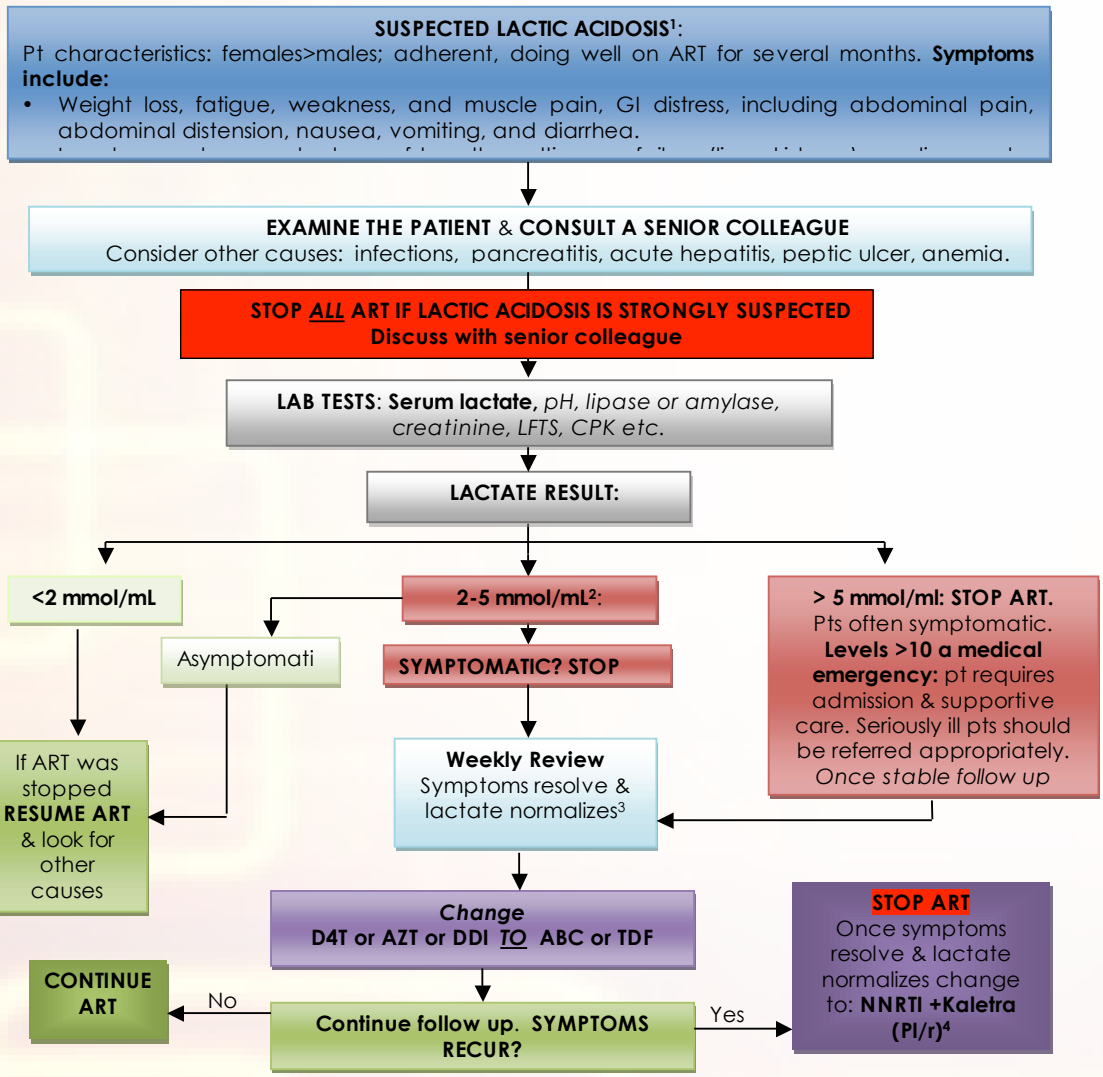


Rash Severity	Grade 1	Grade 2	Grade 3	Grade 4
Description	Localized itchiness, redness, involving < 50% of body. (pruritus, erythema)	Diffuse maculopapular rash involving >50% body	Diffuse rash with vesicules, limited bullae, superficial ulceration of mucous membranes limited to 1 site	Extensive bullous lesions **or** Stevens-Johnson syndrome (SJS) **or** ulceration of mucous membrane involving two **or** more distinct mucosal sites

[1]Greatest risk of rash in 1st 6 weeks; consider other drugs as potential causes in pts who develop a rash **> 2 mo** after ART initiation. [2]Pts with rash under observation should be reviewed in 2 weeks **OR** earlier at any time if the rash worsens. [3]SJS – Stevens-Johnson Syndrome.[4]Rash together with abnormal LFTs indicates a severe hypersensitivity reaction with multi-system involvement; close monitoring is needed. Note that pts with sulpha allergy are 5X more likely to experience NVP-associated skin rash; use NVP in the standard way & monitor

MANAGEMENT OF LACTIC ACIDOSIS

Lactic acidosis is a relatively rare, late side effect of NRTI use, primarily D4T > DDI > AZT. Fatty liver & pancreatitis may develop; fatal hepatitis can occur mainly if D4T + DDI are combined, more so in pregnancy. Measure serum lactate levels for diagnosis & to monitor pt's recovery. Blood for lactate should be taken > 24hr after exercise without using a tourniquet, the sample transported in ice & tested within 4hr to avoid false high levels. Do NOT use lactate test as a screening tool in asymptomatic pts; mildly elevated levels are common in well pts on ART2.

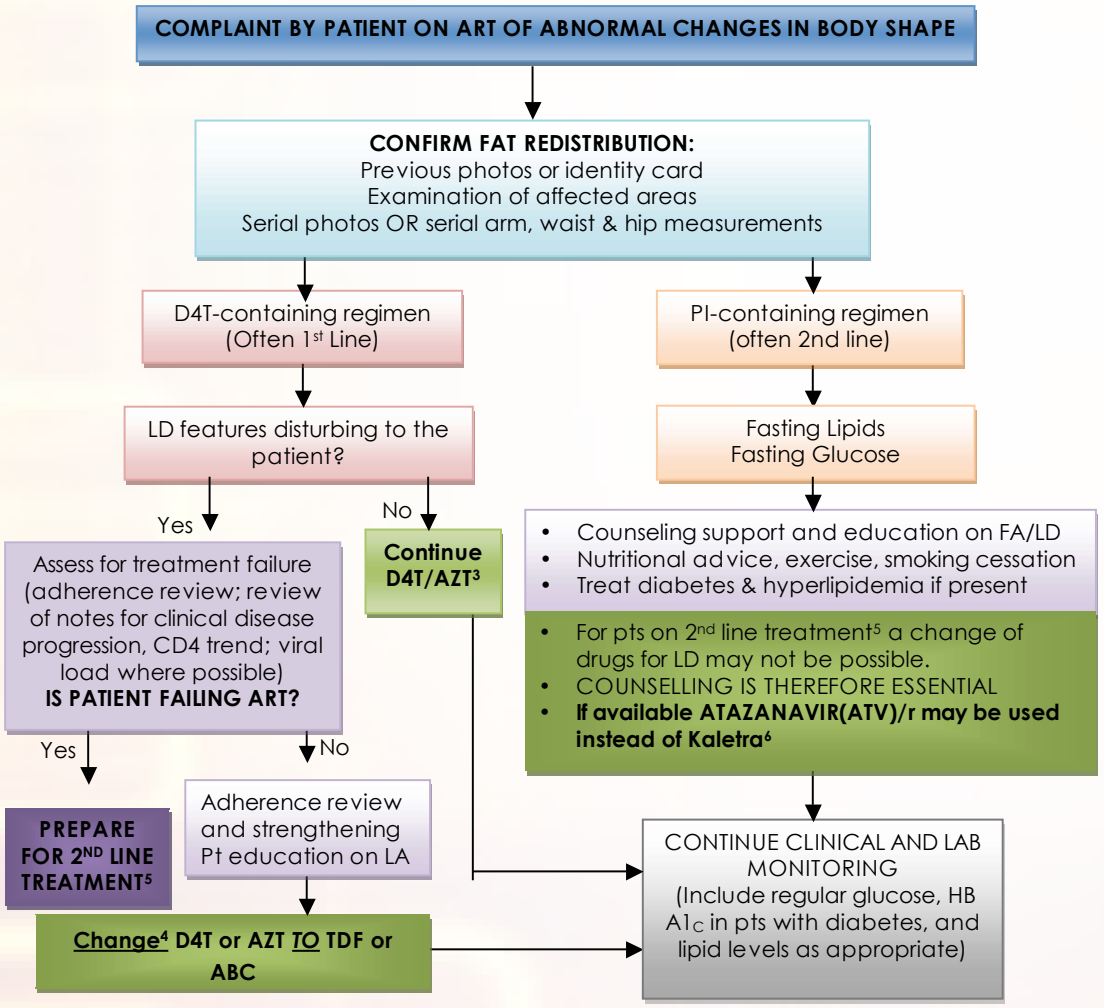


Normal	Mild (2-5Mm)	Moderate (5-10mM)	Severe (> 10mM)
Serum lactate < 2mM	Mild hyperlactatemia in asymptomatic pts requires no intervention. Symptomatic pts need NRTI modification	**STOP ART.** Provide supportive therapy. Substitute offending NRTI once pt recovers. **HIGH MORTALITY.**	**STOP ART.** Provide necessary supportive therapy. Substitute offending NRTI once pt recovers. **VERY HIGH MORTALITY**

[1] A diagnosis of lactic acidosis requires a high index of suspicion because of the non-specific nature of symptoms. Risk factors: women, obesity, duration of ART, use of D4T + DDI, D4T, DDI less with AZT. [2]Lactate levels should not be measured in asymptomatic pts; while lactate is often raised in well pts on NRTIs, mildly raised levels are not predictive of lactic acidosis. [3]Recovery takes a long time; lactate levels may take 4-28 weeks to normalize. **If lactate levels are not available, ART**

MANAGEMENT OF LIPODYSTROPHY

HIV-associated lipodystrophy (LD) consists of both physical (stigmatizing fat redistribution) and metabolic changes. The fat changes include both fat accumulation (FA) in the abdomen, breasts[1] and over the dorso-cervical spine ("buffalo hump"); and fat loss (lipoatrophy, LA) or wasting in the face, arms & legs (with prominence of veins), as well as the buttocks. Metabolic changes including diabetes mellitus and raised lipids may also occur in pts with LD. LA is associated with prolonged use of some NRTIs, D4T >> AZT; FA is more common with PIs although it may also be seen in pts with LA.



