National Guidelines for the Use of Antiretroviral Therapy in Adults and Children

LaoPDR

Second Edition
March 2008

Foreword (NEW)

The first edition of the *National Guidelines for the Use of Antiretroviral Therapy in Adults and Children, Lao PDR* was published in 2005.

During 2006, the World Health Organization (WHO) issued revised guidelines for the use of antiretroviral therapy in adults and children in resource limited settings.

This second edition of the *National Guidelines for the Use of Antiretroviral Therapy in Adults and Children, Lao PDR* is based the following documents

- Antiviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach 2006 revision. World Health Organization, 2006
- Guidelines on Cotrimoxazole Prophylaxis for HIV-Related Infections Among Adolescents and Adults: Recommendations for a Public Health Approach World Health Organization, 2006
- Antiretroviral Drugs for the Treatment of Pregnant Women and Preventing HIV Infection in Infants: Towards Universal Access: Recommendations for a Public Health Approach World Health Organization, 2006
- Antiretroviral Therapy of HIV Infection in Infants and Children in Resource-Limited Settings: Towards Universal Access World Health Organization, 2006
- Clinical HIV/AIDS Care Guidelines for Resource-poor Settings Médecins Sans Frontières (MSF) Second edition, April 2006.
- Clinical HIV-AIDS Care Guidelines, Savannakhet Provincial Hospital, Setthathirath University Hospital, Lao PDR, August 2007
- Management of HIV infection and antiretroviral therapy in children: A clinical Manual. WHO South East Asia Regional Office (SEARO), 2007
- Management of HIV infection and antiretroviral therapy in adults and adolescents: A clinical Manual. WHO South East Asia Regional Office (SEARO), 2007
- National Guidelines for the Management of Opportunistic Infections in Adults and Children Lao PDR. (Unpublished) May 2005
- WHO Case Definitions for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children World Health Organization, 2006

Key new recommendations are:

- Choices for first-line ARVs have been expanded to include newer, safer drugs
- Earlier initiation of ART before CD4 count drops below less 200 cells/mm^3
- **D4T should be dosed at 30 mg BID to everyone irrespective of weight. D4T 40 should never be used.**
- Stavudine (d4T) is no longer a preferred fist line ARV due to its side effect, predominantly lactic acidosis, lipoatrophy and peripheral neuropathy
- D4T will continue to be used in many countries due to its low cost and wide availability in fixed dose combination tablets
- The updated recommendations in this second edition provide guidance on the recognition

and management of the d4T toxicities and how to use the newer ARVs.

- Dosing of d4T is changed following new WHO recommendations that 30mg BID should be given to all patients irrespective of body weight. The previous recommendation was 40 mg BID for those ≥ 60kg and 30mg BID for those< 60 kg[1]
- Recognition and management of Immune Reconstitution Inflammatory Syndrome (IRIS) is essential in the first few months or ART.
- Clear guidelines are provided on how to safely stop NNRTIs in chronic HIV infection and in the setting of PMCT to limit the development of NNRTI resistance
- Expanded PMCT interventions
- Post exposure prophylaxis (Occupational and non-occupational)

The first edition of these guidelines promoted a “seek advice” system where physicians were advised to call a mentor when complications presented. This system has been deleted in the second edition and additional guidance provided so that a suitably trained physician can make more independent decisions on patient care.

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Introduction

The first HIV infection in the Lao People's Democratic Republic was identified in 1990 in a returning Lao female. The first AIDS case was reported in 1992 in a person with a history of frequent travel to Bokeo, a province adjacent to Chiang Rai, a northern Thai province. From 1990 to December 2003, a total of about 98,016 persons were screened/tested for HIV infection and 1212 were found to be positive, with 670 AIDS cases reported, including 486 deaths. The majority of the identified HIV infections were in persons with clinical illnesses and who were suspected of having acquired their infection outside of the country via heterosexual intercourse. IDU is believed to be very low or non-existent, but no studies have been conducted to confirm this impression.

The results of the first complete HIV sentinel surveillance round in the Lao People's Democratic Republic, was carried out in 2001. More than 800 "service women", considered to be indirect sex workers, were tested in three sites. In the capital city of Vientiane, about 1% of the almost 300 service women were found to be HIV positive in Savannakhet, the same rate of HIV-positivity was observed among the same number of service women tested. Overall, less than 1% of indirect sex workers tested was found to be HIV-positive.

Cumulatively, from 1990 to 2007, HIV positive persons are totally 2,630 cases found in 163,653 blood samples tested in 17 provinces nation wide. Out of the total positives cases, there were 1,675 with AIDS and 820 died of AIDS. The transmission mode remained mainly through sexual intercourse that give a proportion of 85% compared to other modes while the consistently use of condoms appears relatively low. Currently there are approximately 700 patients receiving ART in Lao PDR.

The low numbers notwithstanding, it has been recognized that there is no room for complacency in the response to HIV/AIDS. A study of 108 female sex workers showed infection rates of 43% for Chlamydia, 26% for gonorrhoea, and 15% for mixed infection -representing a total infection rate of 54%, which is higher than reported anywhere else in Southeast Asia. Of the 108 sex workers, only 22% reported consistent condom use.

Introduction to the Guidelines

This is the second edition of the ART guidelines; the first version was developed in 2005 but since some of the regimens have changed it was felt that these guidelines should be updated to meet the requirements of National Guideline for the treatment of HIV infection in Adults and Children in Lao People's Democratic Republic.
These guidelines are based on the ART protocol used in the Savannakhet Provincial Hospital. They have been adapted to meet the requirements of a National Guideline for the Treatment of HIV Infection in Adults and Children in Lao People's Democratic Republic.
This is a revised version of the ART protocol used in the Savannakhet Hospital and other hospitals that may be used in the care of people living with HIV/AIDS (PLWHA) in other provinces in the future. It is largely based on the work that is presently conducted in the virology unit in Savannakhet Hospital and MSF-CH. However, these guidelines are designed to be a simplified, easy to use document, developed for a general practice care facility.

The basic principles of these guidelines are:

- ART may be **initiated and monitored** on the basis of clinical staging and/or CD4 count

- **First line ART with back-up system (seek advice)**: Only clinicians with experience in the use of antiretroviral therapy will initiate standard first line treatment, and manage most side-effects. Follow up of stable uncomplicated patients may occur at community level. Using a system of mentoring, treating physicians will be able seek advice from the experienced physicians through telephone or e-mail.

- HIV testing, ART and laboratory monitoring of patients on ART should be provided **free of charge to all patients** eligible for the National ARV program.

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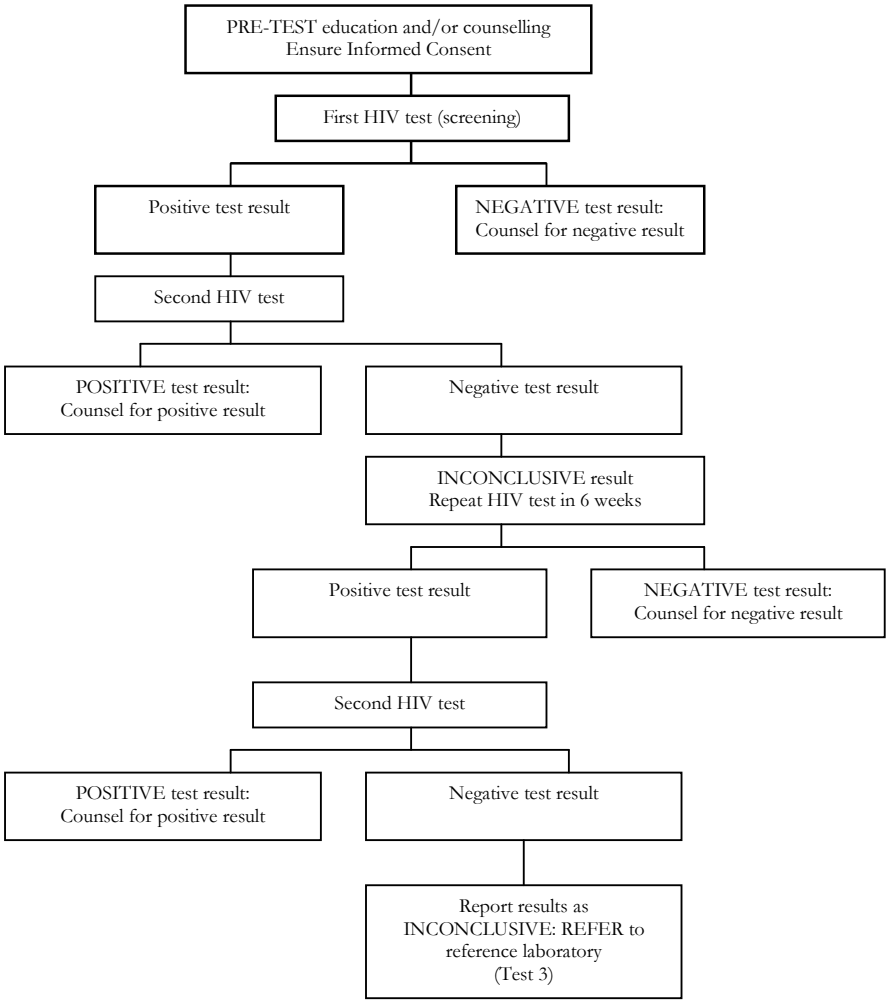
Abbreviations and acronyms

3TC	Lamivudine
AB	Antibody
ABC	abacavir
ALT	alanine transferase
ART	antiretroviral treatment
ARV	antiretroviral
AZT	zidovudine
BID	Twice daily
CBC	complete blood count
CD4	CD4 cell count
d4T	Stavudine
ddI	Didanosine
EFV	Efavirenz
FDC	Fixed drug combination
FTC	Emtricatabine
HAART	Highly Active Antiretroviral Therapy
Hb	Haemoglobin
INH	Isoniazid
IDV	Indinavir
IRIS	Immune recovery inflammatory syndrome
LP	Lumbar Puncture
LPV	Lopinavir
MAC	Mycobacterium Avium Complex
MTCT	Mother to Child Transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NsRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OD	Once daily
OI	Opportunistic infection
PI	Protease inhibitor
PLWHA	People living with HIV/AIDS
PMCT	Prevention of Mother to Child transmission
RTV	Ritonavir
Rx	Treatment
SQV	Saquinavir
TB	Tuberculosis
TDF	Tenofovir
TLC	Total lymphocyte count
TID	Three times daily
TMP-SMX	Trimethoprim-sulfamethoxazole (cotrimoxazole)

National Guidelines for the use of Antiretroviral Therapy in Adults and Adolescents

HIV Testing

Algorithm for HIV Rapid Testing and Counselling



Methods of HIV Testing*

- Test 1: Determine HIV ½
- Test 2: Uni-Gold
- Test 3: ELISA

***Refer to National Guidelines on HIV testing**

NOTES:
In the context of late pregnancy or labour in a MTCT-prevention setting, it is advised to give a single dose of nevirapine on the basis of a single positive rapid test. Post-test counselling should focus on the possibility of the test being performed during the "window period", i.e., when antibodies have not yet formed after actual exposure to HIV. All those with inconclusive results should be encouraged to avoid future risk behaviour and be offered in 6 weeks time to allow for the window period to have passed.

Initial assessment and patient management plan

Clinical manifestations suggestive of HIV infection (See Annexes 6 and 7)

- Weight loss > 10% of base line body weight
-
- Fever (continuous or intermittent) more than one month
-
- Diarrhea (continuous or intermittent) more than one month

- Persistent Generalized lymphadenopathy (PGL) is defined as palpable lymph nodes > 1 cm in 2 or more extra inguinal sites, present for more than 3 months.

- Skin conditions (some conditions, such as genital warts and psoriasis, are common in HIV-infected patients but not necessarily HIV-related.
- *Skin conditions marked with strongly suggestive of HIV infection.

1. Fungal infections:	oral candidiasis (thrush) fungal skin infection vaginal candidiasis (recurrent)
2. Viral infections:	herpes zoster (shingles) recurrent or involving more than one dermatome genital herpes (recurrent) molluscum contagiosum condyloma (genital warts)
3. Bacterial infections:	folliculitis
4. Other skin conditions:	seborrheic dermatitis papular pruritic eruption (PPE) psoriasis icthiosis diffuse skin dryness*

- Respiratory manifestations
  - cough more than one month
  - dyspnoea
  - tuberculosis
  - recurrent pneumonia
  - chronic or recurrent sinus disease
  -
- Neurological manifestations
  - worsening headache (continuous and unexplained)
  - febrile convulsion

  Declining cognitive function

WHO Clinical Staging of HIV Disease

The revised WHO clinical classification of HIV-associated disease is designed to be used in patients with **confirmed HIV infection**. Along with CD4 count testing, where available, the staging system is used to guide decisions on when to start opportunistic infection (OI) prophylaxis and when to start and switch ART. The WHO Staging system is not reversible. For example, once a person is stage 4 they cannot go back to stage 3 even if the patient becomes asymptomatic.

Clinical stage 1 (Asymptomatic)
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2 (Mild disease)
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular chelitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
Clinical stage 3 (Moderate disease)
Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9 /L) and or chronic thrombocytopenia (<50 X 10^9 /L^3)
Clinical stage 4 (Severe disease)
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Penicilliosis
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Recurrent septicemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

WHO Clinical Staging of HIV Disease

Source: Revised WHO Clinical Staging and Immunological Classification of HIV and case definition of HIV for surveillance, May 2006

Medical History and symptom check list

The following checklist is a guide to key information to ask the patient at the initial (and subsequent) visits. The information will guide in deciding the need for HIV testing if HIV status is unknown and allow disease staging (WHO Clinical Staging of HIV Disease) which is the basis of the management and follow up plan

HIV Testing	**HIV Risk**
Ever tested for HIV in the past? Date and place of first HIV test Reason for the test Documentation of the result Date of any negative HIV test Prior CD4+ cell counts (if available)	Unprotected sexual contact Injection drug use Occupational exposure Perinatal transmission Recipient of blood products Unknown
System Review	**Past history of HIV-Related Illnesses**
Unexplained weight loss Swollen lymph nodes Night sweats and fever Unusual headaches or poor concentration Changes in appetite Skin rashes Sores or white spots in mouth Painful swallowing Chest pain, cough or shortness of breath Stomach pain or Vomiting or Diarrhea Numbness or tingling in hands or feet Muscle weakness and changes in vision	Oral candidiasis *or Candida* esophagitis Persistent diarrhea Varicella zoster (shingles) Oral hairy leukoplakia *Pneumocystis jiroveci* pneumonia (PCP) Recurrent bacterial pneumonia Cryptococcal meningitis Toxoplasmosis Kaposi's sarcoma Disseminated *Mycobacterium avium* complex Cytomegalovirus (CMV) infection Tuberculosis Invasive cervical cancer
Tuberculosis History	**Sexually Transmitted Infections**
Last chest X-ray History of past TB Treatment given (drugs and duration) History of exposure to TB BCG and PPD skin test and result	Genital ulcer or other lesion Genital discharge
Gynecologic History	**General Medical History**
Last PAP smear Menstrual irregularities Pelvic pain or discharge	Any other past medical condition such as diabetes, hypertension, cardiovascular disease Hepatitis B, Hepatitis C
Pregnancy and Contraception history	**Vaccination History**
Previous pregnancies and terminations Living children and HIV status of children Exposure to ARV during pregnancy Drugs and duration of ART Contraception used Last menstrual period	BCG Hepatitis B vaccine
Medication	**Allergies**
Past drugs and reasons for taking them Current drugs and reasons for taking them Opioid substitution therapy	Known allergies to drugs or other substances or materials
ART History	**Psycho Social History**
Current and past exposure to ART Which drugs taken and for how long Understanding and readiness to commence ART if never taken	Family history, e.g. other immediate family member with known HIV infection Social history, e.g. marital status, education, occupation, source of income Financial and family support status Disclosure status, readiness to disclose
Substance use	**Functional status**
Alcohol, stimulant, opiate and other drug use Smoking history	Able to work, go to school, do housework Ambulatory but not able to work Amount of day to day care needed

Management and follow up plan based on WHO staging

WHO Clinical Stage	Management
Stage 1	Patients are followed up every 6 months Check for clinical signs of progression Informed of the clinical signs of progression that would alert them to go back to their medical doctor. • enlargement of lymph glands • fever lasting more than 2 weeks • weight loss • diarrhoea for more than 2 weeks • cough lasting more than 3 weeks or shortness of breath • persistent headache Total lymphocyte count or CD4 cell count if available CD4 3 monthly if CD4 is low Diagnosis and treatment of sexually transmitted infections STIs Counsel on safer sexual practices and contraception
Stage 2	Patients are followed up every 3 months Check for any symptom of disease progression (stage III symptoms) • Fever lasting more than 2 weeks • weight loss >10% of body weight • diarrhoea lasting of more than 2 weeks • oral thrush • persistent headache • persistent cough • mucocutaneous manifestations (seborrheic dermatitis, prurigo, recurrent oral ulceration) Symptom directed laboratory evaluation (if available) • Full blood count • ALT • Sputum smear for TB when productive cough • Total lymphocyte count or CD4 cell count Follow up STI management counselling as for stage 1 patients Cotrimoxazole PCP and Toxoplasmosis prophylaxis Start prophylaxis in all patients with WHO stage 2, 3 and 4 disease If CD4 testing is available, start prophylaxis in patients with: • Any WHO clinical stage and CD4 < /350 cells/mm^3 where the aim of cotrimoxazole prophylaxis is the prevention of PCP and toxoplasmosis. • Any WHO clinical stage CD4< 350 cells/mm^3 where the aim of cotrimoxazole prophylaxis is the reduction of morbidity and mortality associated with malaria, bacterial diarrhoeal disease and bacterial pneumonias in addition to the prevention of PCP and toxoplasmosis Dose One double strength tablet or two single strength tablets once daily Total daily dose is 960 mg (800 mg SMZ + 160 mg TMP) Fluconazole (200 mg twice weekly) antifungal prophylaxis
Stage III and IV	Frequency of follow up depends on the patient's individual condition. Frequent visits are recommended at initiation of ART (1-2 weekly) then 1-3 monthly once the patient is stable on ART. The main objectives of examination are to detect signs and symptoms of Immune Inflammatory Reconstitution Syndrome (IRIS) and OIs including pulmonary or extra pulmonary tuberculosis. Symptom directed laboratory evaluation (if available) • Full blood count • ALT • Sputum smear for TB when productive cough • Total lymphocyte count or CD4 cell count Start opportunistic infections (OI) prophylaxis as in stage 2 above Start cotrimoxazole (sulfamethoxazole 800 mg and trimethoprim 160 mg) P0 daily if symptom of stage III or stage IV.

Starting Antiretroviral therapy

The decision to initiate ART in adults and adolescents is based on clinical and immunological assessment. Viral Load is **not** recommended to guide decisions on when to start ART.

