

NATIONAL MANUAL FOR THE MANAGEMENT OF HIV-RELATED OPPORTUNISTIC INFECTIONS AND CONDITIONS

A HEALTHCARE WORKERS' MANUAL

MINISTRY OF HEALTH

1st Edition 2008

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FORWARD

The past 20 years have seen Kenya go through the rise of the HIV epidemic during which millions of Kenyans have succumbed to, and continue to suffer and die from opportunistic infections (OIs), which are responsible for most HIV-related illnesses and deaths. This situation pertains despite the fact that most OIs are preventable and/or treatable. The main contributing factors to this continued loss of life of PLHA are failure to diagnose HIV infection early, which would allow for interventions to prevent and treat OIs as well as ART to be instituted opportunistically; lack of standardized guidelines and protocols to support the management of OIs; lack of access to laboratory support for the management of OIs and lack of a consistent supply of good quality drugs needed to effectively manage common OIs.

While Kenya has made great strides in HIV treatment with affordable ARV drugs becoming more widely accessible, and widespread use of cotrimoxazole prophylaxis for PLHAs enrolled in care, more needs to be done to develop protocols that standardize the prevention and management of OIs and to make drugs required to effectively treat the common OIs and conditions more widely accessible. The benefits of improved management of OIs are additional to the benefits of ART; both of these interventions constitute important tenets of the comprehensive care of PLHA and should be offered in all comprehensive HIV care centres.

The development of this **National Manual for the Management of HIV-related Opportunistic Infections and Conditions** for use by health care workers at the frontline of our fight against HIV/AIDS is intended to improve their understanding of the causes, prevention and appropriate management of opportunistic infections and conditions in adults and adolescents (OIs in children is covered effectively in the Integrated Management of Childhood Illnesses – IMCI – materials). It is also intended to be a practical guide at the clinic level, so as to improve quality of life, treatment outcomes and survival of PLHA. Crucially, this manual uses a “symptom-based” approach to support health care workers at the most basic primary level to be able to effectively initiate the care of PLHA with OIs and refer patients as appropriate (effective triage of patients at the primary care level). The result of this will be to move the management of OIs closer to the patient while ensuring that referral links with higher-level facilities and care is cultivated.

We at the Ministry of Health appreciate the role of our partners, in particular USAID, together with the highly capable and committed experts from various institutions, whose contributions in realising this manual. It will no doubt provide a basic standard of care, which we hope, all practitioners in the HIV/AIDS management arena, whether in the private or public sector will adopt, to ensure optimal prevention and treatment is provided to those who need them. This too will encourage better comparison of outcomes from various regions or health care sectors and by different practitioners and provide an opportunity for all to learn from each other and improve our standards of care.



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NASCOP Website <http://www.aidskenya.org>

LIST OF ABBREVIATIONS

ABECB	Acute bacterial exacerbation of chronic bronchitis
AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral (drugs)
ATT	Anti-TB treatment
BD	Twice daily
BMI	Body mass index
BP	Blood pressure
CBC	Complete blood count
CD4	CD4+ T-cell (T-lymphocyte bearing CD4+ receptor)
CM	Cryptococcal meningitis
cm	centimetre
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRAG	Cryptococcal antigen
C/s	Culture and sensitivity
CSF	Cerebrospinal fluid
CT	Computerized Tomography
CTX	Cotrimoxazole
CXR	Chest X-ray
DBP	Diastolic blood pressure
D4T	Stavudine
DBS	Dried blood spot
Ddl	Didanosine
DNA	Deoxyribonucleic acid
DOT	Directly Observed Therapy
DS	Double strength
EC	Enteric-coated
ECG	Electrocardiogram
EFV	Efavirenz
EIA	Enzyme Immunoassay Assay
EPI	Expanded Program for Immunization
EPTB	Extra pulmonary tuberculosis
FBC	Full Blood Count
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FQ	Fluoroquinolone
Hb	Haemoglobin
HBV	Hepatitis B virus
HCF	Health care facility
HCV	Hepatitis C virus
HCWs	Health care workers
HIV	Human Immunodeficiency Virus
ICF	Intensive case finding
ICU	Intensive care unit
IM	Intramuscular
IPT	Isoniazid Preventive Therapy
INH	Isoniazid
IRIS	Immune Reconstitution Inflammatory Syndrome

IV	Intravenous
JVP	Jugular venous pulse
LIP	Lymphocytic Interstitial Pneumonitis
LN	Lymph nodes
LP	Lumber puncture
LRTI	Lower respiratory tract infection
MPs	Malaria parasites
MRI	Magnetic resonance imaging
MTCT	Mother-to-child transmission (of HIV)
NASCOP	National AIDS and STD Control Program
NSAIDS	Non-steroidal anti-inflammatory drugs
NTLPT	National Tuberculosis and Leprosy Program
NTS	Non-typhi salmonellae
NVP	Nevirapine
O/c	ova and cysts
OIs	Opportunistic Infections
PCP	<i>Pneumocystis</i> pneumonia
PI	protease inhibitor
PITC	Provider initiated testing and counselling
PLHA	People living with HIV/AIDS
PML	Progressive Multifocal Leukoencephalopathy
PMTCT	Prevention of Mother-to-child Transmission (of HIV)
PR	Pulse rate
PRN	As required
Pt	Patient
PTB	Pulmonary tuberculosis
RBS	Random Blood Sugar
RFT	Renal function tests
RNA	Ribonucleic acid
RR	Respiratory rate
RTI	Respiratory Tract Infection
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
SIADH	Syndrome of inappropriate ADH
SJS	Stevens-Johnson syndrome
SOB	Shortness of breath
SOBOE	Shortness of breath on exertion
SS	Single strength
TB	Tuberculosis
TLC	Total Lymphocyte Count
VL	Viral Load
UNAIDS	Joint United Nations Program on AIDS
USAID	United States Agency for International Development
WHO	World Health Organization

INTRODUCTION

Over the past 2 decades, better understanding of the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS), as well as the development of antiretroviral treatment (ART) have led to tremendous improvements in the management of HIV infection. Consequently, this has resulted in improved quality of life and survival of people living with HIV/AIDS (PLHA). While HIV, by and large, does not directly kill those it infects, it ravages their immune system allowing the entry of opportunistic infections (OIs), to which most patients eventually succumb. Prior to the advent of potent combination ART, it was recognized that prevention and effective treatment of OIs was associated with reduction in morbidity and mortality in PLHA. Even in the era of effective ART, OIs remain the most common cause of morbidity and mortality in PLHAs. The prevention and management of OIs remain important in the chronic care of PLHA whether or not they have access to ARV drugs.

Recognition of the first case of AIDS in Kenya in 1984 heralded the entry of HIV into our society. The gains made by the nation in most health indicators including child mortality and life expectancy have largely been eroded since then. HIV/AIDS has stretched the healthcare provision infrastructure and human resources to the limit. This impact on the health care sector has highlighted the need for improvement in infrastructure as well as in how services are delivered, including decentralization of services and the utilization of all levels of health care facilities and providers in the fight against this disease as some of the key responses to the epidemic.

The improvement in the capacity of health care workers (HCWs) to manage OIs could make a huge contribution in reducing HIV-associated disease burden and improve overall health in the society. The need to provide tools that would empower HCWs inspired the appraisal of an earlier edition and creation of a new and more inclusive, **National Manual for the Management of HIV-related Opportunistic Infections and Conditions**, by a multi-disciplinary team under the auspices of the National AIDS and STI Control Program (NASCO). The aim of this manual is to fill the extant gap in materials that HCWs at all levels of health care service delivery need to enable them to better provide care for PLHAs. It adopts a symptom-based approach to care, consistent with the approach used by the World Health Organization (WHO) in the Integrated Management of Adult and Adolescent Illnesses, which ensures that it is accessible and of practical use to all cadres of HCWs, to ensure that the management of OIs begins at the most basic level, closest to the patient. It emphasizes the fact that the management of OIs, as part of the comprehensive care of PLHA, starts within the home and community and requires specific interventions, many of which can be delivered through all levels of the health care system. To this end, it is necessary that both PLHA and the wider community be educated on basic information on prevention, the first line of defence against OIs, failure of which often results in the need for care beyond the community in a health care facility (HCF). The manual provides the information that HCWs need firstly, to equip PLHAs and their communities, with the necessary information on how they can better stay healthy and secondly for them to be able to provide preventive and treatment interventions at HCFs when the need arises.

We recognize that there are several books and manuals that address the management of HIV related opportunistic conditions at length; these books remain inaccessible to most of our HCWs. This **Manual** is not intended to be a comprehensive text on the management of HIV-related diseases, nor is it intended to replace the need for training and continued mentoring of HCWs in common acute and chronic conditions seen in PLHA presenting to our HCFs; it is anticipated that it will act as an accessible quick reference to help optimize service provision and improve outcomes of common OIs and conditions seen in PLHA. Although many of the conditions discussed occur in HIV-uninfected individuals as well, and are managed in the same way in these patients, it must be emphasized that Kenya is a high HIV-prevalence country and, as such, a significant proportion of patients seen in our medical facilities will be HIV-infected. Consequently, **all individuals seeking care whose HIV status is unknown should be offered HIV counselling and testing**. It is important to remember that, while HIV infection may predispose one to many other infections, these are not only limited to the-HIV infected.

The **Manual** is laid out in eleven chapters broadly based on the body systems, each with an introduction; where appropriate an algorithm(s) or a table summarizing the key issues, a narrative on the common disease(s) encountered in PLHA involving that system and the treatment. The exception is Chapter 1, which is an introduction to OIs in general.

An attempt has been made to put together a **Manual** that is comprehensive enough to answer the information needs of healthcare workers at all levels of service, yet keep it as a portable companion and reference. The solution to that challenge lay in giving up a little on depth in the narrative sections. This document should therefore, where found to be deficient, be used with other guidelines and references.