[1]Enlarged, sometimes painful breasts is seen as part of FA in women. Men may also develop gynecomastia in which case they should be assessed for tumor & hypogonadism; it is not clear exactly which ARVs are responsible for gynecomastia. [2]Confirmation of fat changes may be difficult without previous measurements/photos. [3]HCWs should proactively offer a change in ART where possible in pts with LD without complaints. [4]Pts who have had treatment change for LD should be informed that recovery is very slow and may be incomplete. [5]Pts changing to 2nd line may continue to develop further body changes and should be provided with counseling support. [6]ATV has minimal effects on lipids & may have less effects on fat distribution than other PIs

3.1.3 Abacavir Hypersensitivity

- Genetically determined; risk higher in females and those with higher CD4 counts
- Presentation is commonly in the first 2 months following ABC treatment initiation; median time to symptoms developing is 8 days.
- Symptoms are non-specific and include fever, rash, respiratory symptoms, GI symptoms, hepatitis with raised transaminases. Symptoms may worsen with each additional dose of ABC.
- Discontinue drug; admit patient for observation as symptoms may worsen before improving.
- NEVER re-challenge once diagnosis is made; death may occur.

3.2 CO-MORBIDITY IN PATIENTS ON ART

3.2.1 Drug Interactions

- HCWs should be aware of the interactions between ARV drugs and other drugs that are commonly used.
- Drug interactions may be troublesome in patients with opportunistic infections and other medical conditions who also require ART
- Important interactions occur between rifampicin and both the NNRTIs and PIs. (See below)
- Both EFV and NVP drug levels are reduced to some extent, EFV less so than NVP
- PI drug levels are largely reduced so much, or toxicity likely that generally they should not be used in combination with rifampicin
- Patients on rifampicin for TB treatment who need to start ART (ARV naive) should ideally be started on efavirenz. Once rifampicin therapy is completed, patients may if necessary be changed to NVP; in this case NVP should be started at the full dose (e.g. in adults, 200mg BD), 2 weeks after rifampicin has been discontinued.
- If EFV is preferred but is not available, or if EFV is not suitable for instance in children < 3years and/or < 10kg, ARV-naïve patients may be given triple nucleoside regimen with rifampicin and the ART changed to a standard regimen after TB treatment is complete or after the rifampicin is discontinued.
- Evidence is emerging suggesting that NVP can also be used together with rifampicin; HIV treatment outcome seems to be unaffected. Concerns remain with regard to hepatotoxicity. In the absence of alternative drugs NVP may be used with anti TB treatment with close monitoring for toxicity. (WHO ART Guidelines, 2006. Refer to the Guidelines for Antiretroviral Drug Therapy in Kenya, Pgs 112-120 for drug interactions and management)

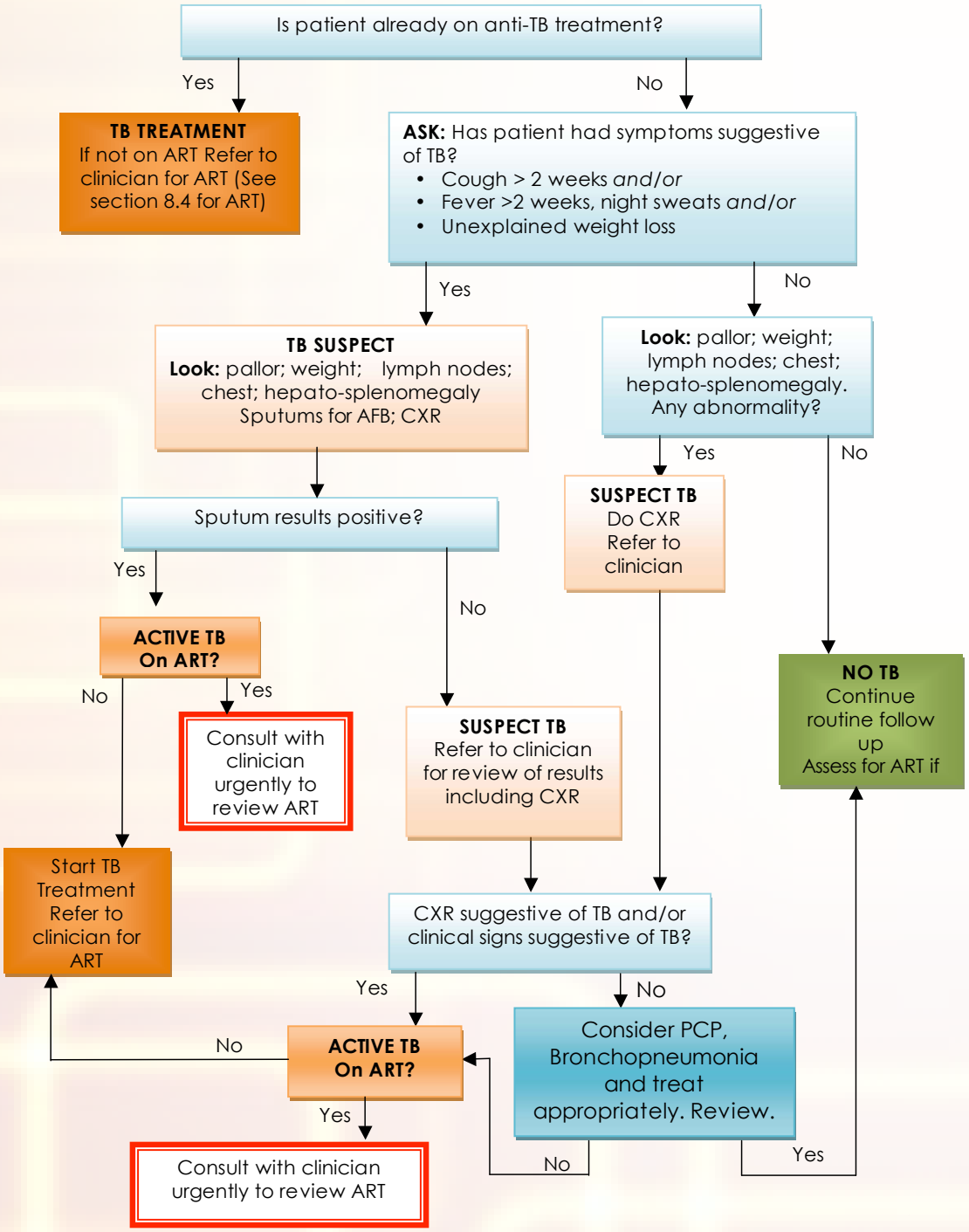
3.2.2 Antiretroviral Therapy and Tuberculosis Treatment

3.2.2.1 TB/HIV Collaborative Management

- Screen all PLHA/CLHA for TB at initial enrolment into HIV care and at each clinical appointment (pg 41)
- Test all TB patients for HIV infection
- Start all TB/HIV co-infected patients on CTX
- Give priority to TB treatment in TB/HIV co-infected patients
- Assess all TB/HIV co-infected patients for ART: start ART during the course of TB treatment in TB/HIV co-infected patients who qualify for ART
- Dual treatment of TB/HIV co-infection is complicated by
  - Drug interactions involving rifampicin with NNRTIs and PIs.
  - Overlapping toxicities e.g. INH and D4T both cause peripheral neuropathy
  - High pill burden of combined ARV and anti-TB drugs.