Recommendations for initiating ART in adults and adolescents based on clinical stage and availability of immunological markers		
WHO Clinical Staging	**CD4 testing not available**	**CD4 testing available**
1	Do not treat	Treat if CD4 cell count < 200/mm^3
2*	Do not treat	
3	Treat	**General rule** Consider treatment if CD4 cell count < 350 cells/mm^3 Start ART before CD4 cell count drops below 200 cells/mm^{3**} **Pregnancy** Start ART in all pregnant women with WHO stage 3 disease and CD4 < 350 **Pulmonary TB** Start ART HIV infected patients with CD4 < 350 and pulmonary TB (WHO stage 3) or severe bacterial disease
4	Treat	Treat irrespective of CD4 cell count

When to start antiretroviral therapy in adults and adolescents

*Consider treatment in WHO stage II disease and total lymphocyte count < 1200 cells/mm^3 but TLC does not correlate well with CD4 count.
**Disease progression is greater in patients who commence ART with a CD4 cell count <200/mm^3 compared to those persons who start therapy above this level.[2 3 4 5 6 7]

	Regimen	**Comments**
First line regimen	d4T + 3TC + NVP	EFV is substituted for NVP intolerance and if patients are receiving rifampicin EFV is preferred in women with CD4 >250. If NVP is used, it should be used with caution, close clinical monitoring and monitoring of liver function and in women with CD4 >250 If EFV is not available, option in patients receiving rifampicin are NVP, a PI based or a tripled nucleoside regimen EFV may be used in women if they use consistent and reliable contraception EFV cannot be used in the first trimester and may be used in the second and third trimester of pregnancy
Alternative first line regimens	AZT/3TC/EFV	NVP and d4T toxicity
	AZT/3TC/NVP	D4T toxicity
	D4T/3TC/EFV	NVP hypersensitivity and/or hepatotoxicity
	(D4T or AZT) + 3TC + LPV/r	NVP and EFV toxicity
	TDF+ 3TC + (NVP or EFV)	Intolerance to AZT and d4T
	TDF+ 3TC + EFV	Hepatitis B co-infection

Recommended first line antiretroviral regimens

Notes

All patients must receive a triple combination regimen. Single and dual therapy should never be given except in the setting of the prevention of mother to child transmission

Abbreviation	Brand name	Strengths	Origin
d4T +3TC +NVP	Triomune 30®	30mg d4T + 150mg 3TC + 200mg NVP	Cipla
	Triviro 30®		Ranbaxy
d4T + 3TC	Lamivir S30® Coviro LS 30®	30mg d4T + 150mg 3TC	Cipla Ranbaxy
AZT + 3TC	Combivir® Duovir®	150mg 3TC + 300mg AZT	Cipla Ranbaxy
TDF + FTC	Truvada®	300 mg TDF + 300 mg FTC	Gilead

Examples of Fixed dose combinations

Abbreviation	Generic name	Strengths	Dosage	Food restriction
3TC	Lamivudine	150mg tab	150mg 2 times daily	No
d4T	Stavudine	30mg caps[1]	30mg 2 times daily	No
AZT	Zidovudine[2]	300mg 250mg	300mg 2 times daily 250mg 2 times daily	No
NVP	Nevirapine	200mg tab	200mg 2 times daily	No
EFV	Efavirenz	600mg caps	600mg once daily	No
TDF	Tenofovir	300 mg tabs	300 once daily	No
FTC	Emtricatabine	200 mg tabs	300 once daily	No

First line drugs and doses

1. d4T 40mg is no longer recommended. All patients, irrespective of body weight, receive d4T 30mg BID
2. AZT can be given as 250mg BID or 300mg BID. Anaemia may be less with 250 mg BID dosing

Starting and stopping non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Starting Nevirapine		
Lead in NVP dose for the first 2 weeks	**AM**	**PM**
	d4T + 3TC	d4T + 3TC + NVP
Escalate to full NVP dose after 2 weeks	FDC One pill (d4T + 3TC + NVP)	FDC One pill (d4T + 3TC + NVP)
Stopping either NVP or EFV		
Stop NVP or EFV Continue NRTI backbone (2 drugs only) for 7 days then stop all drugs. This is to cover the long half life of NNRTI decay and reduce the risk of NNRTI resistance		

Note: Lead in NVP dosing at 200 mg once daily for the first 2 weeks produces adequate NVP drug levels. Due to enzyme auto induction, NVP levels decline over 2 weeks and dose escalation to 200 mg BID is required to maintain adequate levels. Starting NVP 200 mg BID without lead in dosing results in high serum concentrations of NVP and increased risk of rash and hepatoxicity. If nevirapine is restarted after more than 14 days of treatment interruption, lead-in dosing (200mg OD for 2 weeks, then200mg BID) is again necessary

Managing opportunistic infections before starting antiretroviral therapy

Do not commence ART in the presence of an active opportunistic infections (OI). In general, the OI should be treated or stabilized before commencing ART. For details on starting ART in patients with HIV/TB co-infection, see section on the management of HIV/TB. An exception is Mycobacterium Avium Complex (MAC) when commencing ART may be the preferred treatment, especially in situations where specific MAC therapy is not available. Other conditions which may regress following the commencement of ART include candidiasis and cryptosporidiosis.
The following opportunistic infections and HIV-related illnesses need treatment or stabilization before commencing ART.

If patient has this condition	Do this
Tuberculosis (TB)	Treat TB first (see TB section)
Pneumocystis pneumonia (PCP) Bacterial pneumonia Cryptococcal meningitis, Toxoplasmosis, Penicilliosis, Invasive fungal diseases, Significant diarrhoea which may reduce absorption of ART (e.g. more than 5 loose stools per day) Malaria	Treat these illnesses first Start ART when treatment is completed
Oesophageal candida	Treat oesophageal candida first. Start ART as soon as the patient can swallow comfortably
Any undiagnosed active infection with fever and patient is unwell	Diagnose and treat first Start ART when stable
Drug reaction	Do not start ART during an acute reaction
Elevated ALT 3-5 times higher than normal limit	Look for cause and treat if possible (Hep B and C)
Anaemia: Hemoglobin (Hb) < 8 g/dl	Look for treatable cause (blood loss, MAC). If no treatable cause, commence ART with non-AZT regimen (HIV is often the cause of the anaemia)
Pregnancy	If severely ill and early therapy clearly outweighs any potential fetal risk, commence NVP-containing ART EFV should be avoided for pregnant women in the first trimester or women with childbearing potential

Monitoring patients on first line ART

In principle, all patients will be followed up at least once a month until stable on ART. The first follow up consultation is after 2 weeks, to check for side effects before changing NVP to full dose.

Depending on the conditions, additional follow-up visits can be scheduled, should it be patient-initiated, or doctor-initiated. If the patient is on treatment for more than 6 months and do not have any complaints, the follow up frequency could be once every 3 months instead of once a month.

The follow-up serves several purposes

1. Drugs and adherence. Does the patient take the drugs regularly? Does the patient need more counselling and support?
2. Side effects. Do the drugs cause any side effects? Can the patient tolerate them? Should ART regimen be changed?
3. Assessment for signs and symptoms of Immune reconstitution Inflammatory Syndrome
4. Assessment of disease progression and signs and symptoms of first line failure

Evaluation	Before or at ART start	W 2	W 4	W 8	W 12	W 24	Every 6 months	As needed
Clinical								
Clinical evaluation	✓	✓	✓	✓	✓	✓	✓	✓
Fundoscopy[5]								✓
Weight	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓
Check ART adherence		✓	✓	✓	✓	✓	✓	✓
PAP SMEAR	**Annual PAP smears are recommended**							
Laboratory								
HIVAB test[1]	✓							✓
Serology for hepatitis B & C	✓							✓
Crypto Ag (CD4<100)	✓							
CD4 count	✓						✓	✓
Haemoglobin[2]	✓		✓	✓	✓			✓
Pregnancy test[3]	✓							✓
VDRL/RPR	✓							✓
Crypto Ag[6]								
ASAT/ALAT	✓	✓						✓
Creatinine	✓				✓		✓	✓
Other chemistry								✓
Serum lactate								✓
Viral Load[4]								✓

1. Historical documented HIV antibody test is sufficient to commence ART. In the absence of documented, confirmed HIV antibody test, testing prior to commencing of ART is recommended
2. For patients receiving AZT; Haemoglobin monitoring prior to commencing AZT and at weeks 4, 8 and 12 and as required when taking AZT
3. Pregnancy testing for women initiating a first-line regimen containing EFV. Do not commence EFV if pregnancy test is positive and the woman is in the fist trimester
3. Pregnancy testing if pregnancy is suspected in women who are receiving an EFV-based regimen. Change to a non –EFV based regimen if the if the pregnancy test is positive and the woman is in the first trimester
4. HIV-RNA measurement is currently not recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. It may be considered to make the diagnosis of treatment failure earlier or to assess discordant clinical and CD4 findings in patients suspected of failing ART.
5. CD4 < 50
6. CD4<100

Promotion of adherence

Very strict adherence to treatment is required for good viral suppression. A patient who is 95% adherent will have treatment success in 80%. A patient should be considered non-adherent if he/she missed 3 or more out of 60 drug doses over a 1 month period (95%). Several strategies may be used

to maximise adherence. These include, (1) good patient-doctor relationship, (2) good patient-pharmacist relationship, (3) having an “accompagnateur”, (4) peer support groups.

ARV combinations **not** recommended

ARV combinations	Reason not to use
Monotherapy or dual therapy to treat chronic HIV infection	Rapid development of resistance
d4T + AZT	Antagonism (reduced levels of both drugs)
d4T + ddI	Overlapping toxicities (pancreatitis, hepatitis, lipoatrophy) Deaths reported in pregnant women
3TC + FTC	Interchangeable, but should not be used together
TDF + 3TC + ABC **or** TDF + 3TC + ddI	High incidence of early virological failure
TDF + ddI + any NNRTI	High incidence of early virological failure

Immune reconstitution inflammatory syndrome (IRIS)

Definition	A reaction against a foreign antigen (alive or dead) soon after starting ART in a patient who has undergone a reconstitution of their immune responses against this antigen.
Frequency	• 10% of all patients initiating ART • Up to 25% among patients initiating ART with a CD4 cell count < 50 cells/mm^3.[3 8 9]
Timing	• Typically within 2-12 weeks of initiation of ART but may present later
Signs and symptoms	• Unexpected deterioration of clinical status soon after commencing ART • Unmasking of subclinical infections such as TB, which present as new active disease • Worsening of co-existing infections such a flare of hepatitis B or C
Most common IRIS events	• 60% of IRIS events are M.Tuberculosis, MAC or cryptococcal disease [10]
Management	• May be mild and resolve without treatment. Continue ART if possible. • Treat unmasked active OI, such as TB. • Temporary interruption of ART may be needed until the patient is stable on TB drugs, then reintroduction of ART • Steroids: Prednisone 0.5mg/kg/day for 5-10 days in moderate to severe cases of IRIS with tapering of prednisolone dose when stable.[11]

Overview of common IRIS conditions and management

IRIS condition	Clinical presentation	Onset after staring ART	Management
MAC	Lymphadenitis, fever, lung infiltrates	1-12 weeks	Resolves with ART/MAC Give steroids
CMV	Retinitis, vitritis, uveitis	1-8 weeks	Resolves with ART
Herpes zoster	Typical attack	1-12 weeks	Resolves with acyclovir
TB	Fever, Lymph Nodes, lung infiltrates	1-6 weeks	Resolves with ART/TB Give steroids
Cryptococcal meningitis	Typical symptoms	1week-8 months	Resolves with ART and antifungal treatment
Penicillium marneffei	Typical symptoms	1week-8 months	Resolves with ART and antifungal treatment

Antiviral drug toxicities and management **new combined ARV toxicity table.**

Common ARV side effects (first and second line drugs)

Drug	What to expect	When	What to do
NRTIs			
Lamivudine (3TC)	Generally well tolerated		
Abacavir	Hypersensitivity reaction	90% in the first 6 weeks	Stop ABC and NEVER restart. Rechallenge after a hypersensitivity reaction can be fatal
Tenofovir (TDF)	Renal toxicity	Any time	• Serum creatinine at baseline. Stop TDF if creatinine clearance ≥ 70 mL/min (Cockcroft-Gault formula). • Switch to AZT or d4T
Stavudine (d4T)	Peripheral neuropathy	6-12 months	Stop d4T at early signs lipoatrophy or peripheral neuropathy Stop if lactic acidosis is suspected
	Lipoatrophy (fat loss) and progressive weight loss. Pancreatitis	6-24 months	
	Lactic acidosis	Anytime	
Zidovudine (AZT)	Nausea, headache, fatigue	At start often resolves after 2 weeks	Take with food Paracetamol
	Anemia, neutropaenia, Lactic acidosis	Anytime	Check CBC 2-4 weeks after starting and regularly Stop AZT if grade 3 or 4 anaemia and start d4T or TDF (or ABC if available)
	Myopathy – muscle pain and muscle loss	6-24 months	
NNRTIs			
Efavirenz (EFV)	Rash often self limiting	2-4 weeks	• Try to treat with antihistamines • If no response, stop EFV. • Consider switch to NVP with careful clinical and laboratory monitoring in females with CD4 >250 • Last option is to switch to Kaletra
	CNS symptoms Dizziness and drowsiness	In the first weeks	• Often resolves spontaneously within 2-8 weeks. • If cannot tolerate, consider switch to NVP with careful clinical and laboratory monitoring in females with CD4 >250 and males > 400 • Last option is to switch to Kaletra
Nevirapine (NVP)	Rash Hepatotoxicity	At start of NVP or at time of dose escalation at 2 weeks	• Stop if grade 3 or 4 • Switch to EFV • If rash or hepatoxicity on EFV • Last option is to switch to Kaletra
PIs			
Lopinavir/r	Lipodystrophy, hyperlipidaemia, nausea, vomiting	Nausea, vomiting in the first weeks Lipodystrophy 6-24 months	Treat hyperlipidaemia if gd 3 or 4 No options until new protease inhibitors become available in LaoPDR

Note: Calculated creatinine clearance (CL_{Cr}) (Cockcroft-Gault formula).

Male: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{Cr}$ (mL/min)

Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = CL_{Cr}$ (mL/min)

Strategies to maximize the safe use of d4T

Training health care workers to recognize the signs and symptoms of lactic acidosis, lipoatrophy and peripheral neuropathy.	Adequately **educating patients** in the early recognition of d4T side effects and when to expect them
Switching to an alternative NRTI (such as AZT, TDF or ABC) as soon as side effects occur may reduce the severity of d4T toxicities **Commence** with d4T in anaemia patients and switch to an alternative NRTI (such as AZT, TDF or ABC) if anaemia improves on ART	Dose reduction to 30 mg twice daily irrespective of weight has been adopted in some county programs.

ART for specific patient populations

ART for women of childbearing potential or who are pregnant

Clinical Situation	Guiding Principles	Recommendations
All women	Treatment decisions are based solely on the women's medical need	Recommended first-line regimen is a NVP-based plus 2 NRTIs EFV plus 2 NRTIs may be used if women have access to consistent and reliable barrier methods of contraception or after the first trimester of pregnancy
Initiating ART in pregnant women	ART is recommended for pregnant women according to the same eligibility criteria as for non-pregnant adults ART should be initiated in pregnant women with WHO clinical stage 3 or 4 disease, or those with WHO clinical stage 1 or 2 disease with CD4 count < 350 cells/mm^3	Women with WHO clinical stage 3 disease and CD4 count < 350 cells/mm^3 should initiate ART Recommended regimen is 2 NRTIs plus and NNRTI The preferred regimen is AZT+3TC+NVP with careful monitoring women with higher CD4 counts (>250)
Women who are pregnant, are in the first trimester and are taking EFV	EFV should be discontinued and replaced with another drug	NVP is substituted for EFV with close monitoring in women with higher CD4 counts Alternatively a PI-based or a triple NRTI regimen could be substituted
Women who are breast feeding	ART is recommended for postpartum breastfeeding women who meet the WHO criteria for initiation of therapy for their own health	The preferred regimen is AZT+3TC+NVP
Women who received ART as part of PMCT intervention	Women who have previously received single-dose NVP prophylaxis for prevention of MTCT should be considered eligible for NNRTI-based regimens. Alternatives may be considered for women whose exposure to single dose NVP (SDN) was <6 months before ART was initiated	SDN > 6 months NNRTI-based regimen SDN <6 months A triple NRTI regimen or PI-based regimen also can be considered

Notes on nevirapine use in women

Women with CD4 counts between 250 and 350 are at increased risk of NVP hypersensitivity with fatal hepatic toxicity. This applies to pregnant and non-pregnant women. NVP should be used with caution and with careful clinical and monitor liver function monitoring in this population

Interaction between ART and hormonal contraceptives

NVP, RTV, LPV/r and SQV/r result in reduced ethinyl oestradiol levels. [12] [13] Oestrogen levels are slightly increased by ATV and IDV and EFV. Consistent use of condoms is recommended women in all HIV-infected women also when taking ART. Limited data show no interaction between medroxyprogesterone acetate and NVP and EFV.[14]

Initiating ART in pregnant women

When to start ART in pregnant woman		
WHO Stage	**CD4 testing not available**	**CD4 testing available**
1	Do not treat	Treat if CD4 count < 200 cells/mm^3
2*	Do not treat	
3	Treat	**Treat if CD4 count < 350 cells/mm^3**
4	Treat	Treat irrespective of CD4 cell count

Recommendations only differ from general adult guidelines in that ART should be initiated in pregnant women with a CD4 count < 350. Many women with a CD4 200-350 will require ART within the first year postpartum and efficacy of NNRTI-based ART initiated less than 6 months following exposure to single-dose NVP viral suppression may be compromised due to NVP resistance. Once initiated, ART should be continued post-partum.

Close monitoring of AST/ALT is recommended during the first few months after commencing NVP-containing ART in pregnant women. Recommended testing schedule is at weeks 0, 2, 4, 6, 8 and then monthly until delivery. NVP should be discontinued if ALT >2.5X ULN, a lower threshold than normally recommended in adults.

Preferred NRTIs for use in pregnant women are AZT and 3TC. The combination of d4T/ddI should not be used. There are no data on use of FTC in pregnancy. Studies have associated TDF with decreased foetal growth and bone demineralization. [15] [16]

The preferred NNRTI is NVP, due to extensive clinical experience with this drug in pregnant women and its proven efficacy in reducing mother to child HIV transmission. SQV/r and NLF are the preferred PIs if women cannot tolerate NVP .EFV may be considered after the first trimester

ART in Tuberculosis/HIV co-infection

Initiating ART in patients with active TB

CD4 Cell Count	ART recommendations[1]	Timing of ART in relation the start of TB treatment
CD4 < 200	**Start ART**	Between 2-8 weeks **and stable on TB drugs**
CD4 between 200-< 350	**Start ART**	After 8 weeks
CD4 > 350	**Defer ART**	Re-evaluate patient at 8 weeks and at the end of TB treatment
CD4 not available	**Start ART**	2-8 weeks

Choice of NRTI
This is the same as for all HIV infected persons.

Choice of NNRTI
EFV is the preferred NNRTI. EFV blood levels are decreased in the presence of rifampicin. There is evidence standard EFV dosing of 600 mg/daily in patients with a weight <60 kg is adequate. [17] [18] [19] [20] [21] Pending more data on EFV dosing for those ≥60 kg, WHO also recommends the standard 600 mg dose of EFV.
NVP levels are also decreased in the presence of rifampicin. However, standard NVP dosing is recommended.[22] [23] [24] [25] [26] Due to concerns about hepatotoxicity, nevirapine-containing regimens should only be used when no alternative is available for women on rifampicin-containing regimens, with CD4 cell count 250-350 cells/mm^3 who need to start ART.
A triple NRTI regimen (AZT+3TC+ABC or AZT+3TC+TDF) can be used with rifampicin. AZT, 3TC and TDF have no or minimal interactions with rifampicin but triple NRTI regimens are less potent than NNRTI-based regimens

Recommendations for patients on ART who develop active TB

First or second line ART	ART regimen at the time TB occurs	ART Options
First line	2 NRTI + EFV	Continue with 2 NRTI + EFV
	2 NRTI + NVP	Substitute to EFV or Substitute to triple NRTIs or Continue with 2 NRTI + NVP
	Triple NRTI	Continue triple NRTI
Second line	2 NRTI + PI	Continue (if already being taken) LPV/r containing regimen and adjust dose of RTV

Notes: Switching back to NVP after rifampicin completed can be considered. If a pregnant woman develops active TB and she is in the second or third trimester, an EFV containing ART regimen can be considered. An alternative in women with active TB in the first trimester is a triple NRTI regimen or a NVP containing regimens, with careful monitoring in women with higher CD4 counts or when CD4 count is unknown.
Second line ART for patients with TB indicating first-line ART failure
Unboosted PIs cannot be used with rifampicin-containing regimens because protease inhibitor levels are sub-therapeutic. [27] [28] If a patient needs to switch to or is already on a PI-based regimen, lopinavir 400 mg/ritonavir 400 mg twice daily in combination with rifampicin could be considered under close clinical and laboratory supervision for hepatic toxicity. Recommendations and precautions for the use of PI-based regimens in combination with rifampicin in women of childbearing potential and pregnant women are the same as for other TB patients.
Concomitant administration of rifampicin with fluconazole results in significant changes in the pharmacokinetic parameters of fluconazole and co-administration these drugs should be separated by 12 hours

Antiretroviral therapy for IDUs (ANNEX)

Initiating ART	Criteria for initiating ART in substance using patients are the same as all patients with HIV Before starting ART, specific factors which may affect the timing of initiation and the choice of ART should be considered. These include, social instability, active use of illicit drugs and presence of co-morbidities such as mental problems and hepatitis viruses co-infections Unavailability of OST or active use of illicit drugs should not preclude access to ART for those IDUs in need Effective links between ART and harm reduction programs are essential Unless the person is severely unwell, initiation of ART is not urgent Adequate time spent preparing to start ART, understanding treatment goals, adherence and the nature of life long ART will maximize treatment outcomes
Choice of ART	WHO-recommended regimens can be chosen for the majority of IDUs The choice of specific antiretroviral drugs depends on: • Co-morbidities (especially hepatitis B/C and psychiatric disorders) • Drug interactions (methadone, buprenorphine) • Adherence (fixed dose combinations
Preferred first line regimen	**AZT + 3TC + (EFV or NVP)**
Choice of NNRTI	Hepatitis C (and hepatitis B) infection are extremely common in IDUs. Monitoring hepatotoxicity is strongly recommended in IDUs receiving NNRTI based ART, especially NVP **EFV** EFV is recommended by some experts the due the high prevalence of hepatitis B and C infection in IDUs and less risk of hepatic complications with EFV compared to NVP.[29] EFV is preferred in patients with clinical and/or laboratory evidence of significant (grade 3 or 4) hepatic dysfunction. EFV should used or used with caution in patients with depression or other significant psychiatric conditions **NVP** NVP is recommended in patients with no other significant comorbidities. Specifically, patients with no clinical signs of hepatic dysfunction or elevation of hepatic transaminases (grade 3 or 4). If NVP is the only NNRTI available, use with careful clinical and laboratory (liver enzyme) monitoring
Alternative first line regimen	**TDF + (3TCor FTC) + (EFV or NVP)** Patients who are HBsAg +ve and TDF is available AZT may be replaced by d4T in any regimen in case of toxicity or contraindication
Second line regimen	Recommendations are the same as for all patients with HIV (ddI or TDF) + ABC+ PI/r or TDF + 3TC (± AZT) + PI/r
Adherence	With experienced staff and adequate support, IDUs can adhere to ART and have clinical outcomes comparable to those of HIV patients who do not use drugs [30] [31]
Methadone	Administration of methadone with EFV, NVP or RTV decreases plasma levels of methadone which may precipitate opiate withdrawal.[32] Patients receiving methadone and commencing ART may require increased doses of methadone

Choice of NNRTI component

Patients, particularly women, with increased CD4+ cell count at initiation of NVP therapy (>250 cells/mm^3 in women and >400 cells/mm^3 in men) are at higher risk for the development of symptomatic hepatic events, often associated with rash. The risk of symptomatic hepatic events regardless of severity is greatest in the first 6 weeks of therapy. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels Patients who have infection with hepatitis B or C and/or increased liver function tests at the start of therapy with NVP are at greater risk of later symptomatic events (6 weeks or more after starting NVP) and asymptomatic increases in AST or ALT.