We hope you will find this OI Guide a useful tool in your daily interaction with those seeking services in your health facility.

A handwritten signature in blue ink, appearing to read 'I. Mohamed', with a horizontal line underneath.

Dr. I. Mohamed
Head, National AIDS and STI Control Program

CHAPTER 1: OVERVIEW OF OPPORTUNISTIC INFECTIONS AND CONDITIONS

CHAPTER 1: OVERVIEW OF OPPORTUNISTIC INFECTIONS AND CONDITIONS

1.1 Introduction

Human Immunodeficiency Virus (HIV) infection is a complex condition affecting the patient, their family and their community as a whole; it is a social problem that is often associated with stigma and discrimination; a psychological problem primarily because of the response of the infected individual, their family and community to the diagnosis; an economic set back due to the burden it places on families, communities and nations as a result of the cost of lost earnings, caring for and eventually, in many cases, losing infected individuals, the majority of who are in their most productive years; it often impacts negatively on individuals' sexual and reproductive health and capacity; and finally it is a complex medical problem associated with opportunistic infections and conditions which are often the cause of morbidity and mortality in PLHA. The diagnosis of HIV infection is therefore often the beginning of serious distress and concern to the infected individual and their family. Consequently, the care of persons living with HIV/AIDS (PLHA) needs to be as comprehensive as possible, providing a wide range of services beyond the provision of specific medical treatment, involving a multidisciplinary team of caregivers to encompass all the important aspects of this multifaceted condition.

Opportunistic infections (OIs) are the most important cause of morbidity and mortality in HIV-infected individuals. Improvement in the recognition, treatment and prevention of these conditions in PLHA has been shown to reduce morbidity and mortality in both industrialized and resource-limited settings. For the care of PLHA to be effective in its reach, it is essential that the community, all levels of the health care system and all cadres be involved in the provision of this package. These services should ideally be provided in a seamless and integrated way to avoid missed opportunities, multiple patient appointments and loss to follow up.

1.2 Natural History of HIV Infection and Opportunistic Infections

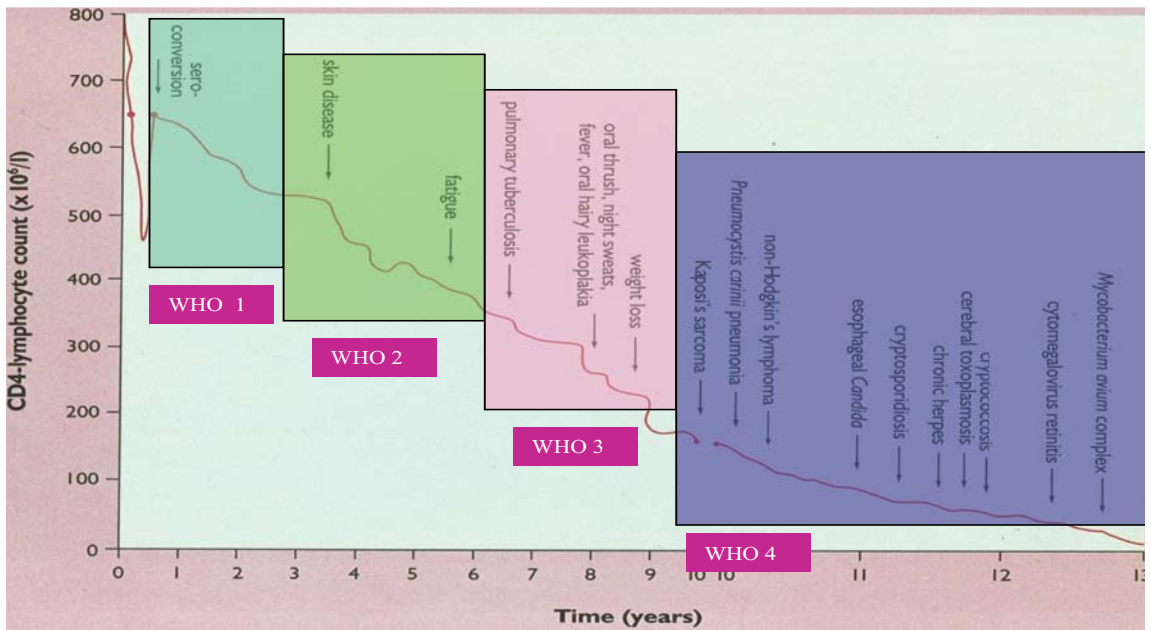
The natural history of untreated HIV infection is characterized by a period of time following infection with the virus during which the patient remains relatively well. The duration of this period of "clinical latency" varies between patients but on average lasts between 8-10 years from the time of infection with HIV. Despite the apparent wellness of patients during this period, there is continued HIV replication and an increasing rise in the amount of the HIV particles in the body (viral load). Persistent HIV replication results in a progressive destruction of the CD4+ T lymphocytes (CD4 cells). The viral load determines the rate of CD4 cell decline and, because of the centrality of these cells in the overall functioning of the immune system, the rate of destruction of the immune system.

It is the impairment of the immune system that results in PLHA becoming ill with repeated, more frequent and increasingly severe infections. In the early phase of HIV disease the conditions afflicting PLHA are no different from those commonly seen in HIV-negative individuals; as the immune suppression becomes more profound, unusually severe or recurrent forms of common infections or more atypical infections and conditions, begin to present in PLHA. Many of these conditions are rarely seen in patients without HIV infection. These conditions, such as *Pneumocystis pneumonia* (PCP) give opportunistic infections their name; they take advantage or are opportunists of a weakened immune system, causing disease, which they would otherwise not cause in healthy individuals. Patients with a severely compromised immune system, classified as WHO stage 4 disease and often associated with a CD4 less than 200 cells/ mm³ will on average die within a 2-4 year period unless effective antiretroviral treatment is provided.

An understanding of the natural history of HIV infection is essential in helping HCWs manage OIs because of the correlation between different OIs and the immune status of patients (see Figure 1). As important as the presenting symptoms and signs are in determining the diagnosis, knowledge of the previous clinical history of a patient as well as the CD4 count or trend is also critical in determining the differential diagnosis of an illness in an HIV infected patient. For instance, a PLHA presenting with cough, fever and increasing shortness of breath over a 4-week period, with no history of previous WHO Stage 3 or 4 illnesses and a CD4

count that has consistently been above 350 cells/mm³ in the preceding months, is unlikely to have PCP. On the contrary, a patient with the same symptoms and a recent CD4 count of 150 cells/mm³ is likely to have PCP as a probable diagnosis.

Figure 1.1 Natural History of HIV Infection: CD4 Decline and Opportunistic Infections



Because of the inexorable and predictable progression of HIV disease in most patients, **early knowledge of one's HIV status** is essential to help with the assessment of sick patients in this high prevalence set-up and allow the institution of interventions that will help improve the quality of and prolong the life of PLHA.

Table 1.1: CD4 and Risk of Opportunistic Infections and Conditions

CD4 Count (cells/mm ³)	Likely Opportunistic Infections and Conditions
Any CD4	HIVAN, KS, TB
> 200	Bacterial pneumonia, TB, sensory polyneuropathy, HAD, PPE, thrush, EPTB
100- 200	Above plus PCP, EPTB
< 100	Above plus Toxoplasmosis, PML, NHL. Cryptococcal meningitis
< 50	Above plus MAC, CMV retinitis, , primary CNS lymphoma

HIVAN = HIV associated nephropathy; KS = Kaposi's Sarcoma; PPE = Papular Pruritic Eruptions; HAD = HIV associated dementia; EPTB = Extrapulmonary TB; PML = Progressive multifocal encephalopathy; NHL = Non-Hodgkin's Lymphoma; MAC = Mycobacterium Avium Complex; CMV = Cytomegalovirus

1.3 Essentials for the Prevention and Treatment of Opportunistic Infections in PLHA

1. **Identification of exposed infants and HIV-infected individuals of all ages**, through appropriate counselling and testing (CT) services. These include voluntary counselling and testing (VCT), routine testing and counselling of pregnant women and HCF-based extensive provider initiated testing and counselling (PITC) services. **All** health care workers should be able to provide diagnostic or provider-initiated testing and counselling to patients presenting to HCFs, especially in TB, Family Planning/Sexually Transmitted Infections (FP/STI), outpatient and in-patient services. The aim should be to ensure that all entry points in HCFs are used to identify PLHA early so that they can be enrolled into care in a timely way. All HCWs should also be able to provide basic counselling and support of patients newly diagnosed with HIV infection, prior to referral to the HIV care clinic.
2. **Education and empowerment of PLHA to foster patient self-management**
 - PLHA should be provided with basic and general information on HIV infection and disease progression; and indications for, benefits of and how to take ART; opportunistic infections and how to prevent them. Well-informed patients are likely to be able to
 - Live “positively” and cope effectively with their illness (see section 1.3.1).
 - Be able to prevent and manage common ailments in the home.
 - Know when to attend a HCF should they be unwell. PLHA should be educated about OIs so that they can recognize important symptoms and present early to HCFs for assessment and care.
3. **Community level uptake of recommended preventive interventions.** Preventive measures against common infections and other OIs including basic hygiene, immunization and chemoprophylaxis should be made available to all PLHA as part of the **basic care package**. The basic care package can largely be advocated for and provided at the community level and includes:
 - Appropriate immunization (important especially in children)
 - Cotrimoxazole prophylaxis
 - Multivitamin supplements
 - Routine screening for TB at each clinical visit and if patient is symptomatic
 - Insecticide treated net for each patient
 - Clean drinking water (treated)
 - Prevention of onward transmission of HIV
4. **Nutritional advice, counselling and support** as appropriate and based on available resources should be made accessible to PLHA. This should include information and practical support on access to clean water, basic personal and environmental hygiene around and within the home and hygiene around food preparation and storage.
5. **Health care worker training, support and continued mentoring** to build capacity and enable them to
 - Provide basic emergency care for various infections and life threatening conditions.
 - Determine what can be done at the particular HCF and HCW level and what needs referral to the next level of HCW and/or HCF (effective triage of patients).
 - Provide PLHA with information on basic prevention of common infections within the home.
 - Provide PLHA with immunization and chemoprophylaxis as recommended by national guidelines.
 - Manage common OIs and conditions as appropriate to their skills and HCF capacity.
6. **Improvement of health care infrastructure** to facilitate chronic patient management at the most appropriate level including effective decentralization of services supported by appropriate supervisory and logistics framework, including improved patient referral systems.