SCREENING FOR TB

Review TB status at baseline, at each clinical appointment and in symptomatic patients



3.2.2.2 Recommendations for When to Start ART in HIV/TB Co-infected Patients

Adults and Adolescents

CD4 COUNT	TREATMENT RECOMMENDATION
NOT available	Start anti-TB treatment Start ART as soon as practicable, preferably in the continuation phase. If EPTB1 start ART in the intensive phase where feasible
CD4 <100/mm3	Start anti-TB treatment Start ART as soon as possible
CD4 count 100-350/mm3	Start anti-TB treatment Start ART after intensive phase of TB treatment
CD4 count >350/mm3	Treat TB. Defer ART and follow up patient

1EPTB = extrapulmonary TB other than TB lymphadenitis

Children

CHILD'S CLINICAL &/OR IMMUNOLOGICAL CONDITION	TREATMENT RECOMMENDATION
Stable but ART is needed	Complete 1st 2 months of anti-TB treatment. Start ART in Continuation phase
Advanced HIV Disease; likely to succumb if ART delayed	Start Anti-TB treatment Start ART in the intensive phase as soon as feasible

3.2.2.3 Choice of ARV Drugs in TB/HIV Co-infected ARV-naïve Patients

PATIENT CATEGORY	RIFAMPICIN-BASED TB TREATMENT (INTENSIVE PHASE OR ENTIRE TB REGIMEN)	NON RIFAMPICIN-BASED CONTINUATION PHASE
Adults & Adolescents	AZT or D4T + 3TC + EFV[1]	AZT or D4T + 3TC + NVP
Pregnant Women	AZT + 3TC + ABC[2] at any gestation OR AZT or D4T +3TC + EFV1 if ≥ 12 weeks gestation	AZT or D4T + 3TC + NVP
Children age below 3 years & weight < 10kg	AZT[4] + 3TC + ABC[2,3]	N/A
Children age above 3 years & weight > 10kg	AZT[4] + 3TC + EFV	N/A

[1] Do a pregnancy test in all pre-menopausal women prior to initiation of EFV. EFV should not be given to women at risk of pregnancy unless effective contraception is used, or in those in the first trimester of pregnancy. For women who commence EFV in the 2nd trimester, if treatment with EFV is to continue post partum, effective contraception should be provided.
[2]Patients who are started on triple nucleoside regimen should be changed to a standard regimen once the TB treatment is complete. (Replace ABC with NVP)
[3]Children who failed prophylaxis (exposed to SDNVP) with TB and who also need ART as well should be started on the triple nucleoside therapy and changed to PI/r-based regimen once anti-TB treatment completed.

3.2.2.4 Choice of ART if patient develops TB while on a successful 1st Line ART

- For adults and adolescents, if on NVP switch to EFV
- For pregnant women on NVP-based ART
  - If in the first trimester switch NVP to ABC; once TB treatment is complete switch ABC back to NVP.
  - If in the second or third trimester, switch NVP to EFV
- For children
- If on NVP switch to ABC (if < 3 years & < 10kg) or EFV (if above 3 years and > 10kg). Once the child completes anti-TB treatment, they should revert back to the national first-line regimen (switch from ABC back to NVP).

Where dual treatment is difficult and is likely to affect adherence to either the TB or the ARV treatment, or where toxicity of dual treatment is a problem, consider delaying/interrupting ART. Start/resume ART after completion of anti-TB therapy.

3.2.2.5 Choice of ART in Patients who develop TB while failing a 1st line ART OR are on a 2nd Line Regimen

- Patients who develop TB on a failing first line regimen need to be changed to 2nd line ARV drug treatment. However, 2nd-line ART regimens are PI-based, and PIs should generally not be used with rifampicin.
- Patients on second line PI-based treatment who develop TB should not be started on anti-TB treatment until the ART regimen is reviewed. Treatment plan for these patients should be agreed upon urgently with a senior clinician.
- While rifabutin is the preferred rifamycin for use in patients on PIs who also need anti-TB treatment, unfortunately it is currently not widely accessible. The following table presents some alternative options for use in patients who have dual infection and need or are receiving PI-based ART.

ART in patients developing TB while on /needing 2nd Line ART

ART Regimen at TB Diagnosis	TB Treatment: Ethambutol-based Continuation Phase	TB Treatment: Rifamycin-based Short Course Regimen*
Failing Standard 1st-Line Regimen	Continue failing 1st-line regimen & commence anti-TB treatment (if on NVP change to EFV). Change to 2nd line regimen during the continuation phase	**Use RIFABUTIN1-based anti-TB treatment. Stop failing first line regimen when 2nd line regimen available. Start 2nd Line treatment.**
Patient on PI-based 2nd-Line Regimen	Stop all ARVs. Start 3TC alone and then start anti-TBs. Stop 3TC and resume 2nd-line treatment in the continuation phase	**Start RIFABUTIN[1]-based anti-TB treatment. Continue 2nd-Line ARV treatment**

*National TB treatment guidelines are in the process of changing to a rifampicin based short course treatment.

1. 1Replace rifampicin with rifabutin and use with PI/r; in the absence of rifabutin Saquinavir/ritonavir may be used at the dose of 400mg SQV/400mg RTV BD with rifampicin. Watch for Hepatotoxicity.
2. Adult dose for rifabutin when used with standard LPV/r dose: rifabutin 150 mg 3X per week
3. Patients who have previously failed 1st-line ARV drug treatment should never be given triple nucleoside therapy if they also need concomitant TB treatment.

3.2.3 Renal and Hepatic Dysfunction and ART

Ideally all patients on ART should have baseline renal function tests (RFTs) - urinalysis and creatinine - for future reference. Patients with impaired renal function should be assessed and investigated in the standard way. The assessment should include determination of:

- Whether the problem is acute (oliguria, anuria, hematuria, recently normal RFTS, oedema, hypertension)
- Whether it is chronic (prolonged symptoms/signs of uraemia, oedema, broad casts, small kidneys on u/s); nephrotic syndrome (proteinuria >3.5g/1.73m2/day, hypoalbuminemia, oedema)
- History of hypertension or diabetes mellitus.
- Drugs used (nephrotoxic drugs as well as those that will need adjustment/ discontinuation)

NRTIs are secreted unchanged through the kidneys; thus, impairment of renal secretory function impairs NRTI excretion, and if severe necessitates dose adjustment. The severity of renal dysfunction is best measured by the glomerular filtration rate (GFR) or the creatinine clearance. If GFR is not available serum creatinine, though less accurate, can be used instead to determine degree of renal dysfunction as illustrated in the rough guide below.

Liver function tests should be carried out as recommended above (See Table 14)

Table 19: Grading of Renal Dysfunction

Grade of Severity of Renal Function	Glomerular Filtration Rate (ml/minute)	Serum Creatinine (µmol/litre)
Mild	20-50	150-300
Moderate	10-20	300-700
Severe	<10	>700

Table 20: ARV Drug Adjustment in Renal and Hepatic Dysfunction

Drug	Daily Dose	Mild Renal Failure (GFR 20-50) Moderate	Renal Failure (GFR 10-20) Severe	Renal Failure (GFR <10)	Hepatic Dysfunction[1]
AZT	600 mg	Unchanged	Unchanged	300mg OD	Caution
D4T	60 mg	20 mg daily	20 mg daily	15 mg daily	Caution
3TC[1]	300 mg	150mg daily	100 mg daily	50 mg daily	Unchanged
DDI >60/ <6okg	400/250 mg	200/125mg daily	125/100mg daily	125/75mg daily	Unchanged
TDF	300 mg	300 mg 48 hourly	Do not use	Do not use	Unchanged
ABC	600 mg	Unchanged	Unchanged	Unchanged	Avoid if severe
FTC	200 mg	200 mg q48h	200 mg q72h	200 mg q96h	Not defined
PIs	Standard dose	Unchanged	Unchanged	Unchanged	Use with caution (avoid TPV/r in severe liver dx)
NNRTIs	Standard Dose	Unchanged	Unchanged	Unchanged	Avoid NVP in severe liver dx; use EFV with caution

[1]Exclude lactic acidosis as a cause in patients with hepatic dysfunction

CHAPTER 4:

Antiretroviral Drugs in Pregnancy & Contraceptive Options for HIV Positive Women And Couples

4.1 General Principles for the Care of HIV Positive Pregnant Women

- Enrol all HIV + pregnant women into care and start them all on CTX (unless contraindicated) and multivitamins; provide insecticide-treated nets (ITNs) in malaria endemic areas. Additional SP is NOT required in women on CTX.
- Screen all HIV + pregnant women for TB (history, exam, sputum; CXR where essential). If active TB is found, anti-TB treatment should be prioritized and started immediately. See pg 41
- Screen all pregnant HIV + women for STIs and treat syndromically if present. Sexual partner(s) should be treated as well and encouraged to be tested for HIV infection
- Assess all HIV + pregnant women clinically and, where possible, immunologically; ARV drugs should then be used for treatment of the mother and/or PMCT as appropriate
- Efavirenz should not be used in women at risk of pregnancy unless effective contraception is provided.
- ART should be optimized in HIV + women who fall pregnant while on ART:
  - Do not discontinue ART in patients planning, or in those with an established a pregnancy.
  - Switch EFV to NVP *as early as possible in the 1st trimester* in women who fall pregnant on EFV.
  - Assess all patients for treatment failure; where confirmed, ART should be changed as early in pregnancy as feasible to allow adequate time for maximal suppression of viral replication before delivery. PMCT options for patients with TF should be discussed with a senior clinician.
  - Hyperemesis gravidarum may very occasionally necessitate discontinuation of ART.
- Prepare pregnant women for ART thoroughly, through education, counselling and support to ensure adherence and treatment success; involvement of partner is very useful in ensuring treatment success.
- Generally delay initiation of ART until women are in the 2nd trimester of pregnancy; the benefits of starting ART in the 1st trimester in severely ill patients may however outweigh the risks.
- **For all pregnant women who need to start ART, a NVP-based regimen can be used; careful clinical and frequent monitoring for hepatotoxicity is recommended in all pregnant women on NVP (see table 14).**
- Where possible use AZT instead of d4T for initiating ART in pregnant women
- Encourage health facility-based delivery for HIV+ pregnant women
- Continue ART during labour in women already on treatment
- Women who do not qualify for or have not been able to access ART should be given one of the short-course regimens for PMCT as outlined below in Table 22.
- Urgently discuss pregnant women who develop TB while on PI-based ART with a senior clinician.
- Using HAART in all pregnant women, regardless of clinical, immunological or virological status, while effective, may not be a feasible option for Kenya at present and is therefore not recommended.