Serious psychiatric adverse experiences have been reported in patients treated with EFV. These include severe depression (2.4%, 0.9%), suicidal ideation, aggressive behavior, paranoid reactions and manic reactions.

Viral hepatitis and chronic liver disease

Co-infection with Hepatitis C is common in HIV infected IDUs. Chronic active infection with Hepatitis B and alcoholic liver disease are also common. Hepatotoxicity associated with these conditions complicates the choice of ART. The NRTIs with most hepatotoxicity are AZT, ddI or d4T. Both available NNRTIs can cause hepatotoxicity. NVP is more commonly associated with severe hepatotoxicity and should be avoided if possible in all patients with chronic liver disease.[33] Efavirenz can be administered at full doses in patients with liver insufficiency. Protease inhibitors are also associated with hepatotoxicity**.** PI dosing is complex in patients with hepatic insufficiency[34].

If drugs are available, the recommended treatment for HIV/HBV co-infection is TDF in combination with 3TC or FTC as part of the ART regimen. 3TC should not be used alone due to rapid development of HBV resistance. Fatal cases of acute flare of HBV have been documented in HIV/HBV coinfected patients who discontinue 3TC monotherapy.[35] [36]

Opioid substitution therapy

OST is the most effective treatment for opioid dependence with substantially higher retention rates, suppression of drug use and improved psychosocial functioning. Its use in the context of HIV treatment has been associated with improved adherence and outcomes to treatment. Detoxification and abstinence based programs are unlikely to achieve similar levels of clinical effectiveness and may prove counterproductive in the context of ART. If possible, stabilization of substance use with substitution treatment is recommended prior to commencement of ART. Where substitution therapy is available, consideration should be given to offering HIV care and dispensing HIV medication at the same site where substitution therapy is delivered. This approach can achieve maximal levels of treatment supervision which should enhance efficacy and reduce the risk of HIV drug resistance. In addition co-location of these services facilitates management of the drug-drug interactions between methadone and ART.

Outcomes of OST in a structured program include:

- Decreased heroin use and reduced chaotic drug taking
- Decreased needle sharing
- Stabilization of client's lives
- Improved quality of life and the chance to lead a productive life in the community
- Improved ability to commence and adhere to ART

HIV and Hepatitis Co-infection

Hepatitis B infection

Choice of ART	Drugs with anti-HBV therapy should be included in first line ART regimen for HIV-infected patients who are HBsAg+ (and HBeAg+ if known)
Preferred first line ART	TDF + (3TC or FTC) + EFV
Alternatives if TDF is unavailable	(AZT or d4T) + (3TC or FTC) + EFV (AZT or d4T) + (3TC or FTC) + NVP (See *Choice of NNRTI* below) In this case, 3TC (or FTC) will be the only drug with activity against hepatitis B
Choice of NNRTI	• EFV is the preferred NNRTI option • NVP should be used with care and regular monitoring in patients who have known HIV/HBV co-infection and grade 1, 2 or 3 elevation of ALT/AST • NVP is not recommended for patients with grade 4 or greater elevations of ALT/AST
Second line regimen	3TC be continued as part of second-line ART following initial ART failure, even if it was used in first-line regimen
HBV Resistance	• Ideally, 3TC should be used either with TDF or not at all • This may not be feasible in resource limited settings • HBV resistance to 3TC will develop in 50% of patients after two years and in 90% after four years of treatment if 3TC is the only active anti-hepatitis B drug in the ART regimen.
Hepatic flares (IRIS)	• Soon after initiation of ART as part of IRIS • Discontinuation of 3TC also may result in hepatic flares

Hepatic flares

Hepatic flares may occur

- Following initiation of ART as part of the immune reconstitution inflammatory syndrome (IRIS).
- When ART is stopped

Flares typically present as unexpected increase in ALT/AST and symptoms of clinical hepatitis (fatigue, nausea, abdominal pain and jaundice) within 6-12 weeks of commencing ART. Flares may be difficult to distinguish from ART-induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare. If it is not possible to distinguish a serious hepatitis B flare from grade 4 drug toxicity, all ART should be stopped until the patient stabilizes.

Hepatitis C infection

HCV therapy	No ARVs are directly active against HCV. However, ART has been shown to delay progression of HCV liver disease in HCV/HIV co infection The only effective treatment is pegylated interferon and ribavirin which are generally not available in resource limited settings[37]
Therapy outcomes	Clinical trial outcomes • HCV genotype 1: 15-28% sustained virological response rates • HCV genotype 2 and 3: 60-70% virological response rates
Side effects of interferon	Up to 60% of individuals treated with IFN will experience mental health issues, mostly commonly depression. Monitor mental health closely.
Timing of HCV therapy	• Commence anti-HCV therapy before CD4 count drops to levels where ART is required • If ART is required in HCV-positive patients, they should be stable on ART with a CD4 count >200 cells/mm^3 before anti-HCV therapy is considered [29]
Preferred first line ART	• NRTI choice is the same as for HCV uninfected patients • EFV is the preferred NNRTI option • NVP should be used with care and regular monitoring in patients who have known HIV/HBV co-infection and grade 1, 2 or 3 elevation of ALT/AST • NVP is not recommended for patients with grade 4 or greater elevations of ALT/AST
Drug interactions	• Ribavirin and d4T/ddI - pancreatitis/lactic acidosis o do not co-administer • Ribavirin and AZT - anaemia o monitor closely • Interferon and EFV - depression o Monitor closely
Hepatic flares	Soon after initiation of ART as part of IRIS

ART failure and when to switch therapy

Defining failure

Switching ART can be considered if there is clinical failure, CD4 failure OR virological failure.

Clinical failure	New or recurrent WHO stage 4 condition after at least 6 months on ART Exceptions are TB, oesophageal candidiasis and severe bacterial infections which may not always represent ART failure Review response to therapy first and if response is good, do not switch
Immunological failure	• CD4 count <100 after one year on ART • Return to or a fall below the pre-therapy CD4 baseline after one year of therapy • 50% decline from the on-treatment peak CD4 value (if known) Before considering failure, ensure that the patient is adherent to ART, there is no active OI to explain the fall in CD4 count.
Virological failure	**VL 1,000-10,000** • Reinforce adherence and repeat VL 3months later • If still 1,000 -10,000, switch to second line **Viral load >10,000 copies** Viral load >10,000 copies after at least 6 months on ART in a patient who is adherent to ART, switch to second line

Notes: ART failure cannot be diagnosed on clinical criteria grounds in the first 6 months on ART.

Clinical events that occur before the first 6 months of therapy often represent IRIS and not failure.

Choice of second-line regimens for treatment failure

First Line Regimen	Second Line Regimen	
	RTI Component	**PI Component**
(AZT or d4T) + 3TC+(NVP or EFV)	**TDF + 3TC (± AZT)** **Or** **ddI + ABC**	**LPV/r**

- The entire treatment regimen needs be changed in the setting of treatment failure
- A ritonavir-boosted PI (PI/r) is the backbone of all second line regimens

Clinical and laboratory monitoring on second line ART

Evaluation	Before or at ART switch	Week 2	Week 4	Week 8	Week 12	Week 24	Every 6 months	As needed (symptom-directed)
Clinical								
Clinical evaluation	✓	✓	✓	✓	✓	✓	✓	✓
Weight	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓
Check ART adherence	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory								
CD4 count	✓						✓	✓
Haemoglobin	✓		✓	✓	✓			✓
Pregnancy test	✓						✓	✓
Creatinine	✓						✓	✓
Fasting lipids	✓						✓	✓
Fasting glucose	✓						✓	✓
Serum lactate								✓
HIV RNA (viral load)								✓

Post exposure prophylaxis

Occupational Post- Exposure Prophylaxis

Treatment of Exposure Site

Skin	✓ Let the wound bleed without scrubbing or squeezing ✓ Immediately wash wound and surrounding skin with water and soap, **without scrubbing**. ✓ Rinse
Eyes and mucous membrane exposure	✓ Rinse the exposed area immediately with isotonic saline solution for 10 minutes

Assessment of Risk

	HIGH RISK	LOW RISK	NO RISK
Body fluids	• Blood • Semen, vaginal secretions • Cerebro-spinal fluid • Amniotic liquid • Other body fluids (synovial, peritoneal, pleural, pericardial) contaminated with visible blood	• Saliva • Urine	Contact with skin or mucous membrane with no injury
Type of exposure	• **Per-cutaneous exposure** Injury with contaminated hollow needle or sharp object. • **Muco-cutaneous exposure** Direct contact between contaminated body-fluid and eye or mucous membrane		

Risk of Transmission and Post-Exposure Prophylaxis

HIV	Per-cutaneous: 0.3% Muco-cutaneous: 0.03-0.09%	PEP (see below)
HBV	Per-cutaneous: 10-30%	Vaccination *(Availability of gamma-globulines in Lao?*)
HCV	Per-cutaneous: 0-10%	None

Assessment of Source Patient

HIV-status unknown	➢ Counseling and HIV-testing as soon as possible.
HIV negative	➢ No PEP
HIV positive	➢ PEP according to exposure risk (see chart) Higher risk of transmission if advanced HIV disease, high viral load, no ART

Assessment and Counseling of Exposed Person

Counselling

- Give health care worker pre test counseling.
- Test the health care worker (baseline tests)
  - HIV
  - Hepatitis B and hepatitis C
  - Haemoglobin, ALT
- **Inform HCW that PEP is not 100% effective.**
- Counsel HCW that they must not give blood and must practice safer sex and safer injecting practices until outcome is known.
- Review HCW (post test counseling) and give baseline results.
- Offer hepatitis B vaccination if HBsAg negative and HBsAg negative.
- Provide counseling on further HIV transmission including condom use, avoiding pregnancy and breast feeding and not donating blood until the person is tested HIV negative three months after the exposure.
-

Documentation of the incident

- Record date and time of exposure, exposure source, details of the event
- Details of PEP treatment if given
- Follow up

Post-Exposure Prophylaxis

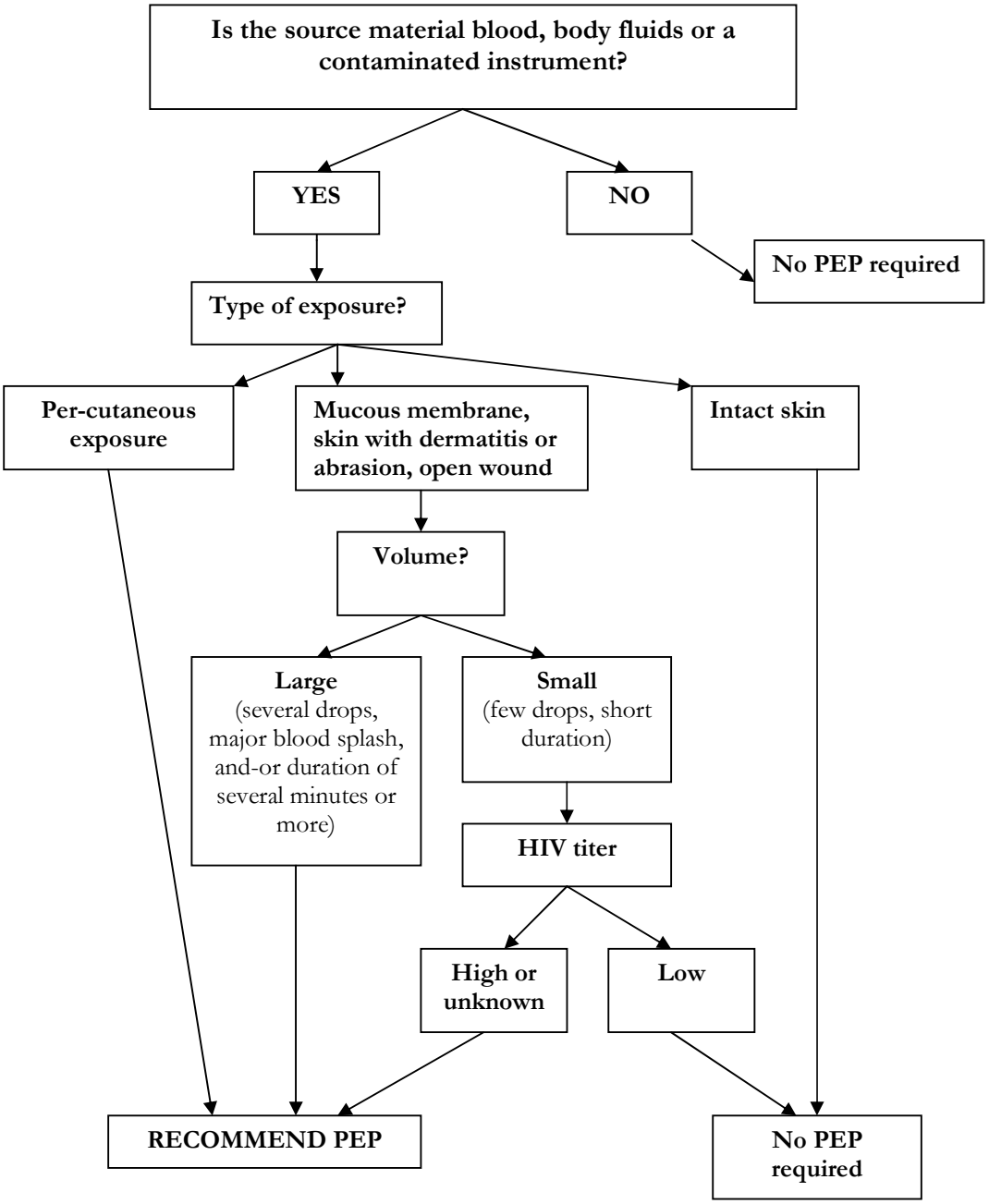
Starting PEP	As soon as possible after exposure, preferably during the first 4 hours and before 72 hours Consider PEP > 72 hours after a high risk exposure
Duration of PEP	28 days
Three drug regimen	(AZT 300mg+ 3TC 150mg) 1 tablet bid + (lopinavir-ritonavir) 2 tablets bid
Side effects	• Nausea, diarrhea, muscular pain, headache: usually mild and transient (inform the patient to avoid drug interruption) • Anemia, neutropenia, thrombocytopenia

Monitoring and Follow-Up

- **Clinical**
  Signs indicating an HIV-seroconversion usually appear 3-6 weeks after exposure: fever (96%), adenopathy (74%), pharyngitis (70%), rash (70%), myalgia (54%).

- **Laboratory**
  - ✓ Baseline (within 8 days after exposure): HIV, Hb, ALT, HBV (HBsAg, HBsAb, HBcAb), HCV serology
  - ✓ Week 2: Hb, ALT

RECOMMANDATIONS FOR PEP



Non Occupational Post-Exposure Prophylaxis

Situations where nPEP may be provided

- Unprotected sexual exposure including rape
- Needle sharing by IDUs
- Injuries from needles discarded in public places. [38]
- Human bite injuries

Situations where nPEP should not be provided

nPEP should not be provided in case of persistent potential exposure to HIV such as discordant sex partners who rarely use condoms, repeated unprotected sex with sex workers or other non regular partners or injection-drug users who often share injection equipment. Persons who engage in frequent, recurrent risk exposure behavior should be counseled and provided with appropriate risk-reduction interventions.

Antiretrovirals for nPEP

The choice is the same for occupational and non-occupational PEP.

Counselling

- Assess extent of risk exposure, frequency of exposure and timing
- Try to ascertain the HIV status if the source (often unknown)
- Evaluate for sexually transmitted infections
- Assess the need for emergency contraception ("morning after pill")
- Give HIV pre test counseling
- Test the individual (baseline tests)
    - HIV
    - Hepatitis B and hepatitis C
    - Swabs and cultures for gonorrhea and Chlamydia if available
    - VDRL and TPHA
    - Pregnancy test (if available) following appropriate counselling
- Counsel the individual that they must not give blood and must practice safer sex and safer injecting practices and not breast feed until outcome is known
- Review and give baseline results
- Offer hepatitis B vaccination if HBsAg negative
-

Classification of antiretroviral drugs by class

Nucleoside Reverse Transcriptase Inhibitors	**Non-nucleoside Reverse Transceriptase Inhibitors**	**Protease Inhibitors**
Zidovudine (ZDV, AZT)	Nevirapine (NVP)	Saquinavir (SQV) soft gel cap
Didanosine (ddI)	Efavirenz (EFV)	Saquinavir (SQV) hard gel cap
Stavudine (d4T)		Saquinavir (SQV) tablets
Lamivudine (3TC)		Ritonavir (RTV, r)[1]
Abacavir (ABC)		Indinavir (IDV)
Nucleotide Reverse Transcriptase Inhibitors	**Entry Inhibitors**	Lopinavir/ritonavir (LPVr)[2]
Tenofovir (TDF)	Enfuvirtide (T20) and Maraviroc	Darunavir
Fixed Combination Antiretrovirals[3]		
Zidovudine + Lamivudine Stavudine + Lamivudine + Nevirapine Zidovudine + Lamivudine + Nevirapine Tenofovir + Emtricatabine + Efavirenz (Atripla)		

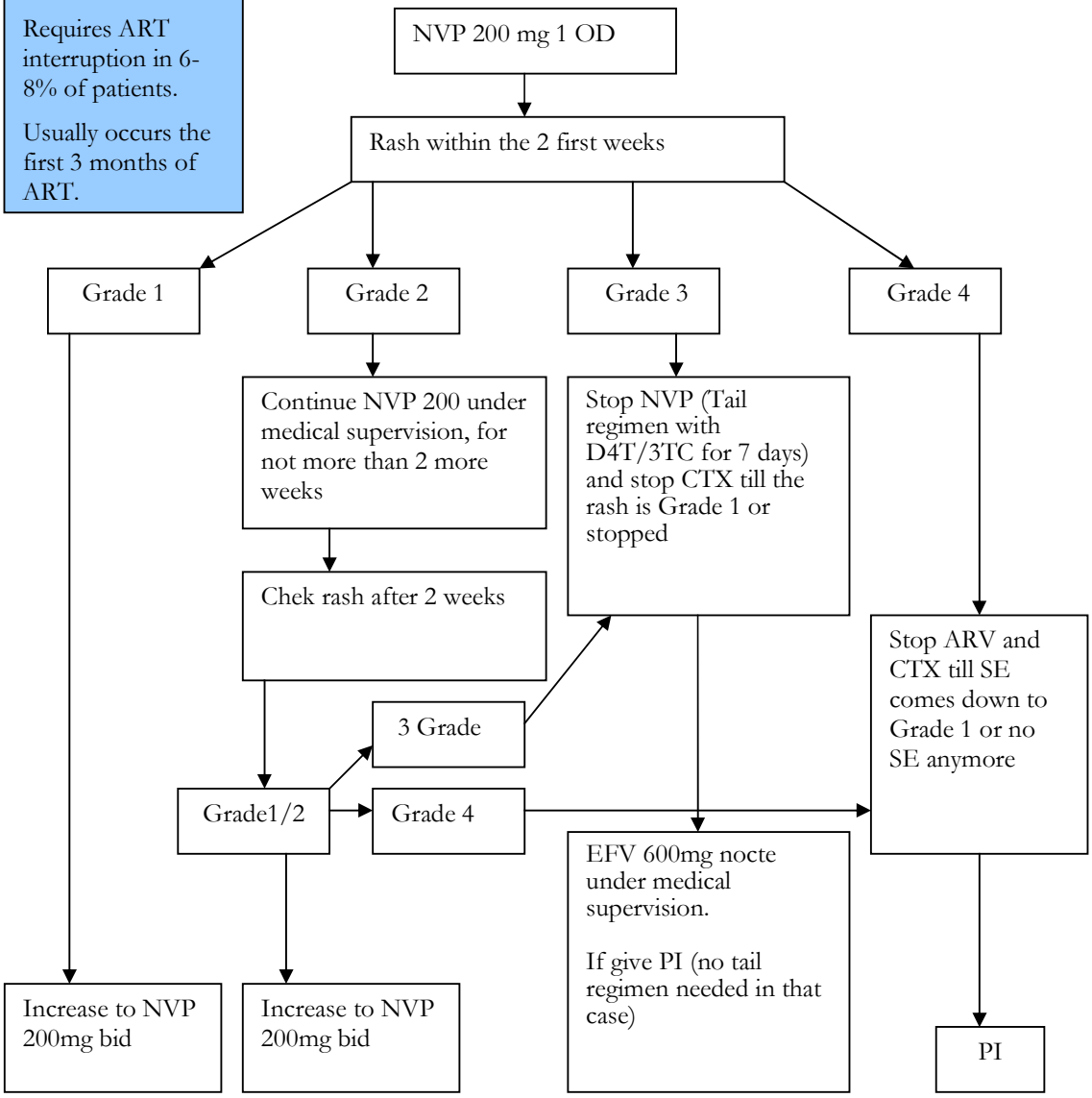
1. Ritonavir is only recommended as a booster of other protease inhibitors
2. Two formulations are available: Original capsules (refrigeration required) and new heat stable tablets (no refrigeration). Heat table tablets are marketed as *Kaletra tablets* in developed countries and will be marketed as *Alluvia* in resource limited settings. Generic formulations of Alluvia will be available
3. Other combinations may be available in some countries