1.3.1 Positive Living with HIV Infection

Successful living with HIV infection requires that patients accept their diagnosis and provide themselves and their family with an opportunity to look to the future with hope and move forward with their lives. Although individual characteristics may have a bearing on a person's capacity to deal with this often-devastating diagnosis, there are other controllable external factors that may contribute to a positive outlook in life with HIV infection. They include:

- Adequate counselling and support at diagnosis and thereafter as required.
- Supportive atmosphere at home, which often entails disclosure to a member or members of the family and/or close friend. Providing HIV care for affected families together as a unit may be very useful in fostering a supportive atmosphere at home.
- Patient taking care of him- or her-self; this requires patient education and empowerment and results in patients being able to address their nutritional requirements within their means, taking regular exercise and dealing with drug, alcohol and tobacco use.
- Supportive community environment with active addressing of stigma through community sensitization and education, patient support groups, etc. Patients should be encouraged to be part of these activities where possible.
- Supportive health care workers. HCWs should develop an open and honest relationship with the PLHA that recognizes and supports their role in the management of their own illness through education and empowerment.
- Provision of reproductive health care services that address the needs of PLHA including STI prevention and treatment, provision of effective contraception for those who need them, comprehensive advice on pregnancy for couples living with HIV and prevention of mother child transmission. Reproductive health services should also address the specific reproductive desires and hopes that individual patients may have.
- Prevention and timely treatment of OIs (addressed in the rest of the document)
 - Prevention of OIs involves patient education, behaviour modification as well as judicious use of chemoprophylaxis.
 - Successful treatment requires early recognition of symptoms and signs of impending disease severity both by patients and primary health care workers, and appropriate referral of patients for treatment at the most fitting level of care.
- Availability of effective ART and systems and structures that support successful ART. Patients who develop severe OIs need to start ART as part of their care. Ideally ART should be commenced before the "onset" of severe immunosuppression and the onset of severe life-threatening OIs.

In order to support affected Kenyan families and individuals to live a fulfilled and productive life after the diagnosis of HIV infection, it is important that all HCWs be skilled in the providing education and support on the issues listed above, be knowledgeable on various aspects of HIV care and be able to educate communities and PLHA to enable the PLHA, their family and community see the future beyond a positive HIV test.

1.4 Prevention of Opportunistic Infections

Many of the common OIs that affect PLHA are preventable. Involvement of PLHA is essential in preventing various OIs and to this end PLHA education to foster behaviour change to support prevention of OIs should be part of the routine discourse between HCWs and PLHA.

1.4.1 Nutrition

- A balanced diet adequate in calorific (energy) requirements is essential for all individuals, including PLHA, to maintain their health and wellbeing. Malnutrition is a risk factor for development of and increasing the severity of various illnesses including infections such as TB.
- PLHA are more likely to have inadequate intake of food due either to illness or an inability to obtain adequate food.

- The nutritional requirements of PLHA are likely to be higher than that of people without HIV, especially during periods of illness.
 - **It is therefore necessary to assess food availability and adequacy of all HIV positive individuals.**
 - Nutritional assessment and supplementation is part of the comprehensive care of HIV infection. A nutritional assessment should be carried out at initial patient evaluation and regularly during follow up. Any weight changes, abnormal blood tests (e.g. anaemia, hypoalbuminaemia), should necessitate an in-depth review of diet as part of the overall patient evaluation.
 - Simple and reproducible methods of nutritional assessment should be used (weight, BMI, mid-upper arm circumference).
 - Based on each individual's assessment, nutritional education and counselling should be provided; it is evident that even where food options are limited nutritional advice can improve the quality of an individual's diet.
- Food and/or micronutrient supplementation should be provided where necessary and where available. **Routine use of prescribed multivitamins in HIV-infected patients in resource-limited settings is recommended** because of the likely micronutrient deficiency of most diets as well as evidence of immunological benefits demonstrated in various patient groups in this setting.

1.4.2 Prevention of specific infections

○ Vaccine preventable illnesses

Where vaccines can be used to prevent common infections, they should be used as per local recommendations, for instance the childhood vaccines.

All attempts should be made to help the patient improve their home environment, as this will contribute to overall improvement in their health through reduction of common infections.

○ Bacterial Respiratory Tract Infections.

- Respiratory tract infections (RTIs) are more frequent, have a tendency to recur and are more likely to be severe in PLHA (especially as their immune system deteriorates) than in HIV-negative individuals.
- Early diagnosis and treatment can prevent a large proportion of deaths due to acute RTIs.
- It is important that both patients and HCWs be educated and informed to ensure early presentation of patients to HCFs and assessment and appropriate management of patients at the most appropriate level of services by HCWs.
- *Effective use of cotrimoxazole (CTX) prophylaxis in PLHA contributes tremendously to a reduction in RTIs.*

○ Tuberculosis (TB) See pg

○ Diarrhoeal diseases.

- Poor hygiene around the home, which includes poor handling and disposal of faecal matter, contributes to the spread of diarrhoeal diseases through contamination of drinking water and food.
- The incidence of bacterial and parasitic diarrhoeal diseases can be reduced through improvement of basic hygiene. Use of boiled or treated water for drinking; washing hands after using the toilet, handling animals or soil and before handling food; thorough and adequate cooking of food; avoidance of soft cheeses, unpasteurized milk (or boiling milk before use) should be emphasized to PLHA and practical tips provided where possible to empower them to adopt these changes in their lifestyle.
- *Effective use of cotrimoxazole (CTX) prophylaxis in PLHA contributes tremendously to a reduction in diarrhoea due to some bacterial and parasitic infections.*

o Malaria.

- HIV increases the risk and severity of, as well as deaths from, malaria in adults and children. It is important that all HIV-infected patients, along with pregnant women and children, living in malaria-endemic areas be provided with insecticide-treated nets.
- *Effective use of cotrimoxazole (CTX) prophylaxis in PLHA contributes significantly to a reduction in clinical malaria.*
- *ART used appropriately also further reduces the incidence of malaria in severely immunocompromised PLHA*

1.4.3 Chemoprophylaxis

1.4.3.1 Cotrimoxazole Prophylaxis

All HIV-infected individuals, regardless of age, ARV drug treatment status or immunological status, should be given cotrimoxazole unless it is contraindicated.

Adult Dose: 960 Mg OD (2 SS Tablets Or 1 DS Tablet Per Day)

Cotrimoxazole (CTX) prophylaxis is a cost-effective intervention, effective against the following infections in HIV positive patients:

- o Common bacterial infections, including bacterial pneumonia, septicaemia
- o Diarrhoea including that caused by *Isospora belli*
- o Malaria
- o Toxoplasmosis (primary or recurrent)
- o *Pneumocystis pneumonia* (PCP; primary or recurrent)

CTX has been shown to be effective despite prevailing high-level bacterial resistance in the setting where it is used. Further, it has been shown to be effective in patients with relatively well-preserved immune system as well, although the benefit derived is greater the more severely immunocompromised an individual is. In addition, it is now also apparent that even in patients on ART, bacterial infections remain a major cause of morbidity and mortality, suggesting that the benefits of CTX are likely to persist in patients on ART with recovering immune system.

CD4 cell measurement has been shown to be useful in the decision of whether to start or stop CTX prophylaxis in PLHA in industrialized countries where the spectrum and burden of infectious diseases is different from that in resource-limited settings. The evidence to support the use of CD4 measurement as an entry or exit criterion in resource-limited settings, with high background morbidity from infectious diseases is however unclear. Apart from this, limited availability of reliable CD4 testing in the early phase of scale-up of treatment and care in many parts of the country would mean that the use of CD4 criteria for CTX use would limit access to this effective and affordable intervention.

In view of the broad benefit derived from this simple intervention, even in patients with relatively good immune status, and the complexity of having entry and exit criteria based on CD4 levels in our local health care setting, **it is recommended that all HIV positive patients including those on ART take cotrimoxazole prophylaxis unless contraindicated.** This recommendation is in line with the 2006 edition of the WHO guidelines for use of CTX prophylaxis in resource-limited settings where bacterial infections and malaria are prevalent and cause significant morbidity across a wide immunological spectrum in PLHA.

