MINISTRY OF HEALTH

GUIDELINES FOR HIV/AIDS DIAGNOSIS AND TREATMENT

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ACRONYMS AND ABBREVIATIONS

ABC	Abacavir
AFB	Acid Fast Bacilli
AIDS	Acquired immunodeficiency syndrome
DNA	Desoxyribonucleic acid
ALT (SGPT)	Alanin aminotransferase
anti-HBc	Anti-Hepatitis B core antigen
anti- HBe	Anti-Hepatitis B envelop Antigen
anti- HCV	Anti-Hepatitis C antibody
RNA	Ribonucleic acid
ARV	Antiretroviral drug
AST (SGOT)	Asparate aminotransferase
BCG	Bacillus Calmett-Guerrin
b.i.d	two times per day
CMV	Cytomegalovirus
d4T	Stavudine
ddI	Didanosine
EFV	Efavirenz
DOT	Directly observed therapy
ELISA	Enzyme-linked immunosorbent Assay
HAART	Highly active antiretroviral therapy
HBeAg	Hepatitis B Envelop Antigen
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HPV	Human papiloma virus
HSV	Herpes simplex virus
LIP	Lymphoid interstitial pneumonia
LPV	Lopinavir
MTCT	Mother to child transmission
MAC	Mycobacterium avium complex
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleosid reverse transcriptase inhibitor
NVP	Nevirapine
PCR	Polymerase chain reaction
PI	Protease inhibitor
RTV	Ritonavir
TB	Tuberculosis
TCD4	Lymphocyte T CD4 (+)
TDF	Tenofovir
t.i.d	three times per day
TMP-SMX	Trimethoprim-sulfamethoxazol
3TC	Lamivudine

PART A - DIAGNOSIS, TREATMENT AND CARE FOR ADULTS LIVING WITH HIV/AIDS

I. DIAGNOSIS AND STAGING OF HIV INFECTION IN ADULTS

1. Diagnosis of HIV infection:

HIV infection in adults is diagnosed on the basis of laboratory detection of anti-HIV antibody. A person is defined as infected with HIV when his/her serum specimen is reactive in all three anti-HIV antibody tests, which rely on different antigens or of different operating characteristics (as regulated by the Ministry of Health).

2. Staging of HIV infection

2.1. Clinical staging:

Adults with HIV infection are classified into 4 clinical stages depending on the presence of HIV-related conditions (Table 1).

Table 1: Clinical staging of HIV/AIDS in adults

Clinical stage 1: Asymptomatic
- Asymptomatic - Persistent generalized lymphadenophathy
Clinical stage 2: Mild symptoms
- Moderate unexplained weight loss (less than 10% of body weight) - Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) - Zona (Herpes zoster) - Angular cheilitis - Recurrent oral ulceration - Papular pruritic eruption.

- Seborrhoeic dermatitis
- Fungal nail infections

Clinical stage 3: Advanced symptoms

- Unexplained severe weight loss (more than 10% of body weight)
- Unexplained chronic diarrhoea for longer than one month.
- Unexplained persistent fever (intermittent or constant and lasting for longer than one month).
- Recurrent oral candidiasis.
- Oral hairy leukoplakia.
- Pulmonary tuberculosis.
- Severe bacterial infections (pneumonia, empyema, pyomyositis, bone-joint infection, meningitis, septicemia).
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis.
- Unexplained anaemia (< 80g/L), neutropenia (< $0.5x10^9$/L), and/or chronic thrombocytopenia (< $50x10^9$/L).

Clinical stage 4: Severesymptoms

- HIV wasting syndrome (loss of more than 10% of body weight with prolonged & unexplained fever or diarrhoea of more than one month duration).
- Pneumonia caused by *Pneumocystis jiroveci* (PCP).
- Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month duration, or visceral at any site
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs).
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Diseases due to *Cytomegalovirus* (CMV) in retina or other organs.
- Toxoplasmosis in central nervous system.
- HIV encephalopathy.
- Extrapulmonary cryptococcosis including meningitis.

- Disseminated disease due to *Mycobacteria avium complex* (MAC).
- Progressive multifocal leukoencephalopathy (PML).
- Chronic diarrhea due to *Cryptosporidia*.
- Chronic diarrhea due to *Isospora*
- Disseminated mycosis (penicilliosis, extrapulmonary histoplasmosis).
- Recurrent septicemia (including non-typhoid salmonellosis).
- Cerebral or B cell non-Hodgkin lymphoma.
- Invasive cervical carcinoma.
- Atypical disseminated leishmaniasis.
- HIV-associated nephropathy.
- Myocarditis due to HIV.

2.2. Immunological staging:

Immune status of adults with HIV infection is evaluated by number of CD4 cellsof the patient.

Table 2: Immunological staging of HIV/AIDS in adults

Severity	CD4 cell count/mm^3
Normal or not significant deficiency	> 500
Mild deficiency	350 - 499
Advanced deficiency	200 - 349
Severe deficiency	< 200

2.3. Criteria for diagnosis of advanced HIV infection (including AIDS):

- Any stage 3 or stage 4 clinical condition (presumptive or definitive diagnosis)

and/or

- CD4 cell count < 350 cells/mm^3

AIDS is defined as clinical diagnosis (presumptive or definitive diagnosis) of any stage 4 condition or CD4 cell count < 200 cells/mm^3

II. CLINICAL MANAGEMENT OF PERSONS WITH HIV/AIDS

1. Initial assessment:

1.1. Clinical and laboratory assessment:

1.1.1. Taking present and previous medical history:

- History of HIV testing: time of detection, place of testing, risks behaviour of HIV infection (injecting drug use, unsafe sexual practices), duration of risks behaviours.
- History of TB and TB treatment (time of diagnosis and treatment, place of treatment, treatment regimen and outcome); history of exposure to TB source.
- History of OIs, sexually transmitted and other diseases
- Obstetric, gynecological history, use of contraceptive methods
- History of drug allergy to antibiotics (such as cotrimoxazole) and antiretrovirals
- Recently developing signs and symptoms, their progress and response to treatment, especially TB-related symptoms.
- Medications used recently:
    - OI prophylaxis (cotrimoxazole)
    - ARV treatment: reason for use, duration, specific regimen, drug source, treatment adherence
    - Other medications used
- Status of drug and other substances dependence, including injecting drug and opioid use, substitution treatment (e.g. methadone maintenance therapy); history of alcohol use and cigeret smoking…
- History of nutrition
- History of HIV infection in the family: any other family members with HIV infection; if yes, whether ART is given and where ART is provided; issues of HIV status disclosure of patients and their family members (if any)

1.1.2. Physical examination: Do thorough and meticulous physical examination

- Vital signs, body weight, pain symptoms.

- Assessment of functional status: able to worknormally, ambulatory, or bed-ridden
- General condition, mucocutaneous manifestations
- Visual ability, Ear-Nose-Throat status
- Neurological symptoms: meningeal syndrome, focal neurological signs
- Respiratory and circulatory organs
- Abdominal conditions, enlarged liver and spleen, lymph nodes and abnormal intra-abdominal mass

1.1.3. Laboratory:

- CBC, Hb, ALT
- Chest X-ray, sputum AFB in case of suspected pulmonary TB; other investigations necessary for diagnosis of extrapulmonary TB and other OIs
- CD4 (if available).
- Lab tests supporting selection of ARV regimen such as HBsAg, anti-HCV (if available).
- Creatinin, lipid, glucose in case the patient is using TDF or protease inhibitors
- Pregnancy tests as needed.

1.1.4. Diagnosis of OIs and clinical staging:

- Diagnosis of progressive tuberculosis: (see Chapter V, Section 5: Diagnosis and treatment of TB in patients with HIV).
- Diagnosis of other OIs: see Chapter IV (Approach to common clinical syndromes in people living with HIV/AIDS) and Chapter V (Diagnosis and Treatment of common opportunistic infections).
- Clinical staging (see Table 1).

1.2. Management:

- Provide treatment for opportunistic infections and other conditions, symptom releave
- Provide prophylaxis for opportunistic infections
- Assess for eligibility to ARV treatment. If the patient is eligible, , follow preparation for treatment readiness

- Hospitalize cases with severe conditions; seek consultation orrefer patients to at higher level if in the case is to complicated to manage at the localfacilities ; collaborate with TB services, dermatovenereology and obstetrics specialists, with program for prevention of mother to child transmission of HIV and other specialties as needed.

1.3. Counseling and support:

Counseling and support should be provided to all patients with HIV infection both on ARVs or not receiving the ones. Contents of counseling session arebased on assessment need of each patient's needs:

- Psycho-social support and introduction of supportive services
- Provision of knowledge on HIV/AIDS
- Explanation about life-long care and treatment
- Counseling on positive living and nutrition
- Counseling on pregnancy and HIV-related issues
- Counseling on prevention of HIV transmission and safe practice
- Counseling on treatment adherence: importance and contents of treatment adherence, especially to patients on ARV treatment
- Counseling on the necessity of having a treatment supporter when patient enrolled in the treatment program
- Counseling on disclosure of HIV status to family members and partners.
- Referral of other family members to services such as voluntary counseling and testing, as needed

1.4. Follow-up plan and other necessary supports

1.4.1. Schedule for follow-up visits for each patient:

- For patients not receiving ART: Follow-up visits should be scheduled on the basis of clinical stage and CD4 cell count:
    - ⇒ Clinical Stages 1, 2 and CD4 > 350 /mm^3: follow-up visit at every 3 months and whenever abnormal manifestations occur.
    - ⇒ Clinical Stages 1, 2 and CD4 < 350 /mm^3; Clinical Stage 3 and CD4 > 350 /mm^3: follow-up visit at every 1-2 months and whenever abnormal manifestations occur.

- For patients eligible to ART: follow-up visit should be scheduled to prepare for treatment readiness.
- For patients on ART: follow-up visit as scheduled.

1.4.2. Explan to patients to come to health facilities whenever abnormal manifestations occur in order to be timely managed.

1.4.3. Dispense medications as scheduled by the care and treatment team.

2. Follow-up visits:

Patients should come to HIV care and treatment facilities for follow-up visit as scheduled or whenever abnormal manifestations occur.

2.1. Clinical examination and laboratory testing:

- Taking history: symptoms newly occurred since the last visit, such as fever, weight loss, cough, diarrhea, eruption, etc.; psycho-social issues, treatment adherence.
- Clinical examination: general and specific organsexamination for detection of opportunistic infections and other conditions, side effects of prophylactic and therapeutic medications. Re-assess clinical staging.
- Perform routine tests, CD4 cell count; diagnostic tests for OIs and detection of drug side effects as well as treatment failure, as needed.

2.2. Management:

Management will be provided depending on the clinical condition and test results of the patient.

- Treatment for OIs and management of drug side effects if any.
- Consideration of ARV treatment if patient is eligible.
- Psycho-social counseling and support for treatment adherence.
- Referral for patients to other relevant services.

III. PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS

1. Co-trimoxazole prophylaxis

Objective: CTX is effective to prevent opportunistic infections including PCP, toxoplasma encephalitis, as well as other bacterial and protozoal infections that cause pneumonia, diarrhea.

1.1. Indication of Co-trimoxazole prophylaxis

If CD4 is available, start cotrimoxazole prophylaxis for:

- Persons with HIV infection at clinical stages 3 and 4, regardless of CD4 cell count.
- Persons with HIV infection at clinical stage 1 and 2 if CD4 < 200 cells/mm3

If CD4 cell count not available, start cotrimoxazole prophylaxis for:

- HIV-infected patients at clinical stage 2, 3 or 4.

Pregnant women should start Cotrimoxazole prophylaxis regardless of period of pregnancy. Breastfeeding women should continue cotrimoxazole prophylaxis.

1.2. Dosage for prophylaxis

- Co-trimoxazole 960mg (SMX800mg/TMP160mg) orally once per day or three times per week.
- Alternatives (in case of Co-trimoxazole intolerance): Dapsone 100mg/day. Dapsone is less effective than Co-trimoxazole in preventing PCP.

Note: Co-trimoxazole and ARVs (especially nevirapine and efavirenz) can cause rash. Co-trimoxazole prophylaxis should be given 1-2 weeks prior to ARV treatment tohelp with differentiation of side effects between the drugs if occur.

***1.3. Contraindication*:** allergy to sulphonamides

1.4. Common side effects of Co-trimoxazole:

- Vomiting and nausea can be seen, commonly within 1-2 weeks after starting prophylaxis. Co-trimoxazole rash can be of mild, moderate or severe grade (see Table 3). Severe side effects due to Co-trimoxazole such as anemia, granulocytopenia, hepatotoxicity are uncommon.
- Counsel the patients about potential side effects for self monitoring; tell the patients to come immediately to health facilities when signs of severe side effects occur.
- Perform complete blood count, liver enzyme measurement when anemia or hepatotoxicity is suspected.

Table 3: Grading and management of co-trimoxazole rash

Grade	Clinical manifestations	Management recommendations
Grade 1 (mild)	Erythema	• Continue Co- trimoxazole prophylaxis, with close daily monitoring. • Symptomatic treatment and antihistamines.
Grade 2 (Moderate)	Diffuse maculopapular rash, dry desquamation	
Grade 3 (Severe)	Vesiculation, mucosal ulceration	• **DISCONTINUE** the drug until symptoms resolve (usually after 2 weeks). Symptomatic treatment and antihistamines. • Then CONSIDER TO REINTRODUCEco-trimoxazole with desensitization.
Grade 4 (Very severe)	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	• **PERMANENTLY DISCONTINUE** Co- trimoxazole • Symptomatic treatment and antihistamines

Co-trimoxazole desensitization in adults:

- Co-trimoxazole desensitization can be attempted in patients with mild and moderate allergy (grades 1 and 2); patients with severe allergy (grade 3) should be desensitized cautiously. Desensitize should not be attempted in patients with very severe allergic reactions to Co-trimoxazole or other sulphonamides in history
- Desensitization should be commenced about 2 weeks after discontinuing Co-trimoxazole when patients' symptomes resolved. Desensitization should preferably be performed in hospital, where intensive treatment for anaphylactic shock available if needed
- Desensitization is commenced according to the following protocol (see Table 4); dose of desensitization is increased only if patients do not develop hypersensitivity to previous dose of cotrimoxazole (no rash). If a reaction occurs, the desensitization should be stopped. Once the patient recovers fully, dapsone can be used as substitution.

Table 4: Desensitization protocol for co- trimoxazole

Step	Dosage
Day 1	80 SMX + 16 mg TMP (2ml of oral suspension(*))
Day 2	160 SMX + 32mg TMP (4ml of oral suspension(*))
Day 3	240 SMX + 48mg TMP (6ml of oral suspension(*))
Day 4	320 SMX + 64mg TMP (8ml of oral suspension(*))
Day 5	One single strength (480mg) tablet
From day 6	Two single strength (480mg) tablets or one double-strength (960mg) tablet

(*) Oral suspension of Co-trimoxazole contains 200mg SMX + 40mg TMP in each 5ml. In case oral suspension not available, dissolve 400mg SMX + 80mg TMP tablet and use in dosage as above.

1.5. Duration of co- trimoxazole prophylaxis for adults with HIV infection:

Table 5: Duration of Co-trimoxazole prophylaxis for adults with HIV infection

Patient	Management
Patients not receiving ART	Life-long prophylaxis
Patients on ART	***Discontinuation of prophylaxis:*** Co-trimoxazole prophylaxis should be discontinued if the patient has CD4 $\geq$ 200 cells/mm^3 for at least 6 months. If CD4 cell count is not available, discontinue Co-trimoxazole prophylaxis when the patient receives ARV treatment for at least 1 year with good adherence and without clinical manifestations related to HIV. ***Reintroduction of prophylaxis:*** Co-trimoxazole prophylaxis should be reintroduced when the patient has decreased CD4 count <200 cells/mm^3

2. Prevention of active tuberculosis with isoniazide (INH)

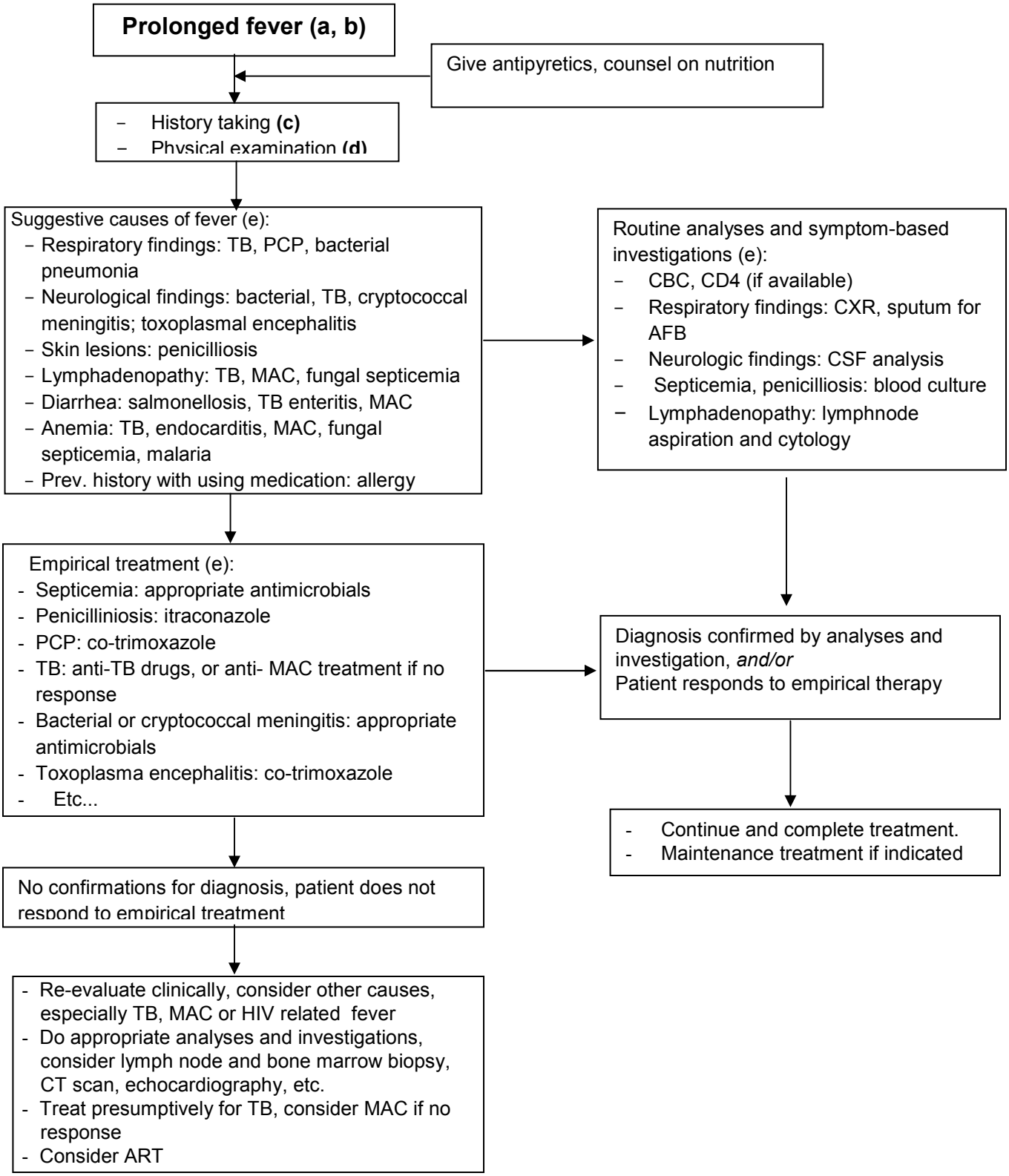
- Objective: prevention of latent TB infection to become active TB disease
- Criteria for prophylaxis: All HIV infected people (adults and children) with no active tuberculosis on TB screening.
- Regimen: oral isoniazide (INH) 5 mg/kg/day (maximal dose in adults is 300 mg per day) given daily for 9 months in combination with vitamin B6, 25 mg daily.
- Monitoring and evaluation: Deliver the drug monthly and evaluate the drug use at least once a month. Management of stopping therapy: lost: if the patient missed less than 50% of total doses, give additional doses

for treatment to be completed; if missed over 50% of total doses, the treatment should be restarted.

- Side effects:
    - Mild: peripheral neuropathy – manage with vitamin B6 100mg/day.
    - Severe: liver involvement (jaundice, anorexia, elevated liver enzymes).
    - Management: stop INH and refer to healthcare facilities for treatment. Advice patients not to drink alcohol or beer during treatment.

IV. APPROACH TO COMMON CLINICAL SYNDROMES IN PATIENTS WITH HIV/AIDS

1. Prolonged fever



Instructions:

(a) Definition: prolonged fever is defined as a fever over 38,5^{0}C lasting for more than 14 days without any causes determined.

(b) Common causes of prolonged fever

- OIs: TB, penicilliosis, cryptococcal meningitis and fungemia, septicemia due to salmonella and other bacteria, MAC, etc.
- HIV related neoplasms, such as lymphoma
- Drug reactions such as hypersensitivity to CTX, NVP, ABC, etc.
- HIV related fever, malaria

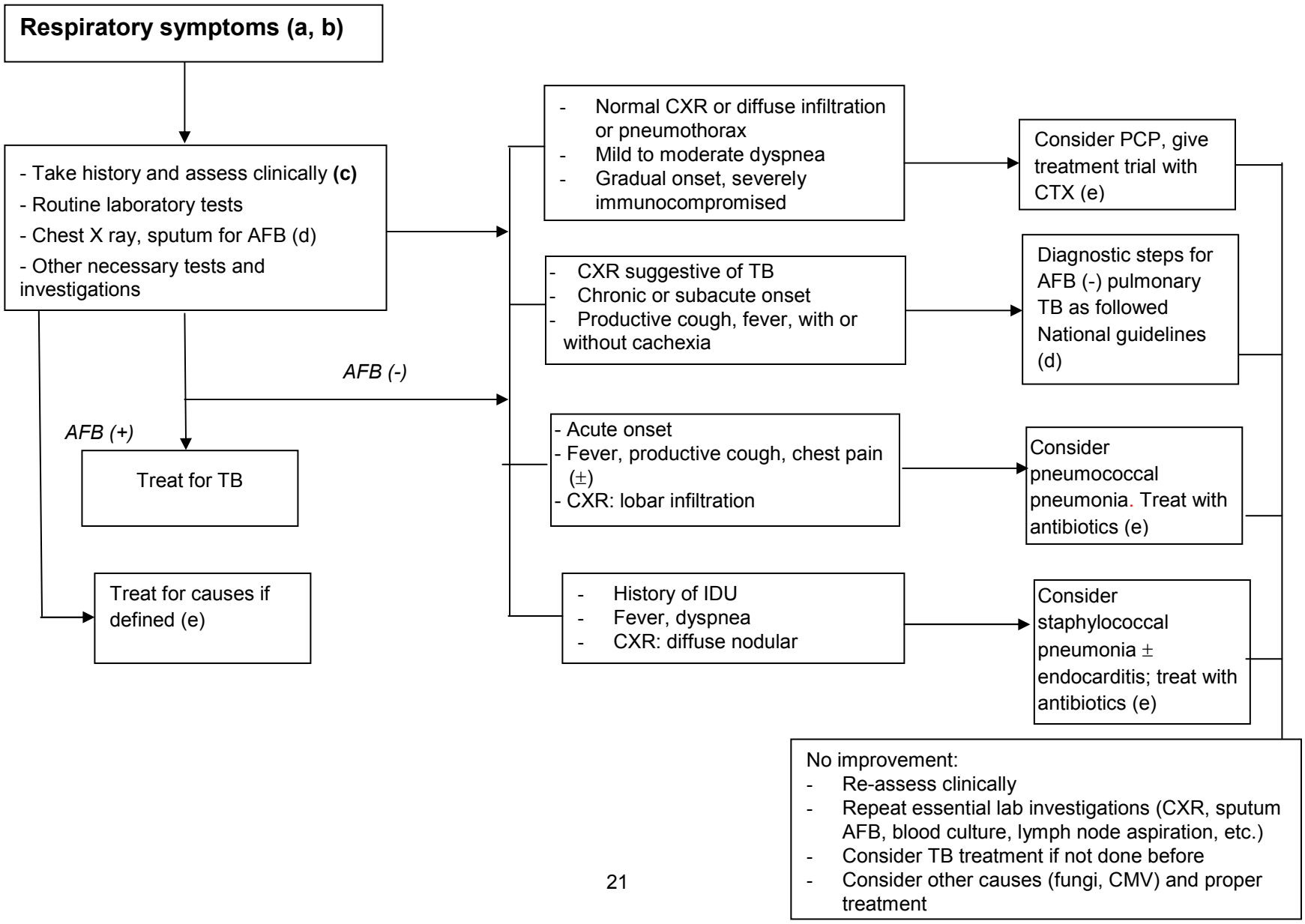
(c) History taking:

- Symptoms from organs and systems: headache (meningitis due to cryptococcus or TB, Toxoplasmosis), diarrhea (salmonella septicemia, MAC, etc.), cough (pulmonary TB), rash (penicilliosis, drug allergy), etc.
- Drugs taken: CTX, ARV, others.
- History of any OI or other HIV associated conditions (potential recurrence of OIs if secondary prophylaxis or ARV treatment not given)
- History of drug allergy and other conditions.
- History of IDU (septicemia with Staphylococcus aureus), unsafe sex (gonorrhea, syphilis, other STIs)
- Family history: TB, cough and other communicable diseases

(d) Clinical examination: Examine all systemsandorgans , focus on the ones with symptoms.

(e) Refer to causes of OIs, investigations and treatment in Section V "Diagnosis and treatment of common Opportunistic Infections".

2. Respiratory manifestations



Instructions:

(a) Respiratory symptoms: cough dyspnea; often associated with fever

(b) Causes:

- Common causes: pleuro-pulmonary TB, PCP, MAC, bacterial pneumonia.
- Other causes: penicilliniosis, cryptococcosis, histoplasmosis (causing respiratory symptoms with systemic fungal infection); cytomegalovirus disease; non-infectious causes: lymphoma, Kaposi's sarcoma.

(c) Considerations in history taking and physical examination:

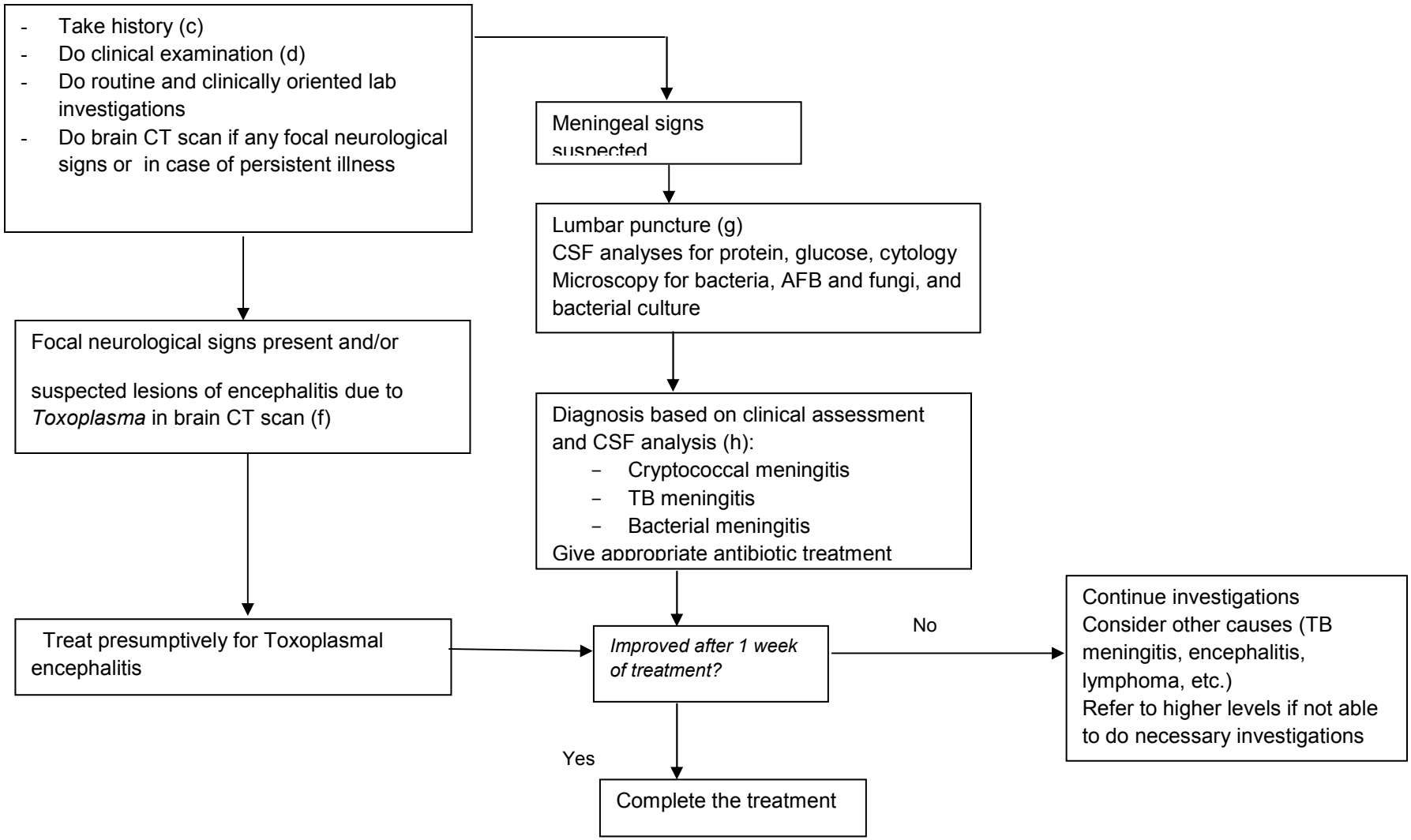
History Taking:	***Physical examination:***
- Onset: acute or chronic - Dyspnea: effort-related or not - Characteristics of the sputum - Accompanied symptoms: fever, chest pain… - History of IDU - TB history of the patient and in family	- Respiratory failure: dyspnea, cyanosis - General conditions: fever, weight loss, skin eruption, lymphadenopathy, etc. - Lungs: crackles, fremitus,… - Findings of immunodeficiency: oral thrush, cachexia…

(d) Investigations: Based on clinical signs & symptoms and history

- Routine laboratory tests, CD4 cell count,
- Chest X-ray, sputum AFB; sputum microscopy and culture to look for other bacteria.
- Blood culture in case of fever
- Pleural tapping and lymph node aspiration in case of pleural effusion and lymphadenopathy; analysis of pleural fluid and lymph node aspirate
- Chest CT scan if available

(e) See the Section V "Diagnosis and treatment of common Opportunistic infections "

3. Neurological abnormalities (a, b)



Instructions:

(a) Neurological signs and symptoms: Headache, altered consciousness, focal neurological signs

(b) Causes:

- Opportunistic infections in CNS: Toxoplasma encephalitis, cryptococcal, TB or bacterial meningitis
- Other causes: lymphoma, HIV-related encephalopathy, progressive multifocal leukoencephalopathy (PML)
- Medications: d4T, EFV

(c) History Taking:

- Duration of symptoms
- Accompanied symptoms: fever, skin eruption, wasting, etc.
- TB history of the patient and in the family

(d) Clinical examination:

- Look for neurological abnormalities: altered mental status, meningeal signs (headache, neck rigidity, photophobia), focal neurological signs (hemiplegia, cranial nerve palsies).
- Look for constitutional signs: fever, lymphadenopathy, skin eruption, manifestations of immunodeficiency

(e) Lab tests and investigations: based on history and clinical examination

- Blood culture if fever presents
- Chest X ray and other lab tests if TB meningitis is suspected

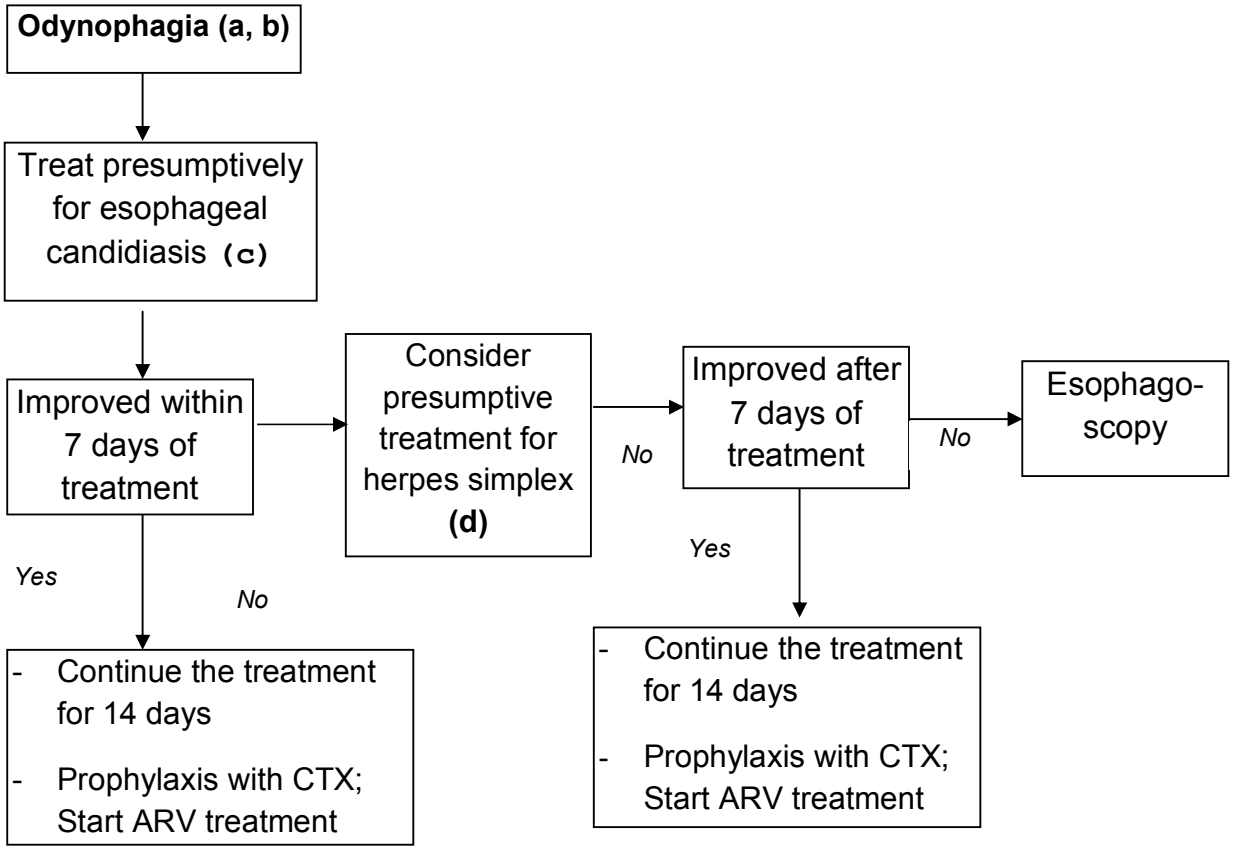
(f) Typical lesions of toxoplasmal encephalitis: treat as indicated in the Section of Opportunistic infections. Other lesions: consider TB meningoencephalitis, bacterial abscess, HIV encephalopathy, etc; perform appropriate assessment and investigations.