NVP Related Rash

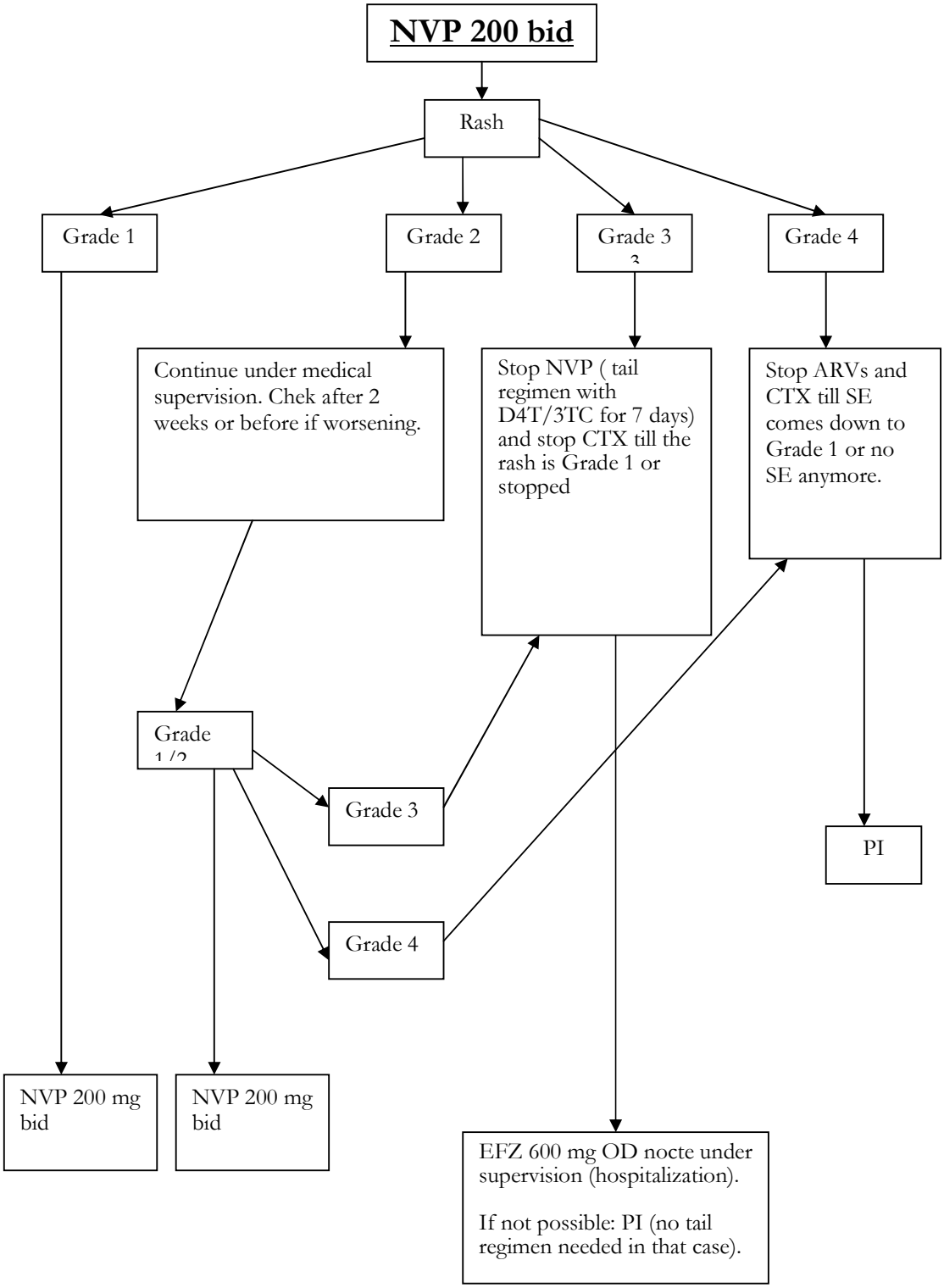
NVP rash occurs in 15-30% of patients.

Requires ART interruption in 6-8% of patients.

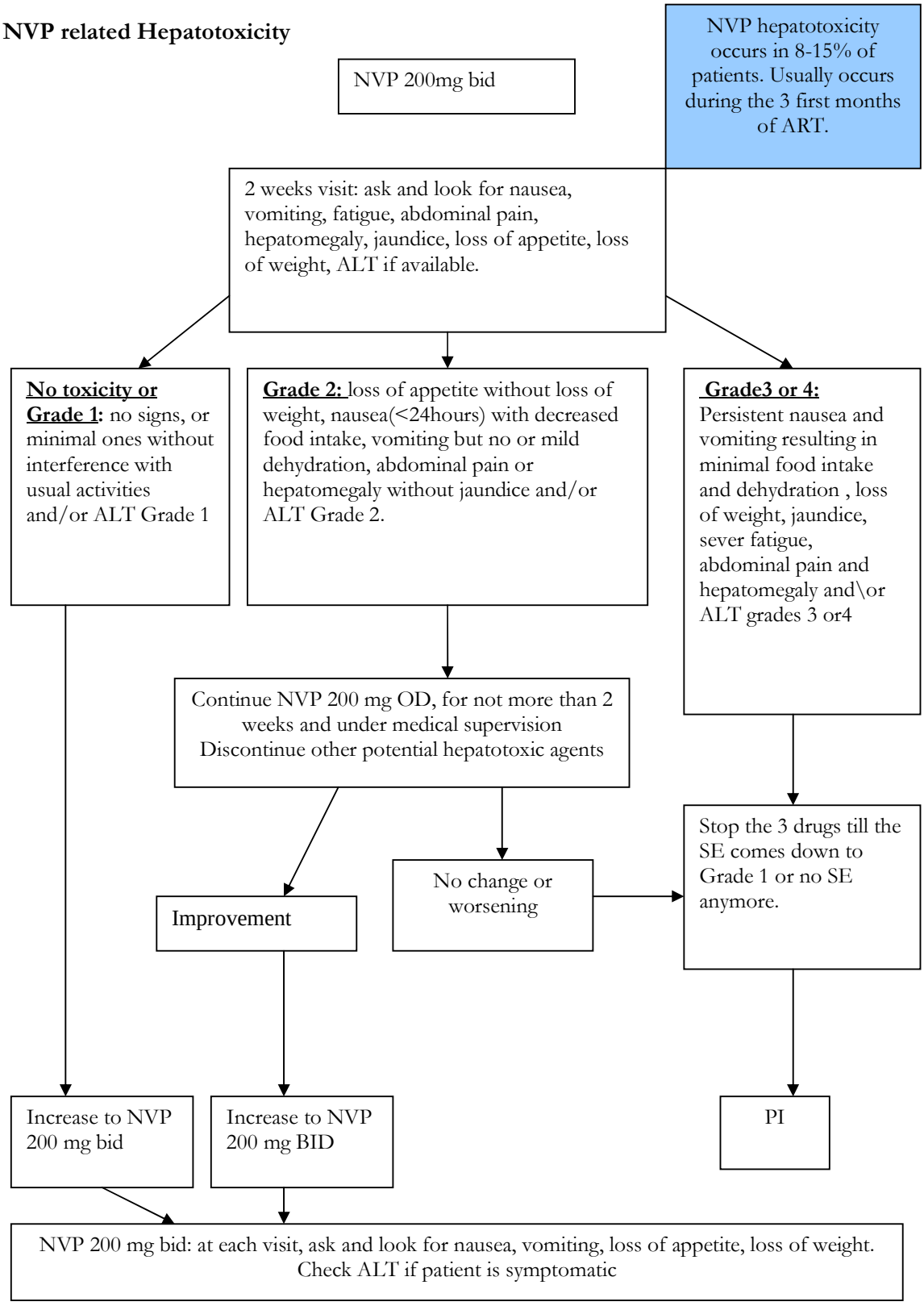
Usually occurs the first 3 months of ART.



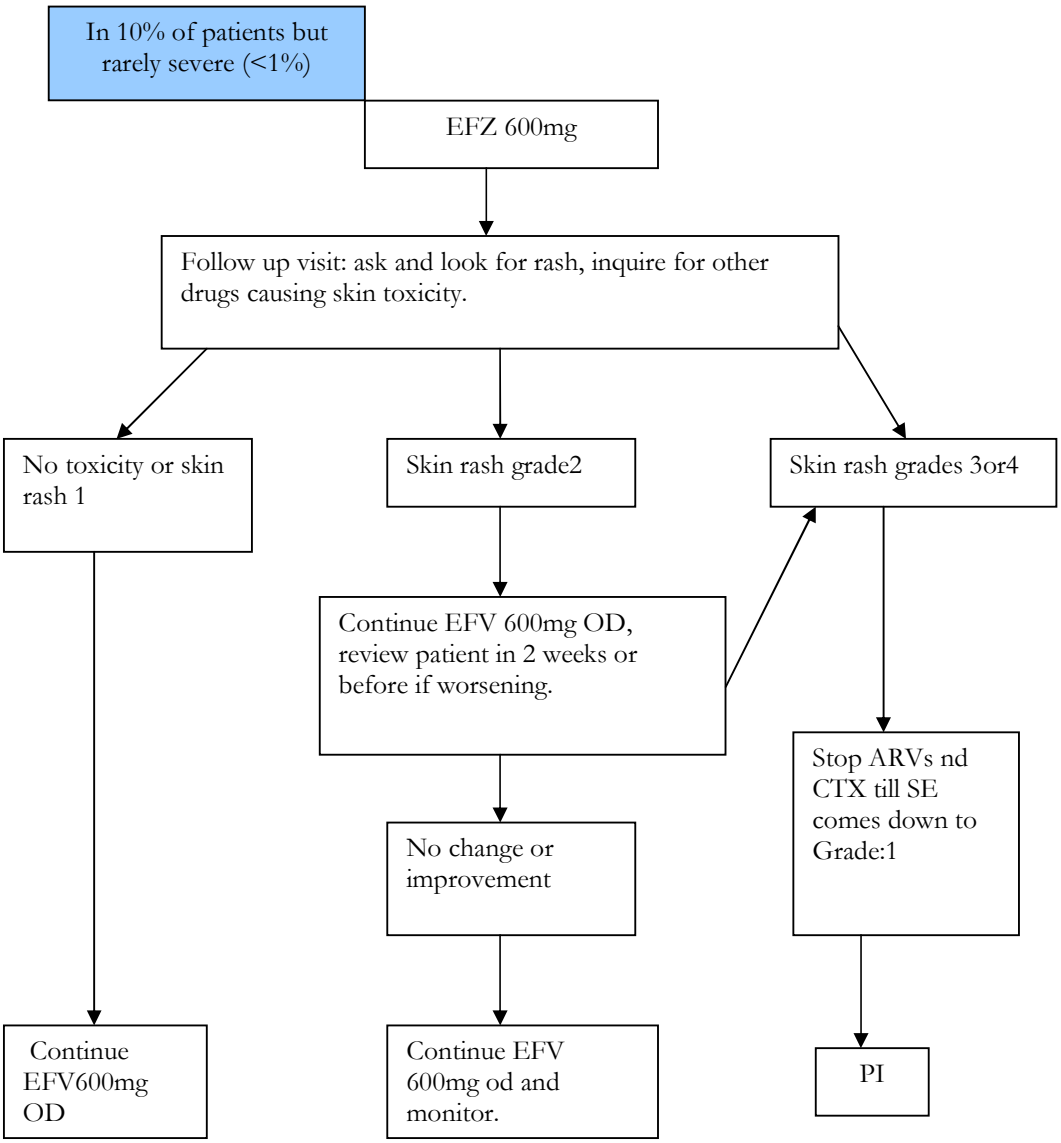
	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous *reaction-rash*	Localized macular rash	Diffuse maculopapular or morbiliform rash OR target lesions)	Diffuse maculopapular or morbiliform rash with vesicles or limited number of bulla OR superficial ulcerations of mucous membranes limited to one site.	Extensive or generalized bullous lesions OR Steven-Johnson syndrome OR Ulceration or mucous membranes involving 2 or more distinct mucosal sites OR toxic epidermal necrolysis


NVP 200 bid
Rash
Grade 1
Grade 2
Grade 3
3
Grade 4
Continue under medical supervision. Chek after 2 weeks or before if worsening.
Stop NVP (tail regimen with D4T/3TC for 7 days) and stop CTX till the rash is Grade 1 or stopped
Stop ARVs and CTX till SE comes down to Grade 1 or no SE anymore.
Grade
1/2
Grade 3
Grade 4
PI
NVP 200 mg bid
NVP 200 mg bid
EFZ 600 mg OD nocte under supervision (hospitalization).
If not possible: PI (no tail regimen needed in that case).

NVP related Hepatotoxicity



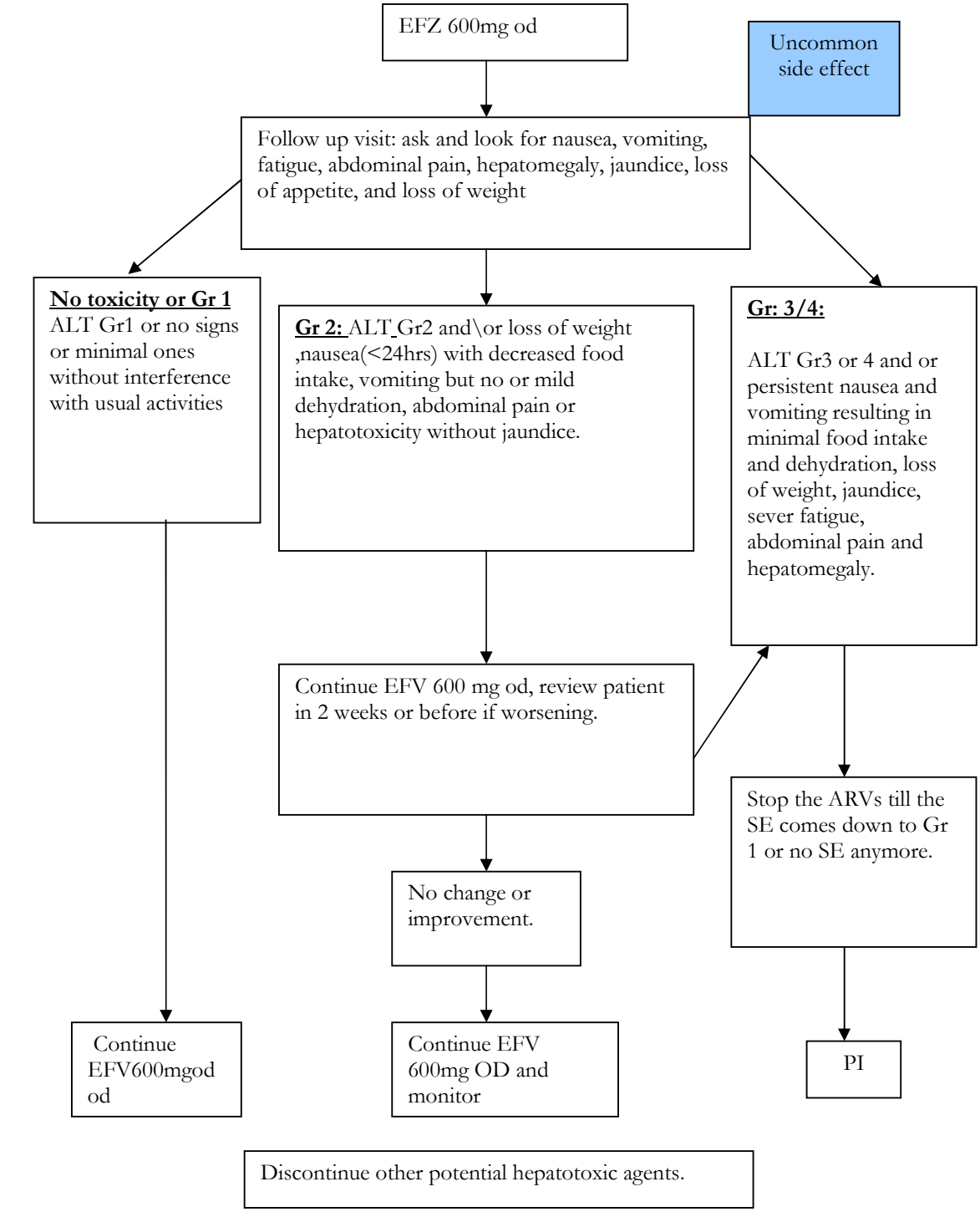
Efavirenz related skin toxicity



	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous *reaction-rash*	Localized macular rash	Diffuse maculopapular or morbiliform rash OR target lesions)	Diffuse maculopapular or morbiliform rash with vesicles or limited number of bulla OR superficial ulcerations of mucous membranes limited to one site.	Extensive or generalized bullous lesions OR Steven-Johnson syndrome OR Ulceration or mucous membranes involving 2 or more distinct mucosal sites OR toxic epidermal necrolysis

Efavirenz Related hepatotoxicity

Routine ALT is not done for patient on EFV, as liver toxicity is uncommon. Algorithm is based on clinical signs and symptoms. Ask for ALT (if possible) in case ALT toxicity values are the same than for NVP. In case ALT toxicity Gr: 3 or 4, EFV will be discontinued and switched for PI.