- While caesarean section, in addition to other methods of PMCT, has been shown to further reduce MCT, it is only recommended in Kenya where it is feasible.

Summary: Care of HIV Positive Pregnant Women

- Optimized antenatal and obstetric care (see PMCT Guidelines)
- CTX prophylaxis, multivitamins, ITNs, basic hygiene
- Screening for TB, STIs
- Early assessment of ALL HIV positive pregnant women for ART by clinical staging and CD4 measurement where possible; ARV drugs should be given for treatment and/or PMCT as appropriate
- Preparation for ART essential to avoid non-adherence and treatment failure.
- Post-exposure prophylaxis for the infant
- Modified infant feeding (see PMCT Guidelines)
- Arrangements for appropriate contraception post partum
- Arrangement for continuing care for mother-baby pair

4.2 When to start HAART in pregnant women

All pregnant women who need ART should be offered effective ART for their own health.

CD4 NOT available: **ALL** patients with WHO Stage 3 and 4 disease

CD4 available: **ALL** patients with **CD4 count < 350** regardless of clinical status

If HAART is not used in HIV positive pregnant women then one of the short course ARV drug regimens for PMCT should be used as appropriate as the minimum standard of care. (See table below)

Table 21: Summary of ARV Drug Use for PMCT in HIV Positive Pregnant Women

	Maternal ART Indicated	Maternal ART Not Indicated	Limited capacity to deliver PMCT or women presents >>36 weeks gestation/ early labour	Mother-babY pair presenting within 72 hours post-partum
Maternal partum	ART[1]	AZT from Ante-28 weeks		
Mother Intra-partum	ART[2]	AZT + SD NVP	SD NVP[4]	
Post partum	ART[3]			
Baby	AZT for 28 days	SD NVP + AZT for 28 days	SD NVP + 28 days	AZT for SD NVP + AZT for 28 days

[1]ART should be started as soon as possible in the 2nd trimester for naïve pts and optimized in those already receiving ART
[2]ART should be continued during labour in women already on ART
[3] All pregnant women should be assessed during pregnancy for ART to ensure that all women who qualify start ART ante-partum. Where ART could not be started during pregnancy, women should be started on ART as soon after delivery as possible.
[4]SD NVP=Single dose Nevirapine should be given as a single dose of 200mg to the mother after the onset of true labour.

4.3 Contraceptive Options for Couples and Women Living with HIV Infection

- HIV+ women and couples living with HIV infection should be encouraged to discuss their reproductive options. Where pregnancy is not desired effective contraception should be offered; if hormonal methods are chosen, dual contraception (use of both hormonal contraception and condoms) should always be encouraged and condoms provided.
- Effective use of contraception in HIV+ women plays an important role in the prevention of unwanted pregnancies and thus the prevention of mother to child transmission (PMCT) of HIV infection.

- Where pregnancy is desired, a couple's status should be considered; if discordance exists, appropriate advice and support should be given. If pregnancy has occurred in a HIV+ woman, as well as PMCT, the mother's own health should be optimized and ART used if indicated.
- The choice of contraceptive methods in HIV+ women is much the same as in HIV-ve women.
- Hormonal contraception may be used in HIV-infected women; however choice of hormonal contraception should take into account ARV drug use.
- HIV + women on Efavirenz should be informed of the risk of foetal abnormalities associated with this drug if pregnancy occurs. Effective contraception should be availed to women at risk of pregnancy if Efavirenz needs to be used

Table 22: Contraceptive Methods for use in Couples and Women Living with HIV Infection

METHOD	COMMENTS	USE IN HIV POSITIVE PATIENTS
Condoms	o Male & female condoms available o Provide dual protection against STIs/HIV & pregnancy. o Require attention & care for correct use each time. o May require co-operation of partner	o **Can and should be used at all stages of HIV infection** o **Can and should be used by patients on ART** o Correct and consistent use by HIV infected patients is recommended regardless of the use of other methods of contraception (dual contraception).
Hormonal Methods	o Very effective and easy to use o Suitable for short- or long-term use o Reversible o Associated with non-contraceptive health benefits o Serious complications extremely rare	o Can be used without restriction in HIV+ women **not** on ART o Can be used without restriction in all HIV+ women for emergency contraception o **Some ARV drugs may reduce method effectiveness.** o **DMPA*/Implants** can however be used with ART; re-injection of DMPA should be done at 10-12 weeks o If hormonal method is chosen, condoms should still be used correctly and consistently

Intrauterine Contraceptive Device	o Highly effective, long-term, reversible method o Remains in place up to 12 years o Almost 100 percent effective o Has no effect on fertility when used by nulliparous women o Should not be provided to women with high risk sexual lifestyle o Bacterial STIs should be screened for and /or treated as a precaution prior to insertion of IUCD	o Attractive method for women with HIV who desire very reliable pregnancy protection o Can be inserted in HIV+ women who do not have WHO Stage 4 disease/ AIDS defining illness o For women with stage 4 disease IUD can be inserted once they are on ART and have controlled symptoms of severe illness
Sterilization	o Good, very effective for couples or individuals who want no more children o Safe, simple surgical procedure o Considered permanent	o No medical reasons to deny sterilization to clients with HIV o Procedure may be delayed in event of acute HIV-related infection or stage 4 disease pending immune reconstitution o Encourage condom use as well

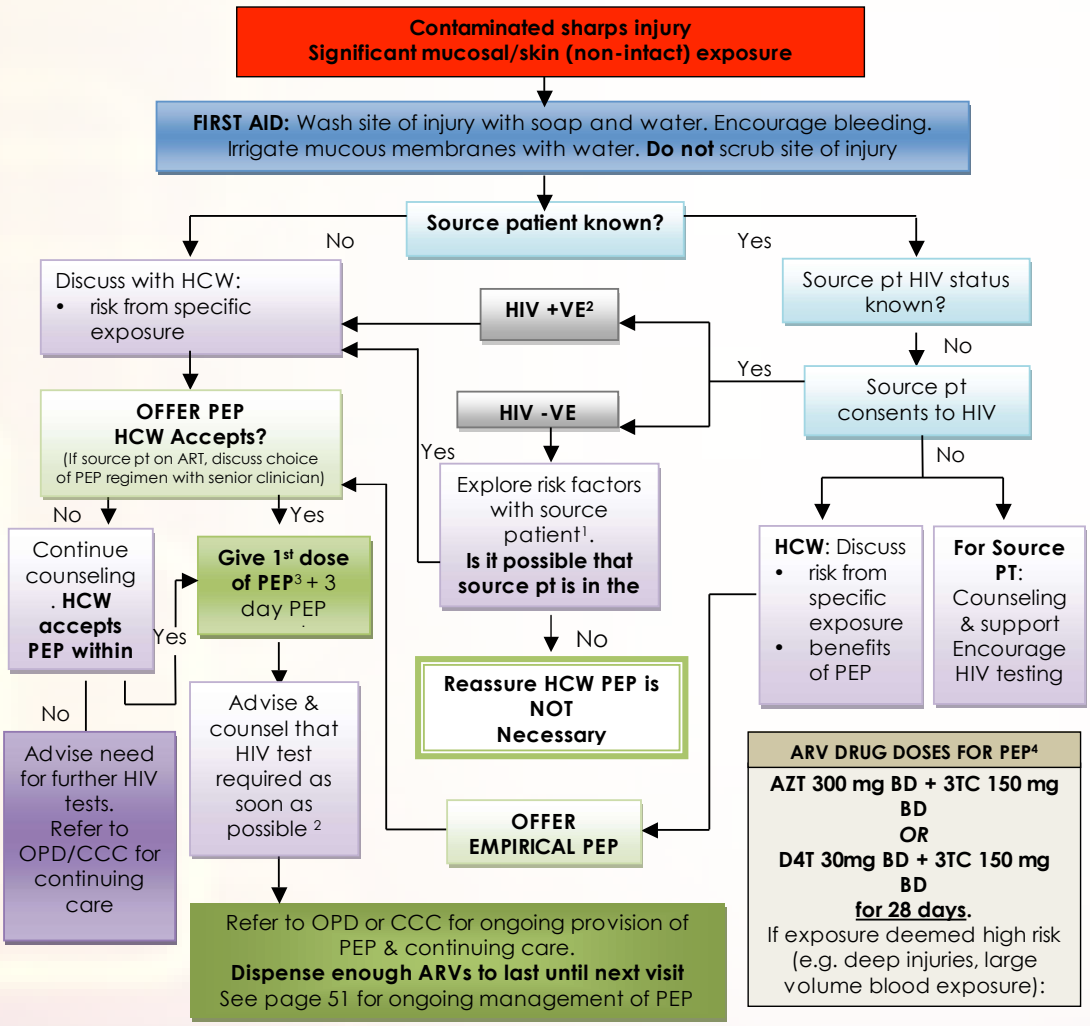
*DMPA = Depot Medroxyprogesterone Acetate (Depo-Provera)