Management of Patients with Cotrimoxazole Allergy

- CTX is effective as a chemo-prophylactic agent against a broad range of organisms; for this reason all effort should be made to ensure that patients, who can, start and continue to use CTX.
- A rash may occasionally develop, usually about 7-14 days following initiation of CTX. It is often a relatively mild maculopapular rash with or without pruritus. Infrequently, more severe rash may develop with severe exfoliation of the skin and Stevens-Johnson syndrome.
- Patients with mild to moderately severe rash should stop the CTX and once recovered should undergo desensitization as shown below in Table 1.
- Patients with severe rash (oedema, vesiculation of the skin, mucosal involvement) should **NOT** be desensitized; CTX should be stopped and never be re-used.
- Desensitization is effective in the majority of patients. The rapid regimen (Table 2) can be used in situations where treatment for PCP needs to be started urgently.
- Dapsone is recommended for use in patients unable to use CTX; unfortunately dapsone is not as effective a chemo-prophylactic agent as CTX and is effective against only PCP when used alone. (Ideally, pyremethamine should be used in addition, to provide effective prevention against toxoplasmosis).
 - Dapsone should be commenced in patients with WHO stage 3 or 4 disease and/or those with a CD4 < 200. It should be discontinued once the CD4 has been greater than 200 cells/mm³ for at least 6 months
 - **Dose** Adults and adolescents: 100mg OD

Cotrimoxazole Desensitization

Table 1.2: Standard Desensitization Regimen (Days) **Table 1.3: Rapid Desensitization Regimen (Hours)**

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

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

1.4.3.2 Isoniazid Preventive Therapy (IPT)

- The risk of new tuberculosis disease in HIV-infected individuals can be lowered, but not eliminated, by reducing exposure to TB, using isoniazid preventive therapy (IPT), and ART.
- INH given for a 6–9 month period reduces incidence of TB by about 60% in PLHA with a positive tuberculin skin test, and by about 40%, when used irrespective of skin-test results.
- Some centres may already be offering IPT routinely to PLHA. **Where IPT is used, it is important that screening for TB is done diligently, adherence counselling is provided and active patient follow-up is possible in the case of defaulters.**
- Where IPT is **NOT** used routinely in PLHA, it **should be offered to all children under 5 years exposed to “open TB” in a close contact** after active TB has been excluded.
- *Consideration should also be given to IPT provision in all HIV infected children after exclusion of TB because of the proven benefits.*

Assessment of PLHA for Eligibility for IPT (See Figure 1.2)

Assess Eligibility for IPT

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

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

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

- **All** children < 5 years exposed to “open” PTB in a close contact, with a negative TB screen should be given IPT regardless of HIV sero-status as a minimum standard of care
- **All** HIV positive children whom TB has been excluded (clinics encouraged to offer this based on available evidence)
- **All** HIV positive patients in whom TB has been excluded (universal use of IPT for PLHA) is an option practiced in some clinics which fulfil the basic requirements for this service

¹ These patients should be investigated for active TB; ² these patients should be treated for PTB

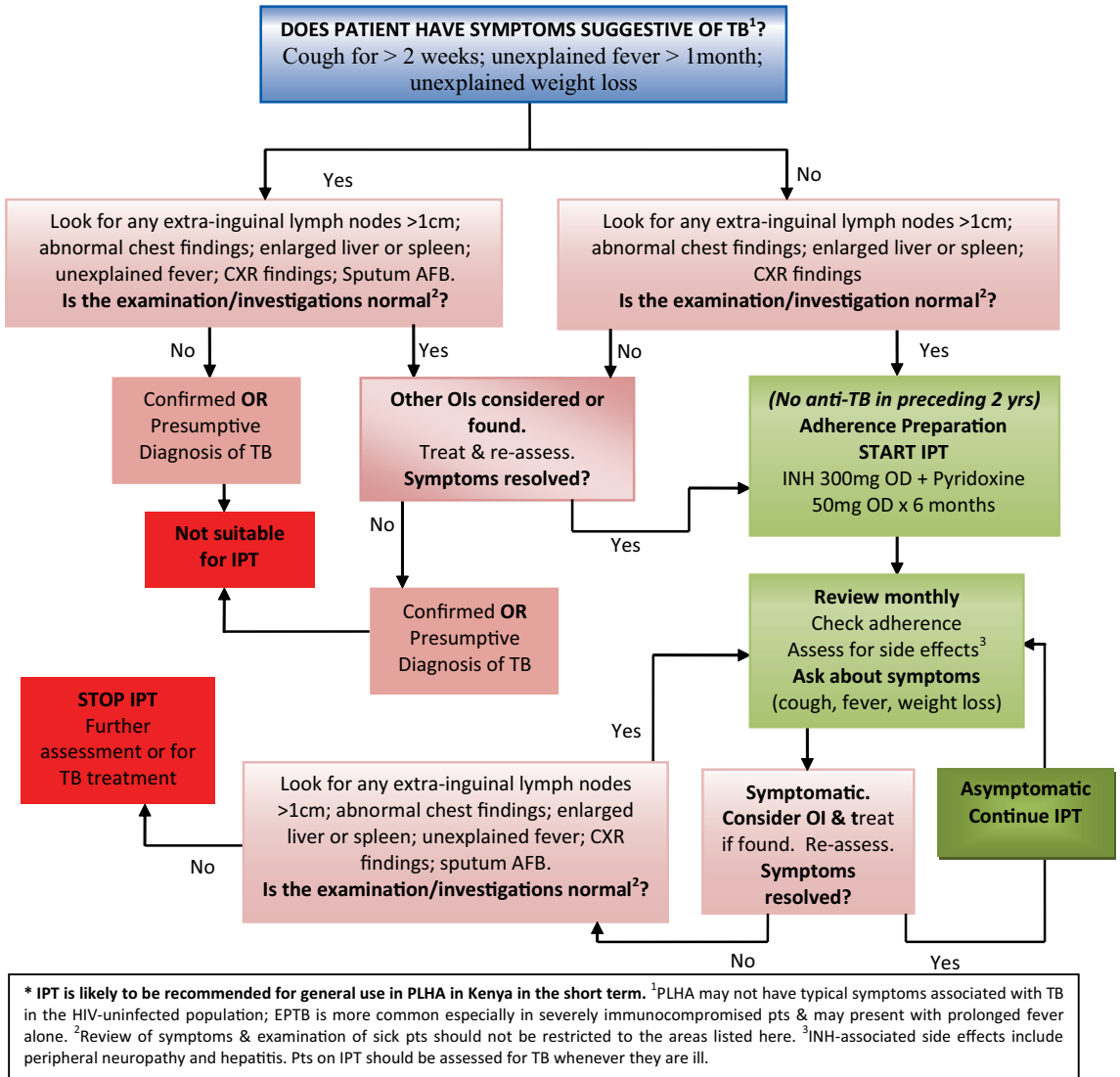
INH DOSE FOR IPT

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

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

Figure 1.2 ISONIAZID PREVENTIVE THERAPY (IPT) FOR PLHA

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



1.5 Principles of Management of Acutely Sick Patients

For effective management of a sick patient it is important that the HCW determines how severely ill the patient is and consequently, the level of care they require. To do these HCWs should always carry out the following in patients presenting with any acute illness:

- Assess for emergency symptoms and signs in **all** acutely ill patients. These are symptoms or signs that indicate that a patient needs emergency treatment started immediately, and also that in-patient hospital treatment might be necessary.
- If symptoms or signs indicative of severe illness are present stabilize the patient first as best as possible, before referral or consultation for further management.

1.5.1 Approach to an acutely ill patient

1. Check for emergency signs (see Table 1.4)
2. If emergency signs are present, institute emergency response immediately according to the presentation, as summarized in Table 1 below, and stabilize the patient
3. After stabilizing severely ill patients, consider referral to the next level of care if the particular HCF and/or cadres of HCWs available are unable to manage the patient. *Complete the clinical assessment as shown in Table 1.5 below when patient is stable.*
4. If patient has no emergency signs a complete clinical assessment should be carried out as per Table 1.6 below.
5. Carry out appropriate laboratory investigations where possible. All patients with an acute illness requiring out- or in-patient hospital care should be offered an HIV test unless their status is already known. Patient who have been tested in the past (> 1 year) but remain at risk (e.g. change sexual partners since last tested, in a sexual relationship where the partner's status is unknown) should be re-tested
6. Provide initial treatment based on the findings of the clinical assessment. Ensure that the patient understands the plan of action and agrees to follow treatment instructions
7. Arrange appropriate follow up for review of the acute illness
8. All HIV positive patients should be started on cotrimoxazole prophylaxis and multivitamins; arrangements should be made to ensure the patient is enrolled into HIV clinical care.

Table 1.4: Emergency Symptoms and Signs and Emergency Response

EMERGENCY SYMPTOMS OR SIGNS	CONFIRM	EMERGENCY RESPONSE
AIRWAYS: Is patient breathing? Is breathing obstructed – wheeze, stridor? Very rapid breathing?	Central cyanosis (blue tongue)? Count number of breaths in 1 minute.	Prop patient up Consider asthma, severe chest infection, and pulmonary oedema. 1.If obstructed breathing/wheeze give salbutamol nebulizer 2.If pulmonary oedema – give IV frusemide 3.If chest infection give first dose of IV/IM antibiotics Refer to hospital
CIRCULATION Any bleeding, diarrhoea? Cold clammy skin? Slow capillary refill (> 2seconds)? Fast, weak or absent radial pulse?	Patient may be in shock if pulse rate (PR) > 120/min, radial pulse weak or absent &/or measured systolic BP (SBP) < 90mmHg	Lie patient with legs higher than chest Insert IV line and give fluids rapidly Consider sepsis and give IV/IM antibiotics If diarrhoea, assess hydration & manage as per section 4.4.8 Pg 71. Refer to Hospital
IMPAIRED CONSCIOUSNESS &/OR CONVULSING Convulsing at presentation Unconscious/impaired consciousness (has patient had a fit?) Confused, agitated Ask about previous fits, poisoning, alcohol or other drug abuse	Measure temperature Measure pulse rate Assess consciousness level	Protect airway Protect patient from injury Insert IV line and give fluids slowly Give IM/IV antibiotics Give IV/IM antimalarial If convulsing give IV/PR diazepam stat and as required (See appendix 2 pg) If convulsions persist > 30min give IVI of phenobarbitone or slow IVI of phenytoin (ECG monitoring required) Refer to Hospital
FEVER: Temp > 40/<35°C	Ask about associated symptoms Measure PR, BP, RR	Depending on associated symptoms manage. If no other symptoms consider malaria or sepsis and give IV/IM antibiotics & antimalarial. Refer

Table 1.5: Summary: Clinical Assessment and Management of Sick Patients

1. HISTORY
Ask patient (or caregiver, if patient unable to provide a coherent history):
<ul style="list-style-type: none"> ○ How have you been? What problems have you developed? ○ Have you had any of the following? <i>If yes, ask for how long (duration)</i> <ul style="list-style-type: none"> - Fever? Night sweats? - Cough? If yes ask about duration, shortness of breath, sputum production? - Diarrhoea? Nausea or vomiting? Poor appetite? Mouth sores? Pain/difficulty swallowing? - Change in weight - New or worsening skin rash? - Headache? Painful neck? Eye pain? Weakness in any part of body? - Fatigue? - Pain passing urine? Passing urine more often than normal? If yes getting up at night to pass urine - Any other pain? If yes, where? - Problems sleeping at night? ○ For adolescent & adults: are you sexually active? Regular partner(s)? Do you know your HIV status? Is partner’s HIV status known? Condoms used consistently & correctly? Do you have genitourinary symptoms? (Discharge, ulcers, pain passing urine? <i>Treat syndromically if symptomatic</i>) ○ For women: when was the LNMP? If sexually active is contraception used? Desired? If needed offer options considering whether or not on ART. Ask whether patient has had cervical screening done. If so when? If not within past 1 year offer VIA/VILI at nearest service ○ Have you been hospitalized before? Treated for a medical problem recently? If yes, ask for & record diagnosis & treatment received. ○ Which medications are you taking and how often? If HIV+, are you on ARVs? Have you started any new medications recently?