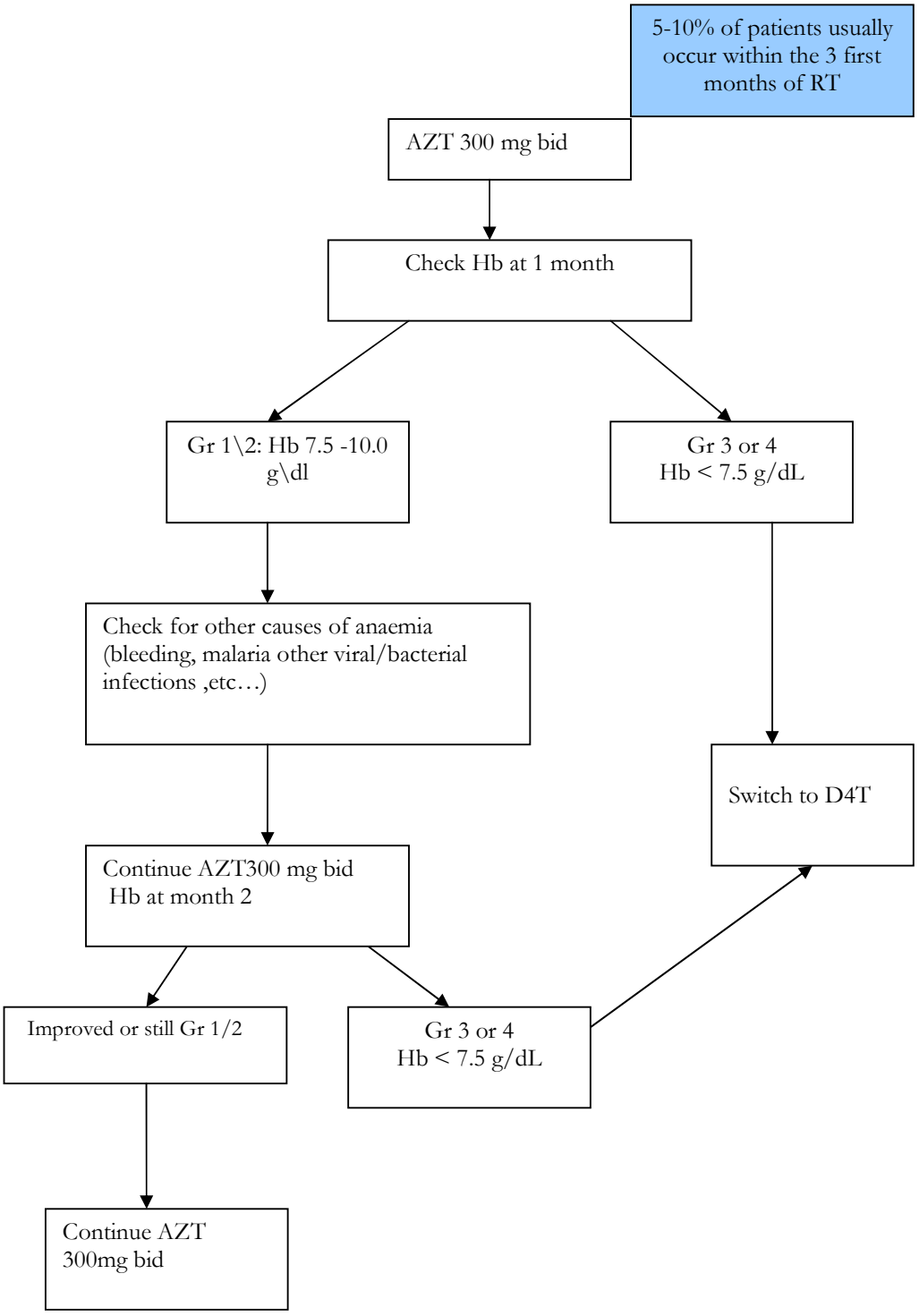


AZT related anemia

Check base-line hemoglobin at M_0. If Hb < 7.5g/dL don't start AZT.

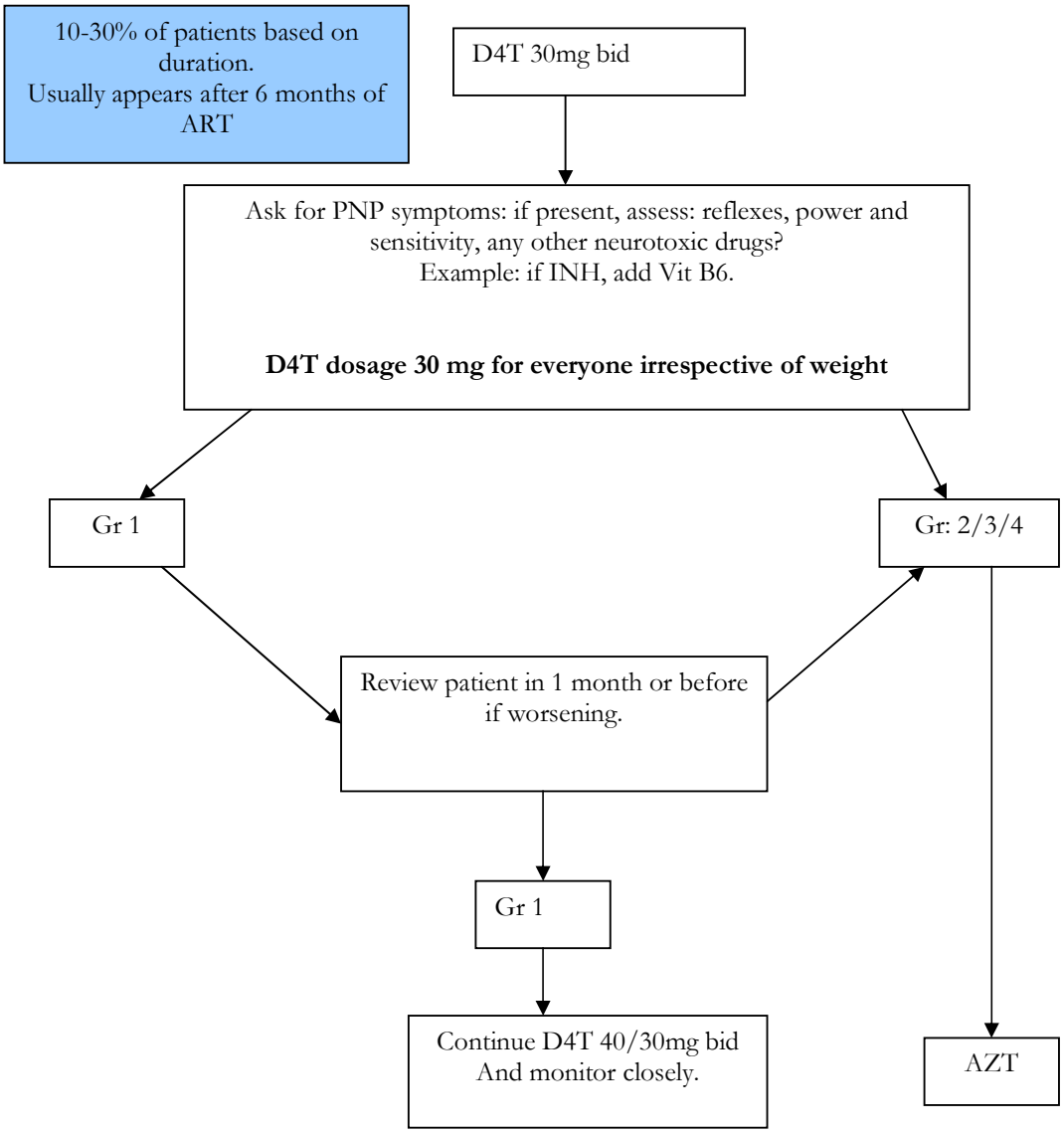
AZT related anemia

Check base-line hemoglobin before commencing AZT.
If Hb < 10.0 g/dL do not start AZT.



D4T related neurotoxicity

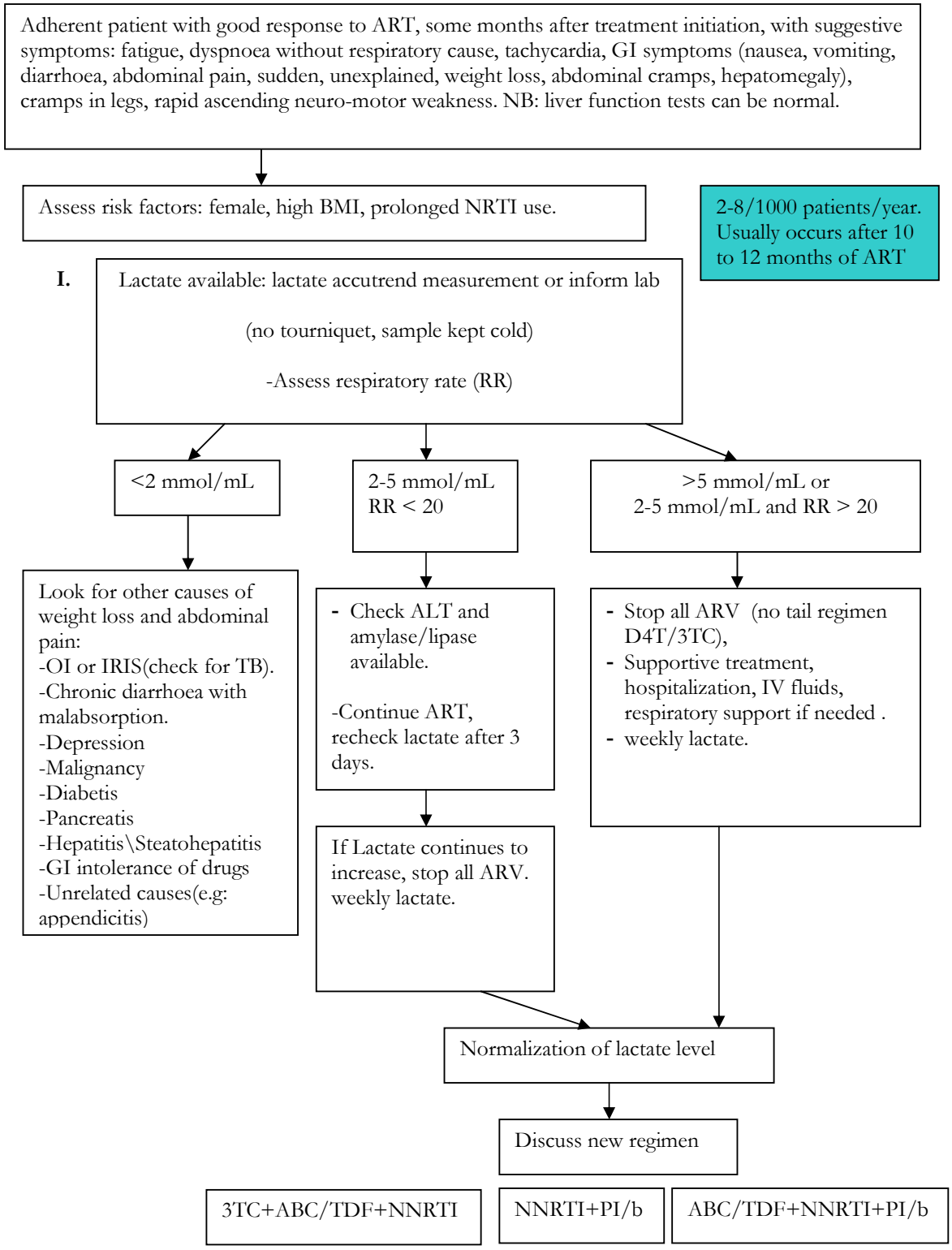
Before starting ARVs, preexisting PNP should be assessed. The baseline neurological examination should be documented in the file. Preexisting PNP due t HIV itself is common among patients with advanced HIV\AIDS disease and may respond to ART.

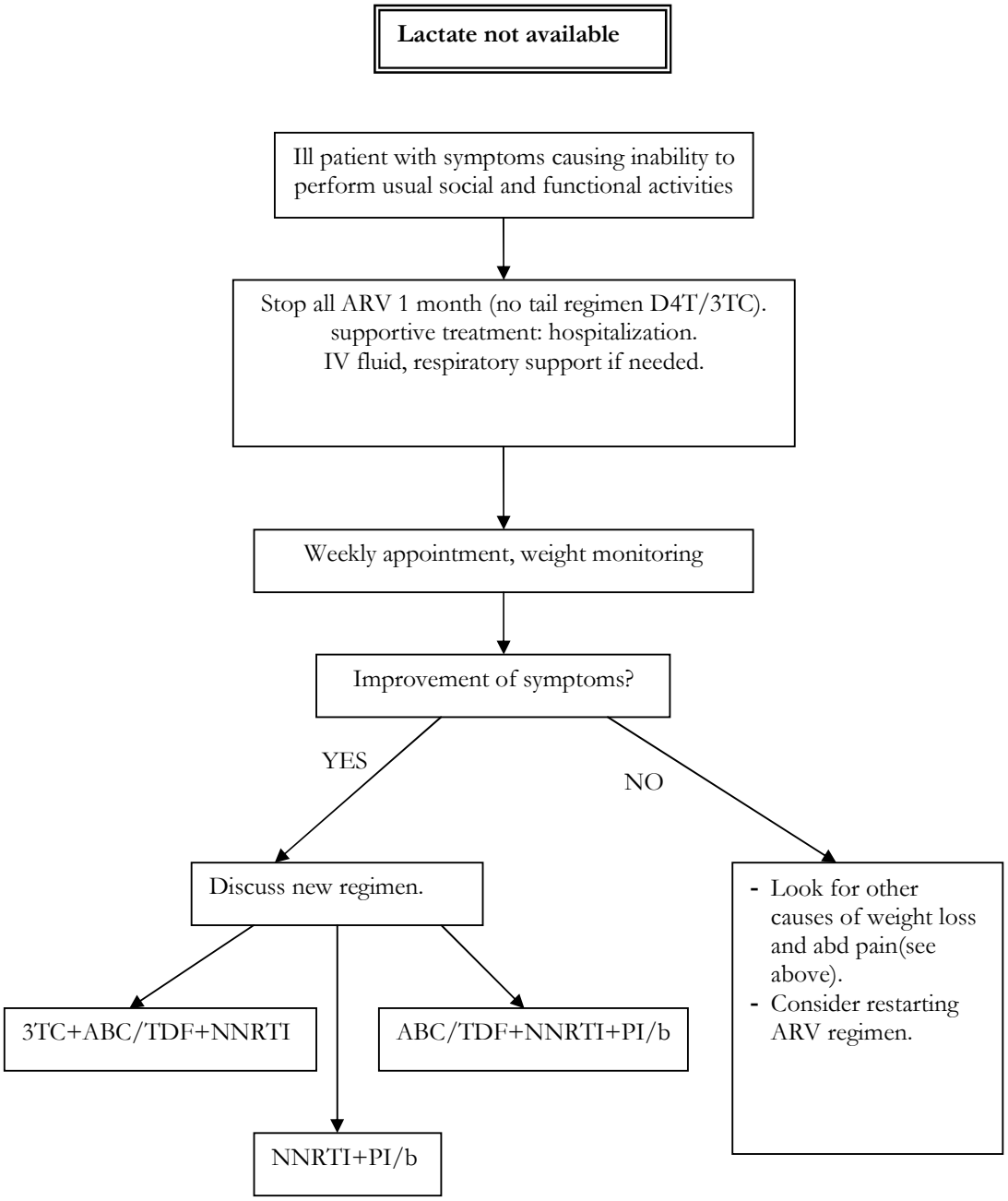


	1	2	3	4
Symptoms: burning, tingling	Mild, does not affect walking.	Moderate. Minimal interference with walking	Severe, continuous, painful, Walking Is difficult.	Incapacitation. very painful. Cannot walk
Sensory	Mild decrease in sensation in toes, symmetrical.	Moderate decrease, not symmetrical	Sever loss of sensation to knees. Other body areas affected.	Sensory loss involves trunk.

NRTI related lactic acidosis

Routine lactic acid monitoring is not recommended as it is not predictive of lactic acidosis in asymptomatic patients




Lactate not available
Ill patient with symptoms causing inability to perform usual social and functional activities
Stop all ARV 1 month (no tail regimen D4T/3TC).
supportive treatment: hospitalization.
IV fluid, respiratory support if needed.
Weekly appointment, weight monitoring
Improvement of symptoms?
YES
NO
Discuss new regimen.
- Look for other causes of weight loss and abd pain(see above).
- Consider restarting ARV regimen.
3TC+ABC/TDF+NNRTI
ABC/TDF+NNRTI+PI/b
NNRTI+PI/b

PART TWO

National Guidelines for the use of Antiretroviral Therapy in Children

Antiretroviral therapy for infants and children

Introduction

The effectiveness of highly active antiretroviral therapy to reduce HIV-related morbidity and mortality in infants and children is similar to that observed in adults.[39] However, treatment of HIV-infected children is more complex than in adults. Reasons include[40]:

- Limited number of pediatric formulations of antiretrovirals
- Differences among individuals in their response to drugs, especially of protease inhibitors
- Adherence to combination therapy for many years is difficult
- Problems taking medication during sleep time or at school
- Unwillingness of young children and adolescents to take medication
- Poor palatability of medication
- Side effects of medication

The general principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons, there are unique considerations needed for HIV-infected infants and children. These include[41]:

- Many perinatally infected children have exposure to zidovudine, nevirapine and other antiretroviral medications, which may result in the development of resistance
- Difficulties in the diagnosis of HIV infection in children <18 months of age in resource limited settings
- Differences in immunologic markers in young children. CD4% and not CD4 count is used to measure immune function. If CD4 is not available, age adjusted CD4 count can be used.
- Changes in drug pharmacokinetics with age caused by the continuing development and maturation of organ systems and changes in body weight

HIV testing in Infants and Children (keep this text or not)

HIV infection can be definitively diagnosed in most infected infants by age 1 month and in virtually all infected infants by age 6 months by using viral diagnostic assays. (Detection of HIV by culture or DNA or RNA polymerase chain reaction [PCR]).[42] These assays may not be available in resource limited settings. Detection of plasma HIV RNA (viral load) is an alternative. WHO also recommends immune-complex dissociated p24 antigen as a second alternative. This test has a high false positive rate in infants less than 4 weeks of age. [43] If available, virological testing should be performed before the infant is age 48 hours, at age 1–2 months, and at age 3–6 months.

HIV infection is diagnosed by two positive HIV virological tests performed on separate blood samples. HIV infection can be reasonably excluded among children with two or more negative virological tests performed at more than one month and more than four months after cessation if breast feeding.,[44].

HIV Antibody Testing

In the absence of viral diagnostic assays, HIV antibody testing is used. However, the diagnosis of HIV infection in infants and children by HIV antibody testing is complicated by the persistence of maternal antibodies in children up to 18 months of age. Two or more negative HIV antibody tests performed at age 6 months with an interval of at least 1 month between the tests also can be used to reasonably exclude HIV infection among children with no clinical evidence of HIV infection. HIV infection can be definitively excluded if HIV antibody is negative at age 18months. Breastfeeding infants are at risk of HIV infection during the period of breastfeeding and a negative virological or antibody test during the breastfeeding period does not exclude the child becoming infected at a later time point. A negative HIV test result at 6 months after discontinuation of breastfeeding rules out HIV infection. A persistent HIV positive test result after 18 months post delivery confirms HIV infection regardless of breast feeding[45].

Who Clinical Staging of HIV/AIDS for Infants and Children

This staging system provides guidance on when to start, stop or substitute antiretroviral therapy in HIV-infected children. Knowledge of HIV clinical staging may also help clinical care providers to offer HIV testing to infants and their parents when children present with conditions where HIV infection is a possible. The clinical staging system is designed for use where HIV infection is confirmed by HIV antibody or virological testing. In children under 18 months, virological diagnostic methods are recommended.

Primary HIV infection
Asymptomatic
Acute retroviral syndrome
Clinical Stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical Stage 2
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Fungal nail infections
Clinical Stage 3
Moderate unexplained malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5 intermittent or constant, for longer than one month)
Persistent oral candida (outside first 6- 8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node TB
Pulmonary tuberculosis
Severe recurrent presumed bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8g/dl), neutropaenia (<500/mm^3) or chronic thrombocytopenia (<50 000/ mm^3)
HIV-associated cardiomyopathy or HIV-associated nephropathy
Clinical Stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe presumed bacterial infections
Chronic herpes simplex infection; (orolabial or cutaneous > month's duration or visceral at any site)
Extrapulmonary tuberculosis
Kaposi sarcoma
Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (outside the neonatal period)
HIV encephalopathy
Cytomegalovirus (CMV) retinitis or CMV infection affecting another organ, with onset at age >1 month
Extrapulmonary cryptococcosis including meningitis
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
Chronic Cryptosporidiosis
Chronic Isosporiasis
Disseminated non-tuberculous mycobacteria infection
Acquired HIV-associated rectal fistula
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy

Initiation of cotrimoxazole prophylaxis in infants and children

Situation			
HIV exposed infants and children[1]	**Confirmed HIV infected infants and children[2]**		
	under 1 year	**1-4 years**	**5 years and older**
CTX prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of HIV transmission and exclusion of HIV infection.	CTX prophylaxis is indicated regardless of CD4 percent or clinical status.[3]	WHO stages 2, 3 and 4 regardless of CD4 percent **OR** Any WHO stage and CD4 <25%	Follow adult recommendations

Notes

1. Defined as a child born to an HIV-infected mother or child breastfeeding from an HIV-infected mother and extends until HIV exposure stops (6 weeks after complete cessation of breast feeding) and infection can be definitively excluded. Programme efforts should focus on CTX prophylaxis in first 6 months of life when the risk of PCP is greatest.
2. In children under 18 months HIV infection can only be confirmed by virological testing[46]
3. Once started on CTX, all children should continue until 5 years regardless of clinical symptoms

When to start ARV therapy in infants and children

Because of the difficulties in making a laboratory diagnosis of HIV infection in infants aged <18, WHO recommendations for initiation of ARV therapy in children are divided into categories related to

- age
- availability of virological diagnostic tests

When CD4 cell assays are available, CD4 cell percentage rather than absolute CD4 cell should be used to determine when to start ARV treatment in children as CD4 cell percentage varies less with age.[47],[48] As in HIV-infected adults, total lymphocyte count significantly correlates with the risk of mortality in HIV-infected children.[49] [50] When CD4 cell count cannot be assessed, total lymphocyte count may be used as a substitute indication for treatment for infants or children with documented HIV infection in the presence of symptomatic disease

When to Treat
WHO stage 3 or 4 **Age related CD4% indicates advanced or severe immunodeficiency** **Total lymphocyte count indicates severe immunodeficiency**

Clinical criteria

WHO clinical disease staging	
Classification	**WHO Clinical Stage**
Asymptomatic	1
Mild	2
Advanced	**3**
Severe	**4**

Immunological Criteria[1]

WHO classification of HIV-associated immunodeficiency using CD4				
Classification of HIV-associated immunodeficiency	**Age-related CD4 values**			
	< 11 months (%)	**12 - 35 months (%)**	**36-59 months (%)**	**≥ 5 years (cells/mm^3)**
Not significant	**> 35**	**> 30**	**> 25**	**> 500**
Mild	**30 - 35**	**25 - 30**	**20 - 25**	**350−499**
Advanced	**25 - 30**	**20−25**	**15−20**	**200−349**
Severe	**<25**	**<20**	**<15**	**<200 *or* <15%**

CD4 Criteria for Severe HIV Immunodeficiency in Children

Immunological Marker [a]	**Age-Specific Recommendation to Initiate ART [b]**			
	≤11 months	**12 months to 35 months**	**36 months to 59 months**	**≥5 years**
%CD4+ [c]	<25%	<20%	<15%	<15%
CD4 count [c]	<1500 cells/mm ^{3}	<750 cells/mm ^{3}	<350 cells/mm ^{3}	<200 cells/mm ^{3}

a - Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.
b - ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.
c - %CD4+ is preferred for children aged <5 years.