(g) Suggestive differential diagnosis based on cerebrospinal fluid (CSF) changes:

CSF	Opening Pressure	Protein content	Cell count	Microscopy	Culture
Cryptococcal meningitis	Very high	Slightly elevated or normal	Slightly elevated or normal	+ India ink stain	+
TB meningitis	High or normal	Slightly elevated to very high	Elevated (lymphocytes predominate)	+/- - -	+/-
Bacterial meningitis	High	Very high	Granulocytes predominate	+/-	+
Toxoplasmal encephalitis	Normal	Normal or slightly elevated	Normal	-	-
Lymphoma	Normal	Normal	Normal	-	-

(h) See the Section V "Diagnosis and treatment of common Opportunistic infections"

4. Odynophagia



Instructions

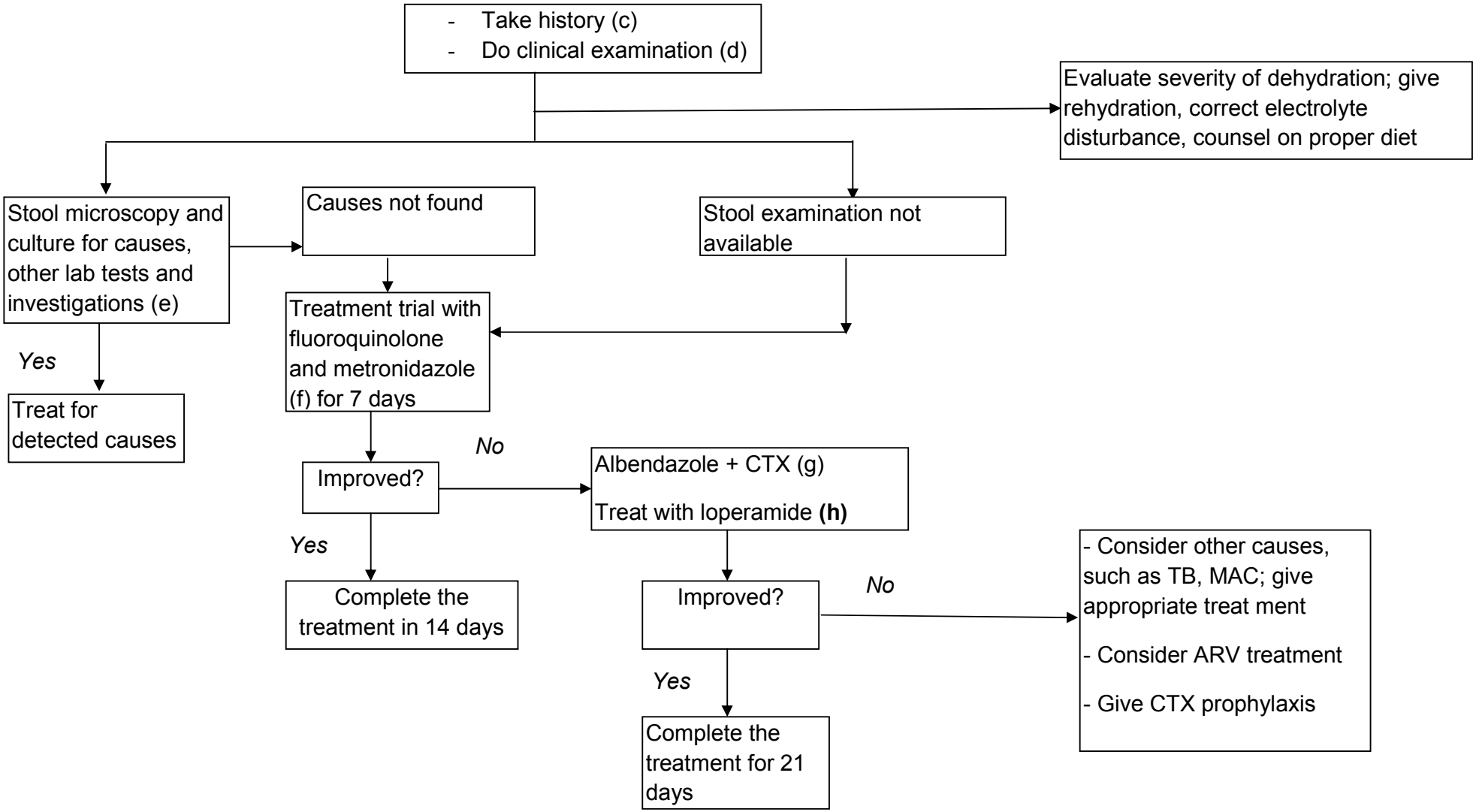
(a) Definition: odynophagia is painful feeling in the throat and retrosternal space on swallowing food, with or without dysphagia, which usually is a symptom of esophagitis.

(b) Causes of odynophagia in HIV patients:

- Candida esophagitis
- Herpes simplex virus esophasitis
- Cytomegalovirus esophasitis
- Aphthous ulcer
- Kaposi's sarcoma, lymphoma of esophagus

(c) Treatment for esophageal candidiasis and Herpes simplex - see the Section V "Diagnosis and treatment of common Opportunistic Infections".

5. Chronic diarrhea (a, b)



Instructions:

(a) Definition: Chronic diarrhea is defined as loose or watery stool of more than 3 times per day, lasting for more than 14 days

(b) Causes of diarrhea:

- Bacterial infections: Salmonella, Shigella, Campylobacter
- Protozoal and helminthic infections: Giardia, Entamoeba, cryptosporidium, Isospora, Microspora, Strongyloides
- Mycobacterial diseases: TB, MAC
- Viral diseases: CMV
- HIV-related malignancies: Kaposi's sarcoma, lymphoma
- HIV itself

(c) History Taking:

- Frequency of bowel movement each day, characteristics of stools
- Accompanied symptoms: fever, abdominal pain, location and characteristics of pain
- History of ARV treatment and using other drugs; antibiotics used for diarhea treatment
- History of TB and other communicable diseases in the family

(d) Clinical examination:

- Evaluate general condition, dehydration and nutritional status
- Look for constitutional symptoms: fever, lymphadenopathy, examination of respiratory and cardiovascular systems
- Examine the abdomen: tenderness, ascites, hepatosplenomegaly, enlarged intra-abdominal lymph nodes

(e) Lab tests and investigations:

- Stool microscopy for erythrocytes and white blood cells (invasive diarrhea); protozoal parasites (entamoeba, giardia), strongyloides larvae, hookworm and other helminthic eggs; formalin-ether concentration and modified acid-base staining for Cryptosporidium and trichrome staining for Microsporidium and isospora; AFB (TB and MAC) if available
- Blood culture if febrile and septicemia associated diarrhea suspected

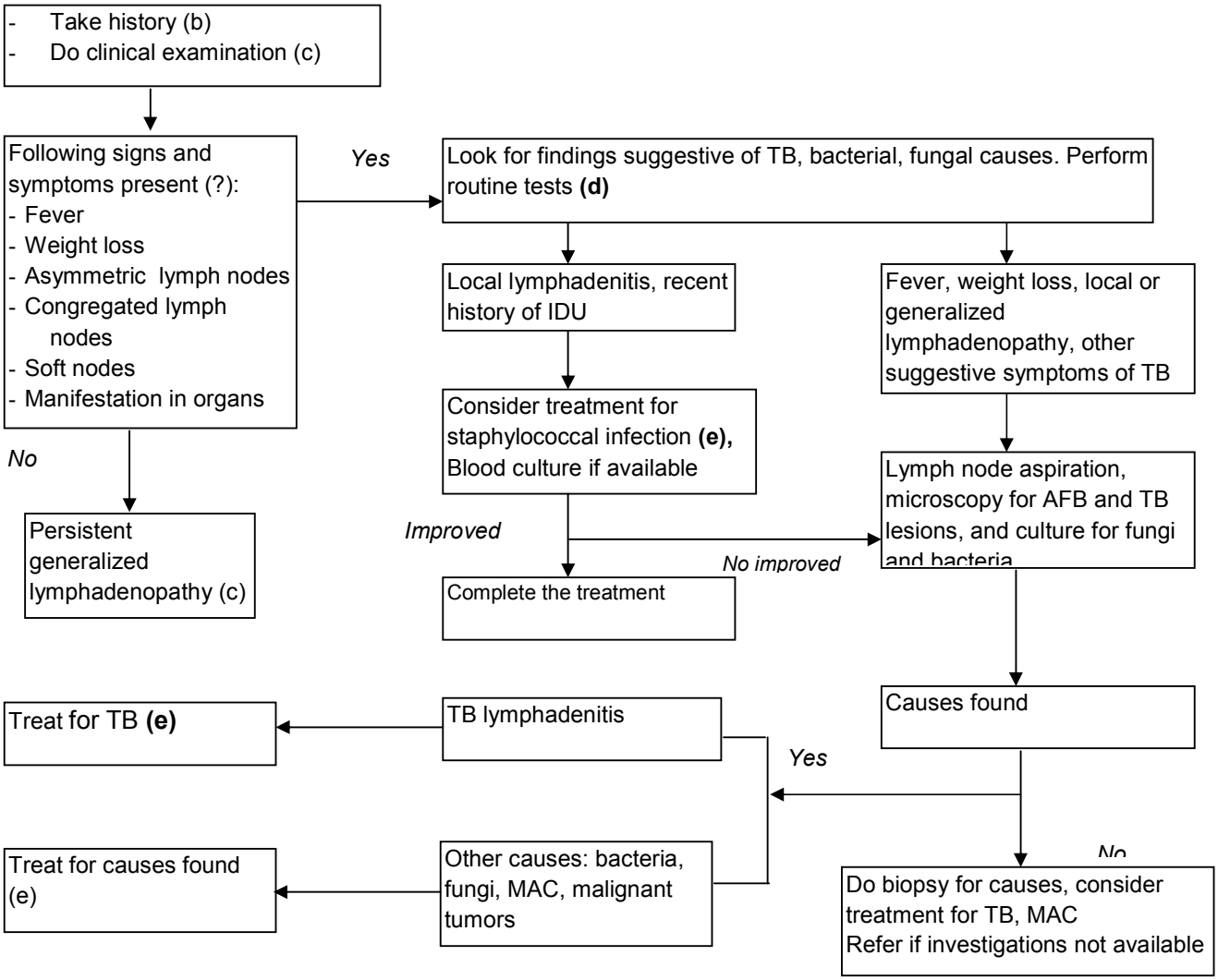
- Chest X ray, sputum examination if having respiratory findings or TB is suspected
- Abdominal ultrasound if available to confirm hepatosplenomegaly, abdominal lymphadenopathy and ascites

(f) Oral Fluoroquinolone (oral ciprofloxacin 500mg or ofloxacin 200mg twice daily) + metronidazol 500 mg twice daily. Effective against shigella, salmonella, campylobacter, entamoeba and giardia. TB should be excluded before treatment with fluoroquinolone

(g) Albendazol 200 mg 2- 4 times/day + co-trimoxazole 960 mg 1-2 times/day. Active against isospora, microsporidia, strongyloides

(h) Loperamide initially 4 mg, then 2 mg after each 4 hours if unformed stool continues; maximal dose: 16 mg/day. Do not use loperamide in patients with bloody and mucous diarrhea.

6. Lymphadenopathy (a)



Instructions:

(a) Causes: enlarged lymph nodes in symptomatic patients are often caused by infections or malignancies. Infectious causes: TB, Penicillium, Cryptococcus, Staphylococcus, maybe MAC; Nocardia, syphilis, histoplasma, leishmania. Malignant causes: lymphoma, Kaposi's sarcoma. HIV itself (persistent generalized lymphadenopathy in asymptomatic HIV infected patients).

(b) History Taking:

- Duration of lymphadenopathy, accompanied symptoms: fever, pain around swelling node, skin eruption, cough, etc.

- History of diagnosis and treatment for OIs (penicilliniosis, TB, etc.) and other diseases

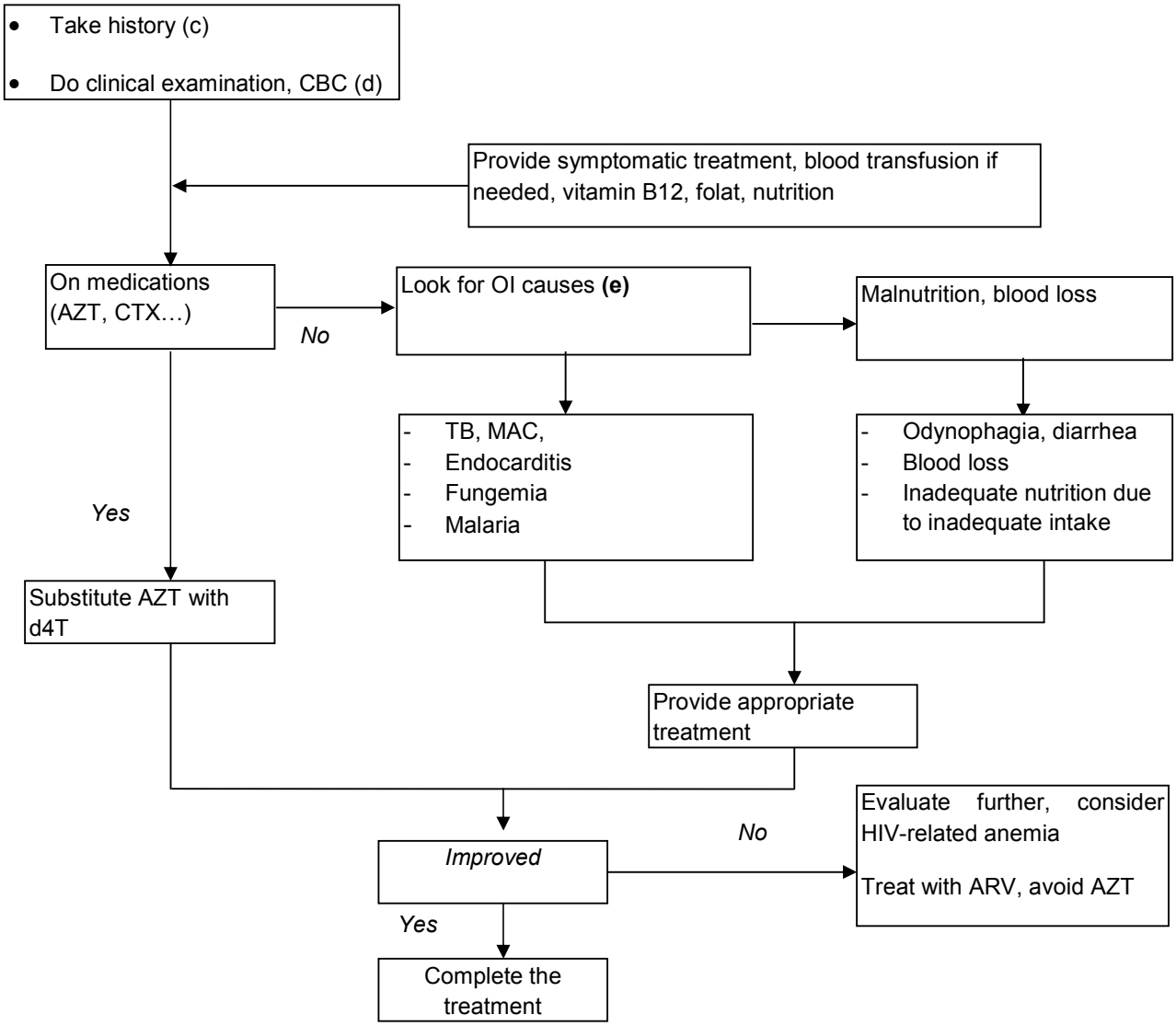
(c) Physical Examination: Assess general condition, look for constitutional manifestations, s.a. fever, cachexia, throat thrush, skin eruption, anemia, etc...

- Examine lymph nodes, evaluate their size and characteristics
- Look for manifestations in other organs, enlarged abdominal lymph nodes, hepatosplenomegaly

(d) Routine lab tests: complete blood count, CD4 cell count if available, CXR

(e) See the chapter on Diagnosis and treatment of Opportunistic Infections

7. Anemia (a, b)


Take history (c)
Do clinical examination, CBC (d)
Provide symptomatic treatment, blood transfusion if needed, vitamin B12, folat, nutrition
On medications (AZT, CTX…)
No
Look for OI causes (e)
Malnutrition, blood loss
- TB, MAC,
- Endocarditis
- Fungemia
- Malaria
- Odynophagia, diarrhea
- Blood loss
- Inadequate nutrition due to inadequate intake
Yes
Substitute AZT with d4T
Provide appropriate treatment
Improved
No
Evaluate further, consider HIV-related anemia
Treat with ARV, avoid AZT
Yes
Complete the treatment

Instructions:

(a) Definition: Anemia is defined as having hemoglobin of < 120g/l for males and < 100 g/l for females.

(b) Causes:

- Infections: TB, systemic fungal disease, endocarditis, MAC, malaria.
- Malnutrition, dysphagia, chronic diarrhea
- Drugs: AZT, CTX, etc.
- Blood loss, medical conditions causing bone marrow depression
- Malignancy and due to HIV itself

(c) History Taking:

- Duration of symptoms associated with anemia, (fatigue, tinnitus, dazzle, dizziness)
- Other symptoms, s. a. fever, diarrhea, odynophagia, cough, skin eruption, etc.
- History of opportunistic infections
- History of using co-trimoxazole, AZT and other drugs
- History of IDU and traveling to malaria areas
- History of blood loss, nutritional uptake

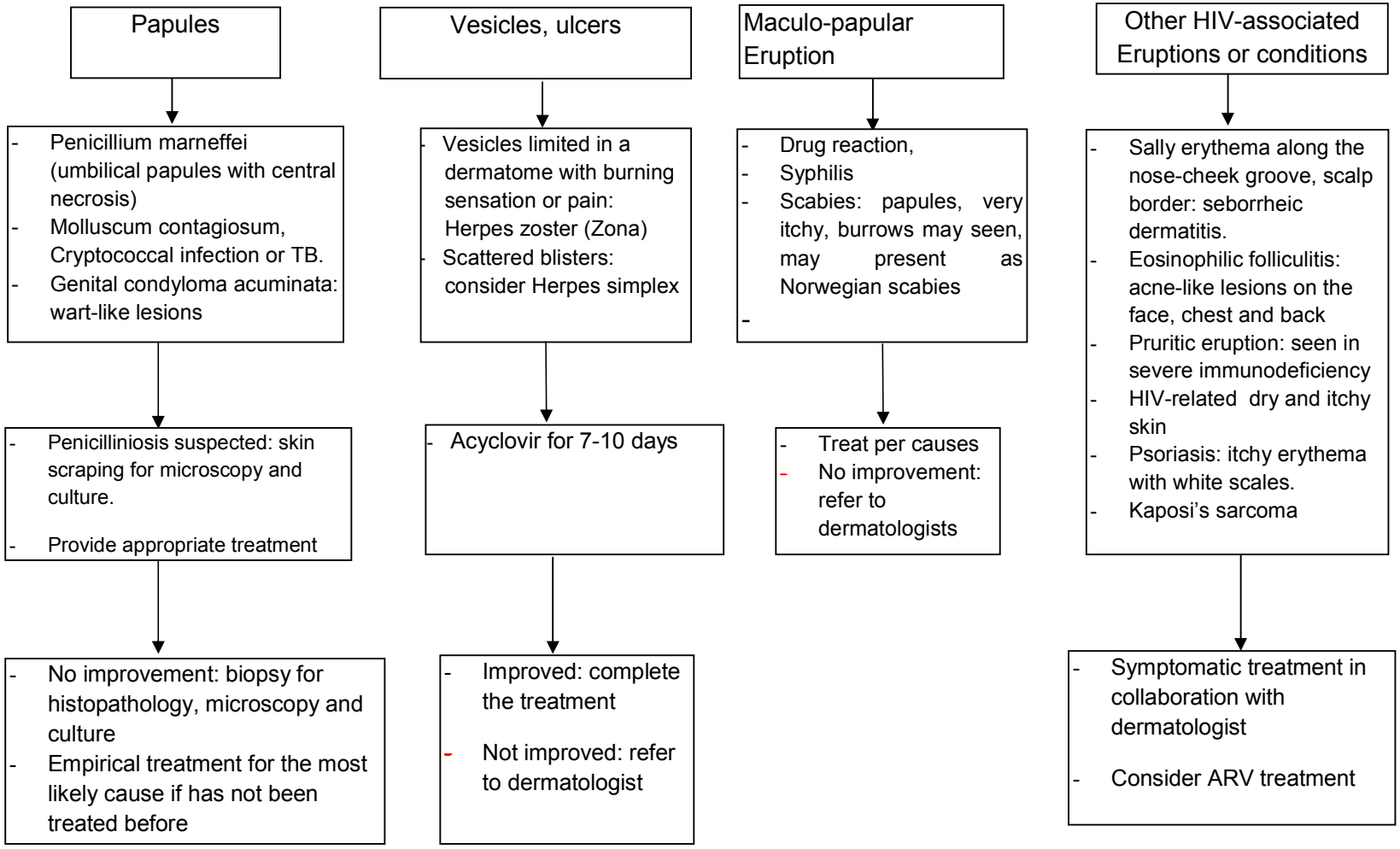
(d) Clinical examination

- Evaluate the severity of anemia, nutrition and look for manifestations of OIs

(e) Laboratory analyses and investigations:

- CBC: Hb, other cell lines; mean corpuscular volume (MCV) (macrocytic anemia suggests vitamin B12 deficiency, co-trimoxazole and AZT associated anemia; microcytic anemia suggests OIs, blood loss).
- Malaria film.
- Diagnostic tests for OIs: sputum AFB, tests for fungi
- Bone marrow analysis, lymph node biopsy, bone marrow biopsy and other investigations if available

8. Mucocutaneous manifestations



Instructions:

1. Causes of skin and mucosa lesions:

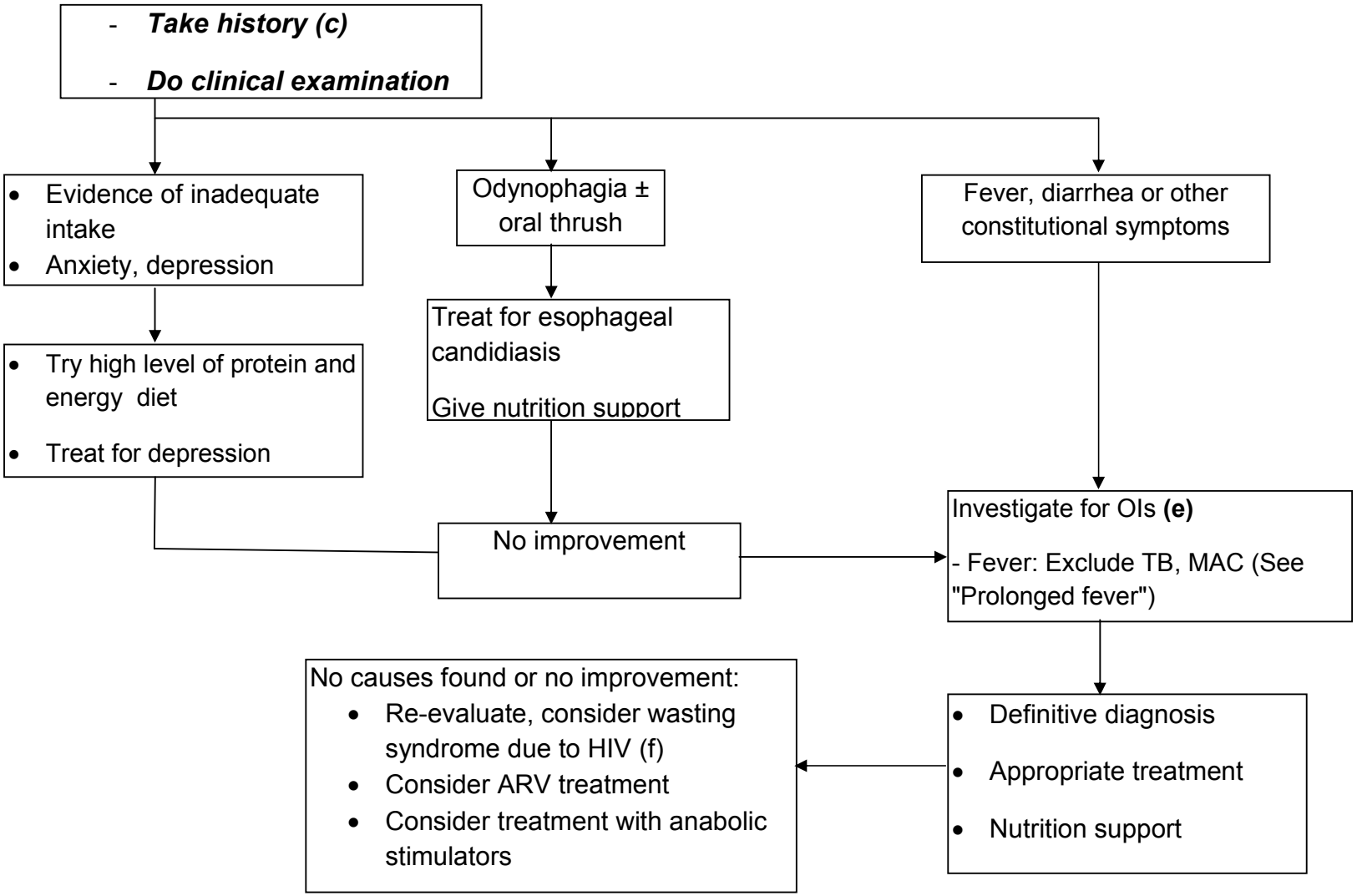
- Bacterial infection: folliculitis, furuncles, cellulitis, TB-associated skin lesions.
- Viruses: Herpes simplex, Herpes zoster (Zona), Molluscum contagiosum (poxvirus), human papiloma virus (HPV), oral hairy leukoplakia (Epstein-Barr Virus)
- Fungi: Candida, Penicillium, dermatophytes (ringworm, onychomycosis), Cryptococcus,
- Parasite: scabies
- Neoplasms: Kaposi's sarcoma, lymphoma
- Other dermatitis: eosinophilic folliculitis, seborrheic dermatitis, pruritic papular eruption (PPE), psoriasis, xerosis.
- Drug reaction: Co-trimoxazol and ARVs can cause eruption, generalized erythroderma, scalded or desquamated skin.

2. Considerations in taking history and examination:

-	Clinical examination:
-	- Type of lesions: papule, blister/vesicle, ulcer, maculae.
-	- Distribution of rash
-	- Evolution of lesions
-	- Other manifestations of immunodeficiency, s. a. oral thrush, cachexia
-	- Accompanied symptoms, s. a. fever, hepatosplenomegaly, neurological abnormalities

3. Etiological diagnosis and treatment: (See Section V "Diagnosis and Treatment of common Opportunistic Infections")

9. Wasting (a, b)


- Take history (c)
- Do clinical examination
• Evidence of inadequate intake
• Anxiety, depression
Odynophagia ± oral thrush
Fever, diarrhea or other constitutional symptoms
• Try high level of protein and energy diet
• Treat for depression
Treat for esophageal candidiasis
Give nutrition support
No improvement
Investigate for OIs (e)
- Fever: Exclude TB, MAC (See "Prolonged fever")
No causes found or no improvement:
• Re-evaluate, consider wasting syndrome due to HIV (f)
• Consider ARV treatment
• Consider treatment with anabolic stimulators
• Definitive diagnosis
• Appropriate treatment
• Nutrition support

Instructions:

(a) Weight loss is defined by comparing the present and previous body weight of the patient, if available, or estimated weight by height.

(b) **Causes**:

- Infections: OIs such as TB, chronic diarrhea due to protozoan parasites, systemic fungal infections and MAC
- Malnutrition due to inadequate intake
- Poor intake due to odynophagia (esophageal candidiasis)
- Psychiatric conditions: anxiety, depression

(c) History taking:

- Duration and grade of wasting
- Symptoms such as fever, diarrhea, painful swallowing, cough, etc.
- History of opportunistic infections
- Nutrition
- Manifestations of anxiety and depression

(d) Physical examination

- Evaluate the severity of wasting, look for edema, anemia
- Look for manifestations of OIs (oral thrush, enlarged lymph nodes, etc.)