2. EXAMINATION
<ul style="list-style-type: none"> ○ Measure temperature & blood pressure. Count number of breaths in 1 minute (respiratory rate, RR). ○ Look for pallor, lymphadenopathy (swollen glands), look at mouth for oral lesions/sores, thrush ○ Further assessment should be based on the presenting symptoms
3. LABORATORY TESTS
<ul style="list-style-type: none"> ○ Ensure patient is stable before ordering or waiting for lab tests (Table 1.4) ○ Choice of lab tests should be based on the history and examination findings ○ If HIV status is unknown or unconfirmed a diagnostic HIV test should be done. ○ If patient is known to be HIV+ and is already enrolled in care, find out the most recent CD4 count; if newly diagnosed or no CD4 arrange CD4 test
4. QUICK ADHERENCE ASSESSMENT IF ON ART
<p><i>Involve treatment supporter in discussions.</i></p> <ul style="list-style-type: none"> ○ Have you had any problems taking your medication? If so what? ○ How are you taking your medications? Can you demonstrate? ○ Carry out pill count and document ○ Are you taking any other drugs (traditional or herbal remedies, anti-TB treatment -ATT, illicit drugs etc)? ○ Relate adherence to clinical presentation and any available biological markers (CD4 trends, weight, VL if available) as well as current illness if appropriate. ○ Report adherence assessment in discharge summary ○ Confirm next appointment date to CCC prior to discharge from clinic/hospital
5. TREATMENT
<ul style="list-style-type: none"> ○ Provide emergency treatment if patient is severely ill (Table 1.4) and refer to the next level if required after emergency response ○ Decide on the appropriate treatment based on the comprehensive clinical assessment including the history, physical examination and any laboratory test results available. Review current treatment to ensure medication chosen poses no risks of untoward drug interaction ○ Explain the problem found (working diagnosis) to the patient. ○ If there are tests pending, discuss these and inform patient if they are likely to influence further management ○ Discuss any other measures necessary for the treatment of the patient ○ Agree with the patient on the management plan ○ Dispense medication; ensure the patient clearly understands how to take the medication, including correct dosing and any food or fluid restrictions ○ Reconcile ARV drugs dispensed with drugs patient has (as per the pill count, to avoid accumulation of drugs at home)
6. ARRANGE PATIENT FOLLOW UP
<ul style="list-style-type: none"> ○ Arrange a follow up appointment for review of the acute problem. ○ Advise the patient of symptoms and signs that should prompt them to attend earlier than planned. ○ PLHA who have never been enrolled should be given both cotrimoxazole and multivitamin and advised where and when they can be followed up for their HIV care.

1.6 When to Start ART in Patients with Acute OIs

The benefits of starting ART in the setting of an acute OI include

- Improvement in the immune function, potentially improving the chances of recovery from the OI. Conditions for which improvement of immune function has been shown to result in improved treatment outcome comprise conditions for which limited effective specific treatment is available such as Kaposi's sarcoma, progressive multifocal leucoencephalopathy (PML), chronic diarrhoea (due to cryptosporidiosis, microsporidiosis). In these cases the benefits of starting ART outweigh any considerations of some of the problems associated with starting ART during acute OI listed below; ART should therefore be started as soon as possible in patients with the above conditions.
- Reduction in chances of developing a second OI

Reasons against starting ART during an acute OI include

- Drug-drug interactions
- Pill burden
- Overlapping drug toxicity and difficulty determining which drug is responsible for a given toxicity
- Immune reconstitution inflammatory syndrome (see below).

While the above may make treatment of OIs and concomitant use of ART challenging it is still beneficial to start ART after 2 or so weeks of initiating specific OI treatment particularly for severely immunocompromised patients with TB and PCP. For most patients with OIs including those with cryptococcal meningitis it is reasonable to stabilize the patient prior to initiation of ART. **The decision as to whether or not to start ART in patients with acute OIs should be made by clinicians experienced in the management of HIV infected patients.**

1.6.1 Immune Reconstitution Inflammatory Syndrome

ART strengthens the immune system and restores that capacity of the body's defense mechanisms to fight against specific organisms (i.e. ART restores protective pathogen-specific immune responses), resulting in less frequent episodes of OIs. If there are pre-existing sub-clinical infections in the body at the time ART is started, the improving immune system begins to fight against these organisms. This can result in unexpected clinical worsening of a condition either not previously diagnosed or already being treated. The immune reconstitution inflammatory syndrome (IRIS) is the term used to describe the group of clinical symptoms and signs associated with the



unexpected worsening of a pre-existing condition under treatment or the presentation of a hitherto sub-clinical/undiagnosed condition in a patient recently started on ART, despite an adequate response to ART.

Risk factors for developing IRIS include starting ART in patients with severe immunodeficiency ($CD4 < 50$ cell/mm³), starting ART early in the course of treating an OI and starting ART in the presence of undiagnosed OIs.

The infectious organisms commonly implicated in the syndrome are mycobacteria, *Pneumocystis jiroveci*, Cryptococcus, herpes viruses including varicella zoster, hepatitis B virus and cytomegalovirus (CMV). IRIS can also occur in association with malignancies like KS.

Clinical Presentation of IRIS

The clinical presentation of IRIS depends on the inflammatory or infective pathology that is responsible for causing it, the particular organism involved and the site of disease. Generally a patient who has been improving develops worsening of or new symptoms and signs, which may or may not be typical of the underlying cause.

Differential diagnoses of IRIS include a new OI, ARV drug toxicity, ART failure and failure of the specific antimicrobial therapy. In order to arrive at the correct diagnosis a high index of suspicion is required and a thorough clinical assessment necessary. The following should be determined in the history

- Specific symptoms
- Recently and previously diagnosed or treated OIs; treatment initiation and completion dates
- ART history including regimen, when initiated, prior ART
- Adherence history and assessment for all medications, is essential.
- CD4 count at treatment initiation

Clinical examination and investigations should be carried out as guided by the symptoms. A clinician should

review patients recently starting ART who develop new or worsening symptoms or signs suggestive of OIs. ART failure is unlikely to be responsible for OIs presenting in an adherent patient on ART for period less than 6 months; however treatment failure should always be considered and where necessary and possible a viral load should be done to help in the diagnosis.

Table 1.6: Clinical Presentation of IRIS

Responsible Condition	Clinical Presentation of IRIS
TB	IRIS presents from 1-6 wks after starting ART. Commonly high fever, cough, dyspnoea; new or increased lymphadenopathy (peripheral or mediastinal); lymph node abscesses; worsening of pulmonary disease with new or increased infiltrates or effusion; new or worsening CNS presentation; other new extrapulmonary lesions
Herpes Zoster	Within the first 4 months of ART. Presents with herpes zoster,
Cryptococcus	Presents 1 wk to 11 months after ART initiation. Fever, worsening headache, lymphadenitis, new or worsening signs of meningitis; pulmonary disease; skin lesions,
PCP	Fever, cough, dyspnoea in patients on treatment, those recently treated or those undiagnosed. CXR may show worsening radiographic picture
Skin	New or worsening PPE, eosinophilic folliculitis, new presentation or chronic mucocutaneous herpes lesions
Malignancies	New or worsening KS lesions
Hepatitis B	Worsening hepatitis, confirmed by rising ALT AST. Can present late, up to 9 months after ART initiation. "May be associated with re-appearance of positive HBSAG and HBeAG in patients previously positive HBc Ab/HBsAb"

Treatment

No single treatment option exists for IRIS and management depends on the underlying condition, as well as whether the patient is already on specific antimicrobial therapy. Where treatment for the suspected underlying cause has not been started this should be done and the patient observed carefully. No modification of OI treatment is required in patients with IRIS already on the appropriate treatment; further, recently completed treatment for OI should not be re-initiated in patients with IRIS unless treatment failure has occurred. Mild IRIS symptoms should be managed with NSAIDs as well as the specific treatment for the particular OI. ART should be continued. Severe IRIS requires steroid treatment (prednisolone 1-2mg/kg/day; duration depends on response) as well as specific treatment for the underlying condition and continuation of ART. Occasionally it may be necessary to discontinue ART in patients with life-threatening IRIS (e.g. encephalitis, rising intra-cranial pressure, severe respiratory distress, eye disease with imminent loss of sight).

1.7 Pregnancy and OIs

There is no data that suggests that the OIs experienced by pregnant women are different in spectrum from those experienced by non-pregnant HIV infected women with comparable CD4 counts. Although CD4 counts fall during pregnancy, this is likely to be a dilution effect; CD4 percentage should be used in pregnant women in whom inconsistency between the clinical presentation and the CD4 count exists. Because of the serious prognosis of OIs in HIV positive patients, the diagnostic procedures and appropriate therapy should be used as indicated even in pregnancy. The common radiological and nuclear medicine procedures do not result in radiation exposure more than the threshold limits. Effective treatment should be used taking into account issues of teratogenicity.