CHAPTER 5:

Post-exposure Prophylaxis

EMERGENCY MANAGEMENT OF POSSIBLE EXPOSURE TO HIV INFECTION

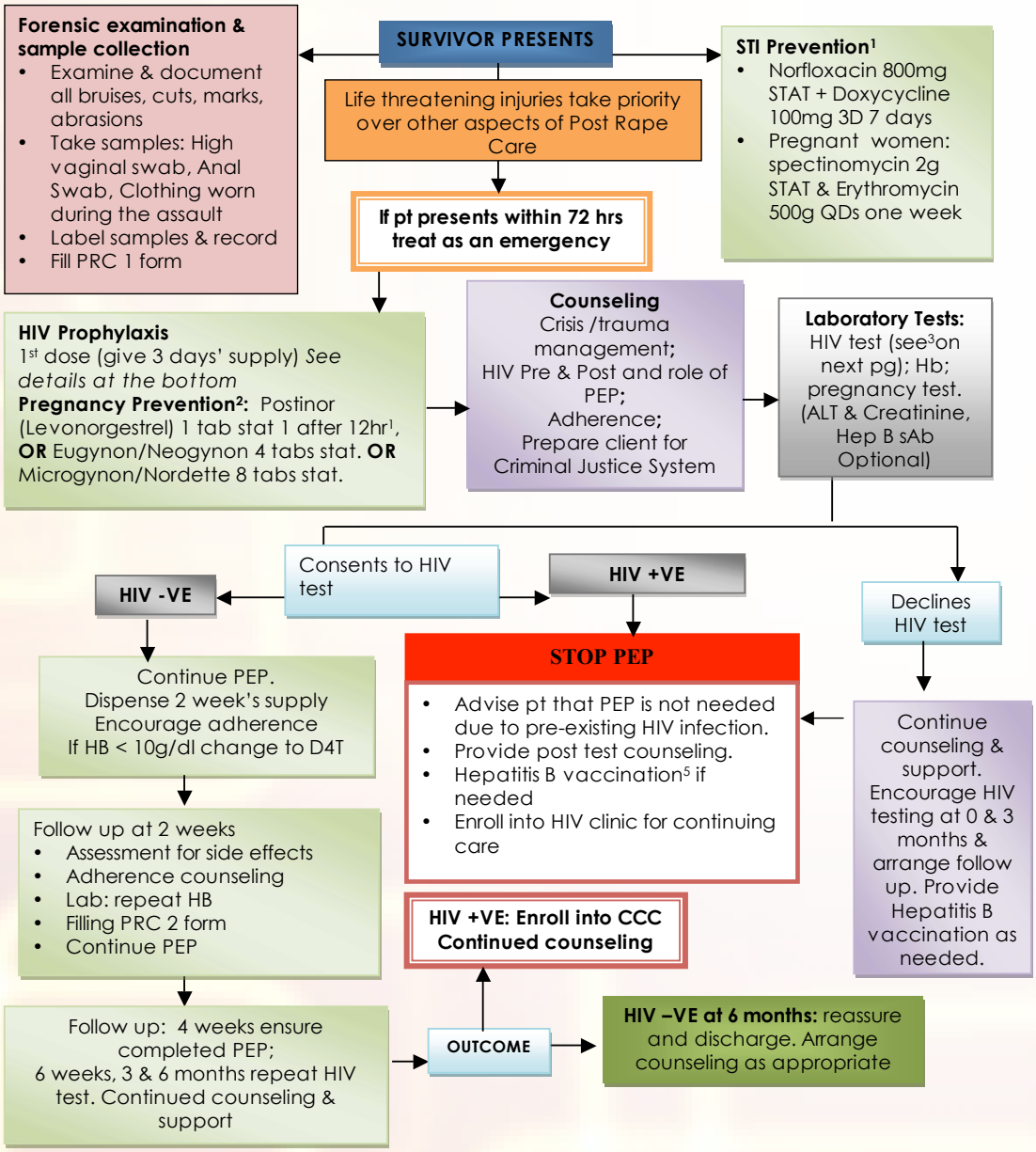
The risk of acquiring HIV infection from a contaminated needle is very small, at approximately 0.09 - 0.3%. Post-exposure prophylaxis (PEP) given correctly, after occupational exposures to contaminated bodily fluids, can dramatically reduce infection rates.



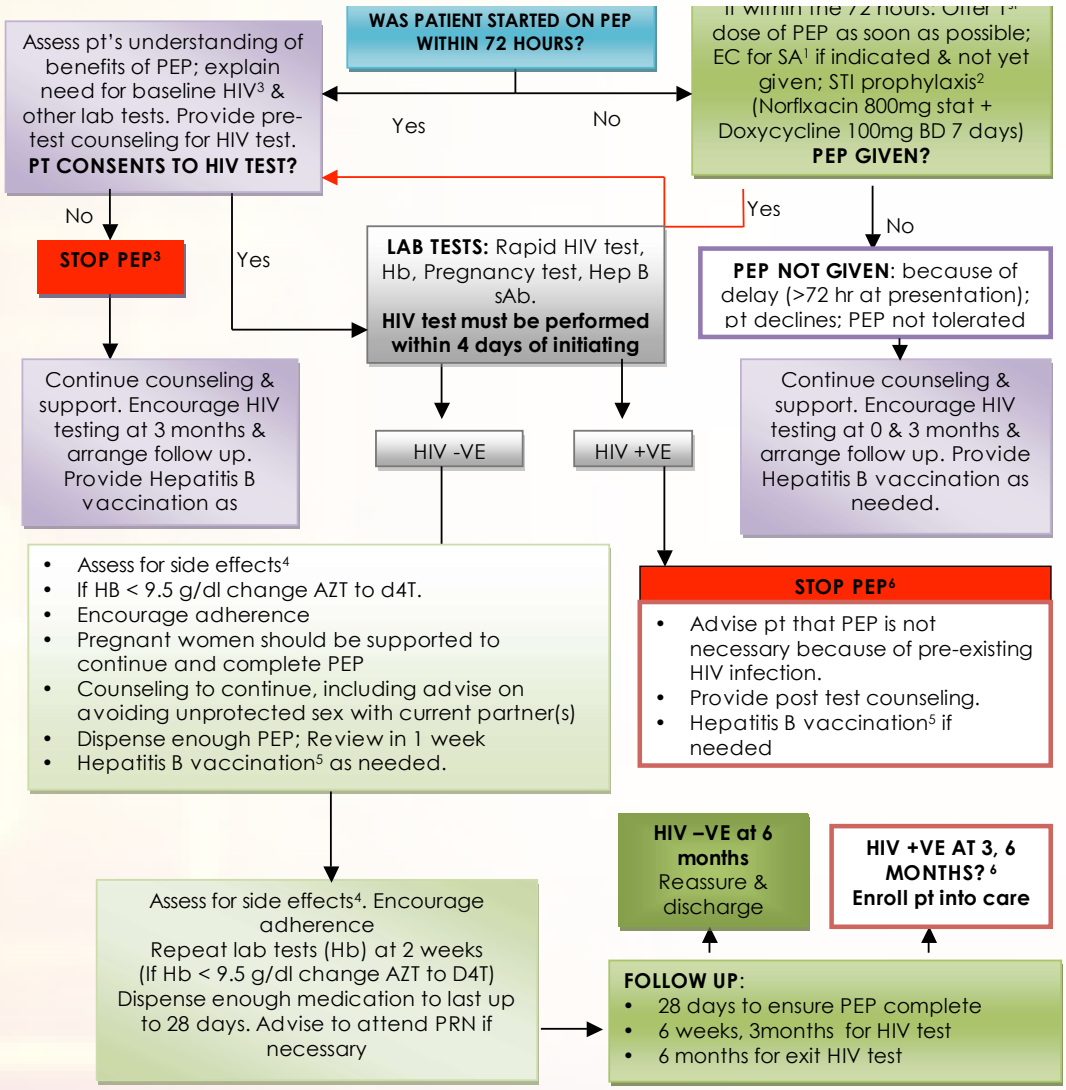
[1]Source pt should not be coerced into having an HIV test if they decline; they should be encouraged to be tested for their own benefit. Counsel source pt appropriately; if source HIV test negative but window period likely, arrange repeat in 3 months. [2]If source pt is on ART the choice of PEP regimen for HCW should be discussed with a senior colleague. [3]The 1st dose of PEP should be offered as soon as possible **within 72hrs**; the earlier it is given the better it works. Lack of HIV test should **NOT** delay the 1st dose; HIV test should however be done as soon as possible **within 5 days** of initiating PEP. [4]Use FDCs where possible to support adherence.