(e) Analyses and investigations:

- Chest X ray, sputum AFB if TB suspected
- Blood culture if bacterial or fungal septicemia suspected
- Stool examination for protozoas

(f) Wasting syndrome due to HIV:

- Weight loss of more than 10% body weight
- Accompanied by
- chronic diarrhea (loose stool more than twice per day) for at least 30 days
- **or** prolonged fever for at least 30 days

    - No any other explainable cause (e.g. TB, cancer) of these manifestations found

V. DIAGNOSIS AND TREATMENT OF COMMON OPPORTUNISTIC INFECTIONS

Table 6: Diagnosis and treatment of common OIs

OI	Clinical manifestations	Diagnosis	Treatment
1. Fungal diseases			
Candidiasis	Oral candidiasis: Multiple creamy-white, easily removable patches or pseudomembraneous plaques on the tongue, gums, buccal mucosa, and palate, anterior surface of tonsils, posterior wall of throat.	Diagnosis clinical Fungal microscopy and culture should only be performed if clinical manifestations are atypical or treatment is ineffective	Fluconazole 100-150 mg per day or Ketoconazole 200 mg b.i.d for 7 days.
	Esophageal candidiasis: painful swallowing	Diagnosis mainly clinical Esophagoscopy if patient does not improve after standard treatment for candidal esophagitis	Fluconazole 200-300 mg/day x 14 days or Itraconazole 400mg/day x 14 days or Ketoconazole 200 mg b.i.d x 14 days

	Vaginal candidiasis: Itching and burning sensation; creamy white vaginal discharge with cheese-like plaques. Vulvo-vaginal area is erythematous, swollen and painful. Recurrence is common.	Diagnosis mainly clinical Fungal microscopy or culture if clinical features are atypical or treatment is ineffective.	Fluconazole 150- 200 mg orally, single dose: higher dose and more prolonged duration of treatment in case of severe immunodeficiency; or: Itraconazole 100 mg orally, b.i.d x 3 consecutive days; or Clotrimazole 100 mg or miconazole 100 mg as vaginal suppositoria, 1suppositorium/day x 7 days, or Clotrimazole 500 mg single vaginal suppositorium, or Nystatin 100.000 units, 1 vaginal suppositorium/day x 14 days
Cryptococcosis	Fungal septicemia: fever, skin papulewith necrosis, lung infiltration, meningitis Meningitis: headache, photophobia, meningeal syndrome, altered consciousness, focal neurological deficits, fever	Skin biopsy or lymph node aspiration for fungi, blood culture CSF analysis, India ink staining and culture for fungi	- Preferred regimen: amphotericin B IV 0.7mg/kg/day x 2 weeks, followed by fluconazole 800- 900 mg/day x 8 weeks. - Alternatives: fluconazole 800- 900 mg/day x 8 weeks (for mild and uncomplicated cases or when amphotericin B is unavailable). Treatment of intracranial hypertension: Do daily CSF drainage by repeated lumbar puncture with removal of 15-20 ml of CSF each time or until the headache is relieved (mannitol and corticosteroids are ineffective).. Maintenance therapy: fluconazole 150- 200 mg/day lifelong; discontinue when the patient is on

			ART and has the CD4 count > 200 cells/mm^3 of ≥ 6 months
Penicilliniosis (Disease due to *Penicillium merneffei*)	- Isolated skin lesions: umbilical papules with central dark necrotic crust, without itching or pain, limited to the face or generalized. - Fungal septicemia: fever, skin lesions, anemia, hepatosplenomegaly, lymphadenopathy, cachexia. - Fungal pneumonia: dry cough, fever; mild to moderate dyspnea may present. Must be differentiated from miliary TB and PCP	- Based on typical clinical features. - Microscopy and culture of skin scrapping, bone marrow and lymph node aspirations. - Do culture of blood and above mentioned specimens in Sabouraud's medium at 25-37^oC.	- Preferred regimen: amphotericin B (0.7 mg/day) for 2 weeks, then itraconazole 200 mg b.i.d x 8- 10 weeks - Alternatives (For mild cases or when Amphotericin B is unavailable): itraconazole 200 mg b.i.d x 8 weeks Maintenance therapy: itraconazole 200 mg/day lifelong; discontinue when the patient is on ART and has CD4 count > 200 cells/mm^3 of ≥ 6 months.
Pneumocystis jiroveci pneumonia (PCP)	Cough, dyspnea, fever, night sweat Subacute onset of symptoms over 1- 2 weeks	Diagnosis clinical Normal chest X ray in over 90% of patients; typical CXR: diffuse bilateral interstitial infiltrations. Response to treatment trial with co- trimoxazole may be exploited for diagnosis If available: aspirate	Co-trimoxazole: 15mg TMP/kg/day in 4 divided doses x 21 days; patients weighed < 40 kg: TMP-SMX 480 mg, 2 tablets x 4 times/day; patients weighed > 40 kg: TMP- SMX 480 mg, 3 tablets x 4 times/day. In case of respiratory failure: prednisone (orally or intravenously) 40mg x 2 times/day x 5 days, then 40mg x once daily x 5 days, then 20 mg x once

		bronchioaveolar lavage fluid for Giemsa or silver or immunofluorescence staining for P. jiroveci.	daily x 11 days). Maintenance therapy: Cotrimoxazole 960 mg orally daily until when the patient is on ART and has CD4 count > 200 cells/mm^3 of ≥ 6 months. Alternatives: Clindamycin 600 mg IV or 450 mg orally t.i.d + primaquine 15 mg orally once daily for 21 days in case of hypersensitivity to sulphonamides
2. Protozoal diseases			
Toxoplasmal encephalitis	Headache, drowsiness, seizures, focal neurological deficits Fever	Focal neurological signs Single or multiple mass-occupied lesions on brain CT or MRI (if available). Response to presumptive treatment can be used to support the diagnosis	Co-trimoxazole: TMP based dosage is 10 mg/kg/day intravenously or orally for 3-6 weeks or Pyrimethamine (200 mg loading dose, then 50-75 mg once daily) + sulfadiazine (2-4g/initial dose, then 1- 1.5 g every 6 hours) for 3-6 weeks. Maintenance therapy: Pyrimethamine (25-50 mg/day) + Sulfadiazine (1g x every 6 hours); discontinue when the patient is on ART with CD4 count > 100 cells/mm^3 of ≥ 6 months.
Protozoal diarrhea (Cryptosporidium, Microsporidia	Chronic diarrhea Vomiting, abdominal pain	Stool examination for parasites	ART is the best treatment Diarrhea due to Microsporidia and Isospora can be responsive to Albendazole 400 mg b.i.d x 3 weeks and Co-trimoxazole 960mg b.i.d x 10 days

Isospora)			
3. Bacterial diseases			
Mycobacterium avium complex (MAC)	Prolonged or recurrent fever, weight loss, fatigue, anemia, hepatosplenomegaly and lymphadenopathy. Do differential diagnosis withTB.	Isolation of MAC from blood or other sites, usually difficult to perform. Consider diagnosis of MAC if the patient is not responsive to TB treatment after 2-4 weeks.	Preferred regimen: oral clarithromycin 500mg b.i.d + ethambutol 15mg/kg/day. Alternative regimen: oral azithromycin 500mg/day + ethambutol ± rifabutin 300mg/day; or azithromycin 500mg/day + ethambutol or ciprofloxacin 500mg x twice per day. ART must be given. Discontinue treatment only if the patient is on ART and CD4 count > 100 cells/$mm^3$for more than 6 months.
Purulent polymyositis	- Causative microorganisms: Staphylococcus aureus, Streptococci; more common in IDUs - Clinical manifestations: pyoderma, folliculitis, cellulitis, abscess of muscle and soft tissues, with or without fever; systemic and other organs involvement.	- Clinical diagnosis; - Microscopy and culture of the pus for bacteria if available	- Treatment depends on severity of the disease: antibiotics oral for mild, and parenteral for severe cases. Choose antibiotics, which are active to staphylococci, streptococci, such as oxacillin, first generation of cephalosporin (cephalothin, cephazolin, etc.), and other antibiotics. - Topical cleaning and wound hygiene in cases of ulcers. Use anti-inflammatory and proteolytic agents.
Pneumonia	- Causative bacteria:	Characteristic clinical features.	Intravenous 3rd generation cephalosporins

and pleuritis	pneumococcus, staphylococcus, *H. influenzae, P. aeruginosae, S. aureus*, etc.; rare: *R. equi, Nocardia* species; - Clinical features: abrupt onset with fever, chills, chest pain, productive cough with thick sputum; dyspnea may present; examination may reveal lung consolidation or pleural effusion, lung crackles;	Investigations: elevated WBC and neutrophils; Chest X ray Sputum microscopy and culture, blood culture, thoracentesis for bacterial microscopy and culture if applicable;	(cefotaxime, ceftriaxone); anti-staphylococcal antibiotics if pneumonia due to staphylococcus; anti-pseudomonas antibiotics if the patient having a history of pseudomonas disease or in severe immunocompromised stage; co-trimoxazole in case of Nocardia disease (nocardiosis), etc..
Bacterial meningitis	- Causative bacteria: pneumococcus, other bacteria including rare pathogens such as R.equi, Chryseobacterium meningosepticum, etc. - Clinical features: abrupt or subacute onset, fever, headache, meningeal signs; brain abscess may develop.	Diagnosis based on clinical manifestations; Lumbar puncture, CSF biochemistry, cytology, microscopy and culture, Blood culture if possible; Brain CT scan if available and brain abscess is suspected	Empirical treatment with ceftriaxone intravenously 3-4g/day; modify the treatment according to bacterial culture and results of antimicrobial susceptibility testing. If no bacteria isolated, choose antibiotics on etiological judgment based on clinical manifestations.
Septicemia	- Bacterial causes: Salmonella species, S. aureus, E.coli, Proteus mirabilis, Serratia marcescens, P. aeruginosae,	Diagnosis on basis of clinical manifestations and blood culture if available [some bacteria require special media or prolonged	- Empirical treatment based on suggestive clinical findings [antibiotics active against Gram (-) bacteria for patients with fever and diarrhea; antibiotics active against staphylococcus for

	R.equi, and other bacteria - Clinical manifestations: fever, chills, diarrhea (Salmonella species, E.coli), cellulitis (S. aureus), abscess in the lung and other organs (S. aureus, R.equi, Nocardia species, P. aeruginosa), meningitis and/or brain abscess (R.equi), etc.	incubation time (nocardia)]; Chest X ray or ultrasound if septic metastases suspected (in lung, liver, spleen, etc.); Aspirate of metastatic sites (abscess in soft tissues or internal organs, meningis) for microscopy and culture for causative bacteria.	IDUs with cellulitis and pneumonia, etc.]. Modify antibiotic treatment according to isolated bacteria and results of antimicrobial susceptibility testing.
Bacterial diarrhea	- Bacteria: Salmonella, Shigella, Campylobacter and other enteric bacteria – Clinical features: fever, frequent bowel movements with watery or bloody mucous stools; colics and tenesmus may present. The diarrhea is often severe, and has prolonged course and frequently accompanied with septicemia; septic metastatic foci may present in lungs, joints, hepatobiliary tract and bone marrow.	– Stool microscopy shows RBC and/or WBC (invasive diarrhea) – Culture of blood, stool or fluids from metastatic foci	- Bacteria can be isolated: treatment according the results of antimicrobial susceptibility testing - Bacteria cannot be isolated: treat empirically with ciprofloxacin or another new fluoroquinolone. Monitor the response to treatment (fever, diarrhea)

4. Viral diseases			
Herpes simplex	Clusters of typical blisters, usually in genital area or face. Systemic involvement (HSV encephalitis) is possible	Typical clinical appearance	Acyclovir 200 5 times (or 400 mg t.i.d) daily for 7 days Local care with gentian violet or chlorhexidine.
Herpes zoster	Typical painful blisters in clusters within a dermatome. Eye can be involved	Typical clinical appearance	Acyclovir 800 mg 5 times daily for 7 days Local care with gentian violet or chlorhexidine. Ophthalmic herpes zoster: acyclovir eye ointment
Cytomegalo-virus (CMV)	- Retinitis: blurred vision, with floating dark spots, scotoma, photophobia, progressing to retinal detachment and blindness if not treated timely. May affect one side, or spread to the other side. Retinal lesions are irreversible. - Colitis. - Esophagitis - Gastritis - Encephalitis - Polyradiculopathy - Skin lesions.	Retinitis: clinical diagnosis based on fundoscopy. Retinal lesions: discrete or diffuse patches of retinal necrosis (white) with or without hemorrhage. Diagnosis of other CMV-related conditions should be based on biopsy and viral culture or PCR of specimens from infected sites, such as brain, CSF, skin craping, blood, if available.	– Acute phase: + Intraocular ganciclovir, 2 mg in 0.05-0.1 ml twice a week for 3 weeks, then maintenance therapy once a week. Collaboration with ophthalmologists is adviced. + Ganciclovir intravenously 7.5 -10 mg/kg/day in 2 divided doses for 21 days or longer if no response Following drugs can be used if available: + Foscarnet 60 mg/kg/every 8 hours, and if effective, continue with 60-120mg/kg/day. + Valganciclovir 900mg orally b.i.d x 21 days; or + Valganciclovir intraocular every 6 months + ganciclovir IV or valganciclovir orally as above – Ganciclovir intraocular implant every 6 months Maintenance treatment: Ganciclovir 5mg/kg/day

			every day, or 6mg/kg/day for 5 days per week; or Valganciclovir orally 900mg/day, or Foscarnet 90-120mg/kg IV daily; or Ganciclovir intraocular implant every 6-9 months + ganciclovir 1-1.5g orally 3 times/day Consider discontinuation of treatment when CD4 count > 100 cells/mm^3. Other diseases caused by CMV**:** similar treatment with above medications.
Molluscum contagiosum	Pedunculated nodular lesions, usually on face, genital area and neck, armpits	Clinically	Removal by enucleating or cryotherapy, prick the centre and apply phenol. Responsive to ART
Genital warts (HPV)	Manifestation: Warts present as soft, moist, pink, cauliflower-like papules with peduncle, painless and easily bleeding. - In men warts are found most frequently at the coronal sulcus, prepuce and penis shaft and occasionally at urethral meatus. - In women, warts often occur at clitoris, minor labia, around urethral meatus, perineum. - Genital HPV infection increases the risk of genital cancer.	Mainly relied on clinical features.	- Consultation with Dermatologist. Topical treatment under specialized supervision with podophyllin, trichloroacetic acid; cryotherapy with liquid nitrogen, carbonic laser or electrosurgery. - Responsive to ART

*Pay attention to interaction between OI drugs and ARVs (see Annex 5)

5. Diagnosis and treatment of TB in patients with HIV/AIDS

The management of patients with TB/HIV co-infection is implemented according to the "Protocol for Collaboration in diagnosis, treatment and management of TB/HIV co-infected patients" promulgated in *Decision No.3116/QĐ-BYT dated August 21, 2007 of the Minister of Health.*

5.1. Diagnosis of TB

5.1.1. TB screening:

HIV infected people must be asked for symptoms suggestive of TB at all visits to health care facilities, including:

- Productive cough, possibly hemoptysis
- Prolonged fever.
- Wasting
- Night sweating.

Suspected TB subjects must be screened for pulmonary and extrapulmonary TB by clinical assessment, chest x ray and sputum AFB.

5.1.2. Diagnosis of pulmonary TB

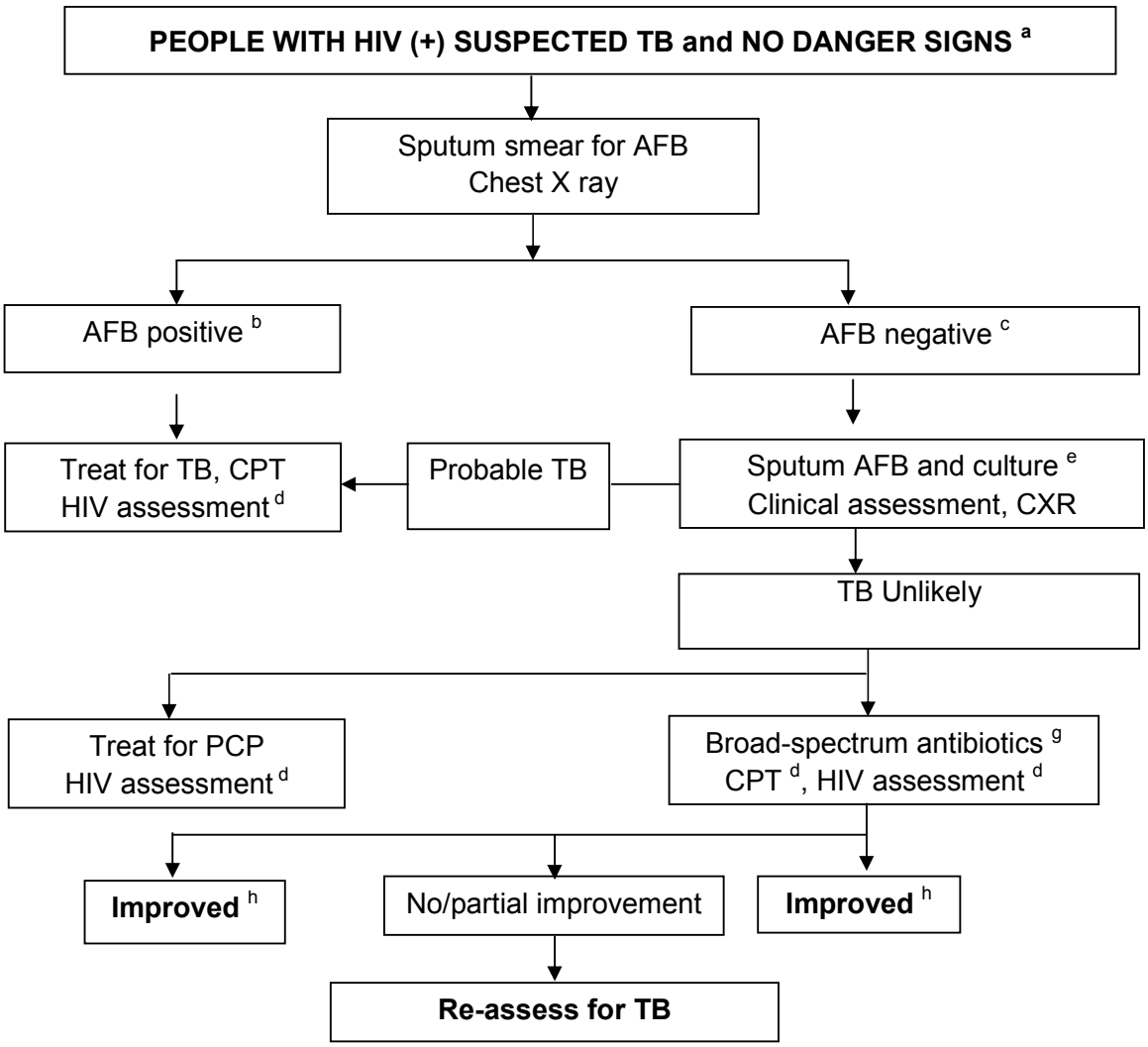
5.1.2.1. Diagnosis of smear positive pulmonary TB

HIV infected people with at least 1 AFB positive sputum smear are considered smear positive pulmonary TB and should be registered and treated as soon as possible *(diagnosis protocol)*

5.1.2.2. Diagnosis of smear negative pulmonary TB

Smear negative pulmonary TB in HIV infected people is defined according to diagnosis procedure and must fulfill following criteria: ***≥ 2 sputum negative smears for AFB, chest x ray suggestive for active TB and the decision of a specialist***.

Diagram 1: Diagnosis procedure of pulmonary TB in HIV infected patients



Note:

a The patient at presentation is not with dangerous signs (able to walk, no dyspnea, no high fever, pulse less than 120 bpm).

b AFB positive pulmonary TB is defined as at least one positive smear,

c AFB negative is defined as at least two sputum negative smears.

d HIV assessment includes: clinical staging, determination of CD4 count and referral for HIV/AIDS care (including ART).

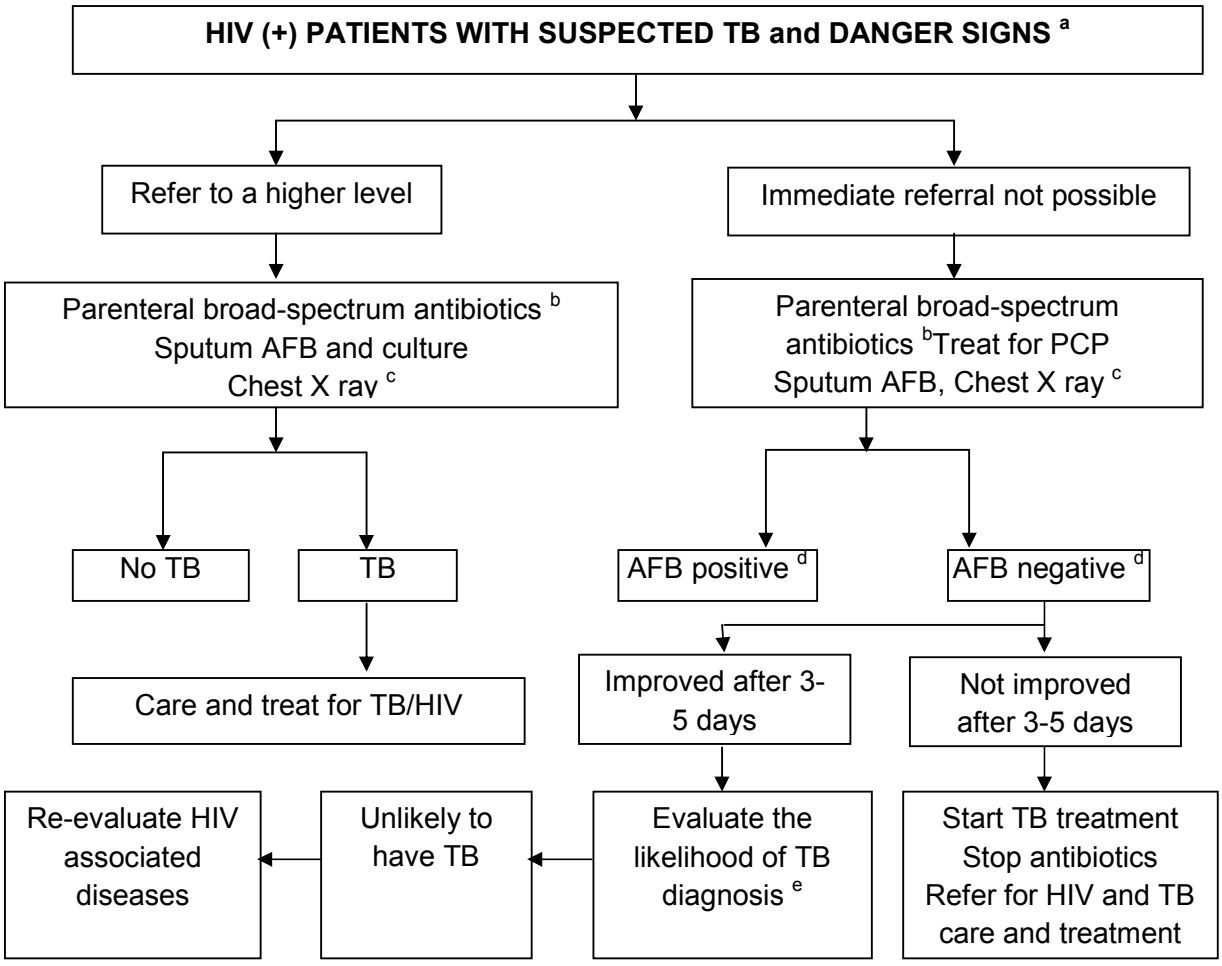
e Only some facilities can do culture for M.tuberculosis.

f It is best to compare the chest X-ray images with the ones from previous visits (e.g. X ray film from the first visit). The patient should be carefully assessed clinically and have chest x ray done to confirm or exclude the diagnosis.

g Broad-spectrum antibiotics except fluoroquinolones.

h Re-assess according to the procedure if symptoms reappear.

Diagram 2: Diagnosis procedure of pulmonary TB in severe patients with HIV infection



Note:

a The danger signs include one of the followings: respiratory rate >30 breaths/minute, fever >39^{o}C, pulse rate >120 beats/minute and unable to walk.

b Broad-spectrum antibiotics except fluoroquinolones.

c These investigations must be done early to speed up the diagnosis.

d AFB positive is defined as at least one smear positive and AFB negative as two or more negative smears.

e Re-assessment for TB includes AFB examination and clinical evaluation.

5.1.3. Diagnosis of extra pulmonary TB

Diagnosis is based on:

- Positive smear for acid-fast bacilli (AFB) or positive culture for *Mycobacterium tuberculosis* with an extra pulmonary specimen

or

- Histological or clinical evidence consistent with diagnosis of progressive extra pulmonary TB **and** is confirmed by a decision of a specialist.

Table 7: Summarized table assistant for diagnosis of common extra pulmonary TB in people with HIV infection

LYMPHNODE TB (PERIPHERAL)	PLEURAL EFFUSION	DISSEMINATED TUBERCULOSIS	PERICARDIAL EFFUSION	TUBERCULOUS MENINGITIS
Suspect TB if • 2 cm or more in size • Asymmetric • Painless swelling • Firm/fluctuant/ fistulated • Cervical location • Weight loss, night sweats, fever **Findings that suggest non TB diagnosis** • Symmetrical (lymphoma or HIV associated lymphadenopathy) • Tender, inflamed, purulent (bacterial or fungal) • Site other than	**Suspect TB if** • Unilateral effusion • Pleural fluid is clear and straw colored **Findings that suggest non TB diagnosis** • Bilateral effusion (possibly heart failure or pneumonia) • Clinical malignancy • Cloudy/purulent pleural fluid (possible empyema) • Blood colored fluid **Essential investigations** • Chest X ray • Sputum smear for AFB if coughing •Fluid aspirate and analysis	**Suspect TB if** • Weight loss, fever and cough • Abnormal chest x ray (possibly miliary pattern) • Hepatosplenomegaly • Night sweats • Anemia **Findings that suggest non TB diagnosis** • Consider Salmonella, pneumococcus, malaria, cryptoccocus • Fever with rigor • Tachypnea (respiratory rate over 30 bpm) • Severe diarrhea • Bloody stool	**Suspect TB if** • Weight loss, night sweats, fever • Evidence of TB elsewhere • Lung fields clear both sides (bilateral pleural effusion may present); symmetrical enlarged heart shape **Findings that suggest non TB diagnosis** • Streaky shadowing in the lungs or heart shape not symmetrical (possibly heart failure) • Hypertension • Electrocardiogram suggests other causes of cardiomegaly (hypertension, coronary disease, valvular diseases, myocardiopathy, etc.) • Fever with rigor (pericarditis with Gram (-) bacteria) **Essential investigations**	**Suspect TB if** • Weight loss, night sweats, fever • Clear CSF with elevated protein, low glucose and lymphocytosis • Cryptococcal antigen (or India ink stain and culture) negative in CSF • Evidence of TB in elsewhere **Findings that suggest non TB diagnosis** • CSF cloudy or neutrophils present on microscopy (possibly bacterial meningitis) • Cryptoccocal tests (+) • Rapid onset • High opening pressure of CSF (possibly cryptococcus) **Essential investigations**

cervical **Essential investigations** • Sputum smears if coughing • Needle aspirate for cytology and AFB **Immediate management** • Aspirate for cytology and AFB microscopy • Lymphnode biopsy if needed	(biochemistry, cytology) •Pleura biopsy and pleuroscopy if needed **Immediate management** **Features of TB only** • Start TB treatment **Non TB features** • Look for other causes • Straw fluid without other diagnosis after 7 days → treat as TB	**Essential investigations** • Chest X ray • Malaria smear • Sputum smear for AFB • Blood culture, complete blood count and cryptococcal antigen **Immediate management** **Features of TB only** • Start TB treatment (+ antibiotics if critically ill) **Non TB features** • Investigate other causes • Start both TB treatment and antibiotics if the patient is critically ill (“surrounding”)	• Chest X ray • Sputum smear for AFB if coughing • Electrocardiography (if ultrasound not available) • Echocardiography (ideally) **Immediate management** **Features of TB only** • Start TB treatment • Refer for urgent aspiration if very breathless/unwell **Non TB features** • Investigate other causes Start TB treatment if pericardial effusion is confirmed by ultrasound and no other diagnosis by 7 days.	• Lumbar punture • CSF microscopy (Gram stain and AFB), CSF protein and glucose • Cryptococcal antigen and stain • Sputum smear for AFB if coughing **Immediate management** **Features of TB only** • Admit to hospital • Start TB treatment **Features of non- TB diagnosis** Treat for cryptococcosis if tests for cryptococcus (+) or no other diagnosis made

5.2. Treatment of tuberculosis

- People with HIV infection should be registered and treated for TB as soon as possible after TB diagnosis.
- TB treatment follows National Guidelines of TB Program, similar for HIV (-) TB patients.
- Provide cotrimoxazole prophylaxis to prevent other opportunistic infections. ART should be considered early and attention should be paid to drug interaction between ARVs and rifampicin, INH .

5.2.1. Essential anti-TB drugs (first line):

National TB Program defines five essential anti TB drugs as follows: Isoniazid (INH), Rifampicin (RMP), Pyrazinamid (PZA), Streptomycin (SM) and Ethambutol (EMB).

5.2.2. Indications of anti-TB regimens:

Regimen I: 2S(E)HRZ/6HE or 2S(E)RHZ/4RH (applied only if direct observation continued in maintenance phase): Intensive phase lasts for 2 months with 4 daily drugs, of which E can substitute for S. Maintenance phase lasts for 6 months with 2 drugs H and E given daily or for 4 months with 2 drugs R and H given daily.

Indications: for newly diagnosed TB cases (never been treated for TB or ever been treated for TB but duration last for less than one month)

Regimen II: 2SRHZE/1RHZE/5$R_3H_3E_3$: Intensive phase lasts for 3 months, of which the first 2 months are with 5 essential drugs given daily (SHRZE), followed by 1 month with 4 drugs (HRZE) given daily. Maintenance phase lasts for 5 months with 3 drugs H, R and E given 3 times per week.

Indications: for cases with recurrence of TB and failure of regimen I, re-treatment after selfdiscontinuation, some severe forms of TB and others special forms of TB (classified according treatment history).

Regimen III: 2HRZE/4HR or 2HRZ/4HR: Intensive phase lasts for 2 months with 4 drugs (HRZE) or 3 drugs (HRZ) given daily, for all TB forms in children. Maintenance phase lasts for 4 months with 2 drugs H and R given daily.

Indications: for pediatric TB cases. In severe forms in children, combination with S can be considered.

VI. ANTIRETROVIRAL THERAPY (ART)

1. Goals and Principles of Antiretroviral Therapy

1.1. Goals of Antiretroviral Therapy:

- To inhibit viral replication and maintain the viral load at the possible lowest level in the blood.
- To restore immune function and reduce the risk of opportunistic infections (OI).
- To improve the quality of life and the survival of people living with HIV/AIDS (PLWHA).

1.2. Principles of Antiretroviral Therapy:

- ART is one part of a comprehensive package of medical care and psychosocial support services for people living with HIV/AIDS.
- ART is primarily provided on outpatient basis and is given only when patients are clinically and/or immunologically eligible and ready to adhere to treatment.
- Any ART regimen must include at least 3 drugs. Antiretroviral therapy is lifelong and the patients must completely adhere to therapy to ensure the effectiveness of treatment and prevent the emergence of drug resistance.
- People with HIV infection commencing ART must continue to apply measures to prevent the transmission of the virus to others.
- People with HIV infection commencing ART must receive prophylaxis of opportunistic infections until their immune system has been reconstituted.

1.3. ARV drug classes available for use in Viet Nam:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside revese transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)

(See Details of common ARV drugs in Annex 4)

2. Criteria for initiating Antiretroviral Therapy

Antiretroviral Therapy is initiated on the basis of clinical staging and CD4 cell count

If CD4 cell count available, ART is indicated when:

- Patients with Clinical stage 4 irrespective of CD4 cell count

– Patients with Clinical stage 3 and CD4 cell count < 350 cells/mm^3 – Patients with Clinical stage 1 or 2 and CD4 cell count < 250 cells/mm^3
If CD4 cell count not available, start ART for HIV-infected patients at clinical stage 3 or 4.

3. Preparation for readiness to commence Antiretroviral Therapy

The preparation for readiness to commence ART must be started from the time the patients first present to the treatment facility. The contents of the readiness preparation should proceed at every patients'visit so that the ART can be initiated immediately should the patients fulfill the criteria for initiating the treatment.

3.1. Pre-ART assessment:

The following is the content of the Pre-ART assessment for the patients who fulfill the clinical and/or immunological criteria for initiating ART:

- Record the pre-treatment cClinical stage and the CD4 cell count (if available)
- Screen for TB and other OIs; provide treatment for TB and acute OIs, if present; collaborate with other healthcare services (e.g. antituberculosis, obstetric and gynecology, etc.) if needed.
- Perform basic laboratory tests and those necessary for selecting ART regimens, such as full blood count/Hb and liver function test (ALT); screen for HBsAg and anti-HCV, if possible.
- Take history of previous ART, if any, the reason for use, the facility provided, actual regimen taken; pay attention to use of suboptimal regimens (such as dual ARV regimen), the adherence to therapy, and the course of disease with the treatment.
- Assess the willingness of the patient to be treated and the availability of the treatment supporter
- choose the suitable ARV regimen for the patient, consider drug interactions between ARVs and OI drugs and other drugs (see Annex 6)
- Inform the patient about the plan for ART-readiness preparation
- Provide Co-trimoxazole prophylaxis, other prophylaxis if indicated and available.

3.2. Education and counseling on adherence to Antiretroviral Therapy

- Provide group counseling and education on the course of HIV infection, prevention of HIV transmission, positive living, nutrition and ART, then individual counseling and education. Each patient should receive 3 counseling and education sessions prior to ARV treatment.
- Provide detail individual counseling on ARV treatment, each patient's regimen, the importance of treatment adherence, plan for adherence support, management of the problems that occur during treatment (e.g. missing a dose, side effects, etc.).
- Provide appropriate counseling for drug users, pregnant women.

3.3. Assessment for treatment readiness

- Assess the patients' understanding about HIV infection, antiretroviral therapy, and the importance of adherence to treatment, what to do when missing a dose.
- Assess the patients' understanding of how to use the drugs, common side effects and its and their management.
- Assess the patients' ability to adhere to treatment by how regularly they attend the counseling sessions and follow-up visits, how well they adhere to co-trimoxazole prophylaxis. Each patient must also have a treatment adherence plan (such as drug taking schedule, reminders for taking doses, availability of treatment supporter), and are willing and commit to participate in treatment program.
- Check other information, such as place of residency, ability to contact when needed.

  ⇨ If the patients fulfill the criteria for treatment readiness, start antiretroviral therapy.

Note:

If the patients are in severe clinical conditions (clinical stage 4 or CD4<100 cells/mm^3), or the patient is pregnant:shorten the preparation period; provide adherence counseling to the treatment supporters and/or the patients themselves in subsequent visits or when the patient's condition stabilizes.

3.4. Initiation of Antiretroviral Therapy

- Review the patients on how to take the drugs, theschedule of drug dispensing and follow-up visits; ensure that patients have a plan to comply with therapy and know how to manage if facing difficulties.

- Prescribe a first-line regimen for HIV-infected patients newly starting antiretroviral therapy;
- For patients with previous history of commencing ART or ART interruption, assess the clinical condition and laboratory parameters to decide appropriate first-line regimen or a second-line regimen in case of treatment failure.

4. First-line Antiretroviral Regimens:

4.1. Prioritized regimens:

AZT + 3TC + NVP

Or

d4T + 3TC + NVP

Indication: Use one of these regimens for all patients starting ART

a. AZT + 3TC + NVP

Dose:

- AZT 300 mg twice daily
- 3TC 150 mg twice daily
- NVP 200mg once daily during the first 2 weeks, then 200mg twice daily

Take the drugs every 12 hours. No diet restrictions required.

Measure Hgb and ALT before starting ART, after 1 month and then every 6 months, and whenever anemia or hepatitis is suspected.

Do not start AZT containing regiment if patients' Hb < 80 g/l. ,Use NVP containing regimen with caution in patients' with ALT > 2,5 upper normal limit, women with CD4 >250 cells/mm^3 and in patient on TB therapy with rifampicin

b. d4T + 3TC + NVP regimen

Usual adult dose:

- d4T 30 mg twice daily
- 3TC 150 mg twice daily
- NVP 200mg once daily in the first 2 weeks, then twice daily

Take the drugs every 12 hours. No diet restrictions required

Measure ALT before starting ART, after 1 month and then every 6 months

Use NVP containing regimen with caution in patients' with ALT > 2,5 upper normal limit, women with CD4 >250 cells/mm^3 and in patients on TB therapy with rifampicin

4.2. Alternative regimens:

4.2.1. AZT + 3TC + EFV or d4T + 3TC + EFV regimen:

Indication: Use one of these regimens if patients cannot use NVP

a. AZT + 3TC + EFV

Normal adult dose:

- AZT 300 mg twice daily
- 3TC 150 mg twice daily
- EFV 600 mg once daily at night

Take AZT + 3TC every 12 hours and EFV at night. Do not take EFV with fatty meal

Measure Hgb before starting ART, after 1 month and then every 6 months, and whenever anemia is suspected.

Do not start AZT containing regiment if patients' Hb < 80 g/l and/or Do not start EFV based regimen for pregnant women during the first trimester.

Avoid using EFV in patients with serious psychiatric problems (current or in the past)

b. d4T + 3TC + EFV

DNormal adult dose:

- d4T 30 mg twice daily
- 3TC 150 mg twice daily
- EFV 600 mg once daily at night

Take d4T + 3TC every 12 hours and EFV at night. Do not take EFV with fatty meal

Do not start EFV based regimen for pregnant women during the first trimester. Avoid using EFV in patients with serious psychiatric problems (current or in the past)

4.2.2. TDF + 3TC+ NVP or TDF + 3TC+ EFV regimen

Indication: this combination is the optimal for patients who cannot use both AZT and d4T.

a. ***TDF + 3TC+ NVP***

DNormal adult dose

- 3TC, NVP: as above.
- TDF: 300 mg once daily.

Note: Measure creatinin/creatinin clearance test prior to ART and every 6 months, change dose when patient has renal failure.

Creatinine Clearance (ML/min) and TDF dose			
≥50ml/min	*30 – 49 ml/min*	*10 – 29 ml/min*	*<10 ml/min*
Once daily *TDF 300mg*	*TDF 300mg every other day*	*TDF 300mg every 3- 4 days or twice a week*	*Contra-indication*

b. ***TDF + 3TC+ EFV***

DNormal adult dose and usage:

- 3TC, EFV: as above.
- TDF: 300 mg once daily.

Note: Measure creatinin/creatinine clearance test prior to ART and every 6 months, change dose when patient has renal failure (as mentioned above)

4.2.3. AZT + 3TC + TDF

Indication: this combination is the optimal for patients who cannot use either NVP and EFV.

DNormal adult dose and usage:

- AZT, 3TC: as above.
- TDF: 300 mg once daily.