CHAPTER 2: FEVER IN HIV INFECTION

CHAPTER 2: FEVER IN HIV INFECTION

2.1 Introduction

Fever is one of the most frequent symptoms reported in HIV-infected individuals and is defined as an elevation of the axillary temperature above 37.2^oC. The presence of fever is not indicative of any particular disease process, but is a pointer that all is not well in the body; consequently, fever should never be ignored. Often times, fever is the most prominent and may be the only manifestation of illness. Because HIV infection is common in patients presenting to out- or in-patient services in our HCFs, **all** patients presenting to a healthcare facility with fever whose HIV status is unknown should be offered a diagnostic HIV test.

Infection is the most common cause of fever in HIV-infected patients; therefore the diagnostic evaluation of such patients should first be directed at the possibility of infection. Conversely, the absence of fever in a sick HIV-infected patient, as in other immunocompromised patients, does not exclude the presence of an infection and a high index of suspicion is required in order to diagnose some of these infections.

The key to the management of fever is in a careful clinical assessment including a detailed history and a thorough physical examination as summarized in Table 1.5 above. Often the clinical assessment will guide the initial management; laboratory investigations, where these are available, should further help in defining the underlying cause of fever. To aid patient management, it is useful to divide the causes of fever as either acute or chronic.

2.2 Acute Fever

Acute fever defined as fever of less than 2 weeks' duration, may be an indicator of severe illness in HIV-infected patients. The commonest causes of acute fever in PLHA as well as in the HIV-uninfected patient in our setting include:

- Malaria
- Upper and lower respiratory tract infections
- Urinary tract infections
- Gastro-intestinal infections
- Skin infections including cellulitis, abscesses
- Septicaemia and occult bacteremia
- Central nervous system infections such as acute bacterial meningitis.

2.2.1 Essential Steps in Management of Acute Fever (See Figure 2.2)

1. Assess for emergency symptoms and signs and stabilize patient
 - a. Always assess the sick patient for emergency symptoms and/or signs and stabilize the patient first by instituting the appropriate emergency response (Table 1.4), before continuing with a more complete clinical assessment. **In a patient with fever the following emergency signs indicate a severe illness requiring admission (Figure 2.1):**
 - Patient unable to walk
 - Patient confused, agitated, has impaired consciousness and/or has had seizure(s)
 - Temperature > 40 or < 35°C
 - Respiratory rate (RR) > 30 breaths/minute in an adult
 - Systolic blood pressure (SBP) < 90mm Hg
 - a. **Does patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*

2. Carry out a clinical assessment (see Table 1.5). A thorough clinical assessment will often elicit information and/or findings that direct the HCW to the likely diagnosis.
 - a. **Ask:**
 - Determine the onset, duration and progression of illness
 - About any associated symptoms in the review of systems
 - About co-morbidity, any recent/current medication including antibiotics and antimalarial treatment.
 - a. **Look:** Carry out a physical examination; this should be directed by the history.
 - Pulse rate, respiratory rate, temperature, BP; systemic examination according to presentation
3. If focal symptoms and/or signs (symptoms and signs pointing to a particular system e.g. cough and abnormal chest signs point to the respiratory problem) are found, the appropriate algorithm should be consulted for the management of the patient. Where patients have fever with no obvious focal signs, a physical examination should be comprehensive and include all systems.
 - It is always important to consider malaria, even in patients who have not travelled to typical endemic areas and even where the history is not typical of malaria.
 - Septicaemia or occult bacteremia must also be considered in febrile patients without an obvious focus of illness or in febrile patients with a focus of infection but with severe illness as indicated by a very rapid pulse (> 120 /minute) low blood pressure (SBP < 90 mm Hg) or altered mental status.
4. Carry out investigations as appropriate.
 - a. Where available, tests chosen should be based on presenting symptoms and/or signs, but will generally include a complete blood count (CBC); peripheral blood film for malaria parasites or serological test for malaria where an experienced microscopist is not available; urine analysis and microscopy; culture of appropriate samples (urine, stool, blood, CSF, sputum). Samples for culture, where this is possible, should ideally be collected before starting antibiotic treatment.
 - b. **Laboratory tests should not delay starting treatment in severely ill patients; where tests are not available, a presumptive diagnosis should be made and empirical treatment started.**
5. Start appropriate treatment
 - a. **Specific treatment** for fever should be directed at the *presumed* cause or causes. This is fairly easy where there are symptoms or signs indicative of a likely diagnosis. Where there is no obvious focus of illness, the possibility of malaria and/or septicaemia or occult bacteremia should be considered and the empirical treatment given should cover these possibilities. Where possible, investigations to support or confirm the diagnosis should be carried out in line with the clinical findings. The choice of drugs depends on the likely cause, known resistance patterns, whether patient has any allergies and availability of the drugs. The dose of drugs may need to be adjusted in patients with renal or hepatic dysfunction.
 - b. **Non-specific treatment for fever:** Antipyretics (paracetamol, non-steroidal anti-inflammatory drugs - NSAIDs) are not necessary in cases of mild fever, except in pregnant women, children with seizures and in patients with impaired cardiac, pulmonary or cerebral function. High fever (temperature $> 40^{\circ}\text{C}$) requires management with tepid sponging and antipyretics. Paracetamol used regularly is normally adequate; non-steroidal NSAIDs should be used where there is an inflammatory component to the illness such as inflammatory joint disease or IRIS. NSAIDs should be avoided in children.
6. Review laboratory results.
 - a. Early test results where available may support treatment choice (malaria tests, CXR).
 - b. Some results require more time, maybe days (e.g. culture results) and sometimes weeks (serology, TB culture); such results should be used when reviewing patient progress on initial treatment and should direct continuing treatment.

7. Review hospitalized patients with fever daily. Their treatment should be amended according to any new clinical and/or laboratory findings.
 - a. For any patient with fever who has failed to improve, the history should be reviewed and the patient re-examined, since disease progression may result in new findings. Similarly, outpatients should be advised to return for re-assessment within 3-5 days if symptoms fail to improve.
8. **Is the patient on ART?**

All HIV positive patients treated for an acute febrile illness should be staged clinically (WHO Clinical Staging) on the basis of the illness. If they are not on ART determine if ART is required.

 - a. If the patient is **not** on ART assess whether they require ART
 - b. If the patient is on ART, their response to the antiretroviral drugs should be assessed based on the acute febrile illness as well as on the CD4 history and other longitudinal clinical parameters.
 - c. All PLHA should be on cotrimoxazole prophylaxis.

The flow chart below (Figure 2.3.) summarizes the approach to the management of a patient with fever

Figure 2.1: Indicators of severe illness requiring admission

<p style="text-align: center;">Indicators of severe illness requiring admission: Patient unable to walk Temp > 40 or < 35°C; PR > 120; RR > 30; BP < 90mmHg Confused, agitated; stiffness of the neck; convulsions Fever associated with co-morbidity (congestive heart failure, diabetes mellitus, severe renal or liver disease)</p>
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Figure 2.2: Management of Acute Fever

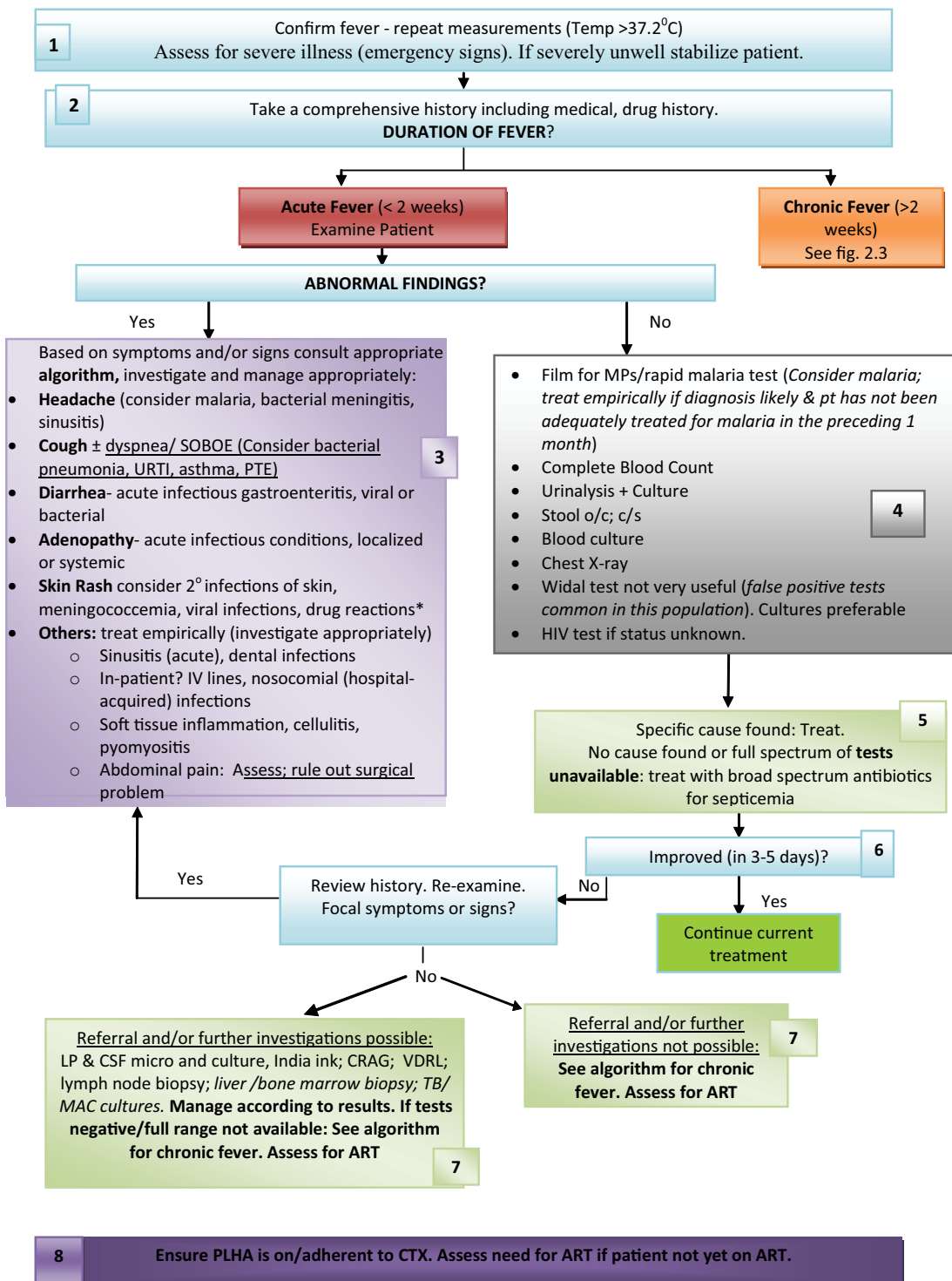


Table 2.1: Specific Treatment for Common Causes of Acute Fever (See Appendix B pg 129)