Total lymphocyte count (TLC)[51]

Classification of HIV-associated immunodeficiency	**Age-related TLC values**			
	< 11 months (cells/mm^3)	**12 - 35 months (cells/mm^3)**	**36-59 months (cells/mm^3)**	**≥ 5 years (cells/mm^3)**
Severe	**<4000**	**<3000**	**<2500**	**<2000**

Notes:

- Clinical staging in children without ART can predict mortality; however, it is heavily dependent on the presence of malnutrition. Clinical staging is used as a guide for cotrimoxazole and ART management particularly in situations where CD4 is not available.
- CD4 is the best measurement for assessing immune deficiency. CD4 should be used in conjunction with clinical assessment; however, CD4 allows an earlier detection of worsening of HIV disease as CD4 decline usually occurs before there is clinical progression. CD4 monitoring can aid in the decision to initiate or switch ART. Younger children normally have higher CD4 than older children and adults. CD4% varies less in children < 6 years old and is the preferred measurement. At age ≥ 6 years, either CD4% or CD4 count can be used. The threshold CD4 levels for severe immunodeficiency in children age 1 year and up corresponds with a 12 month mortality risk of ≤ 5%. In children younger than 1 year and especially < 6 months, CD4 is less predictive of mortality and there is high risk for death even at high %CD4.
- Total lymphocyte count is only used if CD4 measurement is not available and it should only be used to categorize severe immune suppression. Calculation of TLC = % lymphocyte X total white blood cell count.

Recommended first line ART

14 September 2007the United States Federal Drug Administration (FDA) gave tentative approval for a fixed-dose combination (FDC) anti-HIV drug specifically formulated for paediatric use. As a result of this tentative approval, this FDC antiretroviral drug will also be included in the World Health Organisation (WHO) Prequalification Programme and will become available for distribution under the President's Emergency Plan for AIDS Relief (PEPFAR) and Clinton Foundation programmes. Under the trade names of Triomune Baby and Junior, the drug has already been approved and is in use in Zambia.

Preferred first line

Triomune Junior
One tab BID

Alternative first line if side effects from Triomune, especially lipodystrophy

Zidovudine
10 mg / Kg/ dose twice daily

+

Lamivudine
4 mg / Kg/dose twice daily

+

Efavirenz (EFV)
- for children over 3 years **OR**
- > 10kg

Notes:

- **Always give three drugs**
- Drug doses in children are based on weight and dosing must be adjusted as the child grows.
- Formulations appropriate for use by young children who cannot swallow whole tablets or capsules are not currently widely available in resource-limited settings.
- The splitting of adult dose solid formulation ARVs, while suboptimal, should be considered when no other alternatives are available.
- Current adult fixed dose combination formulations may not contain the appropriate doses of each of the component drugs for children on a weight basis.
- Until more research is conducted, children who require ARV therapy and who have previously received ARV as part of prophylaxis for MTCT should be offered standard NNRTI based first line regimens.

Alternative regimen if the child has tuberculosis

Child on rifampicin [a] containing TB therapy who need to start ART	
Preferred regimen	**Alternative regimen**
2 NRTI + EFV (in children ≥ 3 years old)	ZDV or d4T + 3TC + ABC **OR** 2NRTI + NVP [b]

Notes:

a After completion of rifampicin-based treatment, consider switching treatment to standard first line regimen with 2NRTIs + NVP or EFV

b Rifampicin lowers the drug level of NVP by 20–58% and that of EFV by 25%. In children, there is no information on the appropriate dosage of NVP and EFV when used with rifampicin. Standard dosage regimens of EFV can be used.

Children already on first-line ART who develop TB and start rifampicin-containing TB treatment	
Current firstline regimen	**Preferred regimen**
2 NRTI + EFV	Continue the same regimen.
2 NRTI + NVP	Switch to either 2 NRTI + ABC or 2 NRTI + EFV (if age >3 years and >10 kg).

Notes:

- There is no drug interaction between NRTIs and rifampicin
- Apart from rifampicin, other anti-TB drugs do not interact with ARV drugs
- Anti-TB drugs and NNRTIs (especially NVP) can have overlapping hepatotoxicity; therefore, close monitoring of liver functions is required
- If TB is diagnosed first, anti-TB treatment should be started and ART should be started 2–8 weeks after anti-TB treatment to ensure that the treatment is tolerated and to decrease the risk of inflammatory immune reconstitution syndrome (IRIS)
- AZT or d4T + 3TC + ABC have no drug interaction with rifampicin. However, this combination has been shown to be less potent in one study in adults than 2 NRTI + EFV
- ABC is expensive and is therefore not readily available

Assessment of Infants and Children Receiving ARV

Clinical assessment

In addition to the clinical assessments recommended in adults, clinical monitoring of ARV treatment in children should include:

- Nutrition
- Weight and height growth
- Developmental milestones
- Neurological symptoms
- Systematic treatment of intestinal helminth infection is recommended for HIV exposed and HIV infected children >1 year of age.
- Important clinical signs of response to ARV therapy in children include
- improvement in growth in children who are failing to grow
- improvement in neurological symptoms and development in children who are demonstrating delay in developmental milestones or encephalopathy
- decreased frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections)..

Monitoring schedule

	Baseline	2 weeks	Month 1	Month 2	Month 3	Month 6	Every 2-3 months	Symptom directed
Clinical								
Clinical evaluation and HIV staging	X	X	X	X	X	X	X	X
Weight, height	X	X	X	X	X	X	X	
Calculation of ART dose	X	X	X	X	X	X	X	
Nutritional status and needs	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Adherence to ART		X	X	X	X	X	X	
Laboratory								
Hb and WBC*	X				X		X	X
Pregnancy test in adolescent girls	X							X
CD4% or count	X						X	X
ALAT/ASAT	X		X					X
Chemistry								X

- Re-calculation of the dose of ART should be done at every visit. Giving doses of ART that are less than those recommended can lead to rapid development of resistance.
- Check for concomitant drug intake at every visit such as appropriate co-trimoxazole prophylaxis (if indicated) and other drugs. Check for potential drug interactions with ART.
- Assessment for adherence to ART can be done by asking the child and parent/caregiver questions about missed doses and the times at which the child takes ART. Performing a pill count is time-consuming but may be a better measure of adherence, if done correctly.
- Hb and WBC monitoring may be considered in children on AZT at 1, 3, 6 and 12 months and other times is symptoms indicate need.

- Full blood chemistry includes liver enzymes, renal function, glucose, lipids, amylase, lipase, serum electrolytes. Monitoring depends on the symptoms and regimens. Regular monitoring of liver function tests during the first 3 months of treatment should be considered for children on NVP-based regimens, especially in adolescent girls with CD4 cell counts >250 cells/mm^3 as well as infants and children co-infected with hepatitis B virus (HBV), hepatitis C virus (HCV), or with other hepatic diseases.

Changing therapy for individual drug toxicity

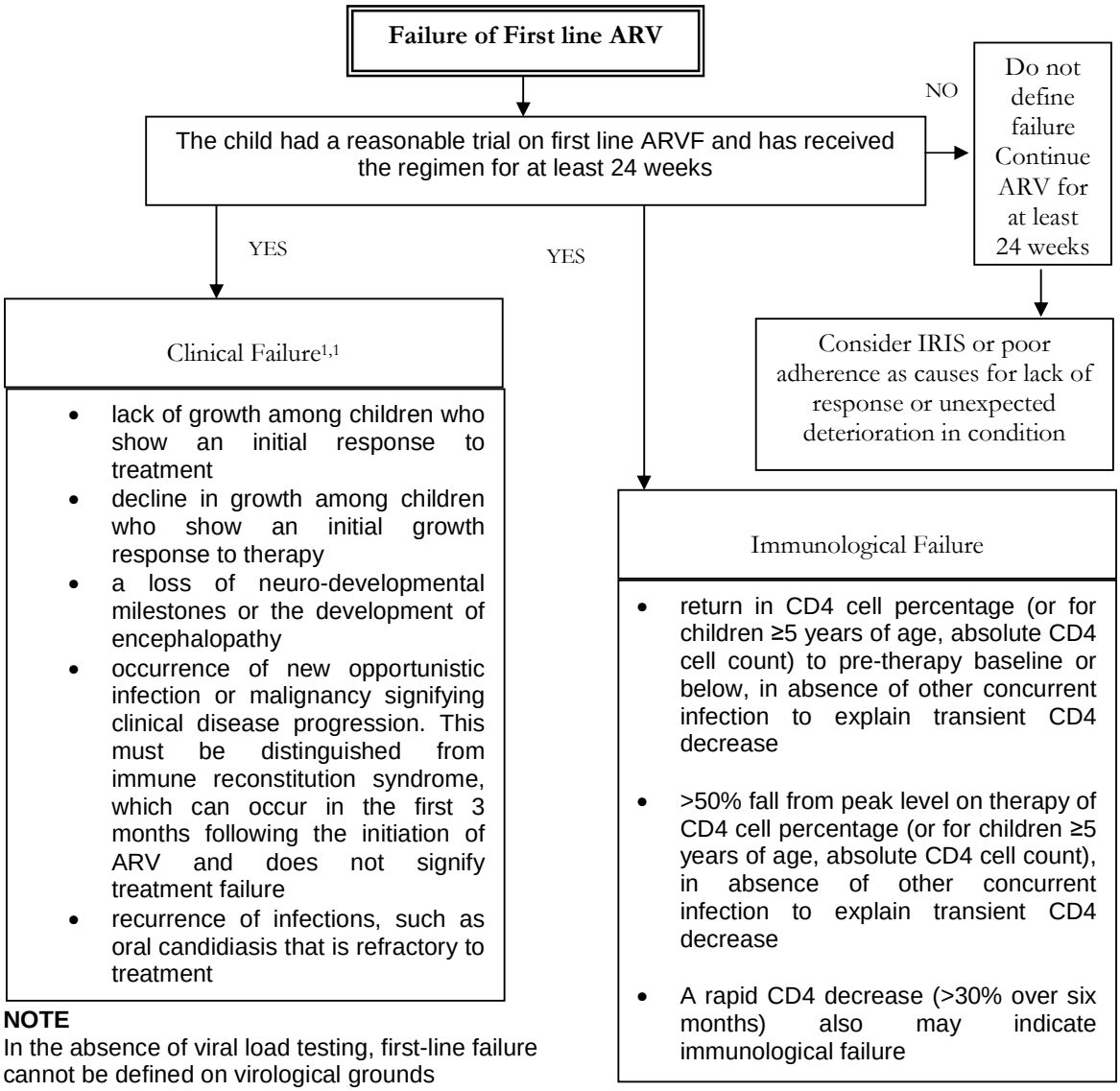
Regimen	Toxicity	Drug substitution
d4T/3TC/NVP	d4T-related neuropathy, pancreatitis or lipoatrophy	Switch d4T to AZT
	NVP-related severe hepatotoxicity	Switch NVP to EFV*
	NVP-related severe rash	Switch NVP to EFV*
AZT/3TC/NVP	AZT-related persistent GI intolerance or severe haematological toxicity	Switch AZT to d4T
	NVP-related severe hepatotoxicity	Switch NVP to EFV*
	NVP-related severe rash	Switch NVP to EFV*
d4T/3TC/EFV	d4T-related neuropathy or pancreatitis	Switch d4T to AZT
	d4T-related lipoatrophy	Switch d4T
	EFV-related persistent CNS toxicity	Switch EFV to NVP
AZT/3TC/EFV	AZT-related persistent GI intolerance or severe haematological toxicity	Switch AZT to d4T
	EFV-related persistent CNS toxicity	Switch EFV to NVP

*EFV should only be given if child >3 or >10kg (if not use Abacavir if available)

Notes:
When rash and/or hepatitis occur with NVP, it is recommended to stop the whole regimen and wait for the rash and/or hepatitis to subside before re-starting with a regimen based on EFV (using the same NRTIs).

Changing ARV Therapy in Infants and Children

The management of drug toxicity and the principles on which to base changes in ARV for children are similar to those in adults.



NOTE
In the absence of viral load testing, first-line failure cannot be defined on virological grounds

Second-Line ARV Therapy for Infants and Children

Second-line therapy for children in the event of first-line regimen failure follows the same principles as for adults and includes a change in nucleoside backbone (e.g., from AZT +3TC to ABC + ddI) plus a protease inhibitor. Use of protease inhibitors other than LPV/r and NFV is more problematic in children due to:

- lack of suitable pediatric drug formulations for IDV and SQV
- lack of appropriate dosing information for ritonavir boosted PIs other than LPV/r

SQV/r can used as an alternative for children who can swallow capsules and are > 25 kg in weight. It should be noted that NFV is the preferred choice among PIs due to the fact that RTV is extremely bitter to taste.

First-Line Regimen	Second-Line Regimen
(d4T or AZT) + 3TC+ (NVP or EFV)	ABC + ddI +/- 3TC Plus LPV/r

Adherence

Children are not small adults, especially in relation to the assessment and support of adherence. Adapted approaches and tools are necessary and should be available and understood by health care personnel. In order to do so, a comprehensive knowledge of the various factors and constraints that influence adherence is essential: factors related to the child itself, the caretaker, the health care provider, the regimen factors and the society in general. Support and assessment of adherence in children is a continuous procedure, starting well in advance of treatment and throughout further follow up. Depending on the stage, whether preparing for treatment or already taking ARV drugs, different issues need to be addressed and adapted approaches applied.

Specific issues to be addressed in supporting adherence in children

Preparation before starting ARV	While on ARV treatment
Related to the child	
How to communicate and evaluate the readiness? • Communication on health, sickness, pain, treatment and adherence issues can be done through fairy tails and games. Depending on the child's maturity, it can include other issues like treatment plan, treatment monitoring, and disclosure and transmission routes. • Any communication should be open and fair, enabling the child to express feelings and to ask questions, whether individually or in groups. • The message should be clear and positive focussing on "AIDS can be treated". • Disclosure should not a prerequisite for good adherence. However, the issue can be addressed through tools. • Assessment of readiness requires proximity in order to sense the child's perspective towards treatment but also to evaluate the willingness / ability to swallow medicines. Swallowing of pills can be taught (starting with smaller pills, see swallowing protocol); alternatives can be found (crushing and mixing of tablets, opening of some capsule, use of syrup). • Prophylactic drugs can be used as a tool to assess adherence prior to starting ART	Communication and evaluation • Plays need to be an integral part of ARV clinics. This helps the children to live positively with HIV/AIDS, provides fun and is a perfect way to provide information, education and communication • Communication can happen individually but also in groups, allowing children to share experiences without compulsory disclosure, e.g., a child shows how he/she swallows tablets. • The importance of adherence is crucial during further follow up and can be addressed through different games and fairy tales. • An evaluation of the child's worries and feelings is essential to adherence, especially at the commencement of treatment. • Adherence assessment can be done through various ways: o open and direct questioning o pill counting o self report of child (e.g. through drawing, stickers in diary) o assessing the understanding of given information • The limitations of adherence assessment should be acknowledged with the focus on support for unconditional adherence from the very beginning. • Tools for adherence support (e.g., diary for self reporting)

Related to the caretaker	
The role of the caretaker is crucial • Identification of a caretaker and evaluation of his/her relationship with the child is a prerequisite • The caretaker should understand and accept his responsibility for all doses of the child's medication Communication with the caretaker should address: o the caretaker's attitude towards HIV/AIDS o caretakers expectations towards ART o all caretakers unanswered questions that might lead to stress or isolation of the child o essential issues like HIV transmission, AIDS can be treated, children can grow, and the importance of adherence o basic knowledge on OI and ARV treatment • Any HIV-infected caretaker should be part of a family-centred model of care and treatment: ARV should be provided if needed.	• • Caretakers should join the children's activities and can apply tools themselves to communicate with their child. • Communication between caretaker and health care provider should take place in a friendly relationship. This can take place in individual sessions but also through group counselling. • Group counselling offers problem sharing and support from peers. • Evaluate the needs and feelings of the caretaker. Other problems, different from the child's health, might be a priority. • The crucial role of the caretaker in ensuring adherence should be acknowledged at every visit. Tools to support adherence (reminders, pill boxes) should be provided to child and caretaker.
Related to the regimen	
• Use a child friendly regimen. o paediatric formulations should be available, e.g., syrups, smaller tablets or even paediatric fixed dose combinations o allow children's preference for adult formulations (tablets, capsules) o learn which adult formulations can be divided and mixed, e.g., some capsules can be opened o use maximum twice daily dosage o take palatability into account o teach child and caretaker how to improve taste e.g., by mixing with juice • Provide knowledge on possible toxicities to caretaker and on appropriate self-management • The child should always be able to see the pills prior to regimen selection	• Integrate intake of medicines with pleasant daily activities o e.g., link with tooth brushing, favourite TV program • Provide tools to remind (funny pill boxes), to express positive/negative feelings (e.g., drawings), to visualize prescription (sticker of medicines and dosage) and to award intake (e.g., stickers) • Offer proximity to health care provider, e.g., hotline in case of toxicities
Related to health care provider	
• Communication tools (fairy tales and games to improve knowledge of caretaker and child, to address adherence issues) and tools to assess and support adherence should be available for the provider. • Address attitude and create understanding for provider by improving their knowledge: o on HIV pathogenesis o rational of ART o importance of adherence, including the message "HIV-infected children can grow, can live normal lives, can attend schools, …"	• Promote a multidisciplinary approach by team working involving doctors, nurses, social workers, pharmacists and PHAs

Annex 1: Dosages of ARVs for adults & adolescents

Generic name	Dose	
Nucleoside RTIs		
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	
Zidovudine (AZT)	250 mg or 300 mg twice daily[1]	
Emtricitabine (FTC)	200 mg once daily	
Didanosine (ddI)[2] buffered tabs or enteric coated (EC) caps	>60 kg: 400 mg once daily <60 kg: 250 mg once daily	
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	
Stavudine (d4T)[b]	30 mg twice daily irrespective of weight[3]	
Nucleotide RTIs		
Tenofovir	300 mg once daily	
Non-nucleoside RTIs		
Efavirenz (EFV)	600 mg once daily	
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	
Proteases inhibitors		
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily	
Lopinavir/ritonavir (LPV/r) [5]	Capsule Lopinavir 133.3mg + ritonavir 33.3mg	three capsules twice daily (400/100mg twice daily) four capsules twice daily when combined with EFV or NVP (533/133,33 mg twice daily)
	Tablet (heat stable formulation) Lopinavir 200mg + ritonavir 50mg	Treatment naïve patients Two tablets twice daily irrespective of co-administration with EFV or NVP (400/100 mg twice daily)
		Treatment experienced patients Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Saquinavir/ ritonavir (SQV/r)[5]	1000/100 mg twice daily	

1. AZT 250mg BID is included as an option in the 2006 WHO guidelines for adult ART and is available as the FDC of AZT 250mg/3TC 150mg/NVP 200mg (*GPOVIR-Z*). New data from Thailand may support a dose of 200mg BID in a Thai population[52]
2. ddI dose should be adjusted when coadministered with tenofovir. If weight >60 kg, the recommended dose is 250 mg once daily. If weight <60 kg, there is no data to make a recommendation (some preliminary PK studies suggest 125-200 mg once daily)[53]. Buffered ddI need to be taken with an empty stomach.
3. d4T 40 mg is no longer recommended **Error! Bookmark not defined.**
4. Other dose regimens in clinical use are 600mg/100mg [54] and 400mg/100mg [55]
5. See TB section for TB-specific dose modifications of lopinavir/r and saquinavir/r