Note: Measure creatinin/reatinin clearance test prior to ART and every 6 months, change dose when patient has renal failure. Measure Hgb test prior to

ART, after 1 month and then every 6 months, and whenever anemia is suspected.

5. Side effects of ARVs drugs and its management:

See ARV related toxicity grading and its management in Annex 6):

***5.1. Mild side effects**:* often occur early after starting ART and self-resolve with the time.

Table 13: Mild side effects of ARV and their management

Symptoms	Management
Nausea	Take drugs with meals
Diarrhea	Give water and electrolyte replacement. Antidiarrheals such as loperamide can provide temporary relief.
Headache	Use paracetamol. If headache continues for 2 weeks patients should see the doctors.
Fatigue	Commonly lasts for 4-6 weeks, if longer, patients should see the doctors.
Abdominal discomfort	If constant, patients should see the doctors.
Mild rash	Use anti-histamine. If rash becomes more severe, consider drug hypersensitivity.
Sleepiness	Take drug before going to bed
Insomnia	Supportive drugs can be used. If patients have severe EFV-related insomnia, the drug can be taken in the morning and avoid driving motorbike or operate machines.
Nightmare, dizziness	Often happens when taking EFV, commonly not lasting for longer than 3 weeks.

5.2. Management of major toxicity of first-line ARV drugs:

5.2.1. AZT related anemia

- Anemia commonly occurs during the first 4-6 weeks of using AZT.

- Exclude other causes of anemia or leucopenia.
- Determine anemia grades and manage:

Grade	Hgb	Management
Grade 1 (Mild)	80 – 94 g/l	Continue with AZT. Supplement with micronutrients, such as vitamin B12, iron and folic acid, counsel on appropriate food intake. Do CBC after 1 and 3 months. If patients' condition is stable or improved, continue with AZT and counsel patients on appropriate food intake.
Grade 2 (Moderate)	70 – 79 g/l	
Grade 3 (Severe)	65 – 69 g/l	Substitute AZT by d4T after excluding other causes which can result in anemia or marrow suppression. Transfuse red packed cells or whole blood. Supplement with micro nutrients, such as vitamin B12, iron and folic acid,
Grade 4 (Severe life threatening)	<65 g/l	

5.2.2. NVP hypersensitivity

- NVP *hypersensitivity* rash often occurs 2-8 weeks after starting ART:
- Monitor patients closely and assess rash severity. Health care workers should counsel patients to go to the clinic immediately if rash is getting more serious or iffever, fatigue present
- Give symptomatic management, use anti- histamin or steroid depending on the severity of rash; monitor closely clinical progress & ALT test
- Management of ART is as follow, depending on the severity of rash:

Grade	Manifestation	Management
Grade 1 (Mild)	Erythema without other symptoms	Continue with NVP, delay escalating dose for several days until rash is

Grade 2 (Moderate)	Diffuse maculopapular or localized dry desquamation	improved *(NVP 200mg/day should not be used over 3 weeks).*
Grade 3 (Severe)	Diffuse erythema over body or vesiculation or moist desquamation	**STOPT NVP immediately**. Continue with other 2 drugs for 7 days, then replace NVP by EFV if the rash improves or If after 7 days, rash does not completely improve, other 2 drugs should be also stopped. Restart with EFV based regimen when the patient is completely stabilized.
Grade 4 (Severe life threatening)	Mucous membrane involvement in orifices, Steven Johnson syndrome Erythema multiforme	**STOPT ALL 3 DRUGS** immediately. Hospitalize or refer to higher level Restart ARV when the patients are completely stabilized. Replace NVP by EFV or TDF or LPV/r

5.2.3. NVP Hepatoxicity

- Measure ALT before starting ART.Screen for HbsAg and anti-HCV if possible.
- Signs of NVP related hepatoxicity during ART include increase in ALT, with or without clinical symptoms, such as rash, fever, fatigue, nausea, vomiting, jaundice, abdominal pain. These signs commonly occur after starting ART several weeks to months.
- High risk of getting hepatoxicity has been observed in: (1) Pregnant women with CD4 >250 /mm^3, (2) patients with high ALT level before starting ART, (3) patients with hepatitis B or C co-infection and (4) patients on TB treatment with rifampicin
- Closely monitor liver function tests for patients using NVP, especially those with higher risks mentioned above.
- Hepatoxicity grading and management:

Grade	ALT	Management
Grade 1(Mild)	1.25 - 2.50 times higher upper normal	Continue with NVP.

	limit	Monitor ALT closely in every 2 weeks
Grade 2 (Moderate)	2.60 – 5 times higher upper normal limit	
Grade 3 (Severe)	5 - 10 times higher upper normal limit	**STOPT NVP immediately**. Continue with other 2 drugs for 7 days, then replace NVP by EFV if ALT improves or If ALT is not improved, stop other 2 drugs. Restart ART only when ALT has been improved; replace NVP with EFV based regimen.
Grade 4 (Severe life threatening)	> 10 times higher upper normal limit	Take into account both ALT and clinical signs and symptoms for appropriate management The ARV regimen can be stopped, patient hospitalized or refered to higher level. Restart ART with NVP substituted with EFV or TDF or LPV/r on case by case basis

5.2.4. d4T- related peripheral neuropathy

- d4T related to peripheral neuropathy can occur after staring ART 3-12 months, usually after 6 months.
- Signs and symptoms of peripheral neuropathy include numbness, tingling, burning, pain, losing sensitivity, usually starting from distal parts of the limbs (mainly at lower limbs, starting from toes); if severe, patients may experience difficulties in movement, lost of sensitivity in many parts of the body. In most of the cases, neuropathy symptoms persist permanently.
- Asking patients and assess at each visit changes in tendon reflexes, decrease peripheral sensation, neuropathy-related dystrophy for early detection of peripheral neuropathy.
- **Replace d4T by AZT after 12 months from starting ART if possible, or replace d4T by AZT or TDF whenever patient presents with manifestations of peripheral neuropathy**.

- When patients on d4T based regimen have signs of peripheral neuropathy, health care workers need to:
    - Check if patients are using other neurotoxic drugs. If patients are on isonazid, ensure that patients are taking pyridoxine 50mg (vitamin B6) daily; DO NOT STOP isonazid.
    - If possible, stop other neurotoxic drugs .

5.2.5. Lipodystrophy

- , Lipoatrophy and lipodystrophy are most commonly associated with NRTIs, especially d4T; usually occur after starting ART 6-12 months or longer.
- Manifestations: loss of subcutaneous fat in the face, arms, legs, buttocks with/without central fat accumulation in abdomen, viscera, breast, neck (often irreversible). If severe, it can cause metabolic disorder such as hyperlipidemia or diabetesmellitus.
- Management:
    - Monitor closely signs of lipoatrophy.
    - Monitor blood glucose and lipid
    - **Replace d4T by AZT after 12 months from starting ART if possible, or replace d4T by AZT or TDF whenever patient presents with manifestations of lipodistroph**y.

5.2.6. Other toxicities of first-line ARVs and management

	Common associated toxicity	**Management**
TDF	Renal toxicity affects bone growth	Give lower dose if patient has renal failure. Replace TDF by AZT or ABC or d4T. Avoid using TDF for pregnant woman and children.
EFV	Persistent and severe central nervous	Replace EFV by NVP, TDF or LPV/r

	system toxicity gynecomasty can be seen in man	
	Rash or hepatoxicity	Manage as as with NVP hepatotoxicity. If grade 3, 4: replace EFV by TDF or LPV/r
	Potential teratogenicity	Do not use EFV for pregnant women during the first trimester of pregnancy (see section on use of antiretrovirals in pregnant women)
d4T	Lactate acidosis: slow progress with non-specific symptoms, such as fatigue, , difficult breathing, abdominal pain, nausea, vomiting, ,lost appetite, weight loss,; Analyses: increased level of lactic acid, ALT, CPK, LDH, and anion gap	Discontinue ART Hospitalize the patient. Restart ART when patients completely recovered. Replacing d4T by TDF
	Acute pancreatitis: Abdominal pain, nausea, vomiting, fever, increased amylasemia.	Discontinue ART; provide supportive treatment and laboratory monitoring. Restart ART with another drug with a lower risk of pancreatic toxicity, such as AZT, TDF, ABC.

6. Monitoring of Antiretroviral Therapy

- Patients initiating ART should be followed and have drugs dispensed according the schedule.
- Frequent follow-up visits should be encouraged at the start of ART for more counseling, adherence support and drug toxicity monitoring.
- When patients adhere well to treatment, tolerate the prescribed regimen, and the clinical symptoms improved, the time frequency of follow-up visits and drug dispensary is once a month; for some cases with specific situations, if patients adhere and respond well to treatment, 2-month follow-up visits can be proposed with the agreement of the care and treatment team. More frequent follow-up schedule is needed if patients develop new OIs, experience drug side effects and , need modification of the regimens or in case patients do not comply with therapy. .

- At each follow-up visit, patients are evaluated for clinical progression , have necessary laboratory analyses repeatedappropriate counseling and support provided.. All information should be recorded in patients' medical chartsand OPC log book.

6.1. Clinical monitoring

At each follow-up visit, patients should be assessed clinically, to monitor the clinical course, to identify and manage the drug side effects or the occurrence of new OIs

- Monitor weight, temperature, pulse, blood pressure and activity performance.
- Monitor drug side effects related signs and symptoms.
- Detect new or recurrent OIs; differentiate IRIS or treatment failure for timely and appropriate management.
- Reassess clinical stage.
- Assess possibility of pregnancy for substituting ARV if indicated (not using EFV in pregnant women in the 1st trimester of pregnancy)

Clinical signs of good response to ART:

- Patients gain weight, have good appetite, and are more active.
- Disappearance of OIs and HIV related conditions

6.2. Laboratory monitoring

	Before initiation of ART	**During ARV treatment**			
		4 weeks	**6 months**	**12 months**	**Every 6 months**
CD4	✓		✓	✓	✓
CBC/Hb, ALT	✓		✓	✓	✓
CBC/Hb, if using AZT containing regimen	✓	✓	✓	✓	✓
ALT, if using NVP containing regimen	✓	✓	✓	✓	✓

Creatinin, if using TDF based regimen	✓		✓	✓	✓
Fasting blood lipid, and glucose if using PI containing or other regimens	✓	once a year or when patients present with manifestations of lipodistrophy			
Viral load* (if available)			✓	✓	✓

Note:

During ART monitoring, if patients present with abnormal signs and symptoms, the doctors can request other tests necessary to support diagnosis and treatment.

6.3. Adherence monitoring

The adherence to treatment should be assessed at each follow-up visit.

- Assess the patients' compliance by counting the number of tablets left, by patients self-report, patients' note book, report of supporters (if available), and by clinical course and laboratory analyses..
- Review with the patients drug taking schedule and management when missing a dose.

If patients have not complied with therapy, find out the causes. The patients need careful counseling on how to overcome the problems and barriers, and timely support to achieve good adherence.

Guide for patients in case of missing an ARV dose:

Right after recognizing missing a dose, take immediately the missed dose. Then calculate the time remained from this moment to the next regular dose (in hours):

- If the time remained is **more than 4 hours**, take the following dose at the scheduled time;
- If the time remained is **less than 4 hours**, DO NOT take the following dose at the scheduled time, but wait until it reaches at least 4 hours to take the next dose.
- If more than 2 doses were missed in a week, discuss with treating doctors..

7. Immune Reconstitution Inflammatory Syndrome (IRIS)

7.1. Definition:

Immune reconstitution inflammatory syndrome (IRIS) is characterized by unexpected deterioration in clinical status of HIV-infected patients after the initiation of antiretroviral therapy, due to recovery of immune system.

The nature of IRIS is the overt inflammatory response of newly reconstituted immune system to live microorganisms in the body or the antigens of these agents.

Common manifestations of IRIS may include:

- The occurrence of OIs which were not recognized before starting ART (such as TB, MAC, Cryptococcus meningitis, etc.)
- The excessive deterioration of OIs which have been treated before starting ART.
- The worsening of co-infections (hepatitis B and C) and autoimmune diseases (psoriasis, dermatitis, etc.).

Timing: IRIS typically occurs within 2-12 weeks of initiation of ART, but can do so at latter time.

7.2. Incidence and risk factors

IRIS occurs in about 10% of patients initiating ART. Risk factors for IRIS include:

- Low CD4 cell count before the initiation of ART (IRIS occurs in about 25% of patients with CD4 count below 50 cells/mm3 at initiation of ART).
- History of OIs before initiation of ART. The closer the time of ART initiation to OI treatment, the higher risk of getting IRIS.
- Use of potent ARV regimen (e.g. PI/r based regimen).

To prevent IRIS, patients should be screened and treated for OIs before starting ART, particularly TB.

7.3. Manifestations of IRIS

Opportunistic infections and non- infectious diseases associated with IRIS:

- Mycobacterial diseases: TB (most common), MAC.
- Fungal infections: Cryptococcus neoformans, Penicillium marneffei, PCP.
- Viral diseases: CMV, Herpes simplex and herpes zoster, HBV, HCV, progressive multifocal leukoencephalopathy

- Prozoal diseases: toxoplasmal encephalitis, leishmaniasis
- Non infectious diseases: psoriasis, thyroiditis

7.4. Diagnosis of IRIS

IRIS should be considered in patients after initiation of ART who adhere well to therapy but present with clinical deterioration, especially if patients have been in advanced stage of immunodeficiency with low CD4 count or OIs before starting ART.

AND it is necessary to:

- Exclude drug toxicity, new OIs
- Exclude treatment failure if patients have been on ART for more than 6 months.

7.5. Management of IRIS

- Some IRIS may be mild and resolve without treatment, and no treatment is required.
- Continue ART if patients can tolerate the regimen.
- Treat unmasking OIs according to causes; modify ARV regimen and doses if there is an interaction between ARV and OI drugs (e.g. replace NVP with EFV if patients are on rifampicine based anti-TB therapy and if EFV is available). Resume the original regimen after completion of OI therapy.
- Discontinue ART temporarily only if patients are severe and cannot tolerate the regimen. Follow ART discontinuation procedure if applicable (stop NVP or EFV first; continue with other NRTI drugs for 7 days and then stop). Restart ARVs when inflammatory syndrome is improved and patients can tolerate the drugs.
- Consider corticosteroid therapy in moderate to severe cases of IRIS. Oral or parenteral prednisolone or methyl-prednisolon can be given at 0.5-1,0 mg/kg/day until the patients' condition improves, then taper over 1-2 weeks.
- Provide other interventions if necessary, such as surgical drainage of lymph node abscess, surgical relief of bowel or tracheal obstruction.

8. First-line treatment failure and second-line regimens

8.1. Treatment failure assessment:

Only consider treatment failure if patients have been on 3-drug ART for at least 6 months and are compliant with treatment. Clinical events that occur during the first 6 months of ART usually include OI, IRIS, or drug toxicity.

Criteria for determining1st line treatment failure:

Table 15. Criteria for determining 1st line treatment failure:

Clinical failure	Occurrence or recurrence of stage 4 diseases or conditions after at least 6 months of therapy [a, b]
Immunological failure [c]	– CD4 count returns to or falls below pre-therapy baseline level or – 50% decline from the on-treatment peak value since the initiation of ART (if known); or – CD4 count < 100 cells/mm3 after a year without any increase.
Virological failure[d]	Plasma viral load > 5,000/ml

Note:

a. Some clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, esophageal candidiasis, recurrent bacterial pneumonia) are not considered indicators of treatment failure. Treat these OIs first, and if response is good, continue with 1st line regimen.

b. Some clinical stage 3 conditions (e.g. TB, severe bacterial infections) can be considered indicatiors of treatment failure. TB occurring 6 months after ART is considered as treatment failure when it presents with immunological or virological failure. If these investigations cannot be done, consider treatment failure if patients have other clinical staging 3, 4 conditions or disseminated TB.

c. Concomitant infections can cause transient CD4 cell decrease; treat these infections first, perform CD4 count when patients are stable.

d. Viral load is best indicator for determining treatment failure. Switch to the regimen if viral load is > 5,000 copies/mml at two tests with at least 1 month interval.

8.2. Procedures when treatment failure suspected:

- Reassess patients' adherence. If adherence is poor, provide enhanced counseling and support; reassess treatment failure criteria after patients adhere well to therapy.
- Assess patients' history of ART, if they ever used suboptimal regimen (e.g. low-dosed, regimen with 2 drugs).
- Check if there is any interaction between current ARV regimen and drugs for OI treatment and prophylaxis or other concomitant drugs.
- Check if there are any factors that influence drug absorption, such as diarrhea, vomiting, drug side effects, etc.
- Assess for OIs and other concomitant conditions, provide timely management.
- Exclude CD4 changes due to variation in performance of CD4 count machines or testing CD4 by different machines.
- If patients present with clinical and immunological failure, viral load testing should be performed if possible before switching to second- line regimen
- Consultantation with ART experts should be conducted when diagnosing treatment failure and switching to second- line regimen considered

8.3. Guide for switching to second-line regimen

Decision to switch to 2nd line regimen is based on integrated consideration of clinical, immunological and viral criteria[a] (if available).

Table 16: Integrating clinical status, CD4 cell count and viral load to guide switching

Treatment Failure Criteria	Clinical Stage 1 and 2	Clinical Stage 3	Clinical Stage 4
CD4 failure (Viral load testing not available)	Do not switch Follow patient for development of clinical signs or symptoms. Repeat CD4 cell count in three months.	Consider switching to second-line regimen.	Switch to second-line regimen.

CD4 and virological failure	Switch to second-line regimen.	Switch to second-line regimen.	Switch to second-line regimen.

8.3.1 Choice of 2nd line regimen:

<table>
<tr><th>1st line regimen</th><th colspan="3">2nd line regimen</th></tr>
<tr><td>d4T/AZT + 3TC + NVP or EFV</td><td>TDF + 3TC (± AZT)
or ddI + ABC</td><td rowspan="3">+</td><td rowspan="3">LPV/r</td></tr>
<tr><td>TDF + 3TC + NVP/EFV</td><td>ddI + ABC
or
AZT + 3TC</td></tr>
<tr><td>AZT or d4T + 3TC +
TDF or ABC</td><td>EFV or NVP + ddI</td></tr>
</table>

- Alternative PI for LPV/r is ATV/r heat stable tablets
- If patients have history of using multiple ARVs in the 1st line regimen, the virus may be already resistant to 2nd line drugs. Do genotyping if possible to guide choice of appropriate regimen.

Toxicity of ARVs of second -line regimens and management

Drugs	Side effects or toxicity	Management
TDF	Renal toxicity Influence into bone growth	Give lower TDF dose when patients have renal failure. Replace TDF by ABC. Avoid using TDF in pregnant women and children.

ddI	Lactic acidosis Pancreatitis Peripheral neuropathy, Fat redistribution: loss of subcutaneous fat (in the face, arms, legs), and central fat accumulation (in visceral, breast, abdomen, neck); increase in blood lipids; alteration in glucose metabolism	Discontinue ART; provide supportive treatment and laboratory monitoring Restart ART when patients are completely stabilized; replace ddI by appropriate NRTI
ABC	Hypersensitivity: commonly occurs in the first 6 weeks of treatment; manifestations: diffuse rash (may presents without rash); fever, fatigue; nausea, vomiting, diarrhea; difficult breathing, cough, sore throat; increase ALT, phosphatasa, LDH	Discontinue ABC and **never give it again** (re-challenge is associated with cardiovascular collapse and death). Give symptomatic treatment
LPV/r	Hepatitis	Assess severity of ALT increase (annex 7). If grade 1, 2: continue with regimen and monitor. If grade 3: change to other PI if available. If grade 4: discontinue ART and monitor; after patient improves, re-start ART, change LPV/r to other PI
	Lipodystrophy: fat accumulation (internal organs, breast, neck); increase in blood triglyceride; disturbance in glucose metabolism (insulin-resistant diabetes mellitus and increased risk of cardiovascular diseases, pancreatitis).	Grade 1 or 2 increase in cholesterol and triglyceride - apply diet, physical exercises and monitor. Grade 3 or 4 - use fibrate drugs (fenofibrate 600mg 1-2 times/day); treat hypecholesterolemia with statin drugs (do not use simvastatin due to interaction with PI).
ATV/r	Elevated indirect- bilirubin,	Usually asymptomatic or mild jaundice without ALT elevation. Replace ATV by other PI
	Central fat accumulation (internal organs, breast, neck; increase in cholesterol and triglyceride, insulin-resistant diabetes mellitus and high risk of cardiovascular diseases, pancreatitis	Management of side effect due to LPV/r

	1st degree atrio-ventricular block (prolonged PR on ECG)	Use with caution in patients with underlying conduction disturbances or on concurrent use of drugs causing prolonged PR

8.3.2. Dosage and administration of 2nd line regimen:

Before switching to 2nd line regimen, it is necessary to:

- Counsel patients to reinforce the adherence to therapy; give the second line regimen when the patients show ability to adhere to the regimen.
- Treat clinical events (stage 3, 4 manifestations).
- Counsel carefully on the new regimen.

Dosage and administration of 2nd line drugs:

- *Tenofovir (TDF):* 300mg once a day p.o.
- *Abacavir (ABC):* 300mg b.i.d orally, every 12 hours or 600mg once daily
- *Didanosin (ddI):* for patients < 60kg – 250mg once a day p.o.; ≥ 60kg – 400mg once a day p.o.
- *Lopinavir/Ritonavir (LPV/r):* 400mg/100mg b.i.d, every 12 hours; LPV/r (capsule) should be taken on full stomach; for LPV/r tablets. : no diet restriction.
- *Atazanavir/Ritonavir (ATV/r):* 300mg/100mg once daily p.o.
- *Lamivudine (3TC) and Zidovudine (AZT):* dosage and administration are similar to that of 1st line regimen.

8.4. Monitoring patients who are on 2nd line regimen:

- Ensure treatment adherence
- Monitor the drug interactions when using LPV/r
- Assess clinical and CD4 response similarly to that of 1st line regimen

9. Antiretroviral therapy for patients with specific conditions:

9. 1. ART for patients with TB/HIV co-infection

- Patients with TB/HIV co-infection have higher risk of death than those with HIV alone, and therefore need timely initiation of ART.
- As TB/HIV co-infected patients often have to take multiple tablets, treatment adherence, interaction between ARV and TB drugs (such as rifampicin) and risk of hepatoxicity should be taken into account.

9.1.1. Initiation of ART in HIV/TB co-infected patients:

9.1.1.1. *Criteria for initiating ART in HIV/TB patients:*

a. The patients are ART naïve and CD4 count available:

Table 18: Initiation of ART for TB patients with CD4 count available

CD4	Management
CD4 >350 cells/mm^3	Start TB therapy first. Assessfor ART after intensive phase or after completion of TB treatment. If the patient is at clinical stage 4, ART can be started after the patient tolerates TB drugs (between 2 to 8 weeks of TB treatment).
CD4 250- 350 /mm^3	Start TB therapy first. Start ART after completion of intensive phase of TB therapy. If the patient is at clinical stage 4, ART can be started after the patient tolerates TB drugs (between 2 to 8 weeks of TB treatment).
CD4 < 250 /mm^3	Start ART as soon as possible, after the patient tolerates the TB drugs (between 2 and 8 weeks of TB treatment).

b. The patients are ART naïve and CD4 count not available:

Table 19: Initiation of ART for TB patients without CD4 count

Clinical status	Management
Pulmonary TB only (no other clinical stage 3 or 4 conditions)	- Complete intensive phase of TB therapy, then assess for ART.
Pulmonary TB with other clinical stage 3 conditions	- Start TB therapy first. - Start ART after completion of intensive phase of TB therapy.
Pulmonary TB with other clinical	- Start TB therapy first.

stage 4 conditions Extra-pulmonary TB.	- Start ART as soon as possible, after the patient tolerates TB therapy (between 2 and 8 weeks).

9.1.1.2. Choice of 1st line ARV regimen for HIV/TB patients:

Table 20: 1st line regimens for HIV/TB patients starting ART

Patients on TB therapy with rifampicin and starting ART: *Preferred 1st line regimens:* AZT/d4T + 3TC + EFV *Alternative regimens:* ▪ If EFV is not available, or for women in the first trimester of pregnancy, and CD4< 250 cells/mm3 AZT or d4T + 3TC + NVP ▪ For women in the first trimester of pregnancy, and CD4 > 250 cells/mm3 AZT + 3TC + NVP with closed monitoring for side effects; or AZT + 3TC + ABC or AZT + 3TC + LPV 400mg/RTV 400 mg ▪ For patients not tolerating NVP and EFV: AZT + 3TC + TDF Note: Avoid using this regimen for pregnant women, if possible. Dose: The same as for HIV patients without TB, increase RTV dose from 100mg to 400 mg.
Patients on TB therapy without rifampicin: use the 1st line regimens as for patients without TB

9.1.2. TB occuring in patients who are on ART:

TB occuring in patients while they are on ART can be IRIS (during first 6 months), new infection, or treatment failure.

9.1.2.1. TB occuring in patients while on ART

- Treat TB in accordance with national TB guidelines. Modify ARV regimen if necessary.

Table 21: ART for TB patients on rifamicin regimen

Current ART regimen	Preferred ART regimen for patients on TB therapy with rifampicine
First-line ART Regimens	
d4T or AZT + 3TC + EFV	– Continue with EFV-based regimen
d4T or AZT + 3TC + NVP	– **Replace NVP with EFV** – If EFV not available, or the patients are pregnant women, or patients cannot tolerate EFV, continue NVP-containing regimen at normal doses, but monitor closely for clinical symptoms of hepatitis and liver enzyme level every 2 weeks, or – Change to AZT + 3TC + TDF regimen
2nd line regimens	
2 NRTI + LPV/r	Switch to or continue (if in use) 2nd line regimen with LPV 400 mg/ RTV 400 mg

– If patients are too severe to continue the ART, discontinue the regimen temporarily and give anti-TB drugs. When patients' condition is stabilized, resume the original ART regimen with consideration of drug interactions (see Annex 5).

– When patients complete rifampicin therapy, consider resuming NVP; in this case, restart with full dose of NVP 200mg, twice per day.

9.1.2.2. Choice of 2nd line ARV regimen for TB patients who have 1st line regimen treatment failure:

– The 2nd line regimen for patients on TB therapy with rifampicin is similar to that for patients without TB with the dose of ritonavir increased: LPV 400mg/RTV 400mg.

– Monitor the patients closely to detect liver toxicity.

9.2. Antiretroviral therapy for HIV patients with viral hepatitis B and/or hepatitis C co-infection:

- The criteria for ART eligibility for patients co-infected with hepatitis B and hepatitis C are the same as for other HIV-infected patients.
- Pay special attention to drug interactions and hepatoxicity in choosing the appropriate ARV regimen.

9.2.1. ART for HIV/HBV co-infection

9.2.1.1. Choice of ARV regimen for HIV/HBV co-infected patients:

Preferred first line regimens: AZT or d4T + 3TC + EFV

Alternative regimens: AZT or d4T + 3TC + NVP

Note:

- EFV is the preferred NNRTI for HIV/HBV co-infected patients, patients with clinical hepatitis or increase in ALT.
- When EFV is not available, NVP can be used for patients with increased ALT with closed monitoring.
- For patients taking NVP, when ALT increases to grade 3 or 4, NVP should be replaced by EFV , TDF or LPV/r

9.2.1.2. Management of HBV hepatic flare when patients are on ART:

Hepatic flares may occur in patients with HIV/HBV co-infection in the first several months of ART as part of IRIS, or as consequences of discontinuation of ARV drugs which also have effect on HBV virus (e.g. 3TC, TDF).

- Manifestations: rapid increase in liver enzyme levels, with signs and symptoms of hepatitis (such as fatigue, abdominal pain, and jaundice). Sometimes it is very difficult to make differentiation with hepatoxicity due to ARV drugs.
- If ALT increases to grade 3 and the clinical status of the patients is stable, continue ART with less hepatotoxic drugs, such as EFV; monitor closely ALT levels (every 2 weeks) and clinical symptoms;
- Monitor closely HIV/HBV coinfected patients if they have to stop ARV drugs, including 3TC, TDF.

9.2.2. Antiretroviral therapy for HIV/HCV co-infected patients:

Choice of ARV drugs is similar to HIV-infected patients without hepatitis C, and EFV is preferred NNRTI.

Notes on using ARV drugs in patients with HIV/HCV co-infection:

- ARVs have no activity against HCV.
- Treat hepatitis C with interferon and ribavirin (RBV), if possible. AZT concentration is increased when used concomitantly with RBV; monitor the AZT toxicity closely. Good response to hepatitis C treatment is observed when patients' CD4 count is more than 200 cells/mm3.

9.2.3. Antiretroviral therapy for patients with high ALT at baseline or unknown HBV, HCV hepatitis status:

- Do ALT testing for all patients before starting ART as regulated.
- Screen for HBsAg and anti-HCV before starting ART or when ALT increases, if feasible.
- When patients' ALT increases with known or unknown HBV, HCV status, EFV based regimen should be used.

9.3. Antiretroviral therapy for injecting drug users (IDUs)

9.3.1. Principles of Antiretroviral therapy in IDUs:

- Criteria for initiating ART for IDUs are similar to other HIV-infected patients.
- Do not delay ART for patients with history of or current IDU.
- Ensure the treatment readiness for patients and their treatment supporters, including readiness to adhere to therapy; provide supportive counseling during treatment.
- Special attention should be paid to drug interaction between ARV and opioid substitution therapy drugs (e.g methadone) and risk of hepatoxicity, especially in IDUs with HBV/HCV co-infection.

9.3.2. Choice of ARVs for HIV infected IDUs.

Choice of 1st line regimen drugs is similar to that for other patients, and includes:

Preferred first line regimens: AZT or d4T + 3TC + NVP

Alternative regimens: AZT or d4T + 3TC + EFV

Notes:

- Screen for HBsAg and anti HCV prior to initiation of ART, if possible. If patients have increased ALT and/or HBsAg (+) and anti-HCV (+): see section on ART for patients with HIV/HCV/HBV co-infection.

- EFV/ NVP decrease the plasma levels of methadone in patients taking methadone substitution therapy, which may precipitate symptoms of opiate withdrawal. Consider increasing doses of methadone.
- Choice of 2nd line regimens is similar to that for other patients; note that LPV and RTV decrease the plasma levels of methadone, resulting in opioid withdrawal syndrome in patients on methadone substitution therapy.

9.3.3. Treatment support:

- Support the patients to stabilize the life and support the adherence to therapy through the help of families, peer groups, healthcare workers, and social support services including vocational support, micro-credit and job creation program.
- Apply DOT (direct observation therapy) approach if possible and if necessary. This activity is easier to be carried out in social support centres.
- Introduce harm reduction intervention programs including outreach services, condom supplies, clean needle and syringe provision, opioid substitution therapy with methadone.
- Coordinate with drug rehabilitation centres and prisons to ensure continuation of treatment for patients on ART being referred from community to closed settings.

VII. ANTIRETROVIRAL THERAPY IN PREGNANT WOMEN AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV (PMTCT)

Principles

- HIV status of pregnant women need to be defined early for timely application of measures to prevent the transmission of the virus to the babies, which include ARV prophylaxis , substitution feeding for the infant and referral for postpartum care and treatment services.
- HIV-infected pregnant women need referral and consultation with HIV/AIDS care facilities for assessment if they are eligible for ART or need ARV prophylaxis for PMTCT.
- Pregnant women are given priority in ART when eligible. The preparation period for ART can be shorten to ensure timely and effective ARV prophylaxis to prevent MTCT.
- Use the most effective regimen for PMTCT. After delivery, the mother need eassessment for clinical and immunology status for ART. If not yet eligible, stop ARV; if eligible, use ART regimen as for other HIV infected adults.

1. ARV therapy for HIV-infected pregnant women

ART for pregnant women is long-term use of ARV to treat HIV infection for the health of pregnant women themselves as well as to prevent transmission of HIV to their babies.

1.1. Initiating ART in pregnant women

1.1.1. Criteria for ART initiation in pregnant women:

The criteria for initiating ART in HIV-infected pregnant women are similar to that for non-pregnant HIV positive adults, as follows:

Criteria for initiation of ART in pregnant women:

- Clinical stage 4: commence ART regardless of CD4 cell count
- Clinical stage 3: commence ART when CD4 < 350 cells/mm3
- Clinical stage 1, 2: commence ART when CD4 < 250 cells/mm3

If CD4 count is not available, ART should be given when pregnant women are at clinical stage 3 or 4

1.1.2. ARV regimens for HIV-infected pregnant women

Preferred regimen:

AZT + 3TC + NVP

- Use during pregnancy, intra-partum and postpartum. Dosage of ARVs for pregnant women is similar to that for other HIV-infected adults.
- Monitor closely ALT level, especially in pregnant women with CD4 from 250 – 350 cells/mm^3. ALT test should be done before starting ART, every 2 weeks in the first month, , once per moth from the second to fouth months and then once every 3 months thereafter. Change to appropriate regimen if patient has hepatotoxicity ;

Alternative regimen:

- When AZT cannot be used: Replace AZT with **d4T or ABC**
- When NVP cannot be used because of hypersensitivity or toxicity, use one of the following options in the priority order:

  + AZT + 3TC + EFV (if gestation age > 12 weeks); or

  + **AZT + 3TC +LPV/r;** or

  + **AZT + 3TC + ABC**

Note:

- HIV-infected pregnant women with active TB and on TB treatment with rifampicin should have drug interaction with NVP or toxicity of EFV in the first trimester of pregnancy considered when selecting ARV regimen (see the Section of ARV treatment for patients with TB/HIV).
- After birth, the mother can continue the same regimen or change to the preferred first line regimen.

1.2. Women who become pregnant while receiving ART

Women who become pregnant while receiving ART: continue original ARV regimen, with the considerations:

- Ifthe women are using EFV and gestation age is <12 weeks: replace EFV with NVP (use 200mg twice a day without lesd-in dose) or appropriate alternative regimens. Counsel on risk of HIV infection with children and discuss the plan of keeping/not keeping fetus with pregnant women.
- EFV based regimen can be continued during 2nd and 3rd trimesters of pregnancy.