Disease	Symptoms	Diagnosis	Treatment
Malaria	Fever, chills, lethargy, joint pains ± diarrhoea and vomiting	High index of suspicion. Blood slide for parasites/rapid test if no experienced microscopist	Antimalarial For <u>very sick</u> patient (with indicators of severe illness) give IV infusion of quinine* OR IM artesunate/artemether combination therapy (ACT)
URTIs (more common in PLHA)	Pharyngitis (sore throat), tracheobronchitis. Sinusitis (pain, nasal discharge/obstruction) Otitis media (ear pain, discharge, fever)	History & exam	Emergency: Unable to swallow or pharyngeal abscess. Give IM/IV antibiotics and refer. Gingivitis – metronidazole OR co-amoxiclav Pharyngitis , tracheo-bronchitis often viral, are self-limiting & do not require antibiotics. Hard to distinguish viral from bacterial pharyngitis. If fever, ↑LN, exudates treat as bacterial with penicillin although these may occur in viral pharyngitis. Otitis media – (red, bulging ear drum; ± discharge). Antibiotics – amoxicillin or erythromycin Acute sinusitis - use saline nasal spray; PLHA often need antibiotics (co-amoxiclav, erythromycin or doxycycline) if sinus pain, obstruction, purulent discharge, headache, fever & no response to nasal decongestants.
Lower Respiratory Tract Infections	Fever, chills, fast shallow breathing ± cough, chest pain	Acute chest symptoms are a pointer + signs on exam. CXR, sputum for TB. Bacterial pneumonia – Strep. pneumoniae (50% of cases) & H. influenzae commonest. Also Staph. aureus, Moraxella Catarrhalis, Klebsiella, and Pseudomonas aeruginosa in late HIV disease	Antibiotics - high dose amoxicillin or benzyl penicillin - erythromycin if pt penicillin allergic; add erythromycin if pt fails to improve within 3 days or if co-morbidity - <u>very sick</u> – ceftriaxone + macrolide - exacerbation of COPD – doxycycline OR erythromycin - nosocomial – ceftriaxone OR ciprofloxacin
Urinary tract infections	Urinary disturbances frequency, dysuria, hematuria & fever. If severely unwell with rigors consider pyelonephritis	History and macroscopic & microscopic examination of the urine	- lower urinary tract infection – nitrofurantoin OR nalidixic acid OR amoxicillin OR oral cephalosporin - <u>very sick</u> – IV amoxicillin + IV gentamicin OR IV ciprofloxacin
Gastro-intestinal infection	Symptoms can be non-specific. Presence of fever plus other symptoms suggests enteric fever. History of antibiotic use?	History; stool exam; blood culture. ETEC, shigella, campylobacter, Non-typhi salmonellae	Antibiotics: not often required in HIV -ve pts but indicated in PLHA - ciprofloxacin OR ceftriaxone - plus metronidazole for amoebiasis/protozoa Antihelminthics if needed - <u>very sick</u> IV amoxicillin + gentamicin + IV metronidazole. Or IV FQ plus IV metronidazole Consider surgical review. - if Clostridium difficile likely: metronidazole
Meningitis	Fever, confusion, agitation, photophobia, skin rash, neck stiffness	Confusion or behaviour that is different from normal in the presence of neck stiffness on examination is a crucial pointer. Microscopic examination of the CSF is mandatory	Acute bacterial meningitis: antibiotics - IV benzyl penicillin plus IV chloramphenicol OR IV ceftriaxone if penicillin allergic
Skin Infections	2° infection of scabies, PPE, VZV; folliculitis, cellulitis, impetigo	Skin cleansing is important. Topical fusidic acid may be used in very localized impetigo. Animal and human bites require TT and co-amoxiclav. Consider rabies	Cloxacillin (± Pen V) OR flucloxacillin (± Pen V) OR erythromycin <u>Very sick or cellulitis:</u> IV benzyl penicillin plus IV flucloxacillin or cloxacillin
Community acquired bacteremia or Septicaemia	Fever but no obvious focus. Treat for malaria as well	Often enteric fever; may be gram+ve associated with sub-clinical bacterial sinusitis or pneumonia	IV amoxicillin + gentamicin OR ceftriaxone alone

2.3 CHRONIC FEVER

Chronic fever, generally defined as fever that has been present for more than 2 weeks' duration, often indicates severe illness in HIV-infected patients. Indeed the conditions likely to be responsible are the most common causes of HIV-related mortality. In the local setting the patient with chronic fever will usually have had treatment for malaria and, in many cases, will have had some antibiotic treatment as well. Despite the limited access to a wide range of laboratory tests it is still possible to manage patients with prolonged fever effectively, using clinical skills and the limited tests available.

2.3.1 Common Causes of Chronic Fever

The most common causes of prolonged fever in PLHA include:

- Tuberculosis, both pulmonary and extra-pulmonary (see Chapter 3).
- *Pneumocystis jiroveci* pneumonia (PCP see Chapter 3)
- Cryptococcal meningitis in severely immunocompromised patients (see Chapter 6)
- Mycobacterium avium complex (MAC) in the severely immunocompromised
- Typhoid, which may present late
- Toxoplasmic encephalitis (see Chapter 6)
- Lymphoma (see Chapter)

2.3.2 Essential Steps in Management of Chronic Fever (See Figure 2.3)

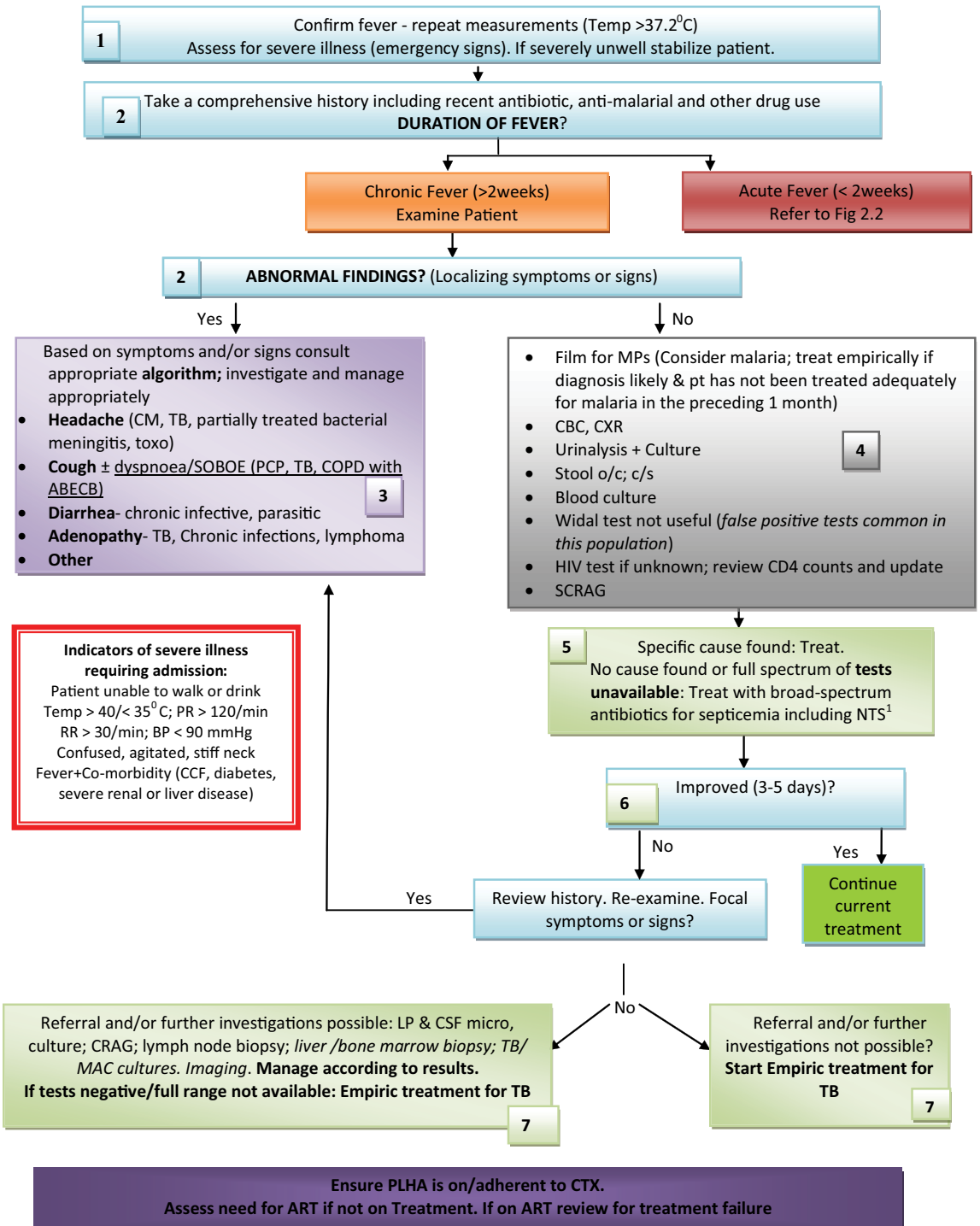
1. Assess for emergency symptoms and signs and stabilize the patient
 - a. Always assess the sick febrile patient for emergency symptoms and/or signs (patient unable to walk, temperature > 40°C, PR > 120/minute, SBP > 90mmHg, RR > 30/minute) and stabilize patient first, before continuing with a more complete clinical assessment and/or referral
 - b. **Does the patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs and with the facilities available at the particular HCF. *If referral to another HCF is required, the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
2. Carry out a comprehensive clinical assessment (see Table 1.5). A thorough clinical assessment will often elicit information and/or findings that direct the HCW to a working diagnosis.
 - a. **Ask about:** onset, duration and progression of fever; associated symptoms in the review of systems with reference to the conditions likely to be responsible (see section 2.3.1); ask if patient has co-morbid conditions (diabetes, hypertension, heart or liver disease etc); ask about previous and current medication and duration of these treatments. Note that some bacterial infections in severe HIV disease may require a longer duration of antibiotic treatment, thus under-treatment is common.
 - b. **Look:** RR, temperature, BP; systemic examination according to history
3. Patients may have fever with no obvious focal complaints; such patients merit a thorough physical examination, which should include all systems. It is always important to consider malaria in febrile patients, although many patients with chronic fever are likely to have been treated before for malaria. Physical examination should be determined by the symptoms elicited. If focal signs are found in the examination, the appropriate algorithm should be consulted to manage the patient.
4. Carry out investigations as appropriate.
 - a. Where available, tests should be chosen based on presenting symptoms and/or signs; generally a complete blood count (CBC), peripheral blood film for malaria parasites or serological test for malaria, urine analysis and microscopy, culture of appropriate samples (urine, stool, blood, CSF, sputum) and a CXR should be performed. (PLHA may have significant chest problems such as PCP or TB without obvious signs on examination). A serum CRAG should also be done.