GUIDELINES FOR THE MANAGEMENT OF RAPE SURVIVORS ATTENDING CASUALTY

Emergency care of post-rape survivors has 4 elements: attending to any injuries sustained; providing trauma counselling and support; prevention of pregnancy where necessary and of STIs including HIV, hepatitis B and bacterial STIs; and addressing forensic issues. Compassion, respect and confidentiality are particularly important in rape survivors due to the intense trauma they have suffered. Emergency doses of ARVs for post-exposure (PEP) and emergency contraception (EC) should be available in ALL health care facilities. (Refer to the National guidelines for Medical Management of Rape and Sexual Violence for extra details)



ONGOING MANAGEMENT OF PEP IN OPD OR HIV COMPREHENSIVE CARE CLINIC



EC=emergency contraception; SA=sexual assault pts. [1]EC should be given as early as possible within 72 hrs of the sexual episode if there are no other episodes of unprotected sexual contact prior to the 72 hr period in one menstrual cycle. [2]STI prophylaxis should be give within 1 week of the assault. [3] HIV test should be done within 5 days of initiating PEP; PEP should not be continued if recipient's HIV status remains unknown. [4]Pts on PEP are likely to discontinue treatment if side effects are not managed; of note are GI side effects like nausea, vomiting due to AZT, which should be controlled. [5]Ideally all non-immune HCWs should be vaccinated against hepatitis B; where this has not been done the pt should be screened for previous exposure to Hepatitis B. if negative a course of vaccination should be given as follows: e.g. Engerix B 1ml deep IM at 0, 1, 2 and 12 months.[6] Rarely PEP may fail especially because of non-adherence or if source pt is on a failing ART regimen with resistance, and the same ARV drugs used for PEP

Appendix 1: Revised WHO Staging Criteria for Adults and Adolescents

Clinical stage	Selected symptoms
Primary HIV infection	1. Unrecognized 2. Acute Retroviral syndrome
Stage I	1. Asymptomatic 2. Persistent Generalized Lymphadenopathy (PGL)
Stage II	1. Moderate weight loss (< 10% of presumed or measured body weight) 2. Minor skin and mucous membrane manifestations (seborrheic dermatitis, prurigo, fungal infection, recurrent oral ulcerations, Herpes Zoster in preceding 2 years) 3. Recurrent upper respiratory tract infections (bacterial sinusitis, bronchitis, otitis media, pharyngitis)
Stage III	1. Severe weight loss (> 10% of presumed or measured body weight) 2. Unexplained chronic diarrhoea > 1 month 3. Unexplained prolonged fever > 1 month 4. Oral candidiasis (Thrush) 5. Oral Hairy Leucoplakia (OHL) 6. Pulmonary tuberculosis (PTB) in past 1 year 7. Severe bacterial infections (e.g. pneumonia, pyomyositis, empyema, bone or joint infections)
Stage IV	*Conditions where a confirmatory diagnostic test is required in italics* 1. Oesophageal candidiasis 2. ***P***neumo***c***ystis Jiroveci ***p***neumonia (PCP) 3. HIV wasting syndrome 4. Recurrent severe bacterial pneumonia (>/= 2 episodes within 1 year) 5. Cryptococcal meningitis 6. Toxoplasmosis of the brain 7. Chronic orolabial, genital or ano-rectal herpes simplex infection for > 1 month 8. Kaposi's sarcoma (KS) 9. HIV encephalopathy 10. Extra pulmonary tuberculosis (EPTB) *11. Invasive cervical cancer* *12. Chronic diarrhoea > 1month -Cryptosporidiosis, Isosporiasis* *13. Lymphoma cerebral or B cell NHL* *14. Visceral leishmaniasis* 15. *Cytomegalovirus (CMV) retinitis or disease of the organs*

Appendix 2: Clinical Staging for HIV-Infected Infants and Children Aged ≤ 12 Years

Clinical stage	Selected symptoms
Stage I	1. Asymptomatic 2. Persistent generalized lymphadenopathy 3. Hepato-splenomegaly (Hepatomegaly, Splenomegaly or Hepato-splenomegaly)
Stage II	1. Parotid enlargement[1] 2. Dermatitis, Verruca Planus[1], Molluscum contagiousum[1], Human papillomavirus[1] 3. Herpes zoster (uncomplicated) 4. Recurrent herpes simplex virus 5. Chronic or recurrent suppurative otitis media 6. Recurrent or chronic sinusitis 7. Thrombocytopenia, not responsive to steroid therapy (Requires lab +/- procedure for diagnosis)
Stage III	1. Low weight for age OR low height for age OR low weight for height 2. Persistent diarrhoea (14 or more days) 3. Recurrent severe bacterial pneumonia (responsive to standard therapy) 4. Non-responsive herpes simplex virus 5. M. tuberculosis (as diagnosed using WHO TB diagnosis guidelines) 6. Systemic varicella infection 7. Complicated Herpes Zoster (recurrent or 2 or more dermatomes) 8. Candida oesophageal/laryngeal or recurrent or refractory oral-pharyngeal Candida (outside the neonatal period) 9. Recto-vaginal fistula *Conditions requiring lab +/- procedure for diagnosis* 1. Anaemia (<8g/dl refractory to hematinics, anti-malarials /anti-helminthics) 2. Symptomatic LIP /Chronic suppurative lung disease
Stage IV	1. Severe refractory wasting/malnutrition 2. Severe multiple or recurrent bacterial infection (excluding pneumonia but including recurrent non-typhi Salmonella) 3. Pneumocystis Jiroveci pneumonia 4. Herpes simplex virus infection (persistent or non-responsive to treatment) 5. Cryptococcal meningitis 6. Cytomegalovirus retinitis 7. Encephalopathy 8. Cardiomyopathy 9. Nephropathy 10. Kaposi's sarcoma (and other HIV related malignancies) *Conditions requiring lab +/- procedure for diagnosis* 1. Cryptococcal infections not diagnosed clinically 2. Cryptosporidiosis infection 3. Histoplasmosis infections 4. Congenital toxoplasmosis (outside neonatal period) 5. Candidiasis and other disseminated fungal infections 6. Non tuberculosis mycobacterial infection including disseminated BCG 7. Progressive multifocal leukoencephalopathy 8. Kaposi's sarcoma and other HIV related malignancies)

1For these conditions only consider ARV therapy if condition very severe and/or affecting quality of life

Appendix 3: Cotrimoxazole Desensitization

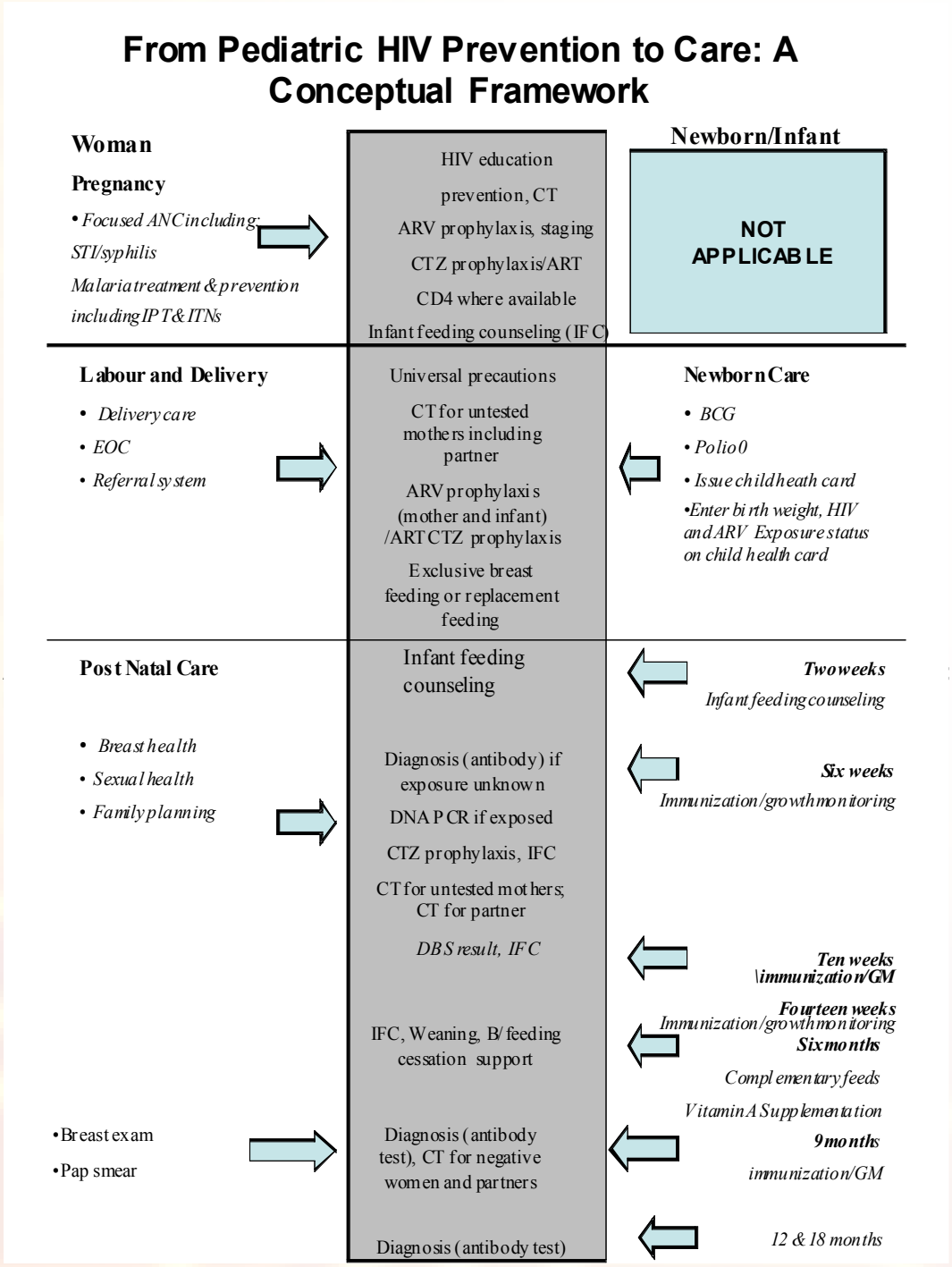
Standard Desensitization Regimen

Day	Dose of TMP/SMX Suspension 40/200 per 5ml
1	0.5ml
2	1ml
3	2ml
4	3ml
5	4ml
6	5ml
7	1 SS tablet
8	2 SS tablets/1 DS tablet per day