1.3. ARV prophylaxis regimen for children borne to mothers who have been taking antiretroviral therapy

If the mothers have been on ART > 4 weeks:

AZT syrup 4mg/kg b.i.d x 7 days

If the mothers have been on ART < 4 weeks:

AZT syrup 4mg/kg b.i.d x 4 weeks

1.4. ART Regimen for post-partum women who had been provided single dose of NVP for PMTCT:

- If the woman meet treatment criteria within 6-12 months after delivery:
  + Use standard 1st line regimen as for other HIV infected adults (see Section on ART for adults)
  + Use AZT + 3TC + TDF; or replace NVP by EFV or LPV/r to avoid drug resistance
- If the woman meet treatment criteria for ART after6-12 months after delivery: use standard 1st line regimen as for other adults.

2. Antiretroviral prophylaxis for preventing mother-to-child transmission of HIV

Antiretroviral prophylaxis for PMTCT is short term use of antiretroviral drugs to prevent the transmission of HIV from HIV-infected pregnant women to their babies.

2.1. Who needs prophylaxis with ARV for PMTCT

- HIV-infected pregnant women not eligible for antiretroviral therapy (those with clinical stage 1-2 and CD4>250 cells/mm3, clinical stage 3 and CD4>350 cells/mm3), or;
- HIV-infected pregnant women eligible for ART, but cannot access ART service or;
- HIV-infected pregnant women not attending antenatal care services or being diagnosed with HIV late during labor and delivery.
- Infants born to HIV positive women

2.2. PMTCT ARV regimens for the mother and newborn

2.2.1. Preferred regimen: AZT + single dose of NVP:

This regimen is given to all HIV (+) pregnant women in antenatal care facilities to prevent HIV transmission from mother to child.

Table 22: Use of AZT + single dose NVP regimen for PMTCT

Mother	**AZT** 300mg b.i.d from week 28 (or as soon as possible thereafter when women are diagnosed with HIV) until labour
Antepartum	
Intrapartum	At the beginning of labour: **NVP** 200mg **+ AZT** 600mg **+ 3TC** 150mg Then **AZT 3**00mg + **3TC** 150mg every 12 hours until delivery
Postpartum	**AZT** 300mg **+ 3TC** 150mg every 12 hours for 7 days
Infants	If the mothers have been on AZT > 4 weeks before birth **Single dose NVP** 6mg, immediately after birth **+ AZT** 4mg/kg b.i.d. x 7 days If the mothers have been on AZT less than 4 weeks before birth **Single dose NVP** 6mg, immediately after birth **+ AZT** 4mg/kg b.i.d. for 4 weeks

Note: Side effect of AZT is anemia, which is not commonly seen in pregnant women with short duration of treatment. Monitor the clinical manifestation of anemia and Hgb level closely, give treatment if needed.

2.2.2. ARV PMTCT regimens if pregnant women diagnosed with HIV during labour:

ARV prophylaxis is indicated when HIV infected pregnant women have not been monitored during pregnancy, or pregnant women diagnosed with HIV lately during labour and at delivery.

Table 23. ARV regimens for PMTCT if the mother appear at labour

Mother	At the beginning of labour: **NVP** 200mg **+ AZT** 600mg **+ 3TC** 150mg Then **AZT 3**00mg + **3TC** 150mg every 12 hours until delivery
During labour	

Postpartum	**AZT** 300mg **+ 3TC** 150mg every 12 hours for 7 days
Infants	**Single dose NVP** 6mg, immediately after birth **+ AZT** 4mg/kg b.i.d. for 4 weeks

Note:

a. *Pregnant women with a positive HIV screening test at labor should be counseled and provided with an appropriate PMTCT ARV regimen; confirmation of infection can be performed later. If the HIV status is not confirmed, stop ARV and other PMTCT intervention.*

b. *Do not give ARV prophylaxis to mothers if delivery is expected to happen within 1 hour; the infants should be provided with ARV as above.*

c. *If AZT is unavailable, give mother single dose NVP during labour and the infants single dose NVP after birth.*

3. Other interventions and referral for the mothers and their infants to care and treatment services after birth

3.1. Interventions for the mothers:

a. Before delivery:

- Give adequate counseling before and after HIV testing
- Counsel on nutrition during pregnancy and on feeding of the baby after birth
- Counsel on psychosocial support
- Train for ARV treatment readiness and ARV adherence

b. During delivery:

- Follow strict measures of aseptics in obstetrics
- Avoid procedures such as amniocentesis, cesarean section, placing electrodes on the fetus' head, etc.
- Wash the newborn right after birth.

c. After delivery:

- Dispense adequate dose of ARV the mother if the mother and infant can be discharged early
- Refer the mother to adult HIV care and treatment facilities for longterm care

3.2. Interventions for the infants:

a. Dispense adequate dose of ARV to the infant and instructing the mother or care-giver about ART adherence. Schedul follow-up visits for dispensing drugs and further counseling if necessary

b. Counsel on Feeding interventions:

- Counsel the mothers about the benefit of breastfeeding and the risk of HIV transmission with breast feeding. Use full replacement feeding for infants if available (source of milk, clean water, food hygiene).
- If breast feeding, counsel adequately on:
    - Feeding position, how to hold the nipples and how to manage when the nipples fissure and breast abscess occurs.
    - Weaning as soon as possible to avoid risk of mother to child HIV transmission.

c. Refer the infant to:

- HIV care and treatment facilities for children, for longterm care and monitoring when the infant is 4-6 weeks of age
- If the infant is orphaned, encourage the family to continue care or refer the child to an orphanage.

VIII. POST-EXPOSURE PROPHYLAXIS

1. Post-occupational exposure prophylaxis

Occupational exposure to HIV is considered when direct contact with HIV contaminated blood or body fluids occurs, which can result in transmission of HIV.

1.1. Modes of exposure:

- Needle stick injuries while performing injection, taking blood sample, body fluid tapping, etc
- Injuries from surgical scalpels and other sharp instruments that have patient's blood or body fluids on.
- Percutaneous injuries from broken tubes which contain patient's blood or body fluids.
- Pre-existing skin lesions (eczema, burn, old ulcers, and inflammation of skin) or mucous membrane (of the eyes, nose and throat) contaminated with patient's blood or body fluids.
- Others: contaminated needle stick injuries when chasing criminals, etc…

1.2. Protocol for post-exposure management

Post-exposure management includes the following steps:

1. Treatment of exposure site
2. Report the exposure to the manager and complete the report form (fill in all the information as required in the Exposure record)
3. Assess the risk of exposure according to the severity of injury and contact.
4. Determine the HIV status of the source of exposure
5. Determine the HIV status of the exposed person.
6. Counsel the exposed person.
7. Provide ARV prophylaxis for the exposed person

a. Treat the exposure site:

- Bleeding wound of the skin:
    + Flush the wound with tap water
    + Let the wound bleed for a short time, do not squeeze
    + Clean the wound thoroughly with soap and water
- Eye exposure: Wash the eyes with distilled water or NaCl 0.9% solution continuously for 5 minutes.
- Mouth and nose exposure:
    + Rinse the nose with distilled water or NaCl 0.9 % solution.
    + Gargle with NaCl 0.9 % solution for several times.

b. Report to the manager and complete the report form:

Indicate the date, time and the context of exposure, describe the wound and assess the level of risk. Get the signatures of the witnesses and the supervisor.

c. Assess the risk of exposure:

- Risk presents with:
    + Bleeding percutaneous wounds caused by containing blood needles: the risk is higher in case of deep wounds caused by large-bore needle containing a lot of blood compared with that of shallow wounds from fine needles with less blood.
    + Deep percutaneous wounds caused by scalpels or broken tubes containing patient's blood and body fluids.
    + Existing lesions, ulcers or scratches on the skin or mucus membranes exposed to patient's blood and body fluids (even when the status of ulcers is unclear): the risk is higher with large ulcers or scratches.
- No risk: normal skin exposed to patient's blood or body fluids.

d. Determine the HIV status of the source of exposure

- If the source patient is HIV (+): get information on the use of and response to ARV treatment
- If the HIV status of the source is unknown: provide counseling and perform HIV test
- In some cases it is impossible to identify the HIV status of the source (being exposed while on duty, the subject ran away).

e. Determine the HIV status of the exposed person.

- Provide pre-test and post-test counseling as regulated
- If the exposed person has positive test result right after the exposure incident: HIV infection occurred before, not due to the exposure incident
- If HIV (-): HIV test is required after 3 months and 6 months.

g. Counsel the exposed person on:

- Risk of infection with HIV, HBV, HCV
- Information and services of the prophylaxis, its benefits and risks.
- Side effects of ARV and signs of primary HIV infection: fever, rash, nausea or vomiting, anemia, lymphadenopathy, etc...
- Prevention of HIV transmission to others: exposed person may transmit HIV to others even if the test is negative (the window period) and they, therefore should practice all prevention measures
- Adherence to treatment and psychological support

h. ARV prophylaxis for the exposed person

Indications: Provide ARV treatment as soon as possible, best within 2 – 6 hours after and before 72 hours after the exposure to all exposure cases with risk. At the same time, assess the HIV status of the source of exposure and the exposed person.

- If the source of exposure is HIV (+): continue the treatment.
- If the source of exposure is HIV (-): it is possible to discontinue the treatment. If the source is suspected as having risk factor and is in the period window, the treatment should be continued..
- If the exposed person is HIV (+): do not provide prophylaxis, refer for follow-up and provide treatment as a normal HIV positive case.
- If the exposed person is HIV (-): continue the treatment.

- Exposure with no risk: no treatment is needed
- If the HIV status of the source of exposure cannot be determined: treat as a case of exposure to the HIV (+) source.

Table 24: Treatment of post-exposure prophylaxis with ARV

	Medications	**Indications**
2 drug regimen (basic regimen)	AZT + 3TC *or* d4T + 3TC	All exposures with risk
3 drug treatment regimen	AZT + 3TC *or* d4T + 3TC *plus:* LPV/r	In case the source of exposure is known with or suspected of ARV resistance
Duration of treatment	4 weeks	

i. Follow-up

- Monitor the side effects of ARV:
- Inform the person on post-exposure prophylaxis about the possible side effects, not to stop taking the medications if the side effects are minor, and visit the treatment doctor as soon as severe side effect(s) occur(s).
- Do CBC and ALT tests on the start of the treatment and after 4 weeks.
- Do HIV test after 3 and 6 months.
- Provide psychological support if needed

2. Non-Occupational Post-Exposure Prophylaxis:

2.1. Definition:

Non-Occupational Exposure is the exposure to blood, body fluid which happens outside of the occupational settings and can result in transmission of HIV.

2.2. Non-Occupational Exposure situations:

- Sexual exposure: Having sex without using condom or the condom slips or breaks down, sexual assaults
- Sharing syringe and needle with injecting drug user (single time);
- Injuries from discarded needles that have visible blood stain on them
- Human bites

2.3. Cases not considered for HIV prophylaxis:

- Post-exposure prophylaxis should not be prescribed for people who repeatedly expose to HIV such as having sex with HIV infected persons, or being sex workers but rarely use condom, injecting drug users that frequently shares syringes and needles.

2.4. Factors requiring assessment for persons who may be exposed to HIV in the non-occupational settings.

- HIV status.
- Situation, frequency and time of exposure. Try to assess the HIV status of the source.
- HIV pre-test counseling.
- Perform HIV and pregnancy testing if needed

2.5. Assessment of the HIV status of the source

If the HIV status of the source is unknown, try to do HIV test. It is possible to start the prophylaxis, and then stop if the source is confirmed as HIV negative.

When the source comes from the population groups with known high HIV prevalence (such as MSM, IDUs, or sex workers), or the person has been sexually assaulted and the HIV status of the source is difficult or impossible to be identified, it is necessary to prescribe prophylaxis after assessing the risks and providing counseling to the exposed person.

2.6. Post-exposure prophylaxis with antiretrovirals:

The procedure for ARV prophylaxis for the non-occupational exposure is similar to that one after occupational exposure; it should be initiated as soon as possible, within 72 hours after the exposure and continued for 28 days. Two-drug ARV regimen should be used.

If the source of exposure has history of taking ARV at presence or in the past, or is known as failing first line regimens, it is recommended to prescribe 3 drug regimens.

Provide counseling on the side effects and treatment adherence prior to prophylaxis.

2.7. Monitoring and support counseling

- Explain about the plan of monitoring and testing after 1, 3, and 6 months, counsel on adherence to treatment during the ARV prophylaxis.
- Counsel on not giving blood, practicing safe sex and safe injection, and non-breastfeed until the HIV status is confirmed or risk is eliminated.
- Counsel on Hepatitis B vaccination if the person is Hepatitis B free, has not been vaccinated or does not have antibody to HBV.
- Counsel on avoiding further exposure to HIV

PART B - DIAGNOSIS, TREATMENT AND CARE FOR CHILDREN LIVING WITH HIV/AIDS

I. DIAGNOSIS, CLINICAL AND IMMUNOLOGICAL STAGING OF HIV INFECTION IN CHILDREN

1. Diagnosis of HIV infection in children

1.1. Diagnosis of HIV infection in infants less than 18 months of age

HIV infection in infants less than 18 month of age, including HIV exposed children (children born to HIV infected mother) and HIV suspected cases is diagnosed on the basis of Polymerase Chain Reaction (PCR for DNA or RNA of virus.

Perform diagnosis followed the Ministry of Health guidelines on diagnosis of HIV infection in infants under 18 months of age

1.1.1. Diagnosis of HIV infection in HIV-exposed infants under 9 months of age

Perform the virological test when the infant is 4-6 week of age, or as soon as possible thereafter .

If the first PCR test is positive, 2nd PCR should be performed to confirm diagnosis of HIV infection, along with clinical assessment for preparation of ARV treatment

If the first PCR test is negative, or 2nd confirmatory test is negative, continue to monitor the child and perform HIV antibody test at age 18 months to confirm/rule out HIV status

If the first PCR test is negative and the infant is breastfed (or stop breastfeeding less than 6 weeks prior to test), PCR test should be perform when infant stop breastfeeding completely for more than 6 weeks.

During follow up, if infants have any sign or symptom suggestive of HIV infection, HIV antibody test should be performed. In case antibody test is positive, PCR test should be performed immediately.

1.1.2. Diagnosis of HIV infection in HIV-exposed infants from 9 to 18 months of age

Perform HIV antibody test first. If the test is positive, PCR should be followed as for infants under 9 months of age to confirmthe diagnosis.

1.2.3. Diagnosis of HIV infection in children under 18 months of age with unclear exposure but having HIV suspected signs:

Follow the guideline for HIV-exposed infants from 9 to 18 months of age

1.2. Presumptive Diagnosis of severe HIV infection (stage IV) in infants less than 18 months of age

Presumptive diagnosis of severe HIV infection is applied when the virological testing is not available, and the infant has:

- PositiveHIV antibody test, AND
- One of the clinical stage 4 diseases or conditions, such as PCP, cryptococcal meningitis, Toxoplasma encephalitis, unexplained severe wasting, extra-pulmonary tuberculosis (excluding axillary lymph node TB as complication of BCG), esophageal candidiasis,

OR

- The infant has at least 2 out of the 3 signs:
  1. Oral thrush (in infants older than 1 month of age)
  2. Severe bacterial pneumonia
  3. Severe sepsis.

Other indicators suggestive of severe HIV/AIDS, such as:

- The mother died from an HIV-related disease, or
- The mother is at advanced HIV/AIDS, or
- CD4 < 20%

Perform HIV diagnosis by virological testing as soon as possible.

1.3. Diagnosis of HIV infection in children ≥18 months of age

HIV infection in children older than 18 months is diagnosed by the serological testing for HIV antibody. HIV infection is diagnosed if the serum sample is reactive in all three anti-HIV antibody tests, which rely on different antigens or of different operating characteristics

Note: *Only laboratories designated by MoH are authorized to inform the HIV positive test results.*

2. HIV infection staging

A child with confirmed diagnosis of HIV infection needs to be assessed for the clinical stage at each follow-up visit and the immunological stage every 6 months (infants with presumptive diagnosis of severe HIVinfection should also have immunological test performed) .

2.1. Clinical staging:

An HIV infected child is classified into 1 of 4 clinical stages, depending on the symptoms and the most severe HIV-associated diseases presented.

Table 1: Clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1: Asymptomatic
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2: Mild symptoms
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infections
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulcerations
Unexplained persistent parotid enlargement[1]
Herpes zoster (Zona)
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Clinical stage 3: Advance symptoms
Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained persistent diarrhea (over 14 days)[1]
Unexplained persistent fever[1] (above 37.5ºC constant or intermittent for longer than 1 month)
Persistent oral candidiasis (after the first 6–8 weeks of life)

[1] Unexplained refers to where the condition is not explained by other causes

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis

Lymph node TB

Pulmonary TB

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis.

Unexplained anemia (<80 g/L), granulocytopenia (<0.5 x 10^9cells/L) or chronic thrombocytopenia (<50 x 10^9 cells/L)[1]

Clinical stage 4: Severe symptoms

Unexplained severe wasting, stunning or severe malnutrition not responding to standard therapy.

Pneumocystis jiroveci pneumonia *(or PCP- Pneumocystis Carinii Pneumonia)*

Recurrent severe bacterial infection (such as empyema, pyomyositis, bone or joint infection, excluding pneumonia).

Chronic herpes simplex infection (orolabial or cutaneous herpes of more than one month's duration or visceral herpes at any site)

Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extra pulmonary tuberculosis

Kaposi's Sarcoma

Cytomegalovirus infection: retinitis or CMV infection affecting other organs, with onset at age > 1 month.

Central nervous system toxoplasmosis (after one month of life).

Extra pulmonary cryptococcosis (including meningitis)

HIV encephalopathy

Disseminated mycosis (endemic fungi such as penicillium, histoplasma)

Disseminated non-tuberculous mycobacterial infections.

Chronic cryptosporidiosis (with diarrhea)

Chronic isosporiasis

Cerebral or B cell non- Hodgkin lymphoma

Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy.

2.2. Immunological staging

The immune status of the HIV infected children is assessed by the absolute number or percentage (%) of CD4 cells (percentage is applied for the children under 5 years of age)

Table 2: HIV/AIDS immunological staging for children with confirmed HIV infection

HIV-associated immuno-deficiency	Percentage of CD4 (or the absolute number of CD4/mm^3)			
	<11 months	12–35 months	36 –59 months	> 5 years (cells/mm^3)
Not significant	>35 %	>30 %	>25 %	> 500 cells/mm^3
Mild	30-35 %	25-30 %	20-25 %	350 – 499 cells/mm^3
Advanced	25-29 %	20-24 %	15-19 %	200 – 349 cells/mm^3
Severe	<25 % <1500 cells/mm^3	<20 % <750 cells/mm^3	<15 % <350 cells/mm^3	<15% < 200 cells/mm^3

If the CD4 count is not available, it is possible to assess the severity of the immunodeficiency based on the total lymphocyte count (TLC) for the children with clinical stage 2 or higher, but is not applied for monitoring the response to ART.

Table 3: Diagnosis of severe immunodeficiency by total lymphocyte count

HIV-associated severe immunodeficiency	Age-related total lymphocyte count cells/mm^3			
	<11 months	12- 35 months	36- 59 months	≥ 5 years
Total lymphocyte count	<4,000	<3,000	<2,500	<2,000
CD4 count	<1,500	<750	<350	<200

3. Diagnosis criteria of advanced HIV infection (including AIDS)

- Any clinical stage 3 or 4 disease (confirmed or clinical diagnosis).

and/or

- CD4 count (or total lymphocyte count if the CD4 count not available) below the age-related thresold of advanced and severe immunodeficiency.

AIDS in a child with confirmed HIV infection is defined as clinical diagnosis (presumptive or definitive) of any stage 4 condition or the CD4 count below the age-related level of severe immunodeficiency.

II. CLINICAL MANAGEMENT OF HIV EXPOSED INFANTS AND CHILDREN WITH CONFIRMED HIV INFECTION

1. Initial assessment:

1.1. Clinical and laboratory assessment

1.1.1. Taking present history and previous medical history:

- HIV history of the parents and measures to prevent mother-to-child transmission
- History of ARV use of mother and infant (reasons for use, duration, specific regimen, treatment adherence)
- If the infant is diagnosed with HIV infection, ask for place of test, testing time and method used
- History of prophylaxis with co-trimoxazole and immunization
- History of opportunistic infections and history of TB in the family
- History of drug allergy to antibiotics such as cotrimoxazole and ARVs, etc.
- History of feeding (breastfeeding or use of formula, nutritional issues); physical and mental development.
- Recently occurred signs and symptoms

1.2.2. General and physical examination:

- Assess general condition, physical development (age-related height, weight, head circumference, motion), mental development and awareness.
- Overall vital signs, skin and mucocutaneous lesions

- Assessthe status of respiratory, circulatory, neurologic organs and ….visual acuity (ear-nose-throat conditions), etc…

1.1.3. Laboratory:

- For infants under 18 months born to mother with HIV infection and infants with HIV suspected but unconfirmed HIV status:
    - Perform HIV testing in accordance with the age of children and as soon as possible (HIV virological and serological testing)
    - Provide pre-test counseling: benefits of HIV testing, procedures and timing of HIV testing. If infant is breastfed, provide appropriate counseling on HIV testing and its results during breastfeeding.
    - Take the specimen and send to the laboratory for testing as regulated
    - Provide counseling when the test result comes back, and manage per protocol.
- For infants with confirmed HIV diagnosis or infants with presumptive clinical diagnosis of severe HIV/AIDS, the following test should be performed:
    - Complete blood count, total lymphocyte count, liver enzymes (ALT).
    - TB screening (such as chest X ray, ESR, Mantoux test, sputum AFB, etc.), or other necessary investigations for diagnosis of other OIs
    - CD4 count (if available).
- If infants present with opportunistic infections or other diseases, appropriate test should be indicated.

1.1.4. Diagnosis of OIs and clinical staging:

- Diagnosis of active tuberculosis: (see Section V “Diagnosis and treatment of common OIs in children with HIV infection”).
- Diagnosis of other OIs: see Section IV (Approach to common clinical syndromes in children) and Section V (Diagnosis and Treatment of common opportunistic infections in children).
- Clinical staging (see Section I, Section 2.1).

1.2. Management:

- Instruct replacement feeding with formula, if available or breastfeeding and other nutritional cares according to age-related needs. For breastfed infants with positive virological test, instruct the mother to continue breastfeeding.
- Provide prophylaxis with co-trimoxazole and immunization as indicated.

- Provide treatment for opportunistic infections, for symptoms and other conditions as well as management of drug side effects (if any).
- Consider indication of ARV treatment if the infants are eligible. If infants have OIs, treat those first. Start ART when condition stabilizes. If infants have first PCR positive, preparation for ART should be done. For infants with severe HIV/AIDS, provide ART without waiting for PCR test results.
- If the children are on ART, assess the regimen in use, and if the regimen is not proper, seek for consultation.
- Admit to hospital the cases with severe OIs or serious side effects
- Seek for consultation from and refer patients to relevant specialized facilities (dermatology & venereology, TB, etc.) or refer to higher levels if beyond treatment capacity of the facility.

1.3. Counseling and support:

Counseling should be provided to the infants' family on following issues:

- Evolution of HIV infection, importance of long-term care and treatment, needs of following-up and HIV confirmative testing for the infants.
- Determine who are the main and supportive care givers for the infants.
- Immunization and prophylaxis for OIs.
- Nutrition issues, including benefits of breast milk and risks of HIV transmission through breast milk, age-related feeding, avoid mixing of breastfeeding and formula feeding, and weaning practices when infants reach 6 months of age to avoid HIV transmission.
- Personal and food hygiene.
- School care, confidentiality and disclosure of HIV infection status of the infants, preventive measures for HIV transmission, safe behavior practice.
- Psycho-social issues and treatment adherence
- Referal of the infants and their family to HIV care and treatment services.
- Supportive solutions for orphaned and abandoned infants

1.4. Follow-up plan and other necessary supports

- Schedule follow-up visit for each patient: every 1-3 months depending on health status of the infant, ability to adhere to CTX prophylaxis, ability of care givers to take care the infants, and on clinical and immunological staging of the infants.
- For infants missing appointments, find out the reasons and establish supportive measures such as further counseling, reminding calls, peer supports, home visits, etc.

- Schedule visits whenever abnormalities occur.
- Dispense drugs as prescribed.
- Coordinate the supports from family and community with available services.

2. Follow-up visit:

HIV infected or exposed children should visit the clinic on regular basis or whenever abnormalities occur. The following should be considered in addition to the above-mentioned requirements:

2.1. Clinical examination and laboratory testing:

- Taking history: symptoms newly occurred since the last visit, such as fever, weight loss, cough, diarrhea, eruption, etc.; psycho-social issues, treatment adherence.
- Clinical examination: assess overall physical and mental development, general and regional examination to detect opportunistic infections and other conditions, side effects of prophylactic and therapeutic medications. Re-assess clinical staging.
- Perform routine tests for infants with confirmed HIV infection (including infants with severe HIV/AIDS), : CD4 cell count every 6 month; diagnostic tests for OIs and tests for drug side effects as well as treatment failure as needed. Regular assessment of treatment outcome in infants on ART should be done as indicated.

2.2. Management:

Management will be provided depending on clinical condition and test results of the children

- Treat OIs and manage drug side effects if any.
- Give ART treatment if the children are eligible.
- Provide nutritional, psycho-social counseling and support for treatment adherence.
- Refer to other relevant services or consult with specialists when needed.

III. PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS, IMMUNIZATION SCHEDULE

1. Prophylaxis with co-trimoxazole (CTX)

a. Objective

Co-trimoxazole prophylaxis is effective to prevent PCP, Toxoplasma encephalitis as well as diarrhea and respiratory tract infection due to some kinds of bacteria.

b. Indications of primary prophylaxis

Table 4: Indications of prophylaxis with co-trimoxazole for HIV exposed and HIV- infected children

HIV exposed children	HIV confirmatively infected children		
	< 1 year	1-5 years	≥ 5 years
• CTX prophylaxis is universally indicated, starting at 4–6 weeks after birth and continued until exclusion of HIV infection • If children are diagnosed with HIV, see next columns	• Prophylaxis is indicated for all infected children	• Clinical stages 2, 3 and 4 regardless of CD4 count Or • CD4 < 25% regardless of clinical stage	If CD4 is available: Clinical stage 3, 4 regardless of CD4 count. Clinical stage 1, 2 with CD4 < 200 cells/mm3 If CD4 is not available: Clinical stage 2, 3, 4

c. Dosage of prophylactic CTX:

Cotrimoxazole consists of trimethoprim (TMP) and sulfamethoxazole (SMX). Prophylaxis dose is 5 mg TMP/kg/day, once a day orally. Dosage can be calculated as in following table:

Table 5: Dose of co-trimoxazole prophylaxis for HIV exposed and infected children

Body weight or body surface area of the children	Syrup (ml) (8 mg TMP/40 mg SMX/1ml)	Tablet (80 mg TMP/400 mg SMX)
3.5 - 4.9 kg (0.21- 0.28 m^2)	2.5 ml	
5.0 - 6.5 kg (0.28- 0.33 m^2)	4	
6.6 - 8.0 kg (0.34- 0.40 m^2)	5	1/2
8.1 - 10. kg (0.41- 0.47 m^2)	6	1/2
10.1 -11.9 kg (0.48- 0.54 m^2)	7	1/2

12.0 - 14.9 kg (0.55- 0.64 m^2)	8	1
15.0 - 16.9 kg (0.65- 0.71 m^2)	10	1
17.0 - 19.9 kg (0.71- 0.83 m^2)	11	1
20.0 - 24.9 kg (0.83- 0.98 m^2)		1,5
25 - 29.9 kg (0.99- 1.15 m^2)		2
30.0 - 35.0 kg (> 1.15 m^2)		2

d. Alternative drugs: Dapson 2mg/kg/day taken everyday or 4mg/kg/time, once a week for the children with allergy to CTX. Dapson is less effective than Co-trimoxazole in preventing PCP and has no effect on preventing toxoplasma.

e. When to stop CTX prophylaxis: When children on ART with CD4 higher than 25% for children 1-5 years old and CD4 > 200 cells/mm3 for children older than 5 years old, for 6 month continuosly.

g. Re-start CTX prophylaxis: when CD4 reduced and reaching the criteria for prophylaxis according to age of infants.

h.Contraindication: Hypersensitivity to sulphonamides including CTX, sulphadoxine- pyrimethamine).

i. Side effects of CTX:

Nausea, vomiting and rash can occur during first 1- 2 weeks after initiation of prophylaxis; severe adverse reactions such as anemia, granulocytopenia, rash and hepatotoxicity can also be seen.

Counsel the care givers and the children on side affects for self monitoring and to seek consultation when suspected signs of severe adverse events occur. Do complete blood count, liver enzymes measuring when anemia or hepatotoxicity is suspected.

Rash due to CTX and how to manage

Table 6: Grading of rash due to CTX and management

Grade	Clinical description	Management
Grade I (Mild)	Erythema	▪ Continue CTX prophylaxis with careful observation and follow up. ▪ Provide symptomatic treatment and anti histamines.

Grade II (Moderate)	Diffuse maculopapular rash, dry desquamation	▪ Continue CTX prophylaxis with careful observation and follow up. ▪ Provide symptomatic treatment and anti histamines.
Grade III (Severe)	Bulla, mucosal ulceration	▪ Hospitalization with supportive treatment ▪ **CTX should be permanently discontinued**
Grade IV (Very severe)	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation	

2. Immunization

Vaccines	Exposed infants	HIV infected children, clinical stages 1, 2 and 3	HIV infected children, clinical stage 4
Vaccines under the National Expanded Program on Immunization (EPI)			
BCG[1]	As scheduled	**Do not give**	**Do not give**
Diphtheria-Pertussis-Tetanus	As scheduled	As scheduled	As scheduled
Poliomyelitis, orally	As scheduled	As scheduled	**Only use injectable vaccine**, if available
Hepatitis B	As scheduled	As scheduled	As scheduled
Measles	As scheduled	As scheduled	**Do not give**
Japanese Encephalitis	As scheduled	As scheduled	As scheduled
Optional Vaccine			
Haemophilus influenzae B	As scheduled	As scheduled	As scheduled
Varicella	As scheduled	As scheduled	**Do not give**
Mumps	As scheduled	As scheduled	**Do not give**
Rubella	As scheduled	As scheduled	**Do not give**

Note:

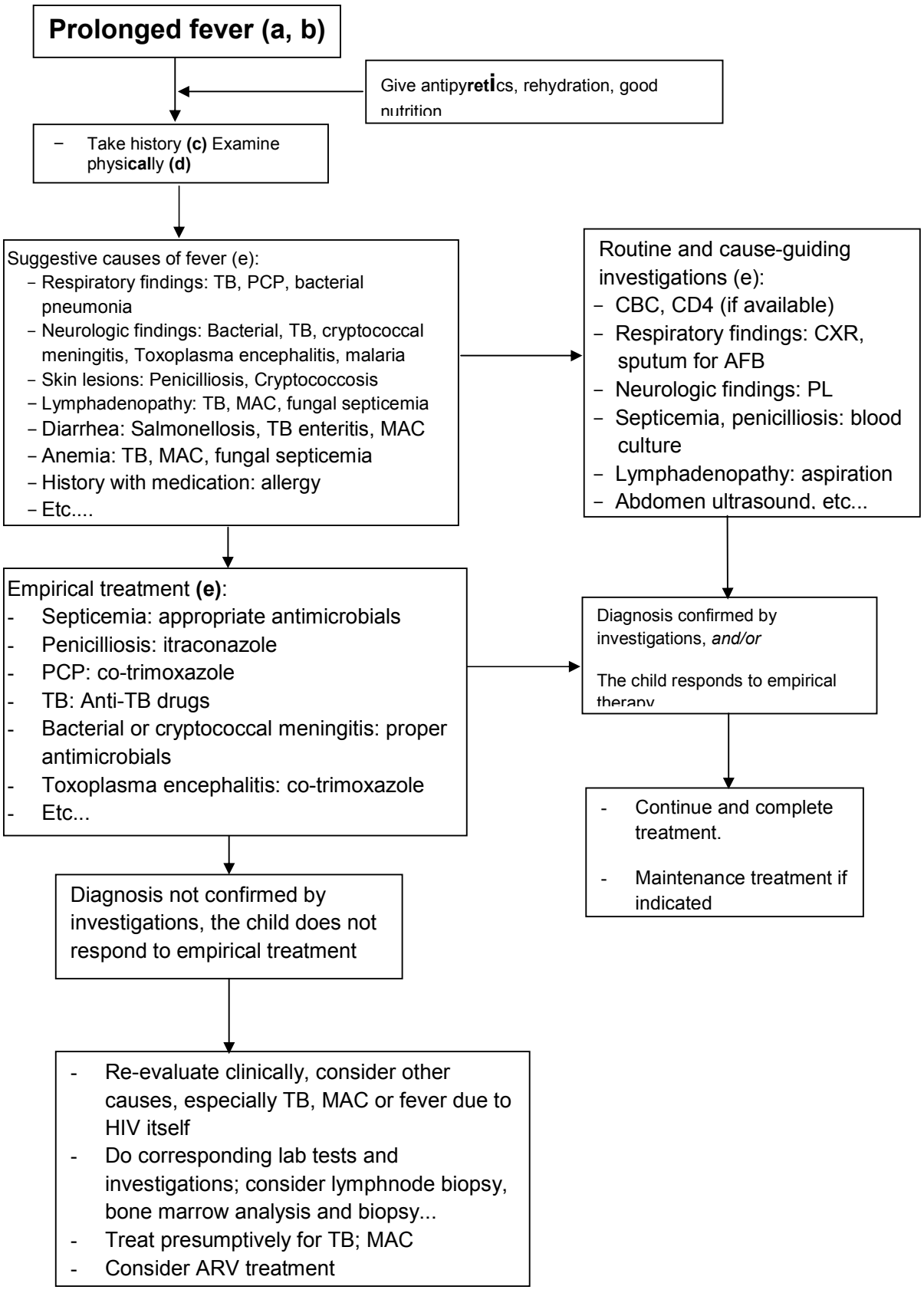
- Give BCG to all HIV-exposed children. Postpone vaccination until HIV infection is excluded in following situations :

  - High risk of HIV infection: The mother and the infant not receiving PMTCT *or*
  - The infant presents with signs or symptoms suggestive of HIV infection. *Or*
  - Low birth weight (under 2500 g) and pre-termed children.