Annex 2: Paediatric formulations and doses

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
Nucleoside analogue reverse transcriptase inhibitors				
Zidovudine (ZDV)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages	< 4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 yrs: 180 mg/m^2/dose twice daily Maximum dose: ≥13 yrs: 300 mg/dose twice daily	Large volume of syrup not well tolerated in older children, Syrup needs storage in glass jars and is light sensitive Can give with food Doses of 600 mg/m^2/dose per day required for HIV encephalopathy Capsule can be opened and contents dispersed or tablet crushed and contents mixed with small amount of water or food and immediately taken (solution is stable at room temperature) Do not use with d4T (antagonistic antiretroviral effect)
Lamivudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages	< 30 days: 2 mg/kg/dose twice daily ≥30 days or < 60 kg: 4 mg/kg/dose twice daily Maximum dose: > 60 kg: 150 mg/dose twice daily	Well tolerated Can give with food Store solution at room temperature (use within one month of opening) Tablet can be crushed and contents mixed with small amount water or food and immediately taken
Fixed-dose combination of ZDV plus 3TC	No liquid available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults	Maximum dose: > 13 yrs or > 60 kg: 1 tablet/dose twice daily (should not be given if <30 kg weight)	Ideally, tablet should not be split Tablet can be crushed and contents mixed with small amount of water or food and immediately taken At weight <30 kg, ZDV and 3TC cannot be dosed accurately in tablet form
Stavudine (d4T)	Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages	< 30 kg: 1 mg/kg/dose twice daily 30 to 60 kg: 30 mg/dose twice daily Maximum dose: > 60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles. Capsules can be opened up and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated) Do not use with ZDV (antagonistic antiretroviral effect)
Fixed dose combination of d4T plus 3TC	No liquid available Tablet: d4T 30 mg plus 3TC 150 mg; d4T 40 mg plus 3TC 150 mg	Adolescents and adults	Maximum dose: 30-60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, tablet should not be split See comments under individual drug components
Didanosine (ddI)	Oral suspension paediatric powder/ water: 10 mg/ml Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg	All ages	< 3 mos: 50mg/m2/dose twice daily 3 mos to < 13 yrs: 90-120 mg/m^2/dose twice daily or 240 mg/m^2/dose once daily Maximum dose: ≥13 yrs or > 60 kg: 200 mg/dose twice daily or 400 mg once daily	Keeps suspension refrigerated; stable for 30 days; must shake well Administer on empty stomach, at least 30 minutes before or 2 hours after eating If tablets dispersed in water, at least 2 of appropriate strength tablets should be dissolved for adequate buffering Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food
Abacavir (ABC)	Oral solution: 20 mg/ml Tablet: 300 mg	Over age 3 months	< 16 years or < 37.5 kg: 8 mg/kg/dose twice daily Maximum dose: > 16 years or ≥37.5 kg: 300 mg/dose twice daily	Can give with food Tablet can be crushed and contents mixed with small amount water or food and immediately ingested MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				hypersensitivity reaction occurs
Fixed-dose combination of ZDV plus 3TC plus ABC	No liquid available Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg	Adolescents and adults	Maximum dose: > 40 kg: 1 tablet/dose twice daily	Ideally, tablet should not be split At weight <30 kg, ZDV/3TC/ABC cannot be dosed accurately in tablet form MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION ZDV/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine (NVP)	Oral suspension: 10 mg/ml Tablet: 200 mg	All ages	15 to 30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m^2/dose twice daily x 2 weeks, then 200 mg/m^2/dose twice daily > 30 days to 13 yrs: 120 mg/m^2/dose once daily for 2 weeks, then 120-200 mg/m^2/dose twice daily Maximum dose: > 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily	If rifampicin co-administration, avoid use (see Tuberculosis section) Store suspension at room temperature; must shake well Can give with food Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with small amount of water or food and immediately administered MUST WARN PARENTS ABOUT RASH Do not dose escalate if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug) Drug interactions
Efavirenz (EFV)	Syrup: 30 mg/ml (note: syrup requires higher doses than capsules, see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 yrs	Capsule (liquid) dose for > 3 yrs: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily 15 to < 20 kg: 250 mg (300 mg = 10 ml) once daily 20 to < 25 kg: 300 mg (360 mg = 12 ml) once daily 25 to < 33 kg: 350 mg (450 mg = 15 ml) once daily 33 to < 40 kg: 400 mg (510 mg = 17 ml) once daily Maximum dose: ≥40 kg: 600 mg once daily	Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste Can give with food (but avoid after high fat meals which increase absorption by 50%) Best given at bedtime, especially in the first 2 weeks, to reduce central nervous system side effects Drug interactions
Fixed-dose combination of d4T plus 3TC plus NVP	No liquid available Tablet: 30 mg d4T/150 mg 3TC/200 mg NVP; 40 mg d4T/150 mg 3TC/200 mg NVP	Adults and adolescents	Maximum dose: 30-60 kg: one 30 mg d4T-based tablet twice daily ≥60 kg: one 40 mg d4T-based tablet twice daily	Ideally, tablet should not be split At weight <30 kg, d4T/3TC/NVP cannot be dosed accurately in tablet form; if tablets are split, NVP dose will be inadequate for very young children and additional NVP is needed to give total of 200 mg/m^2/dose twice daily Since contains NVP, requires dose escalation See comments under individual drug components
Protease inhibitors				
Lopinavir/ritonavir, (LPV/r)	Oral solution: 80mg/ml Lopinavir plus 20 mg/ml ritonavir Capsules: 133.3 mg Lopinavir plus 33.3 mg ritonavir	6 mos of age or older	> 6 mos to 13 yrs: 225 mg/m2LPV/57.5 mg/m^2 ritonavir twice daily or weight-based dosing: 7-15 kg: 12mg/kg LPV/3 mg/kg ritonavir/dose twice daily 15-40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily Maximum dose: > 40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml) twice daily	Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25^{0}C (77^{0}F) for 2 months; at temperature >25^{0}C (77^0 F), drug degrades more rapidly Liquid formulation has low volume but bitter taste Capsules large Capsules should *not* be crushed or opened, but must be swallowed whole Should be taken with food

Name of drug	Formulations	Pharmacokinetic data available	Age (weight), dose and dose frequency	Other comments
				Drug interactions

Note: meter² body surface area calculation: square root of (height in centimetres times weight in kilograms divided by 3600)

Annex 3: Paediatric Dosing Chart

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

WHO recommendations 2006

			Lamivudune (3TC)				Stavudine (d4T)								Abacavir (ABC)					
			Target dose - 4mg/kg/dose twice daily to maximum 150mg/dose twice daily				**Target dose** - 1mg/kg/dose twice daily up to 30mg/dose twice daily								**Target dose** - <16 years or <37,5 kg: 8 mg/kg/dose given twice daily **- Maximum dose**: >16 years or ≥37,5kg : 300 Mg/dose given twice daily					
			10mg/ml solution		150 mg tablets		1mg/ml syrup		15mg capsules		20mg capsules*		30mg capsules		20mg/ml syrup		300mg tablets			
	Bottle	**Top**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**a.m.**	**p.m.**	**Bottle**	**Top**
Weight Range (kg)	**5**	**5,9**	3 ml	3 ml			6 ml	6 ml							2 ml	2 ml			**5**	**5,9**
	6	**6,9**	3 ml	3 ml			7 ml	7 ml			0,5 cap	0,5 cap			3 ml	3 ml			**6**	**6,9**
	7	**7,9**	4 ml	4 ml			8 ml	8 ml			0,5 cap	0,5 cap			4 ml	4 ml			**7**	**7,9**
	8	**8,9**	4 ml	4 ml			9 ml	9 ml			0,5 cap	0,5 cap			4 ml	4 ml			**8**	**8,9**
	9	**9,9**	4 ml	4 ml			10 ml	10 ml			0,5 cap	0,5 cap			4 ml	4 ml			**9**	**9,9**
	10	**10,9**	5 ml	5 ml					1 cap	1 cap					5 ml	5 ml			**10**	**10,9**
	11	**11,9**	5 ml	5 ml					1 cap	1 cap					5 ml	5 ml	0,5 tab	0,5 tab	**11**	**11,9**
	12	**13,9**	6 ml	6 ml	0,5 tab	0,5 tab			1 cap	1 cap					6 ml	6 ml	0,5 tab	0,5 tab	**12**	**13,9**
	14	**16,9**			0,5 tab	0,5 tab					1 cap	1 cap					0,5 tab	0,5 tab	**14**	**16,9**
	17	**19,9**			0,5 tab	0,5 tab					1 cap	1 cap					0,5 tab	0,5 tab	**17**	**19,9**
	20	**24,9**			1 tab	0,5 tab					1 cap	1 cap					1 tab	0,5 tab	**20**	**24,9**
	25	**29,9**			1 tab	1 tab							1 cap	1 cap			1 tab	1 tab	**25**	**29,9**
	30	**34,9**			1 tab	1 tab							1 cap	1 cap			1 tab	1 tab	**30**	**34,9**

* For weight range : 6kg – 10 kg: stavudine 20mg capsules can be dissolved in a measured quantity of water and half the quantity administered to provide dose shown in the table

Nucleoside Reverse Transcriptase Inhibitors (NRTI) WHO recommendations 2006

			Zidovudine (AZT)						Didanosine (ddI)									
			Target dose - 180-240mg/m2/dose twice daily						**Target dose** - Maximum dose:>13 years or >60kg: 400 mg once daily			**Target dose** - <3 months: 50mg/m2/dose twice daily - 3 months to <13 years: 90-120mg/m2/dode Twice daily - Maximum dose: ≥ 13 years or >60 kg: 200 mg/dose Twice daily or 400 mg once daily					
			10mg/ml syrup		100mg capsules		300mg tablets		125mg EC capsules	200mg EC capsules	250mg EC capsules	10mg/ml suspension		25mg chew tablets*			
	Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m. or p.m.	a.m. or p.m.	a.m. or p.m.	a.m.	p.m.	a.m.	p.m.	Bottom	Top
Weight Range (kg)	**5**	**5,9**	6 ml	6 ml								4 ml	4 ml	2 tabs	2 tabs	**5**	**5,9**
	6	**6,9**	7 ml	7 ml								5 ml	5 ml	2 tabs	2 tabs	**6**	**6,9**
	7	**7,9**	8 ml	8 ml								6 ml	6 ml	2 tabs	2 tabs	**7**	**7,9**
	8	**8,9**	9 ml	9 ml	1 cap	1 cap						6 ml	6 ml	2 tabs	2 tabs	**8**	**8,9**
	9	**9,9**	10 ml	10 ml	1 cap	1 cap						6 ml	6 ml	2 tabs	2 tabs	**9**	**9,9**
	10	**10,9**	10 ml	10 ml	1 cap	1 cap			1 cap			6 ml	6 ml	3 tabs	2 tabs	**10**	**10,9**
	11	**11,9**	10 ml	10 ml	1 cap	1 cap			1 cap			7 ml	7 ml	3 tabs	3 tabs	**11**	**11,9**
	12	**13,9**	11 ml	11 ml	1 cap	1 cap			1 cap			7 ml	7 ml	3 tabs	3 tabs	**12**	**13,9**
	14	**16,9**			2 caps	1 cap	0,5 tab	0,5 tab		1 cap		8 ml	8 ml	4 tabs	3 tabs	**14**	**16,9**
	17	**19,9**			2 caps	1 cap	0,5 tab	0,5 tab		1 cap		9 ml	9 ml	4 tabs	4 tabs	**17**	**19,9**
	20	**24,9**			2 caps	2 caps	0,5 tab	0,5 tab			1 cap			5 tabs	5 tabs	**20**	**24,9**
	25	**29,9**			2 caps	2 caps	1 tab	0,5 tab			1 cap			5 tabs	5 tabs	**25**	**29,9**
	30	**34,9**			3 caps	3 caps	1 tab	1 tab			1 cap			5 tabs	5 tabs	**30**	**34,9**

* 25 mg chew tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least two tablets

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

WHO recommendations 2006

			Efavirenz (EFV)	Nevirapine (NVP)							
			Target dose - 15 mg/kg/day (capsule/tablet) - Weight > 40kg: 600 mg once daily	**Induction** Half of daily maintenance dosing - 160-200mg/m2/dose to max 200mg		**Maintenance** Target dosing - 160-200mg/m2 to max 200 mg per dose twice daily					
			50mg capsules, 100mg capsules, 200mg capsules	100mg/ml syrup	200mg tablets	10mg/ml syrup		200mg tablets			
	Bottom	Top	Once daily	Once daily	Once daily	a.m.	p.m.	a.m.	p.m.	Bottom	Top
Weight Range (kg)	**5**	**5,9**		6 ml		6 ml	6 ml			**5**	**5,9**
	6	**6,9**		7 ml		7 ml	7 ml			**6**	**6,9**
	7	**7,9**		8 ml		8 ml	8 ml			**7**	**7,9**
	8	**8,9**		9 ml		9 ml	9 ml			**8**	**8,9**
	9	**9,9**		9 ml	0,5 tab	9 ml	9 ml	0,5 tab	0,5 tab	**9**	**9,9**
	10	**10,9**	200mg cap	10 ml	0,5 tab	10 ml	10 ml	0,5 tab	0,5 tab	**10**	**10,9**
	11	**11,9**	200mg cap	10 ml	0,5 tab	10 ml	10 ml	0,5 tab	0,5 tab	**11**	**11,9**
	12	**13,9**	200mg cap	11 ml	0,5 tab	11 ml	11 ml	0,5 tab	0,5 tab	**12**	**13,9**
	14	**16,9**	200mg cap + 50mg cap		0,5 tab			1 tab	0,5 tab	**14**	**16,9**
	17	**19,9**	200mg cap + 50mg cap		1 tab			1 tab	0,5 tab	**17**	**19,9**
	20	**24,9**	200mg cap + 100mg cap		1 tab			1 tab	0,5 tab	**20**	**24,9**
	25	**29,9**	200mg cap + 100mg cap + 50mg cap		1 tab			1 tab	1 tab	**25**	**29,9**
	30	**34,9**	200mg cap + 200mg cap		1 tab			1 tab	1 tab	**30**	**34,9**
	35	**39,9**	200mg cap + 200mg cap		1 tab			1 tab	1 tab	**35**	**39,9**

Protease Inhibitors (PI) WHO recommendations 2006

	Lopinavir/ritonavir (LPV/r)									
	Lopinavir target doses: 5-7.9 kg: 16 mg/kg/dose twice daily 8-9.9 kg: 14 mg/kg/dose twice daily 10-19.9 kg: 12 mg/kg/dose twice daily 14-39.9 kg: 10 mg/kg/dose twice daily				**Ritonavir target dose** 7-15 kg: 3 mg/kg/dose twice daily 15-40 kg: 2.5 mg/kg/dose twice daily Maximum dose: 400 mg lopinavir + 100 mg ritonavir taken Twice daily					
	80mgLPV/ 20mgRTV per ml solution				133mgLPV/ 33mgRTV per capsule		200mgLPV/ 50mgRTV per tablet			
	Bottle	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	Bottom	Top
Weight Range (kg)	**5**	**5,9**	1 ml	1 ml					**5**	**5,9**
	6	**6,9**	1,5 ml	1,5 ml					**6**	**6,9**
	7	**7,9**	1,5 ml	1,5 ml	1 cap	1 cap			**7**	**7,9**
	8	**8,9**	2 ml	2 ml	1 cap	1 cap			**8**	**8,9**
	9	**9,9**	2 ml	2 ml	1 cap	1 cap			**9**	**9,9**
	10	**10,9**	2 ml	2 ml	1 cap	1 cap			**10**	**10,9**
	11	**11,9**	2 ml	2 ml	1 cap	1 cap			**11**	**11,9**
	12	**13,9**	2 ml	2 ml	2 caps	1 cap	1 cap	1 cap	**12**	**13,9**
	14	**16,9**	2 ml	2 ml	2 caps	1 cap	1 cap	1 cap	**14**	**16,9**
	17	**19,9**	2,5 ml	2,5 ml	2 caps	1 cap	1 cap	1 cap	**17**	**19,9**
	20	**24,9**	3 ml	3 ml	2 caps	2 caps	1 cap	1 cap	**20**	**24,9**
	25	**29,9**	3,5 ml	3,5 ml	2 caps	2 caps	2 caps	1 caps	**25**	**29,9**
	30	**34,9**	4 ml	4 ml	3 caps	3 caps	2 caps	2 caps	**30**	**34,9**
	35	**39,9**	5 ml	5 ml	3 caps	3 caps	2 caps	2 caps	**35**	**39,9**

* This table does not take into account NFV 625 mg tablets, which are rarely available in the field

Fixed Dose Combinations (FDC) WHO recommendations 2006

			Zidovudine (AZT) + Lamivudine (3TC)		Stavudine (d4T) + Lamivudine (3TC)		Zidovudine (AZT) + Lamivudine (3TC) + Abacavir (ABC)		Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP)*			
			Target dose - Zidovudine: 180-240mg/m2/dose twice daily - Lamivudine: 4mg/kg/dose twice daily - Maximum dose: 1 tablet/dose twice daily		**Target dose** - Stavudine: 1mg/kg/dose twice daily - Lamivudine: 4mg/kg/dose twice daily - Maximum dose: 1 tablet/dose twice daily		**Target dose** - Zidovudine: 180-240mg/m2/dose twice daily - Lamivudine: 4mg/kg/dose twice daily - Abacavir: 8mg/kg/dose twice daily - Maximum dose: 1 tablet/dose twice daily		**Maximum dose** one 30-mg d4T-based tablet twice daily			
			300mgAZT/ 150mg3TC per tablet		300mgd4t/ 150mg3TC per tablet		300AZT/ 150mg3TC/ 300mgABC per tablet		300mgd4t/ 150mg3TC 200mgNVP per tablet			
	Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	Bottom	Top
Weight Range (kg)	5	5,9									5	5,9
	6	6,9									6	6,9
	7	7,9									7	7,9
	8	8,9									8	8,9
	9	9,9									9	9,9
	10	10,9			0,5 tab	0,5 tab			0,5 tab	0,5 tab	10	10,9
	11	11,9			0,5 tab	0,5 tab			0,5 tab	0,5 tab	11	11,9
	12	13,9			0,5 tab	0,5 tab			0,5 tab	0,5 tab	12	13,9
	14	16,9	0,5 tab	0,5 tab	1 tab	0,5 tab	0,5 tab	0,5 tab	1 tab	0,5 tab	14	16,9
	17	19,9	0,5 tab	0,5 tab	1 tab	0,5 tab	0,5 tab	0,5 tab	1 tab	0,5 tab	17	19,9
	20	24,9	1 tab	0,5 tab	1 tab	0,5 tab	1 tab	0,5 tab	1 tab	0,5 tab	20	24,9
	25	29,9	1 tab	0,5 tab	1 tab	1 tab	1 tab	0,5 tab	1 tab	1 tab	25	29,9
	30	34,9	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab	30	34,9

* NVP dosing must be adjusted during the induction phase (D1-D14). During this phase, do not use this fixed-dose combination !

NEW WHO DOSING RECOMMENDATIONS FOR EXISTING PEDIATRIC FDCs

Source : *Pediatric Triple Fixed-Dose Combinations for Antiretroviral Therapy* (Clinton Foundation - February 2007)

		Triomune-Baby (Cipla)		Triomune-Junior (Cipla)		Triviro-LNS-Kid (Ranbaxy)		Triviro-LNS-Kid-DS (Ranbaxy)			
Weight (kg)		d4T 6mg 3TC 30mg NVP 50mg		d4T 12mg 3TC 60mg NVP 100mg		d4T 5mg 3TC 20mg NVP 35mg		d4T 10mg 3TC 40mg NVP 70mg		Weight (kg)	
Bottom	Top	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	Bottom	Top
3	3,9	1	1	0,5	0,5	-	-	-	-	3	3,9
4	4,9	1	1	0,5	0,5	-	-	-	-	4	4,9
5	5,9	1	1	0,5	0,5	-	-	-	-	5	5,9
6	6,9	1,5	1,5	1	0,5	-	-	-	-	6	6,9
7	7,9	1,5	1,5	1	0,5	2	2	1	1	7	7,9
8	8,9	1,5	1,5	1	0,5	2	2	1	1	8	8,9
9	9,9	1,5	1,5	1	0,5	2	2	1	1	9	9,9
10	10,9	2	2	1	1	2,5	2,5	1,5	1	10	10,9
11	11,9	2	2	1	1	2,5	2,5	1,5	1,5	11	11,9
12	13,9	2	2	1	1	3	3	1,5	1,5	12	13,9
14	16,9	2,5	2,5	1,5	1	3,5	3,5	2	2	14	16,9
17	19,9	2,5	2,5	1,5	1	4	4	2	2	17	19,9
20	24,9	3	3	1,5	1,5	4,5	4,5	2,5	2,5	20	24,9
25	29,9	4	4	2	2	6	6	3	3	25	29,9
30	34,9	4	4	2	2	6	6	3	3	30	34,9

Annex 4 Storage of Antiretrovirals (Room temperature is 15-25 Deg C)

Drug	Storage requirements
Abacavir (ABC)	Room temperature
Didanosine (ddI)	Room temperature for tablets and capsules. Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.
Lamivudine (3TC)	Room temperature **(15-25 DEG C)**
Stavudine (d4T)	Room temperature. After reconstitution, oral solution should be kept refrigerated; if so, it is stable for 30 days.
Zidovudine (AZT, ZDV)	Room temperature
Zidovudine + Lamivudine + Abacavir	Room temperature
Tenofovir (TFV)	Room temperature
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature
Lamivudine + Stavudine + Nevirapine	Room temperature
Atazanavir	Room temperature
Lopinavir/Ritonavir (LPV/r) capsules	Refrigerate for long term storage At room temperature: stable for 2 months
Lopinavir/Ritonavir (LPV/r) heat stale tablets (Aluvia)	Room temperature
Ritonavir (RTV)	Refrigerate capsules until dispensed; Stable at room temperature for 30 days. Room temperature for oral solution (do not refrigerate)
Saquinavir tabs	Room temperature

Annex 5 Simplified grading of severity of adverse experiences

Alternative explanations for toxicity must be excluded before concluding that it is secondary to the ARV drug.
If side effect grade 3 (GRADE 4 DEPENDING ON THE SIDE EFFECT), stop suspected ARV drug and substitute.
IF GRADE 3 STOP NVP AND CONTINUE WITH TAIL PROTECTION FOR 7 DAYS, IF GRADE 4 STOP ALL SEE ALGORITHMS
If grade 1 or 2 rash after 2 weeks of lead-in dose NVP (200mg/d), continue same dose for max. 2 weeks more and observe whether rash resolved
.