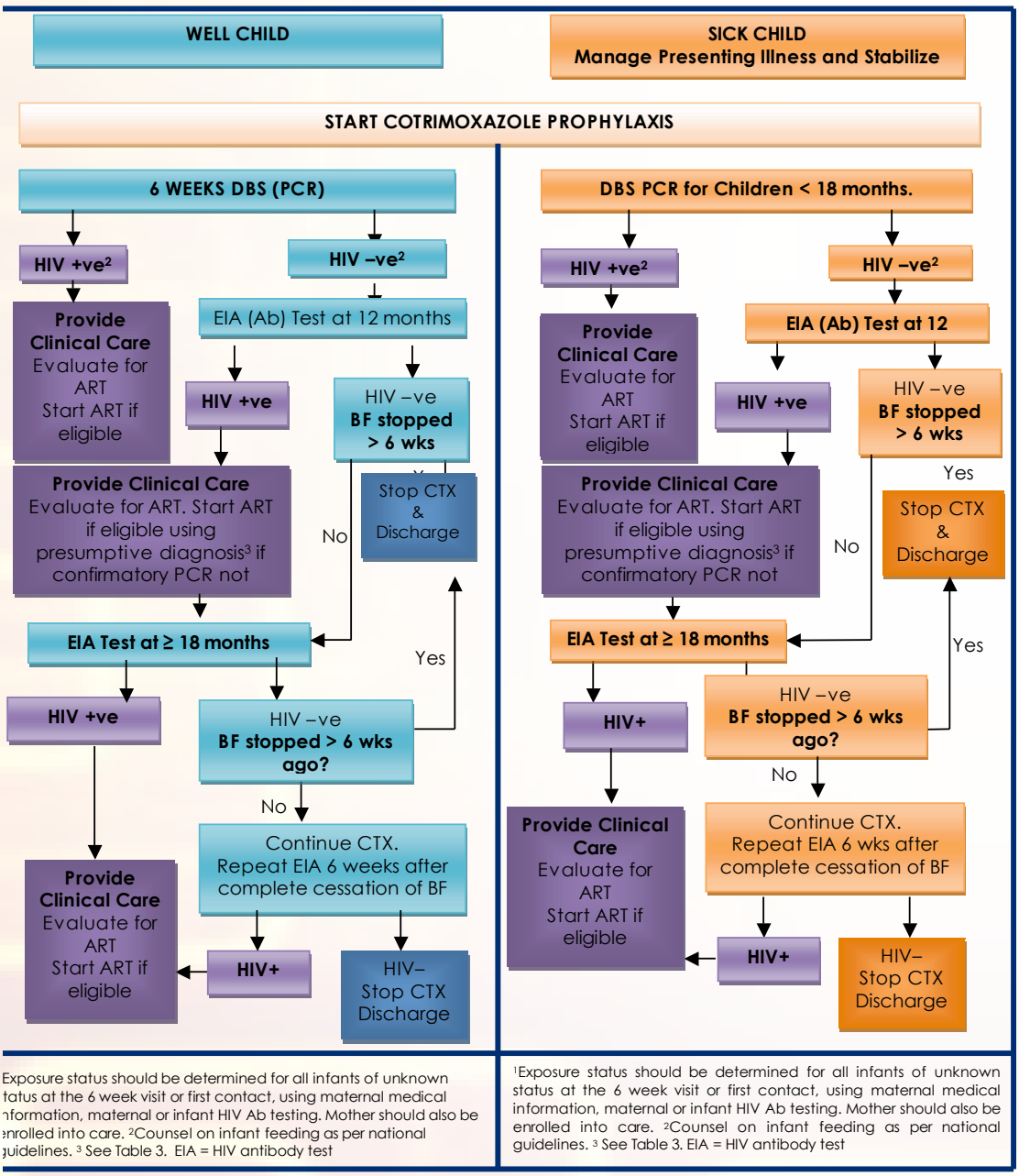
Rapid Desensitization Regimen

Hour	Dose of TMP/SMX 40/200 per 5ml
0	0.5ml
1	1ml
2	2ml
3	3ml
4	4ml
5	5ml
6	1 SS tablet

Appendix 4: Framework for the Management of HIV-positive Mothers and Exposed Infants



Appendix 5: Algorithm for Early Infant Diagnosis for HIV-Exposed1 Children



Exposure status should be determined for all infants of unknown tatus at the 6 week visit or first contact, using maternal medical nformation, maternal or infant HIV Ab testing. Mother should also be enrolled into care. [2]Counsel on infant feeding as per national guidelines. [3] See Table 3. EIA = HIV antibody test

[1]Exposure status should be determined for all infants of unknown status at the 6 week visit or first contact, using maternal medical information, maternal or infant HIV Ab testing. Mother should also be enrolled into care. [2]Counsel on infant feeding as per national guidelines. [3] See Table 3. EIA = HIV antibody test

Appendix 6: Antiretroviral Drugs and TMP/SMZ PAEDIATRIC Dose Chart for use in Resource-limited Settings

eight nge (kg)	Abacavir (Ziagen®, ABC)		Didanosine (Videx®, DDI)			Lamivudine (Epivir®, 3TC)		Stavudine (Zerit®, d4T)		Zidovudine (Retrovir®, ZDV, AZT)			Efavirenz (Storin®, Sustiva®, EFV)	Nevarapine (Viramune®, NVP)			
	8mg/kg/dose TWICE daily		90-120mg/m²/dose TWICE daily	120mg/m²/dose TWICE daily	180-240mg/m²/dose ONCE daily	4mg/kg/dose TWICE daily		1mg/kg/dose TWICE daily		180-240mg/m²/dose ONCE daily			Dose as shown ONCE daily for children 3YEARS AND OVER	INDUCTION DOSE: 160-200 mg/m²/dose ONCE daily		MAINTAINANCE DOSE: 160-200 mg/m²/dose TWICE daily	
	20mg/ml solution	300 mg tablets	10mg/ml solution	25,50,100mg chewable tablets	125,200,250,400 mg EC capsules	10mg/ml solution	150mg tablets	1mg/ml solution	15,20,30 mg capsules	10mg/ml syrup	100mg capsules	300 mg capsules	50,100,200 mg capsules, 600mg tablets	10mg/ml suspension	200mg tablets	10mg/ml suspension	200mg tablets
– 3.9						2 ml		Not recommended	Not recommended	5 ml			Not recommended	5 ml			
– 4.9						3 ml		Not recommended	Not recommended	6 ml			Not recommended	5 ml			
- 5.9	2 ml		4 ml	25mg + 25mg tabs		3 ml		6 ml		6ml				6 ml		6 ml	
– 6.9	3 ml		5 ml	25mg + 25mg tabs		3 ml		7 ml	10mg(as 0.5x20mg)	7 ml				7 ml		7 ml	
– 7.9	4 ml		6 ml	25mg + 25mg tabs		4 ml		8 ml	10mg(as 0.5x20mg)	8 ml				8 ml		8 ml	
– 8.9	4 ml		6 ml	25mg + 25mg tabs		4 ml		9 ml	10mg(as 0.5x20mg)	9 ml	1 cap			9 ml		9 ml	
- 9.9	4 ml		6 ml	25mg + 25mg tabs		4 ml		10 ml	10mg(as 0.5x20mg)	10 ml	1 cap			9 ml	0.5 tab	9 ml	0.5 tab
l – 10.9	5 ml		6 ml	50mg+25mg tabs in am 25mg+25mg tabs in pm	125mg EC cap	5 ml			15 mg cap	10 ml	1 cap		200 mg cap	10 ml	0.5 tab	10 ml	0.5 tab
– 11.9	5 ml	0.5 tab	7 ml	50mg + 25mg tabs	125mg EC cap	5 ml			15 mg cap	10 ml	1 cap		200 mg cap	10 ml	0.5 tab	10 ml	0.5 tab
! – 13.9	6 ml	0.5 tab	7 ml	50mg + 25mg tabs	125mg EC cap	5 ml	0.5 tab		15 mg cap	11 ml	1 cap		200 mg cap	11 ml	0.5 tab	11 ml	0.5 tab
l – 16.9		0.5 tab	8 ml	50mg+50mg tabs in am 50mg+25mg tabs in pm	200mg EC cap		0.5 tab		20 mg cap		2 caps in am 1 cap in pm	0.5 tab	200 mg cap+50 mg cap		0.5 tab		1 tab in am 0.5 tab in pm
' – 19.9		0.5 tab	9 ml	50mg+50mg tabs	200mg EC cap		0.5 tab		20 mg cap		2 caps in am 1 cap in pm	0.5 tab	200 mg cap+50 mg cap		1 tab		1 tab in am 0.5 tab in pm
l - 24.9		1 tab in am 0.5 tab in pm		100mg+25mg tabs	250mg EC cap		1 tab in am 0.5 tab in pm		20 mg cap		2 caps	0.5 tab	200 mg cap+100 mg cap		1 tab		1 tab in am 0.5 tab in pm
– 29.9		1 tab		100mg+25mg tabs	250mg EC cap		1 tab		30 mg cap		2 caps	1 tab in am 0.5 tab in pm	200 mg+100 mg+50 mg caps		1 tab		1 tab
l – 34.9		1 tab		100mg+25mg tabs	250mg EC cap		1 tab		30 mg cap		3 caps	1 tab	200 mg cap (x2)		1 tab		1 tab
– 39.9		1 tab		100mg+25mg tabs	250mg EC cap		1 tab		30 mg cap		3 caps	1 tab	200 mg cap (x2)		1 tab		1 tab