- BCG-associated disease can occur after BCG vaccination, presents with swollen left axillary or left supraclavicular lymphnode, enlarged liver and spleen, and cachexia. Consultation with TB specialists is needed for assessment and treatment.

IV. APPROACH TO COMMON CLINICAL SYNDROMES IN CHILDREN WITH HIV/AIDS

1. Prolonged fever



Instructions:

(a) Definition: prolonged fever is defined as a fever over $37^0 5$ lasting for more than 14 days.

(b) Common causes of prolonged fever

- Common causes in HIV infection with severe immunodefficiency:
  - TB, MAC, candidiasis, penicilliosis, cryptococcal meningitis and fungal septicemia, systemic salmonellosis and septicemia due to other bacteria, CMV diseases, etc...
  - HIV related neoplasms: lymphoma,
  - Fever due to HIV itself, malaria
- Drug reaction: hypersensitivity to CTX or ARVs (NVP, ABC, etc.).

(c) History taking*:*

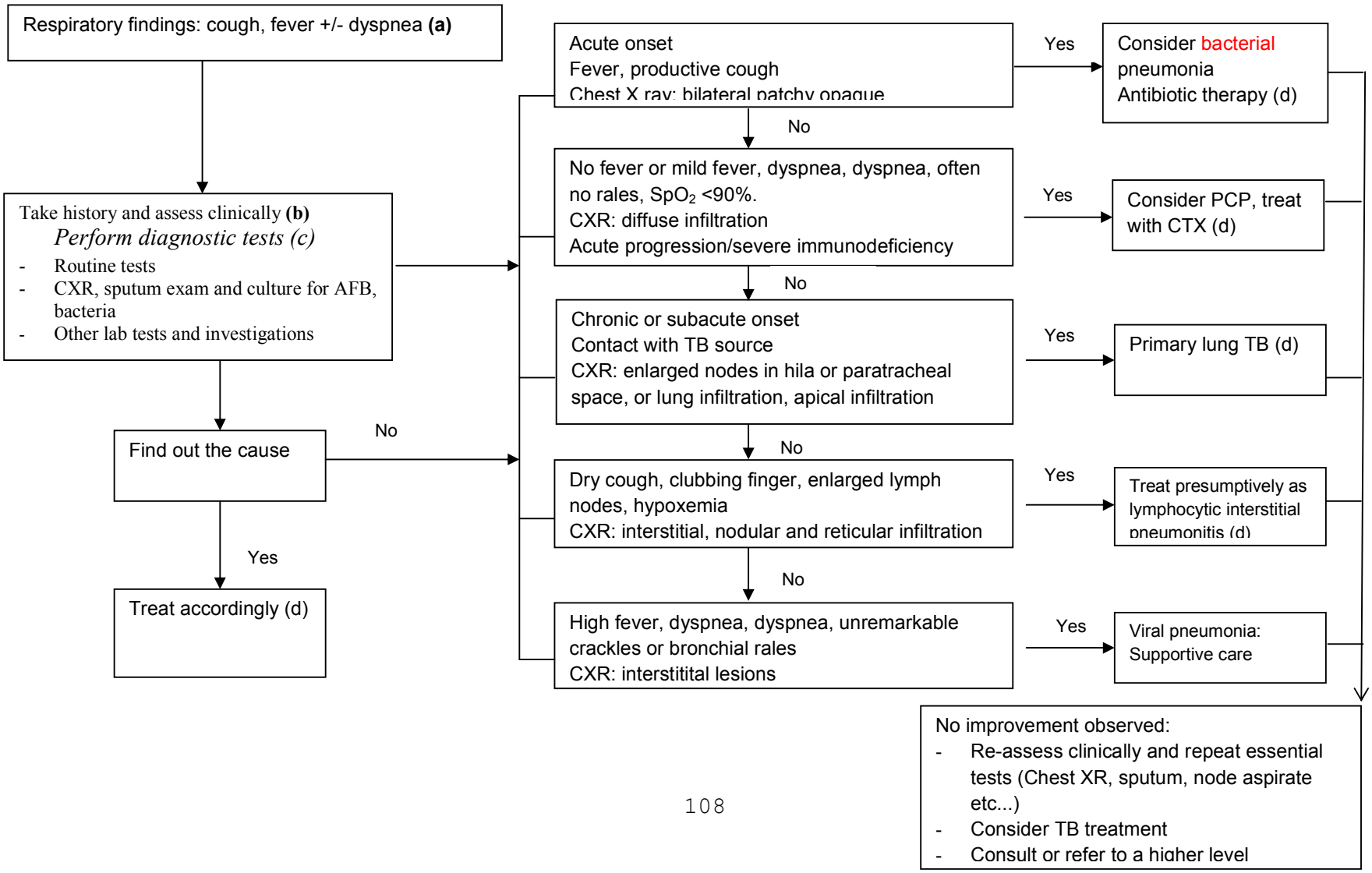
- Duration of illness, characteristics of onset (acute, subacute)
- Symptoms from organs and systems: headache, diarrhea, cough, skin eruption...
- Medications used: CTX, ARV, other drugs
- Previous history of OIs and other HIV associated conditions (potential recurrence of OIs if secondary prophylaxis or ARV treatment not given).
- Previous history of drug allergy and other conditions.
- Family history: TB and other communicable diseases

(d) Clinical examination:

- Examine all organs and body systems; focus on affected organs.
- If the children have low CD4 count, consider examination of the eyes for lesions suggestive of CMV, toxoplasma.

(e) Find out causes of opportunistic infections, request lab tests and other investigations to establish diagnosis and treatment (also see Section V: Diagnosis and treatment of common opportunistic infections in HIV infected children).

2. Respiratory findings



Instructions:

(a) Causes:

- Common causes: Bacterial pneumonia, PCP, primary lung TB, lymphocytic interstitial pneumonitis, viral pneumonia
- Other causes: fungal diseases, non-infectious causes

(b) Considerations in history taking and clinical examination:

Taking history:

- Acute, subacute onset
- Dry or productive cough
- Accompanied findings: fever, weight loss, cold sweating…
- TB history of the patient and his/her family

Clinical examination:

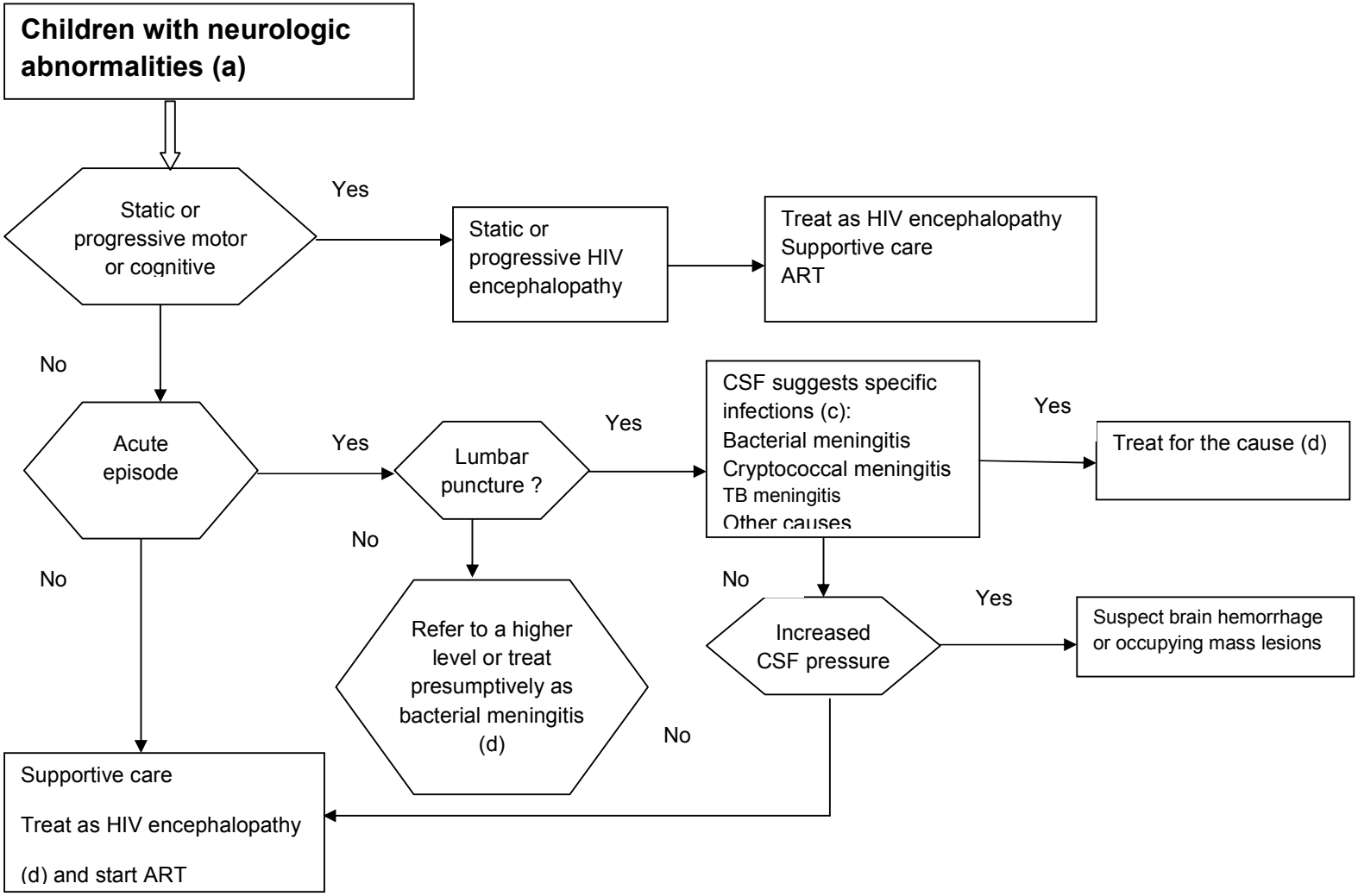
- Respiratory failure: dyspnea, cyanosis
- General conditions: fever, weight loss, eruption, enlarged lymph nodes, clubbing fingers, etc...
- Respiratory examination: crackles, fremitus…
- Other findings: mental-physical development, manifestations of immunodeficiency such as oral thrush, cachexia…

(c) Diagnostic tests: Based on clinical signs & symptoms and history

- Routine tests, CD4 cell count,
- Chest X ray; sputum AFB; sputum microscopy and culture for other bacteria.
- Blood culture in cases of fever
- Pleural tapping in cases of pleural effusion and lymph node aspirate in cases of lymphadenopathy for lab tests
- Chest CT scan if available

(d) See also Section V: “Diagnosis and treatment of common opportunistic infections in HIV infected children”

3. Neurologic findings



Instructions:

(a) Definition: Neurologic diseases in children include:

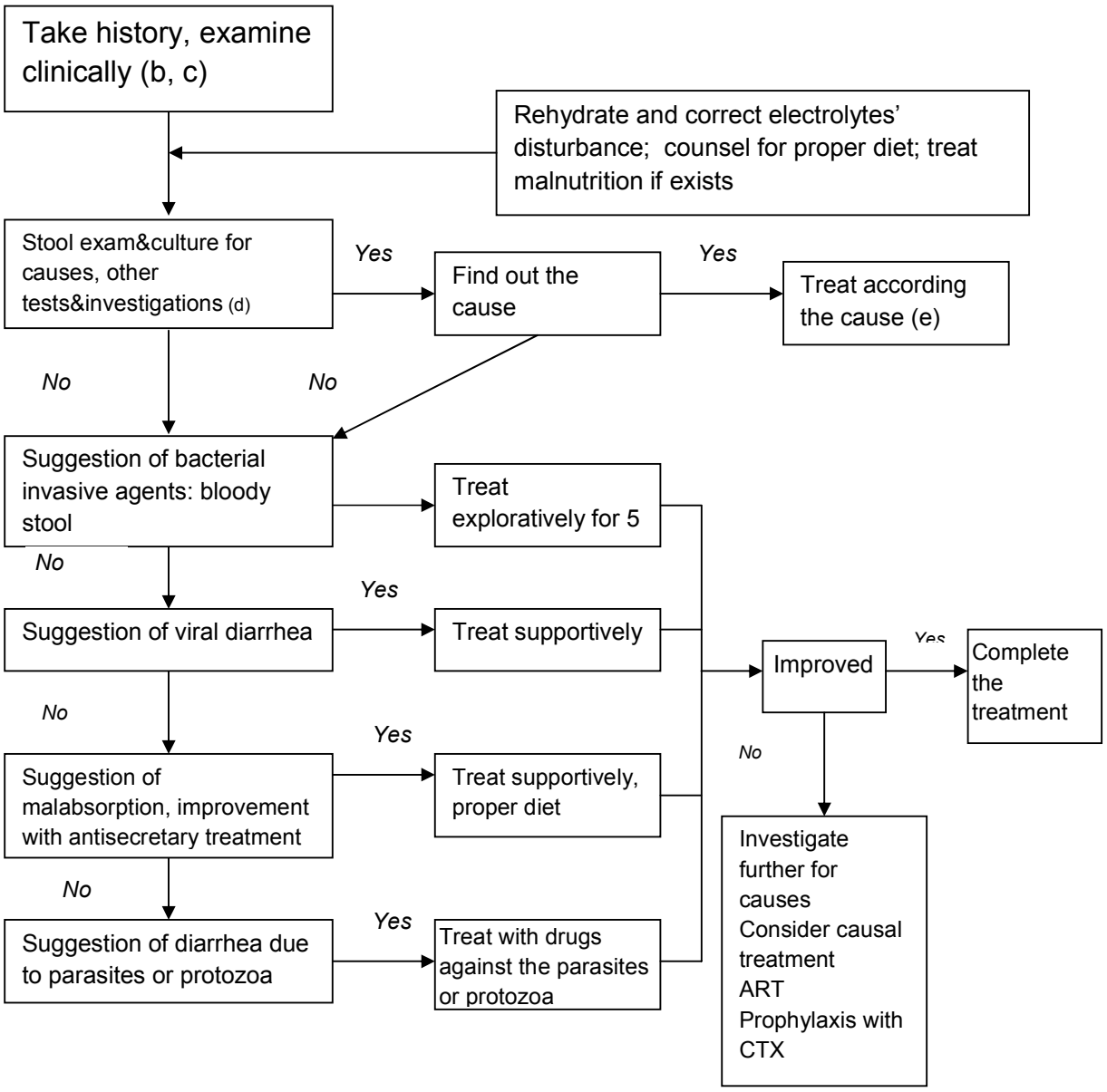
- Progressive encephalopathy: Progressive decline in motor, cognitive or language functions, evidence of loss or increasing delay in achieving developmental milestones; onset can be as early as the first year of life but can occur at any time.
- Static encephalopathy: Motor dysfunction and other developmental deficits of varying severity that is non-progressive as documented on serial neurological and developmental examination.
- HIV static encephalopathy is defined when no other causes of developmental deficits/neurologic dysfunction found, such as premature delivery, asphyxia at birth, use of drugs or alcohol in pregnancy.
- Acute infection: acute onset with seizures, focal motor deficits and meningeal syndrome (such as in bacterial meningitis, cryptococcal meningitis, TB meningitis).

(b) Acute manifestations can occur in previously healthy HIV infected children or superimposed on HIV encephalopathy.

(c) Relied on lab results of CSF for biochemistry, cytology, bacterial and fungal examination and culture to determine

(d) Causes and treatment: See also Section V: “Diagnosis and treatment of common opportunistic infections in HIV infected children”.

4. Persistent diarrhea (a)



Instructions:

(a) Definition: Chronic diarrhea is defined as liquid stools of more than thrice per day, lasting for over 14 days

(b) Taking history:

- Frequency of bowel each day, characteristics of stools
- Accompanied symptoms: fever, abdominal pain, location and characteristics of pain
- Nutritional history of the child.
- History of TB and other communicable diseases in the family

(c) Clinical examination:

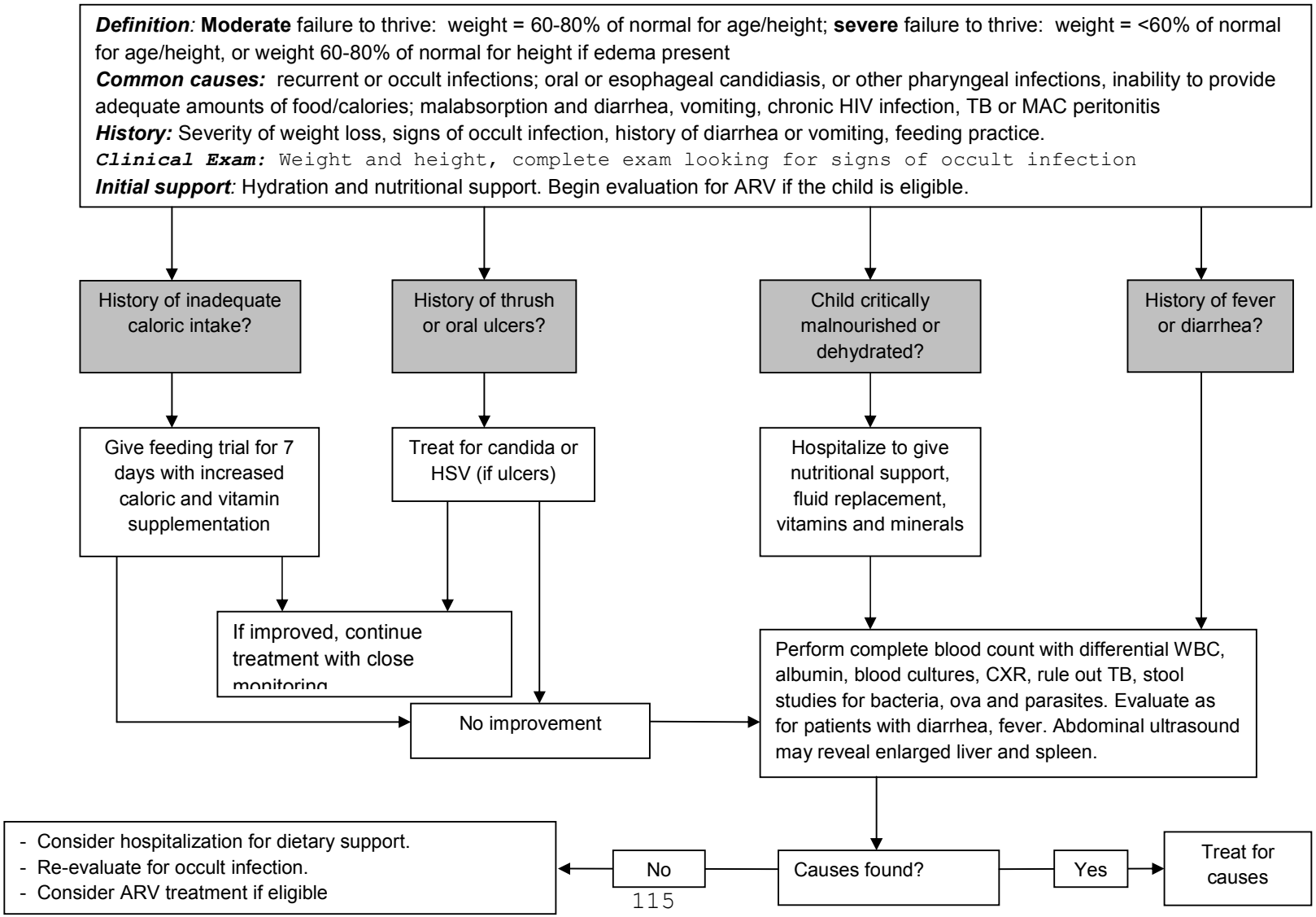
- Evaluate general condition and dehydration and nutrition
- Evaluate developmental status
- Systemic findings: fever, lymphadenopathy, weight loss;
- Examine respiratory and circulatory systems
- Examine the abdomen: tenderness, ascites, hepatosplenomegaly, enlarged lymph nodes in the abdomen

(d) Lab tests and investigations:

- Stool microscopy; look for
  - Red and white blood cells (invasive diarrhea due to shigella and other kinds of bacteria); protozoan parasites (amoeba, giardia, larvae of strongyloides, hookworm, helminthes eggs); AFB (TB and MAC),
  - cryptosporidium by formalin-ether concentration method and modified acid-base staining , microsporidium and isospora by trichromatic stain; if available
- Blood culture if the child is febrile and diarrhea associated with septicemia due to bacteria suspected
- Chest X ray, sputum examination if respiratory findings or suspected TB
- Abdominal ultrasound to confirm hepatosplenomegaly, lymphadenopathy and ascites:

(e) Causes and treatment: See also Section V: “Diagnosis and treatment of common opportunistic infections in HIV infected children”

5. Wasting and Failure to Thrive



V. DIAGNOSIS AND TREATMENT OF COMMON OPPORTUNISTIC INFECTIONS IN HIV INFECTED CHILDREN

OI	Clinical features	Diagnosis	Treatment*
Fungal diseases			
Candidiasis	The disease usually occurs in severe stage of immunodeficiency with severe, refractory course and is prone to relapse. • Oral, pharyngeal and esophageal candidiasis: multiple white, easily removable patches, pseudomembranous plaques located on the tongue, gums, buccal and pharyngeal mucosa. If the lesions spread to the pharynx and esophagus, the child often has dysphagia and/or painful swallowing.	• Based on clinical features • Esophagoscopy: indicated if the symptoms not improved with antifungal treatment • Microscopic exam for fungi when the patient not responding to the treatment. • Culture if the clinical features are atypical.	Oral candidiasis: • Oral Fluconazole 3-6 mg/kg once daily for 7-14 days; • Topical application: Daktarin oral gel (miconazole) or Nystatin 5 times daily for 7-14 days. Esophageal candidiasis: - Fluconazole 3-6 mg/kg once daily for 14 - 21 days or - Ketoconazole 5mg/kg/day orally in 1-2 divided doses for 2-3 weeks Invasive candidiasis: Amphotericin B 0.5-1.5 mg/kg/day for 2-3 weeks
Cryptococcosis	Cryptococcosis is rare in children, and is more common in children > 6 years • Meningitis: fatigue, fever, persistent headache, nausea, vomiting, alteration of mental	• CSF: clear, with high opening pressure; glucose and protein can be normal; cell count slightly elevated with lymphocytes predominate. Staining with India ink for fungi.	• Induction treatment: indicated for severe meningitis (patients with altered consciousness, brain edema, positive CSF microscopy for fungi, etc) Preferred regimen: Amphotericin B 0.7-1.5 mg/kg/day x 2 weeks

	status, epilepsy, coma; occult meningeal signs, possible visual disturbance, hearing loss, etc... • Skin eruption: nodules-papules with central necrosis, ulcerative papules, pustules. • Pneumonia: diffuse interstitial pneumonia. • Other organs involvement: bone, kidney, liver, lymph nodes.	• CSF, blood and tissues culture for fungi. • Skin biopsy for microscopy and culture for fungi. • Cryptococcal antigen in serum.	• Consolidation phase: Fluconazole 5 – 6 mg/kg/day x 8 weeks • Maintenance therapy: Fluconazole 3 mg/kg/day or Itraconazole 3 mg/day. • Discontinue when the patient on ART and CD4 count > 200 cells/mm^3 ≥ 6 months Mild cases can be started immediately with oral fluconazole
Penicilliosis	The disease usually occurs when the patient is severely immunocompromised. Features: • Fever, enlarged lymphnodes, hepatosplenomegaly, weight loss, anemia. • Skin rash: umbilical necrotic papules; mainly distributed on the head, face, upper trunk or throughout the body.	• Based on clinical features if patients present with fever and typical skin lesions • Direct microscopy for fungi with specimens taken from the skin, bone marrow, lymph nodes. • Blood culture and culture of above specimens in Sabouraud media at 25-37^oC. • Skin biopsy.	Combined therapy: Amphotericin B intravenously, 0.7-1.5mg/kg/day for 2 weeks, followed by itraconazole 5- 6 mg/kg twice daily 8 weeks. • Maintenance treatment: Itraconazole 3 mg/day lifelong. Discontinue the maintenance therapy when the patient on ART and CD4 count > 200 cells/mm^3 ≥ 6 months.
Pneumocystis Pneumonia (PCP)	The disease commonly occurs in infants aged less than 1 year, usually with severe clinical course	Characteristic clinical features Definitive diagnosis: microscopy of sputum (induced sputum for high	• Preferred regimen: TMP - SMX 20mg/kg/day (based on TMP) in 3-4 divided doses (every 6-8 hours) for 21

	and high mortality risk. • Acute or subacute onset with fever, cough, tachypnea, cyanosis; physical exam reveals crackles in the base of both sides. Atypical symptoms may be present as cough without fever, dyspnea, anorexia, weight loss. • Lab tests: commonly moderate to severe hypoxemia (low PaO_2), leukocytosis, elevated LDH > 2 UNL. • Chest XR: bilateral diffuse interstitial infiltration, may present with lobar infiltration, miliary pattern or normal.	sensitivity) or bronchial/bronchioaveolar lavage fluid for P.jiroveci; staining methods: Giemsa, silver impregnation, immunofluorescence.	days • Alternative regimen: Clindamycin 20 – 40 mg/kg/day in 4 divided doses intravenously + Primaquin 15- 30mg/day orally. • Supportive treatment with steroids in case of respiratory failure (PaO_2< 70 mm Hg). Prednisone 2mg/kg/day in 2 divided doses for 5 days, then 1 mg/kg/day for 5 days, followed by 0.5 mg/kg/day from day 11 to day 21, then stopped if the child is stable.
Protozoan diseases			
Toxoplasmal encephalitis	Toxoplasmal infection in children may be antenatal (congenital) or postnatal. Early symptoms of toxoplasmosis include fever, sore throat, myalgia, enlarged lymph nodes, skin eruption and hepatosplenomegaly;	• Serology for IgM, IgA, IgE in the first 6 months and for IgG in children over 12 months of age. Serology can be negative in children with toxoplasmal encephalitis. • Isolation of the agent or PCR of	**Initial treatment** • Congenital toxoplasmosis: Co-trimoxazole 10-15 mg TMP/kg/day intravenously or orally, or Pyrimethamine 2 mg/kg/day orally once daily for 2 days, then 1 mg/kg/day daily for 2-6 months, then 1 mg/kg/day 3 times per week + Sulfadiazine 50 mg/kg/day

	Late symptoms include encephalopathy, fever, confusion, seizures and retinal involvement.	blood, CSF, amniotic fluid or tissues involved. • Diagnostic imaging (cerebral CT, MRI) can show specific lesions of abscess	orally in 2 divided doses + Acid folinic 10-25 mg/ day. Duration of treatment is decided by physicians experienced in treatment of toxoplasmosis. • Postnatal toxoplasmosis: Preferred regimen: Co-trimoxazole 10-15 mg TMP/kg/day intravenously or orally, or Pyrimethamine orally, induced dose 2mg/kgBW/day for 3 days, the decreased dose 1mg/kg/day + acid folinic orally 10-25 mg/day + sulfadiazin orally, 120mg/kg/day in 4 divided doses for 3-6 weeks. Alternative regimen: Pyrimethamine + clindamycin **Maintenance treatment:** • Cotrimoxazole 5mg/kg/day (based on TMP) • Pyrimethamine 1 mg/kg/day + folinic acid 5 mg/kg 3 times/week + sulfadiazin 85-120 mg/kg/day in 2-4 divided doses or • Pyrimethamine + folinic acid + clindamycin
Crypto-sporidiosis	Subacute or chronic watery diarrhea often associated with cramps, nausea and vomiting.	Modified acid-fast staining of stool reveals small oocyst (4–6 µm in diameter).	ART is the only effective treatment that controls persistent cryptosporidiosis. Supportive care includes rehydration,

<table>
<tr><td></td><td></td><td></td><td>correction of electrolyte abnormalities and nutritional supplementation.

Nitazoxanide is approved for treatment (aged 1–3 years: 100 mg twice daily, aged 4–11 years: 200 mg twice daily)</td></tr>
<tr><td colspan="4">Bacterial diseases</td></tr>
<tr><td>Tuberculosis</td><td>- Carefully history taking for course of illness, source of infection

- Clinical examination:

+ Prolonged cough, prolonged fever for > 2 weeks, weight loss (or no weight increase), sweating, ….

+ Cervical lymphadenopathy, no pain, with/without fistula

+ Subacute meningitis, with increased intracranial preasure, not responding to conventional antibiotics

+ Pleural, peritoneal, or pericardial effusion

+ Arthritis, spondilitis</td><td>+ Tuberculin test (Mantoux): positive reaction (≥ 5mm)

+ Imaging diagnosis: Chest X-ray, CT, MRI, ultrasound , etc

+ Lymphnode, abscess aspiration or biopsy:

+ CSF, pleural, peritoneal tapping andanalyses

+ M.tb detection (by different methods, such as microscopy for AFB, PCR, culture, etc.) in specimen , such assputum, gastric /bronchial wash, body fluids, lymphnode aspiraton, pus from abscess, etc</td><td>TB treatment for HIV infected children:

- Regimen: 2RHZE/4RH (per National TB program’s protocol)

- Severe tuberculosis (miliary TB, meningitis TB, bone/joint TB), supplement of Streptomycin for 2 months of intensive treatment and prolong period of maintenance therapy.

- Consider interaction between rifampicine and nevirapine (replace with Efavirenz), monitor ALT level during treatment

- TB drugs

<table><tr><td rowspan="3">Drugs</td><td colspan="2">Dose</td></tr><tr><td>Daily</td><td>3 times/week</td></tr><tr><td>mg/kg</td><td>mg/kg</td></tr></table></td></tr>
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<table>
<tr><td>Isoniazid</td><td>5 (4-6)</td><td>10 (8-12)</td></tr>
<tr><td>Rifampicin</td><td>10 (8-12)</td><td>10 (8-12)</td></tr>
<tr><td>Pyrazinamid</td><td>25 (20-30)</td><td>35 (30-40)</td></tr>
<tr><td>Ethambutol</td><td>20 (15-25)</td><td>30 (25-35)</td></tr>
<tr><td>Streptomycin</td><td>15 (12-18)</td><td>15 (12-18)</td></tr>
</table>
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<tr>
<td>Side effects of BCG in HIV infected children (BCGit)</td>
<td>- Abscess at injection site, enlarged lymphnodes at vaccination side. Systemic manifestations with high mortality rate (75%)</td>
<td>Aspiration of lymphnodes for histopathology, culture if possible</td>
<td>- Treat with at least 4 drugs: Isoniazid, Rifampicin, Pyrazinamid, Ethambutol, Ofloxacin or Ciprofloxacin.
- Treat for at least 9 month and consider ARV treatment.</td>
</tr>
<tr>
<td>Atypical Mycobacterial complex (MAC)</td>
<td>Fever, night sweats, weight loss, fatigue, chronic diarrhea and abdominal pain.
Laboratory findings: neutropenia, increased alkaline phosphatase or lactate dehydrogenase (LDH)</td>
<td>Isolation of the causative microorganism or histopathology</td>
<td>Combination treatment:
Clarithromycin 7.5 – 15mg/kg twice daily (maximum 500mg/dose) + Ethambutol 15 – 25mg/kg once daily (maximum 1000mg) + Rifampicin 10-20 mg/kg once daily.</td>
</tr>
<tr>
<td>Severe and recurrent bacterial infections</td>
<td>Pneumonia is a common cause of deaths in children with HIV/AIDS. Septicemia, empyema, osteomyelitis, purulent adenitis, cellulitis, meningitis, etc. can occur.</td>
<td>Characteristic clinical features. Investigations: elevated WBC and neutrophils; chest X ray, sputum microscopy and culture, blood culture, pleural tapping and pleural fluid microscopy and culture for</td>
<td>Frequently used antibiotics as below:
- Ceftriaxone 80–100mg/kg/day in 1-2 divided doses
- Cefotaxime 150–200mg/kg/day in 3-4 divided doses</td>
</tr>
</table>

	• Clinical features: Fever accompanied by manifestations from involved organs such as cough, dyspnea, meningeal signs, red swelling lymphnodes… • Lab findings: WBC often not elevated, diagnostic tests for organ involved as chest x ray, CSF Blood, CSF and pleural fluid should be cultured for causative agents.	bacteria if available.	▪ When enteric Gram negative bacteria are suspected, use: - Ceftazidime 150 – 200mg/kg/day in 3-4 divided doses - Ciprofloxacin 20 – 30 mg/kg/day in 2 divided doses ▪ When methicilline resistant staphylococcal infection is suspected: - Vancomycin 40 – 60 mg/kg/day in 3-4 divided doses - Clindamycin 10 – 20 mg/kg/day in 3-4 divided doses ▪ CTX must be combined if PCP cannot be ruled out ▪ If no improvement after 7–10 days, lab tests for TB and fungal infections must be performed
Lymphocytic interstitial pneumonitis (LIP)	Commonly seen in older children with HIV infection, rarely causing mortality but has persistent course and can cause chronic dyspnea. Gradual onset with following manifestations:	Characteristic clinical manifestations Chest X ray: pulmonary infiltrations as in TB or PCP	Transient improvement occurs with prednisolone 1-2mg/kg/day (if PaO2 < 85-90 mm Hg); taper the dose after clinical response. – Symptoms usually recur quickly after discontinuation of corticosteroid unless the patient has been given ART.

	– Dry cough, dyspnea, finger clubbing, parotitis, lymphadenopathy – Hypoxemia, especially with concomitant respiratory infections – Lab findings: CXR with bilateral reticulonodular interstitial infiltrates, bronchiectasis		– Do not use prednisolone in case concomitant conditions for which corticosteroids are contraindicated
Viral diseases			
Herpes zoster infection (Zona)	Zoster may occur when the TCD4 cell count is still relatively high. Clustered vesicular eruptions with central crust, distributed within a dermatome in one side of the body, commonly on the intercostal areas, chest, back and face, along the path of a nerve. The child often experiences burning pain in affected area, sometimes persistent even after the lesions already resolve, also called postherpetic neuralgia. Fever may present.	Clinical features often typical and not require supportive lab tests.	Acyclovir 20mg/kg orally 4 times per day for 7-10 days. Apply topical antiseptics such as methylene blue, millian for controlling superinfection.