PARAMETER	ARV	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 may be LIFE THREATENING
Hb (g/dl)	**AZT**	**8,0 – 9,4**	7,0 – 7,9	6,5 – 6,9	< 6,5
Neutrophile absolute count (x1000/ mm3)	AZT	1,0 – 1,5	0,75 – 0,99	0,5 – 0,749	< 0,5
Headache	AZT	Mild, no Rx needed	Relieved by non-narcotic Rx	Only responds to narcotic Rx	No relief with Rx
Myopathy	AZT	Mild to moderate pain, not interfering with daily activities		Interfering with daily activities	Bedridden, disabling
AST	NVP, more rarely EFV, NRTI or PI	50 – 100	100 –200	200 – 400	> 400
ALT		50 – 100	100 –200	200 – 400	> 400
Psychological	EFV	Mild to moderate confusion/ anxiety/ depression; abnormal dreams		Severe mood changes	Acute psychosis, hospitalization
Allergic reaction	NVP, less common EFV	Itch, no rash	Some urticaria	Generalized urticaria	Anaphylaxis
Rash		Erythema, itch	Mac-pap rash or dry scaling	Blisters or moist desquamation	Muco-membranous; Lyell and St Johnson S.
Paresthesia (burning, tingling)	D4T, DDI, rarely 3TC	Mild, no Rx needed	Relieved by non-narcotic Rx	Only responds to narcotic Rx	No relief with Rx
Neuro-motor		Mild weakness	Unable to walk on heels and/or toes	Foot drop or unable to dorsiflex toes	Bedridden, wheel chair
Lipodystrophia	D4T, less AZT, PI	1-2 sites		> 2 sites	
Diarrhea (stools/day or /week)	NFV	<4/ day, <1 week	5-7/ day, >1 week	> 7/day, orthostatic hypo tension, requiring IV fluids	

Annex 6Criteria for HIV-Related Clinical Events in Adults and Adolescents

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination.	Not applicable
Persistent generalized lymphadenopathy (PGL)	Painless enlarged lymph nodes >1 cm, in two or more non-contiguous sites (excluding inguinal), in absence of known cause & persisting for ≥3 months	Histology
Clinical Stage 2		
Moderate unexplained weight loss (<10% of body weight)	Reported unexplained weight loss. In pregnancy failure to gain weight.	Documented weight loss <10% of body weight.
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last six-month period)	Symptom complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillo-pharyngitis without features of viral infection (e.g. coryza, cough).	Laboratory studies where available, e.g. culture of suitable body fluid.
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross midline.	Clinical diagnosis
Angular chelitis	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, and usually respond to antifungal treatment.	Clinical diagnosis.
Recurrent oral ulcerations (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane.	Clinical diagnosis.
Papular pruritic eruption	Papular pruritic lesions, often with marked post-inflammatory pigmentation.	Clinical diagnosis.
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin).	Clinical diagnosis.
Fungal nail infections	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discolouration - especially involving proximal part of nail plate – with thickening & separation of nail from nail bed).	Fungal culture of nail/nail plate material.

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 3		
Severe unexplained weight loss (more than 10% of body weight)	Reported unexplained weight loss (>10% of body weight or body mass index <18.5). In pregnancy weight loss may be masked.	Documented loss of more than 10% of body weight.
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month.	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than one month)	Reports of fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarial areas.	Documented fever >37.6. with negative blood culture, negative Ziehl-Nielsen (ZN) stain, negative malaria slide, normal or unchanged chest X-ray (CXR) and no other obvious focus of infection.
Oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off.	Clinical diagnosis
Pulmonary TB (current)	Chronic symptoms: (lasting ≥2-3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, PLUS either positive sputum smear OR Negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease	Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms).
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic.	Isolation of bacteria from appropriate clinical specimens (i.e. usually sterile sites).
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis.

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 4		
HIV wasting syndrome	Reported unexplained weight loss (>10% body weight), with obvious wasting or body mass index <18.5. PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month. OR Reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarial areas.	Documented weight loss >10% of body weight; plus two or more unformed stools negative for pathogens or Documented temperature of > 37.6 ^{o}C or more with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR.
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 months), tachypnoea and fever; AND Chest x-ray evidence of diffuse bilateral interstitial infiltrates AND No evidence of a bacterial pneumonia. Bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more previous episodes in last 6 months .Acute onset (<2 weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	Positive culture or antigen test of a compatible organism.
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than one month duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.	Positive culture or DNA (by PCR) of HSV or compatible cytology/histology.
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidiasis.	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology.
Extrapulmonary TB	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: Pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Miliary TB diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of extra pulmonary tuberculosis.	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from respiratory specimen then must other have evidence of extra pulmonary disease).
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules.	Macroscopic appearance at endoscopy or bronchoscopy, or by histology.
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available)single/multiple intracranial mass lesion on neuro-imaging
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection which might explain the findings.	Diagnosis of exclusion: and (if available) neuro-imaging (CT or MRI)

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually sub acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood.
Disseminated non-tuberculous mycobacteria infection	No presumptive clinical diagnosis.	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung.
Progressive multi focal leukoencephalopathy (PML) PML	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus (JCV) PCR on CSF.
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis.	Cysts identified on modified ZN microscopic examination of unformed stool.
Chronic isosporiasis	No presumptive clinical diagnosis.	Identification of *Isospora*
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis.	Histology, antigen detection or culture from clinical specimen or blood culture.
Recurrent non-typhoid salmonella bacteraemia	No presumptive clinical diagnosis.	Blood culture.
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV associated tumours.	No presumptive clinical diagnosis	Histology of relevant specimen or for CNS tumours neuroimaging techniques
Invasive cervical carcinoma	No presumptive clinical diagnosis.	Histology or cytology.
Visceral leishmaniasis	No presumptive clinical diagnosis.	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen.
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

Source: Revised WHO Clinical Staging and Immunological Classification of HIV and case definition of HIV for surveillance, May 2006

Annex 7 Presumptive and definitive criteria for recognizing HIV-related clinical events

(In infants and children with **established** HIV infection**)**

Clinical event	Clinical diagnosis	Definitive diagnosis
Primary HIV infection		
Asymptomatic infection Acute retroviral syndrome	 Acute febrile illness 2−4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin rashes	In children 18 months or over seroconversion from HIV antibody negative to antibody-positive. A positive virological test for HIV virus or its components (RNA or DNA or ICD HIV p 24 antigen) confirmed by a second virological test obtained from a separate determination. Profound temporary lymphopaenia and other transient blood abnormalities may occur.
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination.	Not required.
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause.	Not required.
Clinical Stage 2		
Unexplained persistent Hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Not required.
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children: scabies and insect bites should be excluded.	Not required.
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Not required
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur.	Not required.
Lineal gingival Erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Not required.
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Not required.
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring.	Not required.
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudomembrane.	Not required.
Unexplained parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.	Not required.
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent.	Not required

Clinical event	Clinical diagnosis	Definitive diagnosis
	Does not cross the midlines.	
Recurrent upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Not required.
Clinical Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to −2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Confirmed by documented loss of body weight of –2SD, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Confirmed by documented fever of >37.5 ^{0}C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Oral candida (outside first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Confirmed by microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	None
Lymph node TB	Non acute, painless "cold" enlargement of lymph nodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain. Culture.
Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. Response to standard anti-TB treatment in one month.	Confirmed by positive sputum smear or culture.
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	None.
Symptomatic LIP	No presumptive diagnosis.	Diagnosed by CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with

Clinical event	Clinical diagnosis	Definitive diagnosis
		cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation;	Confirmed by CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropenia (<1000/mm^3) or chronic thrombocytopenia (<50 000/ mm^3)	No presumptive diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI.
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 SDs, as defined by WHO IMCI guidelines.	Confirmed by documented weight loss of >-3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone.	Confirmed by: CXR typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or BAL or NPA, or histology of lung tissue.
Recurrent severe presumed bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology
Oesophageal candida (or candida of trachea, bronchi or lungs).	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary/disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Responds to standard anti-TB therapy.	Confirmed by positive microscopy showing AFB or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy and histology.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Not required but may be confirmed by : ▪ typical red-purple lesions seen on bronchoscopy or endoscopy; ▪ dense masses in lymph nodes, viscera or lungs by palpation or radiology; ▪ histology.

Clinical event	Clinical diagnosis	Definitive diagnosis
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians: progressive floaters in field of vision, light flashes and scotoma; typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR).
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Not required but confirmed by computed tomography (CT) scan showing single/multiple lesions with mass effect/enhancing with contrast.
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually sub acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	Confirmed by CSF microscopy (India ink or Gram stain), serum or CSF CRAG or culture.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; or - progressive impaired brain growth demonstrated by stagnation of head circumference; or - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Confirmed by brain CT scan or MRI demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Diagnosed by: Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.
Disseminated mycobacteriosis, other than TB	No presumptive diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea lasting longer than one month by microscopic examination.
Chronic Isospora	No presumptive diagnosis.	Confirmed in children with chronic diarrhoea by microscopic examination.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive diagnosis.	Diagnosed by CNS imaging: at least one lesion with mass effect on brain scan; histology of relevant specimen
Progressive multi focal leukoencephalopathy (PML)	No presumptive diagnosis.	Diagnosed by MRI or CT scan, and biopsy. Viral PCR for Jacob Creutzfeldt virus.

Notes:

a. Diagnosis of HIV infection according to recommendations in Section II.

References

[1] Hill A, et al. Meta-analysis of efficacy and safety for clinical studies of d4T 40 mg versus 30 mg BID in 1008 patients. 16th World AIDS Conference, Toronto, August 2006

[2] Egger M, May M, Chene G, et al. Prognosis of HIV1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet, 2002. 360(9327):119-29.

[3] Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunODeficiency virus infection and prior antiretroviral therapy. N Engl J Med, 1997. 337(11):734-9.

[4] Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunODeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med, 1997. 337(11):725-33.

[5] Garcia F, De Lazzari E, Plana M, et al. Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. J Acquir Immune Defic Syndr, 2004. 36(2):702-13.

[6] Teerawattananon Y, Hanshaoworakul W, Russell S, Tangcharoensathien V, Jiamton S. Targeting antiretroviral therapy: lessons from a longitudinal study of morbidity and treatment in relation to CD4 count in Thailand. Asia Pac J Public Health. 2006;18(1):39-48

[7] WoOD E, Hogg RS, Harrigan PR, Montaner JSG. When to initiate antiretroviral therapy in HIV-1 infected adults: a review for clinicians and patients. Lancet Infect Dis 2005;5:407-14.

[8] French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunODeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000; 1:107–15.

[9] Breen RAM, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004; 59:704–707.

[10] Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. Curr Opin Infect Dis 2006;19:20-5.

[11] McComsey G, Whalen C, Mawhorter S, et al. Placebo-controlled trial of prednisone in advanced HIV-1 infection. AIDS 2001;15:321-7.

[12] Winston A, Boffito M. The management of HIV-1 protease inhibitor pharmacokinetic interactions. J Antimicrob Chemother 2005;56:1-5.

[13] Back D, Gibbons S, Khoo S. Pharmacokinetic drug interactions with nevirapine. JAIDS 2003;34 (Suppl 1):S8-14.

[14] Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-Limited Settings: Towards Universal Access. Recommendations for a public health approach; 2006 revision. WHO 2006

[15] Tarantal AF, Castillo A, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). JAIDS 2002;29:207-20.

[16] Hazra R, Gafni R, Madlarelli F, et al. Safety, tolerability, and clinical responses to tenofovir DF in combination with other antiretrovirals in heavily-treatment-experienced HIV-infected children: data through 48 weeks. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 8-11, 2004 (928).

[17] Almond L, Gibbons S, Davies G, Dack D, Khoo S. A retrospective survey of the Liverpool TDM Service: factors influencing efavirenz concentrations in patients taking rifampicin. 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec, April 2005, poster 2.12.

[18] Patel A, Patel K, Patel J et al. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naive patients in India who are coinfected with tuberculosis and HIV-1. J Acquir Immune Defic Syndr. 2004 Sep 1;37(1):1166-9.

[19] Pedral-Sampaio D et al. Efficacy and Safety of Efavirenz in HIV Patients on Rifampin for Tuberculosis. The Brazilian Journal of Infectious Diseases 2004; 8(3):211-216

[20] Manosuthi W et al. A randomized controlled trial of efavirenz 600 mg/day versus 800 mg/day in HIV-infected patients with tuberculosis to study plasma efavirenz level, virological and immunological outcomes: a preliminary result. In: XV International AIDS Conference, Bangkok, Thailand, July 2004 [Abstract MoOrB1013]

[21] Sheehan NL, Richter C, Efavirenz 600 MG is not associated with Subtherapeutic Efavirenz Concentrations when given concomitantly with Rifampin. 6th International Workshop on Clinical Pharmacology of HIV therapy. 28-30 April 2005, Quebec City, Canada.

[22] Autar RS et al. What is the clinical relevance of the drug interaction between nevirapine and rifampin? In: XV Int AIDS Conf., Bangkok, Thailand, July 2004 [Abstract B11784].

[23] Oliva J et al. Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis. AIDS 2003, 17:637-642

[24] Ribera E et al. Pharmacokinetic interaction between nevirapine and rifampin in HIV-infected patients with tuberculosis. J Acquir Immune Defic Syndr 2001, 28:450-453

[25] Dean G L, Back D J, De Ruiter A. Effect of tuberculosis therapy on nevirapine trough plasma concentrations. AIDS 1999; 13: 2489-2490.

[26] Van Cutsem G, Cohen K., Bedelu M., Sarunchuk P., Hilderbrand K., Coetsee D. Boulle A. TB/HIV co-infected patients on rifampicin containing treatment have equivalent ART treatment outcomes, and concurrent use of nevirapine is not associated with increased hepatotoxicity. WePp0303. 3th IAS Conference on HIV Pathogenesis and Treatment. 24-27 July 2005, Rio de Janeiro, Brazil.

[27] Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. AIDS. 2002 Jan 4;16(1):75-83.

[28] Justesen U.S, Andersen A.B., Klitgaard. Pharmacokinetic interaction between rifampicin and the combination of indinavir and low dose ritonavir in HIV infected patients. Clin Infect Dis. 2004 Feb 1;38(3):426-9.
[29] HIV/AIDS Treatment and Care For Injecting Drug Users. Clinical Protocols for the WHO European Region.
[30] Wood E, Hogg RS, Yip B, et al. Rates of antiretroviral resistance among HIV-infected patients with and without a history of injecting drug use. AIDS 2005;19:1189-95.
[31] Wood E, Montaner JS, Yip B, et al. Adherence to antiretroviral therapy and CD4 T-Cell count responses among HIV-infected injection drug users. Antiviral Therapy 2004;9(2):229-35.
[32] Altice, Frederick L.; Friedland, Gerald H.; Cooney, Elizabeth L Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS. 13(8):957-962, May 28, 1999.
[33] British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2005
[34] HIV/AIDS Treatment and Care: WHO protocols for CIS countries. The Regional Office for Europe of the World Health Organization 2004
[35] Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine Clin Infect Dis. 1999 May;28 (5):1032-5
[36] Filippini P, Coppola N, Pisapia R, Scolastico C, Marrocco C, Zaccariello A, Nacca C, Sagnelli C, De Stefano G, Ferraro T, De Stefano C, Sagnelli E. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy AIDS. 2006 Jun 12;20 (9):1253-60.
[37]Alberti A, Clumack N, et al Short statement on the first European Consensus Conference on the Treatment of Chronic Hepatic B and C in HIV Coinfected Patients. Journal of Hepatology 2005;42:615-24.

[39] de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. JAMA 2000; 284: 190–7.
[40] van Rossum A M C, Fraaij P L A, de Groot R: Efficacy of highly active antiretroviral therapy in HIV-1 infected children. Lancet Infectious Diseases 2002; 2: 93–102
[41] Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection: The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), The Health Resources and Services Administration (HRSA), and The National Institutes of Health (NIH) June 25, 2003. www.aidsinfo.com (accessed 21/1/04)
[42] Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection: The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), The Health Resources and Services Administration (HRSA), and The National Institutes of Health (NIH). www.aidsinfo.com (accessed 21/1/04)
[43] Nesheim S, Lee F, Kalish ML, et al. Diagnosis of perinatal human immunodeficiency virus infection by polymerase chain reaction and p24 antigen detection after immune complex dissociation in an urban community hospital. J Infect Dis, 1997.175(6):1333-6.
[44] Centers for Disease Control and Prevention. Guidelines for prophylaxis against Pneumocystis carnii pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. MMWR, 1995. 44(RR-4).
[45] Chokephaibulkit K, Chuachoowong R, Chotpitayasunondh T, Chearskul S, Vanprapar N, Waranawat N, Mock P, Shaffer N, Simonds RJ. Evaluating a new strategy for prophylaxis to prevent Pneumocystis carinii pneumonia in HIV-exposed infants in Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. AIDS. 2000 Jul 28;14(11):1563-9.

[46] Recomemndations for diagnosis of HIV infection in infants and children, WHO 2006

[47] Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 Study. J Allergy Clin Immunol 2003
[48] Embree J, Bwayo J, Nagelkerke N, et al. Lymphocyte subsets in human immunodeficiency virus type 1-infected and uninfected children in Nairobi. Pediatr Infect Dis J 2001;20:397-403
[49] Mofenson LM, Harris DR, Moye J, et al. Alternatives to HIV-1 RNA concentration and CD4 count to predict mortality in HIV-1-infected children in resource-poor settings. Lancet 2003
[50] European Collaborative Study. Gender and race do not alter early-life determinants of clinical disease progression in HIV-1 vertically infected children. AIDS 2003
[51] Shearer WT, Rosenblatt HM, Gelman RS, Oyomopito R, Plaeger S, Stiehm ER, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. J Allergy Clin Immunol. 2003 Nov;112(5):973-80.
[52]Cressey T, Leenasirimakul P, Jourdain G et al: Intensive Pharmacokinetics of Zidovudine 200 mg Twice Daily in HIV-1-Infected Patients Weighing Less Than 60 kg on Highly Active Antiretroviral Therapy. JAIDS 2006;42(3):386-8
[53] Pruvost A, Negredo E, et al. Measurement of Intracellular Didanosine and Tenofovir Phosphorylated Metabolites and Possible Interaction of the Two Drugs in Human ImmunODeficiency Virus-Infected Patients. Antimicrobial Agents and Chemotherapy, May 2005, p. 1907-1914, Vol. 49, No. 5
[54] Cressey TR, Leenasirimakul P, Jourdain G, et al. Low-doses of indinavir boosted with ritonavir in HIV-infected Thai patients: pharmacokinetics, efficacy and tolerability. J Antimicrob Chemother. 2005 Jun;55 (6):1041-4.

Epub 2005 May 9. Cressey TR, Leenasirimakul P, Jourdain G, TOD M, Sukrakanchana PO, Kunkeaw S, Puttimit C, Lallemant M.

[55] Boyd M, Mootsikapun Petal; Pharmacokinetics of reduced-dose indinavir/ritonavir 400/100 mg twice daily in HIV-1-infected Thai patients. Antiviral Therapy 10:301–307.