eight range(kg)	Lopinavir/ritonavir (Kaletra®,LPV)			Nelfinavir (Viracept®,NFV)		Ritonavir (Norvir®,RTV)		Stavudine+Lamivudine	Stavudine+Lamivudine +Nevirapine	Zidvudine+Lamivudine(Combivir®)	Zidovudine+Lamivudine +Abacavir (Trizivir®)
	10 – 16mg/kg/dose TWICE daily			Target dosing <10kg: 75mg/kg/dose >10 kg to 19.9kg: 60mg/kg/dose >20kg: max dose of 1250mg TWICE daily		STARTING DOSE: 250mg/m²/ dose TWICE daily	MAINTAINANCE DOSE: 400mg/m²/ dose TWICE daily	Dose Shown TWICE daily	Dose Shown TWICE daily	Dose Shown TWICE daily	Dose Shown TWICE daily
	80mg lopinavir/ 20mg ritonavir per ml solution	133mg lopinavir/3 3mg ritonavir per ml solution	200mg lopinavir/6 0mg ritonavir per ml solution	250 mg tablets	625 mg tablets	80 mg/ml solution	80 mg/ml solution	30 mg d4T/ 150 mg 3TC tablets	30 mg d4T/ 150 mg 3TC/ 200 mg NVP tablets	30 mg ZDV/ 150 mg 3TC tablets	30 mg ZDV/ 150 mg 3TC/ 300 mg ABC tablets
– 5.9	1ml			2tabs		1ml	1.5ml				
– 6.9	1.5 ml			2tabs		1ml	2ml				
– 7.9	1.5 ml	1cap		3tabs in am 2tabs in pm		1ml	2ml				
– 8.9	2 ml	1cap		3tabs		1.5ml	2ml				
– 9.9	2 ml	1cap		3tabs		1.5ml	2.5ml				
) – 10.9	2 ml	1cap		3tabs		1.5ml	2.5ml	0.5tab	0.5tab		
– 11.9	2 ml	1cap		3tabs		1.5ml	2.5ml	0.5tab	0.5tab		
– 13.9	2 ml	2caps in am 1cap in pm	1tab	4tabs		1.5ml	3ml	0.5tab	0.5tab		
– 16.9	2 ml	2caps in am 1cap in pm	1tab	4tabs		2ml	3ml	1tab in am 0.5tab in pm	1tab in am 0.5tab in pm	0.5tab	0.5tab
– 19.9	2.5 ml	2caps in am 1cap in pm	1tab	5tabs	2tabs			1tab in am 0.5tab in pm	1tab in am 0.5tab in pm	0.5tab	0.5tab
– 24.9	3 ml	2caps	2tabs in am 1tab in pm	5tabs	2tabs			1tab in am 0.5tab in pm	1tab in am 0.5tab in pm	1tab in am 0.5tab in pm	1tab in am 0.5tab in pm
– 29.9	3.5 ml	2caps		5tabs	2tabs			1tab	1tab	1tab in am 0.5tab in pm	1tab in am 0.5tab in pm
– 34.9	4 ml	3caps	2caps	5tabs	2tabs			1tab	1tab	1tab	1tab
– 39.9	5 ml	3caps	2caps	5tabs	2tabs			1tab	1tab	1tab	1tab

Appendix 7: How to Take Tablets or Capsules (useful in children)

NAME	COMMENTS
Abacavir (ABC)	• Tablets may be swallowed whole or crushed and dispersed in water or onto a small amount of food & immediately ingested
Stavudine (D4T)	• Capsules may be opened and dispersed in water or onto a small amount of food & immediately ingested. • Stavudine capsules are not recommended for use in children <7 kg. • Oral solutions need refrigeration for storage. Not suitable for patients without refrigeration facility at home
Lamivudine (3TC)	• Tablets are not scored but can be divided into two equal halves with a pill splitter. • Tablets may be crushed and dispersed in water or onto a small amount of food & immediately ingested. • Oral solution should be used in children < 12 kg for accurate dosing. It is stable at room temperature.
Zidovidine (AZT/ZDV)	• Capsules may be opened and dispersed in water or onto a small amount of food & immediately ingested. • Tablets may be crushed and dispersed in water or onto a small amount of food & immediately ingested. • Oral solution should be used in children < 8 kg for accurate dosing. It is stable at room temp.
Didanosine (DDI)	• The tablets may be dispersed in water before administering. Alternatively, the tablets may be chewed and swallowed. • Must be administered on an empty stomach at least 30 minutes before or 2 hours after eating. • Oral solutions need refrigeration for storage. Not suitable for patients without refrigeration facility at home. • If taken with Indinavir, the drugs must be separated by one hour.
Nevirapine (NVP)	• Tablet is scored and may be divided into equal parts. • Tablet may be crushed and dispersed in water or onto a small amount of food and immediately ingested. • Oral solution is stable at room temperature. Consider using liquid for the induction dose in children < 9 kg for accurate and precise dose.
Efavirenz (EFV)	• Capsules may be opened and dispersed in water or onto a small amount of food and immediately ingested. • Oral solution is stable at room temperature. • Although the liquid may be available in some areas, it is advisable to use the capsule or tablet forms when possible.
Lopinavir/ ritonavir (LPV/r)	• Dose is calculated based on Lopinavir component. • Capsules must be swallowed whole. • Oral solution should be taken with food. • Capsules and oral solution must be refrigerated until dispensed. • After removing from refrigeration capsules and oral solution are stable for 30 days at room temperature (up to 25° C). Heat stable formulation is now available.
Nelfinavir (NFV)	• Tablets may be crushed & dispersed in water or onto a small amount of food & immediately ingested. • Must be taken with food to improve absorption.

Appendix 8: Fixed Dose Paediatric Drugs

Company	Trade name	WHO Abbreviation	Stavudine (d4T) dose/tablet (mg)	Lamivudine (3TC) dose/tablet (mg)	Nevirapine (NVP) dose/tablet (mg)
Cipla	Triomune Baby	FDC 6	6	30	50
	Triomune Junior	FDC 12	12	60	100
Emcure#	Emtri Junior	FDC 10	10	40	70
GPO†	GPO-vir	FDC 7	7	30	50
Ranbaxy	Triviro Kids	FDC 5	5	20	35
	Triviro Kids DS	FDC 10	10	40	70

#Emcure also produces an FDC powder for reconstitution, which needs to be kept at kept at 4°C after mixing

FDC 6 and 12 dosing schedules, used either in combination (first column) or individually (second and third columns)

Weight range (kg)		Formulation	DOSE (tablets)		Formulation	DOSE (tablets)		Formulation	DOSE (tablets)	
			AM	PM		AM	PM		AM	PM
3	3.9	50/6/30 mg tablets	1	1	50/6/30 mg tablets	1	1	100/12/60 mg tablets	0.5	0.5
4	4.9	50/6/30 mg tablets	1	1	50/6/30 mg tablets	1	1	100/12/60 mg tablets	0.5	0.5
5	5.9	50/6/30 mg tablets	1	1	50/6/30 mg tablets	1	1	100/12/60 mg tablets	0.5	0.5
6	6.9	50/6/30 mg tablets	1.5	1.5	50/6/30 mg tablets	1.5	1.5	100/12/60 mg tablets	1	0.5
7	7.9	50/6/30 mg tablets	1.5	1.5	50/6/30 mg tablets	1.5	1.5	100/12/60 mg tablets	1	0.5
8	8.9	50/6/30 mg tablets	1.5	1.5	50/6/30 mg tablets	1.5	1.5	100/12/60 mg tablets	1	0.5
9	9.9	50/6/30 mg tablets	1.5	1.5	50/6/30 mg tablets	1.5	1.5	100/12/60 mg tablets	1	0.5
10	10.9	50/6/30 mg tablets	2	2	50/6/30 mg tablets	2	2	100/12/60 mg tablets	1	1
11	11.9	50/6/30 mg tablets	2	2	50/6/30 mg tablets	2	2	100/12/60 mg tablets	1	1
12	13.9	50/6/30 mg tablets	2	2	50/6/30 mg tablets	2	2	100/12/60 mg tablets	1	1
14	16.9	100/12/60 mg tablets	1.5	1	50/6/30 mg tablets	2.5	2.5	100/12/60 mg tablets	1.5	1
17	19.9	100/12/60 mg tablets	1.5	1	50/6/30 mg tablets	2.5	2.5	100/12/60 mg tablets	1.5	1
20	24.9	100/12/60 mg tablets	1.5	1.5	50/6/30 mg tablets	3	3	100/12/60 mg tablets	1.5	1.5
25	29.9	200/30/150 mg tablets	1	1	50/6/30 mg tablets	4	4	100/12/60 mg tablets	2	2
30	34.9	200/30/150 mg tablets	1	1	50/6/30 mg tablets	4	4	100/12/60 mg tablets	2	2