	The condition is often difficult to treat and frequently relapsed, may appear in both sides and affect multiple areas of the body		
Herpes simplex	Skin and mucosa manifestations*:* vesicular eruptions in crops, quickly progressing to ulcerations; frequently localized in or around the genital organs, can be found in rectum and colon, oral cavity and perioral areas, occasionally spreading to esophagus causing dysphagia, odynophagia; sometimes expanding to trachea and bronchi. The disease is generally more severe with frequent relapses compared with HIV-negative persons. Herpes encephalitis: manifestations are often nonspecific with focal lesions in frontal-temporal lobes.	• Based on clinical manifestations • Tzanck preparation for gigantic cells, viral culture or fluorescent antibody test, PCR, if possible.	• Acyclovir orally 20 mg/kg 3 times per day for 5-10 days for mild cases; • Intravenous Acyclovir 5 -10mg/kg every 8 hours for 10 days for severe cases including encephalitis; or • Famciclovir 125 mg orally twice daily for 5-10 days; • Topical application of methylene blue or gentian violet for controlling superinfection.
Cytomegalo-virus (CMV)	Cytomegalovirus (CMV) disease often occurs when CD4 < 50 cells/mm^3.	Fundoscopy if retinitis suspected. Brain biopsy, CSF, skin lesion, blood for viral culture or PCR.	• Preferred regimen for systemic disease and retinitis: Gancyclovir 10 - 15 mg/kg/day intravenously in 2 divided doses for 14 - 21 days, then 5 - 10 mg/kg/day x 5-7

	Major manifestations of CMV disease in children: retinitis, esophagitis, hepatitis, pneumonia, encephalitis, colitis; fever, failure to thrive, developmental retardation, hearing loss; anemia, thrombocytopenia, elevated LDH.	Children with low CD4 count should have eyes carefully examined to assist in considering treatment for CMV or ARV and to prevent immune reconstitution syndrome	days/week. • Alternative regimen: Foscarnet 180 mg/kg/day in 3 divided doses for 14-21 days, then maintain 90-120 mg/kg/day. • Retinitis in children > 3 years of age: intraocular ganciclovir combined with gancyclovir orally 90 mg/kg/day in 3 divided doses. • Maintain lifelong ganciclovir 5 mg/kg/day intravenously after systemic disease. Maintenance therapy for retinitis is ganciclovir intraocular every 6-9 months + ganciclovir orally 90 mg/kg/day in 3 divided doses. • Discontinue the treatment if ARV treatment has been started and CD4 percentage > 15% for more than 6 months

* Pay attention to interaction between OI drugs and ARVs (see Annex 6)

VI. ANTIRETROVIRAL THERAPY

1. Goals and principles of ART

1.1. Goals of ART for HIV infected children:

- To suppress the virus replication and maintain the viral load at a possible lowest level in the blood.
- To restore immunological function and help decrease the prevalence of opportunistic infections (OI).
- To improve the quality of life for the children and increase the survival.
- To maintain normal growth for children physically and mentally.

1.2. Principles of ARV treatment:

- ART is part of comprehensive package of medical care and socio-psychosocial supports for children living with HIV/AIDS.
- Any ART regimen should must include at least 3 drugs.
- ART is lifelong treatment and the children should adhere absolutely to therapy to ensure treatment efficacy and avoid drug resistance.
- HIV infected children commencing ART should continue prophylaxis for opportunistic infection (OI) when the immune system has not been reconstructed.

1.3. ARV drug classes used in Vietnam:

- Nucleoside and nucleotide reverse transcriptase inhibitor (NRTI)
- Non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Protease inhibitor (PI)

Details for common ARV drugs and their usage, see Annex 3.

2. Criteria for initiating ART

Antiretroviral Therapy is initiated on the basis of diagnostic status of HIV diagnosis, age, clinical and immunological staging of the children.

1. Children with confirmed HIV infection:

- Children < 12 months: ART should be provided immediately regardless clinical staging and CD4 cell count
- Children > 12 months, ART is indicated when:
  - Clinical stage 4, regardless of CD4 count.

- Clinical stage 3, regardless of CD4 count; children with TB, LIP, oral hairy leukoplakia (OHL) and thrombocytopenia, should be treated for these conditions first and ART can be delayed if CD4 count is still above level of "severe immunodeficiency" by age. If CD4 count is unavailable, consider ART.
- Clinical stage 2 and CD4 cell count (or TLC) below the level of "severe immunodeficiency" by age
- Clinical stage 1 and CD4 cell count below level of "severe immunodeficiency" by age

2. Children under 18 months of age who have not diagnosed as HIV infected by virological testing, but are clinically diagnosed with severe HIV/AIDS disease.

3. Preparation for readiness to commence Antiretroviral Therapy

The preparation for readiness to commence ART must be started from the time the patient first presents to the treatment facility. The contents of the readiness preparation should proceed at every patient visit so that the ART can be initiated immediately should the patient fulfill the criteria for initiating the treatment.

3.1. Pre-ART assessment:

The following is the content of the Pre-ART assessment for the HIV infected children who fulfill the clinical and/or immunological criteria for initiating ART:

- Re-assess clinical stage and immunologic status (% of CD4 cell count or total lympho count if CD4 is unavailable).
- Screen for TB and other opportunistic infections; consult with other specialized services (TB, dematology, etc…) if needed. Provide treatment for TB and acute OIs, if present.
- Perform basic laboratory tests and those necessary for selecting ART regimens: CBC/Hgb and liver enzymes (ALT).
- Take previous ART history of the mother and her child, if any, the reason for use (as prevention of mother-to-child transmission or treatment for the mother), specific regimen, treatment adherence, and the course of disease with the treatment.
- Assess nutritional status, family situation of the children, treatment willingness of the family/care givers.
- Choose the suitable ARV regimen for the children

- Inform the family/care givers about the plan for ART-readiness preparation
- Provide Co-trimoxazole prophylaxis, other prophylaxis if indicated and available.

3.2. Education and Counseling prior to ART

Provide counseling to the parents/care givers and the children (if grown up enough) on “Understanding of Antiretroviral therapy” including:

- Course of HIV infection, ARVs and benefits of the treatment
- Importance of treatment adherence and measures for strengthening adherence
- Treatment regimen, how to divide or measure the drugs, how to store drugs
- How to manage vomiting after taking drugs, drug side effects and its management
- Plan for care and follow-up at the treatment facility or at home

3.3. Assessment for treatment readiness

- Assess the parents/care givers about “Understanding of Antiretroviral therapy” to ensure that the children will be given drugs exactly as requirements of treatment. Provide training and counseling again if the parents/care givers show inadequate understanding. Counseling period can be shortened in case of severe conditions requiring early initiation of ART.
- Verify other issues such as place of residency, ability to contact as needed, community supports.
- The parents/care givers sign in the informed consent forms for ART participation of the children.
- Note: If the children need to be given treatment immediately, dispense ARVs for treatment and plan counseling for subsequent follow-up visits, or hospitalize the children.

3.4. Initiation of Antiretroviral Therapy

- Prescribe a first-line regimen for all children newly starting antiretroviral therapy; take into consideration history of exposure to NVP (the mothers or the infants have been given PMTCT with NVP containing regimen within previous 12 months) to ensure appropriate choice of regimen.

- Dispense the ARVs and instruct the parents/care givers about the treatment drugs, how to take the drugs, the schedule of drug dispensing and follow-up visits. Ensure that the parents/care givers have a plan to comply with therapy and know how to manage if facing difficulties.
- Instruct the parents/care givers how to store drugs at home. Cold storage is required exclusively for suspensions of d4T and LPV/r.
- Choice of Pediatric formula of ARVs (suspension or tablet) is based on age or body weight of children. Infants under 10 kg of body weight should be given syrup; tablet formula with fixed dose combination can improve treatment adherence of the children
- Dosage calculation is based on body weight or surface area of children (see Annex 4). Calculation is needed for choosing appropriate dosage in accordance with infant's body weight; an ARV tablet should not be divided into less than a half of the tablet.
- Consider drug interactions when selecting regimen (see Annex 5).

4. First-line Antiretroviral Regimens:

4.1. Regimen for infant newly starting ART (exclude those have exposed to NVP through PMTCT intervention wihin previous 12 months)

4.1.1 Preferred regimen:

AZT + 3TC + NVP

Indications: for all chidren initiating ART, who have never exposed to NVP or have exposed to NVP (through PMTCT intervention) for more than 12 months

Note:

- Lead-in NVP dose should be half of normal dose, increase to normal dose after 2 weeks of treatment
- Take drugs every 12 hours. Drug can be taken before or after meal
- Measure Hgb and ALT level prior to ART, after 1 month and then every 6 months or whenever anemia or hepatitis is suspected.
- Do not start this regimen when children have Hgb < 80 g/l; If during treatment Hgb < 70 g/l, AZT should be replaced
- Cautious when using NVP for children with ALT > 2,5 upper normal limit and children on TB treatment with rifampicin

4.1.2. Alternative regimens:

a. d4T + 3TC + NVP

Indications: children who have contraindications for or intolerance with AZT.

Note:

- Lead-in NVPdose should be half of normal dose, increase to normal dose after 2 weeks of treatment
- Take drugs every 12 hours. Drug can be taken before or after meal
- Measure Hgb and ALT level prior to ART, after 1 month and then every 6 months.
- Cautious when using NVP for children has ALT > 2,5 upper normal limit and children on TB treatment with rifampicin

b. AZT + 3TC + EFV

Indications: children with contraindications for or intolerance with d4T and NVP, or on TB treatment with rifampicin, children over 3 years of age and weighed > 10 kg .

Note:

- Take AZT + 3TC every 12 hours, EFV should be taken one time at night, 2-3 hours after meals.
- Measure Hgb prior to ART, after 1 month and then every 6 months or whenever anemia is suspected.
- Do not start this regimen when children has Hgb < 80 g/l; If during treatment Hgb < 70 g/l, AZT should be replaced
- Do not start this regimen for children under 3 years of age or weighed less than 10 kg or pregnant adolescent at first trimester, children with mental disorders (present or previous problems).

c. d4T + 3TC + EFV

Indications: children over 3 years of age and weighed > 10 kg with contraindications for or intolerance with NVP, or on TB treatment with rifampicin.

Note:

- Take AZT + 3TC every 12 hours, EFV should be taken one time at night, 2-3 hours after meals.

- Do not start this regimen for children under 3 years of age or weighed less than 10 kg, or pregnant adolescent at first trimester, children with mental disorders (present or previoushistory of).

d. Triple NRTIs Regimen: AZT/ d4T + 3TC + ABC

Indications: use only for children with intolerance with or allergic to NVP and EFV, or because of drug interaction (rifampicin). This regimen should be used restrictively.

4.2. Infants under 12 months of age who have exposed to NVP (the mothers or the infants have received NVP containing PMTCT regimen):

4.2.1. Preferred regimen: AZT + 3TC + LPV/r

Indications: Use this regimen to all children under 12 month of age who have exposed to NVP through PMTCT intervention.

4.2.2. Alternative regimens:

a. d4T + 3TC + LPV/r

Indications: children with contraindications for or intolerance with AZT.

b. ABC + 3TC + LPV/r

Indications: children with contraindications for or intolerance with AZT, d4T

c. AZT + 3TC + NVP or d4T + 3TC + NVP

Indications: if LPV/r is unavailable

5. ARV drug side effects and its management

5.1. ARV toxicity: The severity of ARV-related drug toxicity in children is divided into 4 grades: mild, moderate, severe and severe life-threatening, as in adults. Grading of ARV side effects in children is displayed in the Annex 7.

- Grade 1 (Mild): symptomatic treatment, change of therapy not required.
- Grade 2 (Moderate):
  - If children have lipodystrophy or peripheral neuropathy (d4T), substitute the offending drug
  - Other side effects: consider continuation of ART and symptomatic treatment, consider substitution of drug if condition is not improved.
- Grade 3 (Severe): Do not stop ARV, substitute drug that cause side effects.

- Grade 4 (Severe life-threatening):
    - Immediately discontinue ARV drugs, manage the medical event
    - Restart ART, when condition is stabilized, substitute the offending ARV with other.

Note when managing ARV drug toxicity:

1. Determine the severity of the toxicity based on clinical signs/symptoms and laboratory testing
2. Evaluate concurrent medications and verify if the toxicity is attributable to an ARV or other drugs taken at the same time.
3. Exclude other disease' processes that can result in worsened situation.
4. Manage the adverse event according to severity:
5. Emphasize importance of treatment adherence.

5.2. Management of common side effects of ARV drugs

The severity of side effects should be assessed depending on clinical manifestation and laboratory test in order to provide appropriate management.

Table 8: Management of some ARV serious side effects in children

Clinical manifestations	**Laboratory**	**Management**
Severe rash/Stevens–Johnson syndrome (NNRTI class, particularly NVP, less common with EFV)		
- Rash usually occurs during the first 6-8 weeks of treatment - Rash at grade 1,2 - Rash at grade 3 - Rash at grade 4 - life-threatening (Stevens–Johnson syndrome or toxic epidermal necrolysis	- Elevated aminotransferase evels (see Annex 7)	- If mild or moderate rash, ART can be continued without interruption but under close observation - For severe rash: substitute toxic drug, provide symptomatic treatment - For life-threatening rash: discontinue all ARVs and provide symptomatic treatment. Once symptoms resolve,

		restart ART, substitute NVP with a PI-based regimen or triple NRTI (see Section IV, item 4). NEVER using NVP for children again.
Severe anemia, leucopenia (AZT)		
Assess status of: - Skin lesions, membrance - Heart beat - Functional status (fatigue)	- Decreased hemoglobin and neutrophil cell count (see Annex 7)	Give blood transfusion if needed; discontinue AZT if Hb < 70g/l and substitute with d4T or ABC
Severe and chronic CNS toxicity: due to EFV		
Sleep disturbance, depression, behavior change	Lasting for 2-4 weeks	Substitute with NVP
Acute hepatitis due to NNRTI class, particularly NVP, more rarely EFV; NRTIs or PIs		
Usually occurs within 6-8 weeks - Jaundice - Liver enlargement - Gastrointestinal symptoms - Fatigue, anorexia - *May have hypersensitivity component (rash, fever, systemic symptoms)*	- Increased transaminase and bilirubin level (see Annex 7)	Depending on severity: - Monitor and provide symptomatic treatment if at grade 1 or 2 - Substitute toxic drug if at grade 3 (see Section VI, item 10) - If at grade 4 – life-threatening, discontinue all ARVs and monitor; once symptoms resolve, either o Restart ART by changing to an alternative ARV (substitute NVP by EFV) or o Restart current ART regimen under close observation; if symptoms

		recur, substitute the offending drug with an alternative ARV
Acute pancreatitis (NRTIs, particularly d4T, ddI; rarely 3TC)		
Assess for: - Nausea and vomiting - Abdominal pain - May accompany lactic acidosis	- Increased pancreatic amylase and lipase level (see Annex 7)	If at grade 4 – life threatening: - Discontinue all ARVs until symptoms resolve - If possible, monitor serum pancreatic amylase, lipase - When symptoms resolve, restart ART, substitute the offending drug with an alternative NRTI, preferably one without pancreatic toxicity
Hypersensitivity reaction (ABC or NVP)		
- *ABC:* progressive worsening of symptoms soon after starting ABC, usually within 6–8 weeks. Children present with fever, fatigue, myalgia, nausea, vomiting, diarrhea, abdominal pain, pharyngitis, cough, dyspnea; rash (usually mild) - *NVP:* Systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash	- Increased transaminase levels and eosinophil count (see Annex 7)	If at grade 3: replace toxic drug and provide symptomatic treatment If at grade 4 – life threatening: - Immediately discontinue all ARVs and provide symptomatic treatment - When symptoms resolve, restart ART, substite toxic ARV (ABC or NVP) by others. - NVP or ABC should <u>NEVER</u> be readministered to the patient
Lipodystrophy (d4T; PIs)		
Fat loss and/or fat accumulation in specific	- Elevated serum triglycerides;	Monitor closely, especially after 6-12 months of treatment

parts of the body: - Fat deposit in abdomen, buffalo hump, breast hypertrophy - Fat loss from limbs, buttocks and face occurs to a variable extent	- Elevated serum cholesterol; - Low HDL levels - Hyperglycemia	If lipodystrophy occurs, substitute d4T with ABC or AZT Substitute an PI with NVP or EFV
Severe peripheral neuropathy (d4T, ddI; rarely 3TC)		
- Pain, tingling, numbness of hands or feet; inability to walk - Distal sensory loss - Mild muscle weakness and areflexia can occur	- None	Monitor closely, especially after 6-12 months of treatment Substitute d4T with AZT or ABC
Lactic acidosis (NRTI class, particularly d4T)		
- Generalized fatigue and weakness - Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, hepatomegaly, anorexia, poor weight gain and/or sudden unexplained weight loss) - May present with hepatitis or pancreatitis - Neurological symptoms (including motor weakness)	- Increased anion gap - Lactic acidosis - Raised aminotransferase, CPK, and LDH levels	Severe: replace toxicity drug and provide symptomatic treatment Life-threatening: - Discontinue all ARVs and provide symptomatic treatment - When symptoms resolve, restart ART, substitute d4T with ABC or AZT

6. Monitoring Antiretroviral Therapy

- Children with ART should be followed and dispensed drugs as scheduled every 1-2 months.
- Children at the beginning of ART should have frequent follow-up visits for more counseling, adherence support and drug toxicity monitoring. When the children exhibit good adherence and tolerance with the regimen, their clinical conditions improved, the time between the visits can be prolonged. More frequent visits should be scheduled in case children have new opportunistic infections, poor adherence, or need drug substitution .
- At each follow-up visit, the children should be evaluated for clinical course, mental and physical development, occurrence of infectious diseases, drug side effects, and assessed for treatment adherence, provided with necessary counseling, support and testing.

6.1. Clinical monitoring

At each follow-up visit, monitor the the children for clinical course, identify and manage the drug side effects or the occurrence of new opportunistic infections as specified follows:

- Assess milestones of physical and mental development
- Monitor clinical signs and symptoms associated with drug side effects, detect new or recurrent opportunistic infections; differentiate immune reconstitution or treatment failure. Hospitalize for monitoring and treatment or seek for consultation and referral as needed.
- Assess possibility of pregnancy for substituting ARV if indicated in case of female adolescents (not using EFV in the 1st trimester of pregnancy)

6.2. Laboratory monitoring

Table 9: Laboratory monitoring during ART in children

	Before initiation of ART	**During treatment**			
		4 weeks	**6 months**	**12 months**	**Every 6 months**
CD4 and % of CD4	✓		✓	✓	✓
CBC/Hb, ALT	✓		✓	✓	✓

CBC if using AZT containing regimen	✓	✓	✓	✓	✓
ALT if using NVP containing regimen	✓	✓	✓	✓	✓
Pregnancy test for female adolescents	✓	If suspected			
Viral load	(if available)				

Note:

During ART monitoring, if patients present with abnormal signs and symptoms, request immediately other necessary tests to timely detect the disease, make diagnosis and provide treatment.

6.3. Adherence monitoring

The adherence to treatment should be assessed at each follow-up visit, based on the following:

- Reports of the parents/care givers on administering drugs; ask the parents/care giver questions on how to administer drugs and how to manage when missing doses
- Counting the number of tablets left, examination for clinical and laboratory improvement.

If the children are poorly adhere to treatment, reasons should be investigated. The parents/care givers should be provided with adequate counseling on how to overcome barriers to adherence and how to get timely supports to ensure good adherence.

Instructions for missing ARV doses in children:

Right after recognizing missing a dose, **first** take immediately the missed dose. **Then** calculate the time remained from this moment to the next regular dose (in hours):

- If the remained time is **more than 4 hours**, take the following dose at the scheduled time;
- If the remained time is **less than 4 hours**, DO NOT take the following dose at the scheduled time, but wait until it reaches at least 4 hours to

take the next dose.

– If more than 2 doses are missed in a week, report to doctors in charge for more instructions.

6.4. Monitoring ART effectiveness:

Signs of good response to ART:

- Good physical and mental development: gaining weight and height, being physically active, meeting milestones for intelligent development.
- Lower morbidity or absence of opportunistic infections.
- Increase in CD4 count and CD4 percentage (often during 24 weeks after starting ART)

If children respond well to treatment:

- Continue ART regimen, modify ARV doses according children's weight and height
- Regular counseling on and support adherence and nutrition
- Drug dispensing and follow-up schedule

If children do not respond to treatment or have new clinical events:

- Counsel again on adherence, assess treatment adherence and apply measures to support treatment adherence
- Counsel on nutrition, provide measures to enhance nutrition
- Identify causes of no response to treatment or occurrence of new clinical events (distinguish between drug side effects or drug interactions, manifestations of immune reconstitution syndrome or treatment failure), do tests if necessary and provide appropriate treatment.

7. Immune Reconstitution Inflammatory Syndrome (IRIS)

7.1. Definition:

Immune reconstitution inflammatory syndrome (IRIS) is characterized by paradoxical worsening in the overall status of HIV-infected patients after the initiation of antiretroviral therapy, due to recovery of immune system.

The nature of IRIS is the overt inflammatory response of newly reconstituted immune system to live microorganisms in the body or the antigens of these agents.

Common manifestations of IRIS may include:

- The occurrence of OIs, which were not recognized before starting ART (such as TB, MAC, Cryptococcus meningitis, etc.)
- The deterioration of OIs, which have been treated before starting ART.
- The worsening of co-infections (hepatitis B and C) and autoimmune diseases (psoriasis, dermatitis, etc.).

Timing: IRIS typically occurs within 2-12 weeks of initiation of ART, but can do so at later time.

7.2. Incidence and risk factors

IRIS occurs in about 10% of patients initiating ART. Risk factors for IRIS include:

- Low CD4 cell count before the initiation of ART.
- History of OIs before initiation of ART. The closer the time of ART initiation to OI treatment, the higher risk of getting IRIS.
- Use of potent ARV regimen (e.g. PI/r based regimen).

To prevent IRIS, patients should be screened and treated for OIs before starting ART, particularly TB.

7.3. Manifestations of IRIS

Opportunistic infections and non- infectious diseases associated with IRIS:

- Mycobacterial diseases: TB (most common), MAC.
- Fungal infections: Cryptococcus neoformans, Penicillium marneffei, PCP.
- Viral diseases: CMV, Herpes simplex and herpes zoster, HBV, HCV, progressive multifocal leukoencephalopathy
- Protozoal diseases: toxoplasmal encephalitis, leishmaniasis
- Non infectious diseases: psoriasis, thyroiditis

7.4. Diagnosis of IRIS

- IRIS should be considered in children at more than 2 weeks after initiation of ART who adhere well to therapy but present with clinical deterioration, especially if patients have been in advanced stage of immunodeficiency

with low CD4 count or OIs before starting ART. It is necessary to differentiate from:

+ Drug side effects, or drug interaction

+ Manifestations of new opportunistic infections

+ Treatment failure (if patients have been on ART for more than 6 months).

7.5. Management of IRIS

- Some IRIS may be mild and resolve without treatment, and no treatment is required.
- Continue ART if patients can tolerate the regimen.
- Treat unmasking OIs according to causes; modify ARV regimen and doses if there is an interaction between ARV and OI drugs (e.g. replace NVP with EFV if patients are on rifampicin based anti-TB therapy and EFV is available). Resume the original regimen after completion of OI therapy.
- Discontinue ART temporarily only if patients are severe and cannot tolerate the regimen. Restart ARVs when inflammatory syndrome is improved and patients can tolerate the drugs.
- Consider corticosteroid therapy in moderate to severe cases of IRIS. Oral or parenteral prednisolone or methyl-prednisolone can be given at 0.5-1.0 mg/kg/day until the patients' condition improves, then taper over 1-2 weeks.
- Provide other interventions if necessary, such as surgical drainage of lymph node abscess, surgical relief of bowel or trachea obstruction.

8. First-line treatment failure and second-line regimens

8.1. Treatment failure assessment:

a. Principles

- Only consider treatment failure if children are on ART with triple regimen at least for 6 months and have had good adherence.
- Exclude IRIS or drug side effects, or conditions leading to poor drug absorption.

b. Criteria for treatment failure:

Clinical failure	- Lack of or decline in growth rate in children who initially respond to treatment - Loss of neurodevelopmental milestones or development of encephalopathy - Occurrence of new OIs or malignancies or recurrence of

	bacterial or fungal infections that are refractory to treatment
Immunological failure	– CD4 count falls to or below the level of severe immunodeficiency by age after initial recovery response Or – CD4 count falls rapidly below the level of severe immunodeficiency by age as confirmed by at least two consecutive times of testing for CD4 count Or – CD4 count falls to or below the baseline CD4 count. Or – CD4 count falls below more than 50% of the peak level during ARV treatment.

Note: Some conditions of clinical stage 3 such as lymph node TB, pulmonary TB, bacterial pneumonia may not be considered indicators of treatment failure, and do not require to change the regimen.

8.2. Management when suspecting treatment failure with first line regimen:

Continue the first line regimen and re-assess treatment outcome after 1 month, if:

- The children are not complying enough with the regimen, provide counseling and support for their families and caregivers.
- The children develop IRIS, or face drug side effects, or conditions leading to poor drug absorption, find out causes and manage accordingly.
  - Assess OI and concurrent diseases, timely treat and adequately provide prophylaxis.
  - Integrate clinical and CD4 criteria (or measure viral load) and seek for adequate consultation for determining treatment failure and limit as much as possible early switching while 1st line regimen is still in effect.

Table 10: Decision to switch to second line regimen with integrated clinical, immunological criteria

New or recurrent clinical events	Laboratory tests to assess treatment failure	Management

Clinical stage 1 or 2	CD4 not available	• Do not switch
	CD4 available	• Closely monitor clinical events and CD4 if CD4 is closed to severe immunodeficiency level • Consider switching only if at least 2 CD4 results are below severe immunodeficiency level by age
Clinical stage 3	CD4 not available	• Consider switching
	CD4 available	• Closely monitor clinical events and CD4 if CD4 is closed to severe immunodeficiency level • Switch if CD4 is below severe immunodeficiency level, especially if children have ever had good immunological response to ART
Clinical stage 4	CD4 not available	• Switch
	CD4 available	• Switch;

8.3. Choice of second line regimen

Table 11: Switching from 1st line to 2nd line regimens

Choice of switching regimen	
First line regimens	**Second line regimens**
• AZT or d4T + 3TC + NVP • AZT or d4T + 3TC + EFV	• ddI + ABC + LPV/r
• AZT or d4T + 3TC + ABC	• ddI + EFV + LPV/r • ddI + NVP + LPV/r
• ABC + 3TC + NVP or EFV	• AZT + 3TC (can add ddI) + LPV/r • d4T + 3TC + LPV/r

Note on usage of 2nd line regimen:

- *Alternative PI for LPV/r is ATV, which is used only for children over 6 years of age*
- *See drug side effects in Annex 3, dosages of 2nd line regimen in Annex 4 and drug interactions in Annex 5*
- *Didanosine (ddI):* once or twice a day p.o.. Take the drug on empty stomach, at least 1 hour before or 2 hours after meal.
- *Lopinavir/Ritonavir (LPV/r):* twice a day, every 12 hours; LPV/r capsule should be taken on full stomach; for LPV/r tablets, no diet restriction.
- *Atazanavir/Ritonavir (ATV/r):* once daily p.o.

8.4. Monitoring children on second line regimen:

- *Re-counsel care givers and children (for grown up children) to consolidate adherence*
- *Carefully counsel on new regimens*
- *Pay attention to drug side effects: hypersensitivity (abacavir), renal failure (tenofovir), pancreatitis (didanosine), hyperlipidemia and insulin resistant diabetes mellitus (PI drugs)*
- *Monitor drug interaction when using LPV/r*
- *Assess clinical and CD4 response similarly to that of 1st line regimen*

9. ART for children with TB

9.1. TB is diagnosed before starting ART

- TB treatment should be given for children 2 – 8 weeks before initiating ART.
- ARV treatment for children on TB therapy with rifampicin:

  + Children ≤ 3 years and < 10kg of body weight: AZT/d4T +3TC + ABC;

  or consider AZT + 3TC + NVP (if ABC is unavailable);

  + Children > 3 years and > 10kg of body weight: AZT/d4T +3TC + EFV

Note: NVP based regimen can be used again, when TB treatment with rifampicin is completed.

9.2. TB is diagnosed during ART:

- Determine if TB occurrence is IRIS. If yes, assess and mange IRIS.
- Continue with ART and treat TB

- Selection of regimens:
  - If children are on 1st line regimen without NVP, continue the regimen
  - If children are on 1st line regimen with NVP
    - Substitute NVP by ABC if children ≤ 3 years or <10 kg of body weight; change NVP to EFV if children > 3 years and > 10 kg of body weight and return to the standard d4T + 3TC + NVP regimen after completion of TB therapy
    - If ABC and EFV are unavailable, continue with NVP
  - If children are on second line regimen with LPV/RTV: increase ritonavir dose to the same as lopinavir.

10. ARV treatment for children with hepatitis coinfection

- Testing for viral hepatitis B and C coinfection should be done if possible.
- Prior to ARV treatment, measure liver enzymes as regulated.
  - If liver enzymes are elevated ≥ 2.5 times of upper normal limit, consider as follows:
    - For children > 3 years of age: Preferably, use AZT (or d4T) + 3TC + EFV
    - For children < 3 years of age or if EFV is unavailable, use AZT (or d4T) + 3TC + NVP; closely monitoring ALT level.
  - Do not treat with NVP based regimen when ALT > 5 times of upper normal limit.
- During ARV treatment, closely monitor clinical course and liver enzyme levels as regulated.
  - If ALT ≤ 5 times of upper normal limit, continue the treatment
  - If ALT level is between 5-10 times of upper normal limit, continue the regimen but monitor closely liver enzymes every 1-2 weeks ;
  - If ALT level is > 10 times of upper normal limit, in combination with jaundice, replace NVP with EFV or PI

- 3TC has some effects on hepatitis B. In case changing regimen is needed, 3TC should be continued in the new regimen to avoid flare of hepatitis B.
- ARVs have no effect on hepatitis C.

ANNEX

Annex 1 - Clinical and definitive diagnosis criteria of HIV/AIDS-related diseases in adults and adolescents

Diseases	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic	No HIV related symptoms and no signs on examination.	Not required
Persistent generalized lymphadenopathy	Lymph nodes >1 cm, in two or more non-contiguous sites, in absence of known cause and last more than 3 months	Confirmed by histology
Clinical stage 2		
Moderate weight loss	Unexplained weight loss. No weight gained in pregnancy	Confirmed by documented loss <10% body weight
Recurrent upper respiratory tract infection (two or more in past 6 months)	Symptom complex, e.g. unilateral face pain with one-side nasal discharge (sinusitis) or painful swollen eardrum (otitis media), cough with purulent sputum (bronchitis), sore throat (pharyngitis) without the characteristics of viral infection (e.g. cough or running nose)	Sub-clinical laboratory, where available, e.g. culture of suitable body fluid.
Herpes zoster	Painful rash of small fluid filled blisters in distribution of a nerve supply but does not cross midline.	Clinical diagnosis
Angular cheilitis	Splits or cracks on lips at the angle of the mouth, not due to iron or vitamin deficiency and usually responds to antifungal treatment.	Clinical diagnosis
Recurrent oral ulcerations	Aphthous ulceration, typically with a halo of inflammation and a yellow-	Clinical diagnosis

Diseases	Clinical diagnosis	Definitive diagnosis
(occurring 2 or more in past 6 Months)	grey pseudomembrane.	
Papular pruritic eruptions	Papular pruritic vesicular lesions, often with marked post-inflammatory hyperpigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy oily skin condition, particularly affecting hairly areas (forehead, underarms, upper trunk and perineum)	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of nail plate – with thickening and separation of nail from nail bed)	Culture of nail scrapings.
Clinical stage 3		
Severe unexplained weight loss (more than 10% measured body weight)	Unexplained weight loss (> 10% of body weight) without trying, and noticeable thinning of face, waist and extremities or body mass index < 18.5kg/m^2). 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 3 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	Reports of fever or night sweats for more 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	Documented fever >37.5 °C with negative blood culture,

Diseases	Clinical diagnosis	Definitive diagnosis
for longer than one month)	examination. Malaria must be excluded in malarial areas.	negative Ziehl-Nielsen (ZN) stain, negative malaria smear, normal or unchanged chest X-ray (CXR) and no other obvious focus of disease.
Persistent 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 onlateral borders of the tongue, which do not scrape off	Clinical diagnosis
Pulmonary TB (current)	Chronic symptoms lasting for more than 2-3 weeks: cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats and fatigue PLUS either positive 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)

Diseases	Clinical diagnosis	Definitive diagnosis
Severe bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, septicemia and 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
Unexplained anaemia (<8g/dl), neutropenia (<5 $x10^9$/l) or chronic (more than one month) thrombocytopenia (<5 $x10^9$/l) for more than one month	No presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.

Diseases	Clinical diagnosis	Definitive diagnosis
Clinical stage 4		
HIV wasting syndrome	Unexplained involuntary weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5 PLUS unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month OR Reported 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 > 37.5 °C 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 three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND No evidence of 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.

Diseases	Clinical diagnosis	Definitive diagnosis
Recurrent bacterial pneumonia (this episode plus one or more episodes in last six months)	Current episode plus one or more episodes in last six months. Acute onset (under two weeks) of symptoms (e.g. fever, cough, dypsnoea, and chest pain) PLUS new consolidation on clinical examination or chest x-ray, 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, or visceral of any 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 in swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/ histopathology
Extrapulmonary TB (EPTB)	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence of extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy, osteitis. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of EPTB	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from respiratory specimen then must have other evidence of extrapulmonary disease)
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or bloodbruise colour, skin lesions that usually develop into violaceous plaques or nodules	Macroscopic appearance at endoscopy or bronchoscopy, or by histopathology

Diseases	Clinical diagnosis	Definitive diagnosis
		Definitive diagnosis must be made on histopathology
CMV disease (organ other than liver, spleen or lymph nodes)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
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 lesions on neuroimaging (CT scan or MRI)
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) neuroimaging (CT scan or MRI).
Extrapulmonary Cryptococcosis (including meningitis)	Meningitis: usually subacute fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood
Disseminated non-tuberculous	No presumptive clinical diagnosis.	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue,

Diseases	Clinical diagnosis	Definitive diagnosis
mycobacteria infection		excluding lung
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis.	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodensity white matter lesions on neuroimaging or positive polyomavirus (JCV) PCR on CSF
Cryptosporidiosis (with diarrhoea lasting for more than one month)	No presumptive clinical diagnosis.	Identification of Cryptosporidia
Chronic isosporiasis	No presumptive clinical diagnosis.	Identification of *Isospora* with multiple stool examinations
Disseminated mycosis (coccidioidomycosis, 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.

Diseases	Clinical diagnosis	Definitive diagnosis
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV associated tumours	No presumptive clinical diagnosis.	Histology of relevant specimen or neuroimaging techniques for CNS tumours
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

Annex 2 - Clinical and definitive diagnosis criteria of HIV/AIDS-related diseases in children

The following criteria are used for the children less than 15 years with confirmed HIV infection

Diseases	Clinical diagnosis	Definitive diagnosis
CLINICAL STAGE 1		
Asymptomatic	No HIV-related symptoms and no clinical signs on examination	Not required
Persistent generalized lymphadenopathy	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguinal), without known cause	Clinical diagnosis
CLINICAL STAGE 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause	Clinical diagnosis
Papular pruritic Eruptions	Papular pruritic vesicular lesions	Clinical diagnosis
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	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis

Diseases	Clinical diagnosis	Definitive diagnosis
Lineal gingival Erythema	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	Clinical diagnosis
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	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small fleshcoloured or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate more advanced immunodeficiency	Clinical diagnosis
Recurrent oral ulceration	Current event plus at least one previous episode in past six months. Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane	Clinical diagnosis
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and	Clinical diagnosis

Diseases	Clinical diagnosis	Definitive diagnosis
	confluent. Does not cross the midline	
Recurrent or chronic upper respiratory tract infection	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 crouplike cough (LTB). Persistent or recurrent ear discharge	Clinical diagnosis
CLINICAL STAGE 3		
Unexplained moderate mlnutrition or wasting	Weight loss: low weight-for-age, up to −2 standard deviations from the mean, not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management	Documented failure to gain weight or weight loss: body weight of –2 SD, 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	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens

Diseases	Clinical diagnosis	Definitive diagnosis
Unexplained persistent fever (intermittent or constant, for longer than one month)	Fever or night sweats for longer than one month, either intermittent or constant, not responding to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas	Documented fever of >37.5ºC with negative blood culture, negative malaria smear and normal or unchanged CXR, and no other obvious foci of disease
Persistent oral candidiasis (after first 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)	Microscopy or culture
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off	Clinical diagnosis
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	Clinical diagnosis
Lymph node TB	Non-acute, painless “cold” enlargement of peripheral lymph nodes, localized to	Histology or fine needle aspirate positive for Ziehl–Neelsen stain or

Diseases	Clinical diagnosis	Definitive diagnosis
	One region. Response to standard anti-TB treatment in one month	culture
Pulmonary TB	Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adult with smear-positive PTB. No response to standard broad spectrum-antibiotic treatment	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active TB and/or culture positive for *Mycobacterium tuberculosis*
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in drawing, 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)
Symptomatic lymphocytic interstitial pneumonitis	No presumptive clinical diagnosis	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 cor pulmonale and may have increased exercise-induced fatigue.

Diseases	Clinical diagnosis	Definitive diagnosis
		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	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 (<8 g/dl), neutropenia (< 10^9/l) or chronic thrombocytopenia (<50 x10 ^{9}/ l)	No presumptive clinical diagnosis	Laboratory testing not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in WHO IMCI guidelines
CLINICAL STAGE 4		
Unexplained a severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss, stunting or wasting not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of – 3SD, as defined by WHO IMCI guidelines	Documented weight loss for age of more than – 3SD from the mean with or without oedema

Diseases	Clinical diagnosis	Definitive diagnosis
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 with/without prednisolone. CXR typical bilateral perihilar diffuse infiltrates	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage, or histology of lung tissue
Recurrent 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	Culture of appropriate clinical specimen
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 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	Culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea,	Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or

Diseases	Clinical diagnosis	Definitive diagnosis
bronchi or lungs)		macroscopic appearance at bronchoscopy or histology
Disseminated/Extrapulmonary TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features depend on organs involved, such as sterile pyuria, pericarditis, ascitis, pleural effusion, meningitis, arthritis or orchitis. Responde to standard anti-TB treatment	Positive microscopy showing acid-fast bacilli or culture of *M. tuberculosis* from blood or other relevant specimen except sputum or BAL. Biopy 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 redpurple lesions seen on bronchoscopy or endoscopy; • dense masses in lymph nodes, viscera or lungs by palpation or radiology; • histology
CMV retinitis or CMV infection affecting another organ, with onset at age	Retinitis only CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR)

over 1 month	patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis	
Central nervous system toxoplasmosis onset after age 1 month	Fever, headache, focal neurological system signs and convulsions. Usually responds within 10 days to specific therapy	Computed tomography (CT) scan (or other neuroimaging) showing single/multiple lesions with mass effect/enhancing with contrast
Extrapulmonary cryptococcosis including meningitis	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	CSF microscopy (India ink or Gram stain), serum or CSF cryptococcal antigen test 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	Neuroimaging demonstrating atrophy and basal ganglia calcification and excluding other causes

	stagnation of head circumference; **or** • acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances	
Disseminated mycosis (histoplasmosis, coccidioidomycosis, or penicilliosis)	No presumptive clinical diagnosis	Histology: usually granuloma formation Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture
Disseminated nontuberculous mycobacterial Infection	No presumptive clinical 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 clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool

Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis	Diagnosed by central nervous system neuroimaging, histology of relevant specimen
Progressive multifocal leukoencephalopathy	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 neuroimaging or positive polyomavirus JC (JCV) PCR on CSF
Symptomatic HIV-associated Nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptomatic HIV-associated Cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Annex 3 - Summary of ARV drugs

Drug name	Abbreviation	Dosage	Tablet/Day	Interactions with food	Side effects
Nucleoside Reverse Transcripatase Inhibitors (NRTIs) Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)					
Zidovudine	AZT, ZDV	300 mg, twice daily	2	No interaction	Leukopenia, anemia, fatigue, malaise, headache nausea, vomiting, hepatitis, myopathy actic acidosis with hepatic steatosis
Stavudine	d4T	30 mg, twice daily	2	No interaction	Peripheral neuropathy Nausea, vomiting, elevated liver enzymes Lactic acidosis with hepatic steatosis
Didanosine	ddI	< 60kg: 125 mg, twice daily ≥60kg: 250 mg, twice daily	4	Take 30 – 60 minutes before meals	Peripheral neuropathy, headache Pancreatitis, nausea, diarrhea, abdominal pain Rash, fever; lactic acidosis with hepatic steatosis
Lamivudine	3TC	150 mg twice daily or 300mg once daily	2	No interaction	Minimal toxicity Headache, insomnia; rash; lactic acidosis with hepatic steatosis
Abacavir	ABC	300 mg twice daily	2	No interaction; alcohol increases ABC levels 41%	Hypersensitivity reaction (fever, rash, nausea, vomiting, abdominal pain -- can be fatal on rechallenge) Lactic acidosis with hepatic steatosis
Tenofovir	TDF	300 mg once daily	1	No interaction	Nausea, vomiting, diarrhea
Non-Nucleoside Reverse Transcripatase Inhibitors (NNRTIs)					

Efavirenz	EFV	600 mg at bed time	1	Avoid taking after high fat meals	Rash, Stevens-Johnson syndrome CNS symptoms, including insomnia, nightmares, hallucinations, mood disturbance Elevated liver enzymes Teratogenic. Contraindicated in pregnancy.
Nevirapine	NVP	200 mg once daily in the first 2 weeks, then 200 mg twice daily	2	No interaction	Rash, Stevens-Johnson syndrom Elevated liver enzymes
Protease Inhibitors *(PIs)*					
Atanazavir + ritonavir	ATV/r	300 mg /100 mg, once daily	1		Gastrointestinal intolerance, nausea, vomiting, diarrhea, abdominal pain,, elevated bilirubin, elevated liver enzymes
Lopinavir + ritonavir	LPV/r	LPV/r: 133,3 mg/33 mg twice daily	3 tablets each time, twice daily (400 mg/100 mg twice daily 4 tablet each time, twice daily when used with EFV or NVP		GI intolerance, nausea, vomiting, diarrhea Rash; headache; hyperglycemia, fat redistribution and abnormal lipids
		LPV/r: 200 mg/50 mg	For the patients who have never been on ARV 2 tablets/twice daily, even if taken with EFV or NVP (400/100 mg twice daily)		
			For the ARV patient 3 tablets twice daily, even if taken with EFV or NVP (600/150 mg twice daily)		
Ritonavi	RTV	Mostly used to boost other PIs			GI intolerance, nausea, vomiting, diarrhea Altered taste; Hepatitis; Hyperglycemia, fat redistribution and abnormal lipids

Annex 4 - Pediatric ARV dosages – Standardized with Developmental Indexes of Vietnamese Children

NRTIs

Weight (kg) *Surface area[1] ($m^{2)}$*	**Stavudine[2]** (d4T, Zerit)		**Zidovudine** (ZDV, Retrovir)		**Lamivudine** (3TC, Epivir)		**Didanosine[3]** (ddI, Videx)		**Abacavir[4]** (ABC, Ziagen)	
	1 mg/kg x **2 times/day**		180-240mg/m^2 x **2 times/day**		4 mg/kg x **2 times/day**		<3 months: **50 mg/m^2** x **2 times/day** 3 months -13 years: **90-120 mg/m^2**x **2 times/day** ≥13 years *or* > 60kg: **200 mg** x **2 times/day**		8 mg/kg x **2 times/day**	
	Syrup 1mg/ml	*Capsule 15,20,30mg*	*Syrup 10mg/ml*	*Tablet 100, 300mg*	*Syrup 10mg/ml*	*Tablet 150mg*	*Syrup 10mg/ml*	*Tablet 25, 50,100mg*	*Syrup 20mg/ml*	*Tablet 300mg*
3,5–4,9kg *0,21–0,28m^2*	5ml		5ml		2ml		3ml		2ml	
5,0–6,5kg *0,28–0,33m^2*	6ml		6ml		3ml		4ml		2.5ml	
6,6–8,0kg *0,34–0,40m^2*	8ml		8ml		3ml		5ml	2 tablets of 25mg	3ml	

8,1–10,0kg *0,40–0,47m²*	**8-9kg**: 9ml **9-10kg**: 10ml		**8-8,9kg**: 9ml **9-10kg**: 10ml	1 tablet of 100mg	4ml			2 tablets of 25mg	4ml	
10,1–11,9kg *0,48–0,54m²*		1 capsule of 15mg		1 tablet of 100mg	5ml			2 tablets of 25mg	5ml	
12,0–14,9kg *0,55–0,64m²*		1 capsule of 15mg		**12-13,9 kg**: 1 tablet of 100mg **14-14,9 kg**: ½ tablet of 300mg	6ml			(1 tablet of 50mg + 1 tablet of 25mg)	6ml	
15,0–16,9kg *0,65–0,72m²*		1 capsule of 20mg		½ tablet of 300mg	7ml	½ tablet		2 tablets of 50mg morning 1 tablet of 50mg + 1 tablet of 25mg night		½ tablet
17,0–19,9kg *0,72–0,83m²*		1 capsule of 20mg		½ tablet of 300mg	8ml	½ tablet		2 tablets of 50mg		½ tablet
20,0–24,9kg *0,83–*		1 capsule of 20mg		2 tablets of 100mg		1 tablet morning ½ tablet		**20-22kg**:2 tablets of 50mg **22-24,9kg**: (1 tablet of		**20-23 kg**:½ tablet **23,1-24,9 kg**:1

0,98m²						night		100mg+1 tablet of 25mg)		tablet morning, ½ tablet night
25,0–29,9kg *0,99–1,15m²*		1 capsule of 30mg		2 tablets of 100mg		1 tablet		(1 tablet of 100mg+1 tablet of 25mg) x2 times/day		1 tablet morning ½ tablet night
≥ 30,0kg *≥1,15m²*		1 capsule of 30mg		1 tablet of 300mg		1 tablet		**30-60kg**: (1 tablet of 100mg+1 tablet of 25mg) **>60kg**: 2 tablets of 100mg		1 tablet

NNRTIs

Weight (kg) *Surface area (m²)*	**Nevirapine**[5] (NVP, Viramune)				**Efavirenz**[6] (EFV, Sustiva, Stocrin)
	Initial dose – **once daily for 14 days** **160-200 mg/ m²**		**Maintenance dose – 2 times/day** **<8 years**: 200 mg/ m² **≥8 years**: 160-200 mg/ m²		**Once daily at bedtime**
	Syrup *10 mg/ml*	*Tablet* *200 mg*	*Syrup* *10 mg/ml*	*Tablet* *200 mg*	*Capsule* *50, 200, 600 mg*
3,5 – 4,9 kg *0,21 – 0,28 m²*	5 ml		5 ml		

5,0 – 6,5 kg *0,28 – 0,33 m^2*	6 ml		6 ml		**Do not use for children < 3 years** **and** **Weight < 10 kg**
6,6 – 8,0 kg *0,34 – 0,40 m^2*	7.5 ml		7.5 ml		
8,1 – 10,0 kg *0,40 – 0,47 m^2*	9 ml		9 ml		
10,1 – 11,9 kg *0,48 – 0,54 m^2*	10 ml	½ tablet		½ tablet	1 capsule of 200 mg once daily
12,0 – 14,9 kg *0,55 – 0,64 m^2*		½ tablet		½ tablet	1 capsule of 200 mg once daily
15,0 – 16,9 kg *0,65 – 0,72 m^2*		½ tablet		1 tablet morning ½ tablet night	(1 capsule of 200mg + 1 capsule of 50mg) once daily
17,0 – 19,9 kg *0,72 – 0,83 m^2*		1 tablet		1 tablet morning ½ tablet night	(1 capsule of 200mg + 1 capsule of 50mg) once daily
20,0 – 24,9 kg *0,83 – 0,98 m^2*		1 tablet		1 tablet morning ½ tablet night	(1 capsule of 200mg + 2 capsules of 50mg) once daily
25,0 – 29,9 kg *0,99 – 1,15 m^2*		1 tablet		1 tablet	(1 capsule of 200mg + 3 capsules of 50 mg) once daily

≥ 30,0 kg *≥ 1,15m²*		1 tablet		1 tablet	**30 – 39.9kg**: 2 capsules of 200 mg once daily **≥ 40.0 kg:** 3 capsules of 200mg or 1 capsule of 600mg once daily

PIs

Weight (kg) *Surface area (m²)*	**Lopinavir/Ritonavir**[7] (LPV/RTV, Kaletra, Aluvia)			**Trimethoprim/ sulfamethoxazole** (TMP + SMX) **Cotrimoxazole** (CTX)	
	5-7.9 kg: 16 mg/kg x **2 times/day** **8-9.9 kg**: 14 mg/kg x **2 times/day** **10-13.9 kg**: 12 mg/kg x **2 times/day** **14-39.9 kg**: 10 mg/kg x **2 times/day**			TMP 5 mg /kg **once daily**	
	Syrup *(LPV 80mg/ RTV 20 m /ml)*	*Coated tablet Aluvia* *(LPV 100 mg/RTV 25 mg)*	*Coated tablet Aluvia* *(LPV 200 mg/ RTV 50 mg)*	*Syrup TMP 8 mg/SMX 40 mg/ ml* *(TMP 40 mg/ SMX 200ml/ 5 ml)*	*Tablet* *TMP 80 mg/ SMX 400 mg (single strength)*
3,5 – 4,9 kg *0,21 – 0,28 m²*	1 ml			2.5ml once daily	
5,0 – 6,5 kg *0,28 – 0,33 m²*	1 ml			4 ml once daily	

6,6 – 8,0 kg *0,34 – 0,40 m^2*	1.5 ml			5 ml once daily	½ tablet once daily
8,1 – 10,0 kg *0,40 – 0,47 m^2*	1.5 ml	1 tablet		6 ml once daily	½ tablet once daily
10,1 – 11,9 kg *0,48 – 0,54 m^2*	2 ml	2 tablets morning 1 tablet night		7 ml once daily	½ tablet once daily
12,0 – 14,9 kg *0,55 – 0,64 m^2*	2 ml	2 tablets	1 tablet	8 ml once daily	1 tablet once daily
15,0 – 16,9 kg *0,65 – 0,72 m^2*	2 ml	2 tablets	1 tablet	10 ml once daily	1 tablet once daily
17,0 – 19,9 kg *(0,72 – 0,83 m^2*	2.5 ml	2 tablets	1 tablet	11 ml once daily	1 tablet once daily
20,0 – 24,9 kg *0,83 – 0,98 m^2*	3 ml	2 tablets	1 tablet		1 ½ tablets once daily
25,0 – 29,9 kg *0,99 – 1,15 m^2*	3.5 ml	3 tablets	2 tablets morning 1 tablet night		2 tablets once daily
≥ 30,0 kg *≥ 1,15m^2*		4 tablets	2 tablets		2 tablets once daily

Fixed dose combination (FDC)

Weight (kg) *Surface area (m^2)*	Use single ARVs for initial dose **x 14 initial days**			Use fixed dose combinations (FDCs)[8] for **maintenance dose x 2 times/day**		
	d4T: 1 mg/kg *(Syrup 1 mg /ml, Capsule 15, 20, 30 mg)* **2 times/day**	**3TC: 4 mg/kg** *(Syrup 10 mg / ml, Tablet 150 mg)* **2 times/day**	**NVP: 160-20 mg/m^2** *(Syrup 10 mg / ml, Tablet 200 mg)* **Once daily**	**Fixed dose combination d4T-6** *(Tablet d4T 6 mg/ 3TC 30 mg/ NVP 50 mg)* (Triomune Baby)	**Fixed dose combination d4T-12** *(Tablet d4T 12 mg/ 3TC 60 mg/ NVP 100 mg)* (Triomune Junior)	**Fixed dose combination d4T-30** **(***Tablet d4T 30 mg/ 3TC 150 mg/ NVP 200 mg)* (Fixed dose combination for adults)
3,5 – 4,9 kg *0,21 – 0,28 m^2*	5 ml	2 ml	5 ml once daily	**Do not use fixed dose combinations (FDCs) for children < 5kg (use single drugs)**		
5,0 – 6,5 kg *0,28 – 0,33 m^2*	6 ml	3 ml	6 ml once daily	**5 – 5.9 kg**: 1 tablet **6.0 – 6.5 kg**: 1½ tablets morning, 1 tablet night		
6,6 – 8,0 kg *0,34 – 0,40*	8 ml	3 ml	7.5 ml once daily	1½ tablets		

m^2						
8,1 – 10,0 kg *0,40 – 0,47 m^2*	**8-8.9kg**: 9 ml **9-10kg**: 10 ml	4 ml	9 ml once daily	1½ tablets		
10,1 – 11,9 kg *0,48 – 0,54 m^2*	1 capsule of 15mg	5 ml	½ tablet once daily	2 tablets	1 tablet	
12,0 – 14,9 kg *0,55 – 0,64 m^2*	1 capsule of 15 mg	6 ml	½ tablet once daily	2 tablets	1 tablet	
15,0 – 16,9 kg *0,65 – 0,72 m^2*	1 capsule of 20 mg	7 ml or ½ tablet	½ tablet once daily		1½ tablets morning, 1 tablet night	
17,0 – 19,9 kg *0,72 – 0,83 m^2*	1 capsule of 20 mg	8 ml or ½ tablet	1 tablet once daily		1½ tablets morning, 1 tablet night	
20,0 – 24,9 kg	1 capsule of 20 mg	1 tablet morning, ½ tablet night	1 tablet once daily		1½ tablets	

0,83 – 0,98 m^2						
25,0 – 29,9 kg *0,99 – 1,15 m^2*	1 capsule of 30 mg	1 tablet	1 tablet once daily		2 tablets	
≥ 30,0 kg *≥ 1,15m^2*	1 capsule of 30 mg	1 tablet	1 tablet once daily			1 tablet

Annex 5 - Interactions of ARVs

ARV drugs	Interacted drugs	Mechanism/effect	Recommendations
LPV/r	Clarithromycin	Decreased metabolism, clarithromycin concentration increased	Adjust clarithromycin dose only in renal failure
EFV, NVP	Clarithromycin	Increased metabolism, clarithromycin concentration decreased	The efficacy of MAC treatment and prophylaxis may be decreased
EFV	Rifabutin	Increased metabolism, significant decrease in rifabutin levels/ Efavirenz level may decrease	Increase rifabutin dose to 450-600mg daily or 600mg twice weekly. No dosage change necessary for efavirenz.
NVP	Itraconazole	Can affect concentration of both NVP and itraconazole	Adjust dose of NVP and intraconazole
EFV	Intraconazole	Decrease 35-44% maximum & minimum concentration of intraconazole and intraconazole-OH	Adjust dose of intraconazole
ddI	Gancyclovir	ddI level increased up to 100%	Monitor for ddI-related adverse reactions.
LPV/r	Ketoconazole	Decreased metabolism, ketoconazole concentration increased	Use with caution at ketoconazole doses > 200 mg/day
ddI	Fluoroquinolone antibiotics	Mark decrease in quinolone drug levels because of cationization	Administer didanosine at least 2 hours after quinolone.

RTV, LPV/r,	Rifabutin	Decreased metabolism, significant increase in rifabutin levels/ Increased metabolism, saquinavir level may decrease	Decrease rifabutin to 150mg every other day or 3 time per week. Consider increasing indinavir to 1000mg every 8 hours if this is the only PI administered; No dosage change for other PIs.
NVP, LPV/r	Rifampicin	Increased metabolism, significant decrease in NVP and PI levels	
EFV, RTV, NVP	Rifampicin	Increased metabolism, decrease in PI or nevirapine levels	Possible combination use.
d4T, NVP, EFV, RTV, LPV	Methadone	Decreased methadone concentration	Withdrawal syndrome can occur; may require increase in methadone dose
ATV	Contraceptives Norethindrone, Ethinyl estradiol	Increased concentration of contraceptives	No need to adjust doses of contraceptives
NVP, RTV, LPV	Ethyl estradiol	Significant decrease in Ethyl estradiol concentration	Use alternative or supportive contraception methods
ddI	TDF	Increased ddI levels	Decrease ddI dose to 250mg a day

Annex 6 - Severity grading of ARV side effects in adults

Parameters	**GRADE 1 (Mild)** Mild symptoms, no limitation of patients in action, no treatment/ intervention is required	**GRADE 2 (Moderate)** Activity of patients may be limited and need support, no treatment or limited treatment is required	**GRADE 3 (Severe)** Significant limitation in patient's activity; medication treatment is required, hospitalization might be needed	**GRADE 4 (Life-threatening)** Severe limitation in patient's activity, significant support needed, intensive treatment is required, hospitalization or palliative care
HAEMATOLOGY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Haemoglobin	8.0 − 9.4 g/dl	7.0 − 7.9 g/dl	6.5 − 6.9 g/dl	<6.5 g/dl OR
Absolute neutrophil count	1000 −1500/ mm3 OR 1.0 − 1.5/G/l*	750 − 999/ mm3 OR 0.75 − 0.99/G/l*	500 − 749/ mm3 OR 0.5 − 0.749/G/l*	<500/mm3 OR <0.5/G/l*
Platelets	75000 − 99000/mm3 OR 75 − 99/ G/l*	50000 − 74999/mm3 OR 50 − 74.9/G/l*	20000 − 49999/mm3 OR 20 − 49.9/G/l*	<20000/mm3 OR <20/G/l*
CHEMISTRIES	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
SODIUM				
Hyponatraemia	130 − 135 meq/l OR 130 − 135 mmol/l	123 − 129 meq/l OR 123 − 129 mmol/l	116 − 122 meq/l OR 116 − 122 mmol/l	<116 meq/l OR <116 mmol/l
Hypernatraemia	146 − 150 meq/l OR 146 − 150 mmol/l	151 − 157 meq/l OR 151 − 157 mmol/l	158 − 165 meq/l OR 158 − 165 mmol/l	>165 meq/l OR >165 mmol/l
POTASSIUM				

Hyperkalaemia	5.6 − 6.0 meq/l OR 5.6 − 6.0 mmol/l	6.1 − 6.5 meq/l OR 6.1 − 6.5 mmol/l	6.6 − 7.0 meq/l OR 6.6 − 7.0 mmol/l	>7.0 meq/l OR >7.0 mmol/l
Hypokalaemia	3.0 − 3.4 meq/l OR 3.0 − 3.4 mmol/l	2.5 − 2.9 meq/l OR 2.5 − 2.9 mmol/l	2.0 − 2.4 meq/l OR 2.0 − 2.4 mmol/l	<2.0 meq/l OR <2.0 mmol/l
BILIRUBIN				
Hyperbilirubinaemia	>1.0 − 1.5 x ULN	>1.5 − 2.5 x ULN	>2.5 − 5 x ULN	>5 x ULN
GLUCOSE				
Hypoglycaemia	55 − 64 mg/dl OR 3.01 − 3.55 mmol/l	40 − 54 mg/dl OR 2.19 − 3.00 mmol/l	30 − 39 mg/dl OR 1.67 − 2.18 mmol/l	<30 mg/dl OR <1.67 mmol/l
Hyperglycaemia (nonfasting and no prior diabetes)	116 − 160 mg/dl OR 6.44 − 8.90 mmol/l	161 − 250 mg/dl OR 8.91 − 13.88 mmol/l	251 − 500 mg/dl OR 13.89 − 27.76 mmol/l	>500 mg/dl OR >27.76 mmol/l
Triglycerides	200 – 399 mg/dl OR 2.25 - 4.51 mmol/l	400 − 750 mg/dl OR 4.52 − 8.47 mmol/l	751 − 1200 mg/dl OR 8.48 − 13.55 mmol/l	>1200 mg/dl OR >13.55 mmol/l
Creatinine	>1.0 − 1.5 x ULN	>1.5 − 3.0 x ULN	>3.0 − 6.0 x ULN	>6.0 x ULN
Liver enzymes				
AST (SGOT)	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
GGT	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
PANCREATIC ENZYMES				

Amylase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life threatening consequences	Increased lactate with pH <7.3 with life threatening consequences
GASTROINTESTINAL	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for >3 days	Hospitalization required
Vomiting	Mild OR transient; 2−3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4−5 episodes per day OR vomiting lasting >1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR intravenous Rx required	Hypotensive shock OR hospitalization for intravenous Rx required
Diarrhoea	Mild OR transient; 3−4 loose stools per	Moderate OR persistent; 5−7 loose stools per day	Bloody diarrhoea OR orthostatic hypotension	Hypotensive shock OR hospitalization required

	day OR mild diarrhoea lasting <1 week	OR diarrhoea lasting >1 week	OR >7 loose stools/day OR intravenous Rx required	
RESPIRATORY	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O2 therapy
URINALYSIS	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24-hour urine	200 mg to 1 g loss/day OR <0.3% OR <3 g/l	1 g to 2 g loss/day OR 0.3% to 1.0% OR 3 g to 10 g/l	2 g to 3.5 g loss/day OR >1.0% OR >10 g/l	Nephrotic syndrome OR >3.5 g loss/ day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
MISCELLANEOUS	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Fever (oral, >12 hours)	37.7 − 38.5°C	38.6 − 39.5°C	39.6 − 40.5°C	>40.5°C for >12 continuous hours
Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Allergy	Itching, no rash	Limited rash	Diffuse maculopapular rash, phu mao mach	Anaphylactic shock
Rash hypersesnitivity	Erythema, pruritus	Diffuse maculopapular	Vesiculation OR moist	ANY ONE OF: mucous

		rash OR dry desquamation	desquamation OR ulceration	membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25−50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Annex 7 - Severity grading of ARV side effects in children

PARAMETER	MILD	MODERATE	SEVERE	SEVERE, POTENTIALLY LIFE-THREATENING
GENERAL GUIDANCE TO ESTIMATE GRADE OF SEVERITY [a]				
Characterization of symptoms and general guidance on management	Symptoms causing no or minimal interference with usual social and functional activities[b]: No therapy needed, monitor	Symptoms causing greater than minimal interference with usual social and functional activities: May require minimal intervention and monitoring	Symptoms causing inability to perform usual social and functional activities: Requires medical care and possible Hospitalization	Symptoms causing inability to perform basic self-care functions[c]: Requires medical or operative intervention to prevent permanent impairment, persistent disability or death
HAEMATOLOGY ***Standard International Units are listed in italics***				
Absolute neutrophil count	750 – <1.000/mm^3 *0.75 x10^9 – <1x10^9/L*	500 – 749/mm^3 *0.5 x10^9 – 0.749x10^9/L*	250 – 500/mm^3 *0.25 x10^9 – 0.5x10^9/L*	<250/mm^3 *<0.250x10^9/L*

Haemoglobin (child >60 days of age)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 - <8.5 g/dL *1.16 – <1.32 mmol/L*	6.5 – <7.5 g/dL *1.01 – <1.16 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L* or severe clinical symptoms due to anaemia (e.g. cardiac failure) refractory to supportive therapy
Platelets	100.000-<125.000/mm^3 *$100x10^9$ – $125x10^9$/L*	50.000-<100.000/mm^3 *$50x10^9$ – $<100x10^9$/L*	25.000-<50.000/mm^3 *$25x10^9$ – $<50x10^9$/L*	<25.000/mm^3 *< $25x10^9$/L* or bleeding
GASTROINTESTINAL				
Laboratory				
ALT (SGPT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
AST (SGOT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
Bilirubin (>2 weeks of age)	1,1 – 1,5 x ULN	1,6 – 2,5 x ULN	2,6 – 5,0 x ULN	> 5,0 x ULN
Lipase	1,1 – 1,5 x ULN	1,6 – 3,0 x ULN	3,1 – 5,0 x ULN	> 5,0 x ULN
Pancreatic amylase	1,1 – 1,5 x ULN	1,6 – 2,0 x ULN	2,1 – 5,0 x ULN	> 5,0 x ULN
Clinical				

Diarrhoea ≥1 year of age <1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day Liquid stools (more unformed than usual) but usual number per day	Persistent episodes of unformed to watery stools OR increase of 4–6 stools over baseline per day Liquid stools with increased number of stools per day OR mild dehydration	Grossly bloody diarrhoea OR increase of ≥7 stools per day or i.v. fluid replacement Indicated Liquid stools with moderate Dehydration	Life-threatening consequences (e.g. hypotensive shock) Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR hypotensive shock
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 Hours	Persistent nausea resulting in minimal oral intake for >48 hours OR aggressive rehydration indicated (e.g. i.v. fluids)	Persistent nausea with no or minimal oral intake resulting in dehydration and aggressive rehydration Indicated (e.g. i.v. fluids)

Pancreatitis	NA	Symptomatic AND hospitalization not indicated (other than emergency Treatment)	Symptomatic AND hospitalization not indicated (other than emergency treatment)	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. i.v. fluids)	Life-threatening consequences (e.g. hypotensive shock)
ALLERGIC/DERMATOLOGICAL				
Acute systemic allergic reaction	Localized urticaria (wheals) lasting for a few hours	Localized urticaria with indication for medical intervention OR mild angioedema	Generalized urticaria OR angioedema with indication for medical intervention OR symptomatic mild bronchospasm	Acute anaphylaxis OR life-threatening bronchospasm or laryngeal oedema

Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens–Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
NEUROLOGICAL				
Alteration in personality, behaviour or in mood[b]	Alteration causing no or minimal interference with usual social and functional activities[b]	Alteration causing greater than minimal interference with usual social and functional activities[b]	Alteration causing inability to perform usual social and functional activities[b] AND intervention Indicated	Behaviour potentially harmful to self or others or life-threatening consequences

Altered mental status	Altered mental staus causing no or minimal interference with usual social and functional activities[b]	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities[b]	Onset of confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities[b]	Onset of delirium, obtundation or coma
Neuromuscular weakness (including myopathy and neuropathy)	Asymptomatic with decreased strength on examination OR mild muscle weakness causing no or minimal interference with usual social and functional activities[b]	Muscle weakness causing greater than minimal interference with usual social and functional activities[b]	Muscle weakness causing inability to perform usual social and functional activities[b]	Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation

Neurosensory alteration (including painful neuropathy)	Asymptomatic with sensory alteration on examination OR minimal paraesthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paraesthesia causing greater than minimal interference with usual social and functional Activities	Sensory alteration or paraesthesia causing inability to perform usual social and functional Activities	Disabling sensory alteration or paraesthesia causing inability to perform basic self-care functions [c]
OTHER LABORATORY PARAMETERS ***Standard International Units are listed in italics***				
Cholesterol (fasting, paediatric <18 years old)	170 - < 200 mg/dL *4,40 – 5,15 mmol/L*	200 – 300 mg/dL *5,16 – 7,77 mmol/L*	> 300 mg/dL *> 7,77 mmol/L*	NA
Glucose, serum, high: non-fasting	116 – < 161 mg/dL *6,44 – < 8,89 mmol/L*	161 – < 251 mg/dL *8,89 – < 13,89 mmol/L*	251 – 500 mg/dL *13,89 – 27,75 mmol/L*	> 500 mg/dL *> 27,75 mmol/L*
Glucose, serum, high: fasting	110 – < 126 mg/dL *6,11 – < 6,95 mmol/L*	126 – < 251 mg/dL *6,95 – < 13,89 mmol/L*	251 – 500 mg/dL *13,89 – 27,75 mmol/L*	> 500 mg/dL *> 27,75 mmol/L*

Lactate	<2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences or related condition Present	Increased lactate with pH <7.3 with life-threatening consequences (e.g. neurological findings, coma) or related condition present
Triglycerides (fasting)	NA	500 – < 751 mg/dL *5,65 – < 8,49 mmol/L*	751 – 1.200 mg/dL *8,49 – 13,56 mmol/L*	> 1.200 mg/dL *> 13,56 mmol/L*

Notes:

a. Values are provided for children in general except where age groups are specifically noted.

b. Usual social and functional activities in young children include those that are culturally- and

Age appropriate (e.g. social interactions, play activities, learning tasks, etc.).

c. Activities that are culturally- and age-appropriate (e.g. feeding self with culturally appropriate

eating implement, walking or using hands)

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