- b. **Lab tests should not delay starting presumptive treatment in severely ill patients; where they are not available or where results take time, a presumptive diagnosis should be made and empirical treatment started.** Samples for culture, where this is available, should ideally be collected before starting antibiotic treatment. Patients who have had chronic fever for a long time and are clinically stable can wait for results of tests carried out especially where the diagnosis is not obvious.
- 5. **Start appropriate treatment**
 - a. Specific treatment for prolonged fever should be directed at the presumed cause. This is fairly straightforward where there are symptoms or signs indicative of a likely diagnosis. Where there is no obvious focus of illness, the possibility of extra-pulmonary TB should be considered and evidence to support this aggressively searched for clinically and through supportive tests.
 - b. Non-specific/supportive treatment for fever: *Antipyretics* (paracetamol, non-steroidal anti-inflammatory drugs) are not necessary in cases of mild fever, except in pregnant women, children with seizures, patients with impaired cardiac, pulmonary or cerebral function. High fever (> 40°C) *requires* management with tepid sponging and antipyretics, such as regular paracetamol; NSAIDs should be used where there is an inflammatory component such as inflammatory joint disease. NSAIDs should be avoided in children.
- 6. **Review:**

Patients with prolonged fever may be admitted for observation and investigations; however, where investigations are possible and can be done efficiently in the outpatient setting, stable patients with chronic fever may be managed as out patients. Hospitalized patients should be reviewed daily, history re-appraised and re-examined regularly; empirical treatment if started should be amended according to any new clinical and laboratory findings. Where there is no improvement on chosen treatment, the history should be reviewed and the patient re-examined since disease progression may result in new findings. Similarly, outpatients should be given appointments for review to ensure that they are responding to treatment, results are implemented and they are not lost to follow up.
- 7. Patients with prolonged fever not responsive to initial empirical treatment should be re-assessed for the possibility of extrapulmonary TB. In the absence of more extensive laboratory tests to help with this diagnosis, anti-TB treatment (ATT) should be started empirically in the severely ill HIV infected patient with symptoms suggestive of this diagnosis.
- 8. **Is patient on ART?**
 - a. Many conditions causing prolonged fever are classified as WHO Stage 4 illnesses or AIDS defining conditions. As such all PLHA with prolonged unexplained fever should be staged clinically and preparation for ART started as soon as possible (usually from the first visit to the clinic). If the patient is already in care previous CD4 measurements should be reviewed and updated
 - b. ***Patients already on ART developing conditions associated with prolonged fever may be failing ART and should be assessed for failure of their current regimen.***

The flow chart below summarizes the management approach to the HIV positive patient with prolonged fever.

FIGURE 2.3: MANAGEMENT OF CHRONIC FEVER



**CHAPTER 3:
RESPIRATORY
MANIFESTATIONS OF
HIV INFECTION**

CHAPTER 3: RESPIRATORY MANIFESTATIONS OF HIV INFECTION

3.1 Introduction

Respiratory (chest or pulmonary) symptoms are a frequent complaint in HIV-infected individuals and may be due to a wide spectrum of illnesses, including both HIV- and non-HIV-related conditions. The HIV-associated pulmonary conditions include opportunistic infections, such as (recurrent) bacterial pneumonia, tuberculosis, PCP and others caused by viral and fungal pathogens as well as malignancies including Kaposi's sarcoma and lymphoma. While some of these opportunistic conditions may be restricted to the respiratory system, multi-system involvement is not unusual and mandates a complete history and physical examination in patients. Each of these conditions may have specific and suggestive symptoms, signs and X-ray findings; there is however considerable variation and overlap in presentation, which may call for further investigations to help with coming to a definite diagnosis. It should be remembered that non-HIV related respiratory conditions such as asthma, chronic obstructive pulmonary disease, bronchitis, pulmonary embolism, connective tissue disease and non-HIV related malignancies also occur in HIV infected patients; they are not discussed further in this section.

Respiratory tract infections (RTIs) in HIV-infected individuals increase in frequency as the CD4 cell count declines, particularly once it has fallen below 200 cells/mm³. For instance, bacterial pneumonia is more likely to recur and be more severe the lower the CD4 count; while pulmonary TB tends to present "typically" in patients with a well-preserved immune system, TB is more likely to be "atypical" in the severely immunocompromised patient, with unusual pulmonary or extrapulmonary presentations becoming more frequent; PCP is uncommon in patients with CD4 counts above 200 cells/mm³.

3.2 Assessment of patients with respiratory symptoms

The diagnostic approach to the patient with cough begins with a thorough history and physical examination. This together with minimal tests is often enough to suggest differential diagnoses (the likely causes) and a management plan.

Cough is the most common respiratory complaint in HIV-infected patients. Cough most frequently occurs as a result of irritation in the airways caused by infections and inflammation. To facilitate patient management in settings where investigative capacity is limited, the history must be comprehensive enough to help narrow down diagnostic possibilities. The most common causes of cough can generally be categorized according to the duration of the cough.

3.3 Acute Cough

Acute cough (defined as cough present for less than 2-weeks' duration) while commonly due to upper respiratory infections, (acute bacterial and viral pharyngitis or sore throat, common cold), may indicate severe disease, such as bacterial pneumonia. However, most patients with acute cough will have upper respiratory tract infections, many of which are self-limiting viral infections (see Table 1.4 for management). When caused by severe or life threatening conditions acute cough is often associated with additional symptoms such as difficulty breathing and/or fever.

3.3.1 Essential Steps in Management of Acute Cough (See Figure 3.1)

1. Assess for emergency signs and stabilize patient before continuing with a more complete clinical assessment (see Table 1.5)
 - a. Always assess the sick patient for emergency symptoms and/or signs and respond appropriately to stabilize the patient (Table 1.4). Emergency symptoms and signs in patients with acute cough include:
 - Patient short of breath (SOB) at rest, unable to walk or talk in complete sentences, RR > 30/min; central cyanosis (blue lips, tongue) may be present

- Temperature > 40°C
 - SBP < 90mmHg
- b. **Does the patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. *If referral is required patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
2. Carry out a clinical assessment (see Table 1.5). A thorough clinical assessment will often elicit information and/or findings that direct the HCW to the likely diagnosis.
- a. **Ask about:**
- Duration of cough; whether there is sputum production, and if there is blood in the sputum
 - Presence of runny nose, sore throat
 - Presence of fever
 - Presence of shortness of breath (SOB) and its development and progression (sudden vs. gradual onset of SOB; activities that cause SOB); **Shortness of breath (SOB)** is an important discriminating feature in patients with cough; its presence indicates the likelihood of lower respiratory tract conditions, which may be serious. Serious emergencies that may present with SOB include pneumonia, asthma, pulmonary thrombo-embolism (PTE or clot in the lung), cardiac disease and pneumothorax. ***The diagnosis of these potentially serious conditions depends on a thorough history and examination; a working diagnosis can be made clinically in the vast majority of patients and an emergency response instituted. A clinician should review patients with SOB due to the potentially serious diagnoses.***
 - Presence of wheeze (define onset, duration, relation to activity, night or day etc).
 - Weight loss, unusual night sweats
 - Previous chest or heart disease, history of treatment for TB (if treated for TB ask about adherence history)
 - Smoking status, current or past
 - Previous drug history including recent antibiotics, current medication and duration of these treatments.
 - Any co-morbidity
- b. **Look:** PR, RR, temperature, BP; examination of the ear nose and throat, chest and other systems according to the presentation
3. Carry out investigations as appropriate.
- a. Where available, tests should be chosen based on the presenting symptoms and/or signs. In patients with acute cough investigations may not be necessary if the presumed diagnosis is of an URTI. If more severe illness is likely, investigations may include CBC; peripheral blood film for malaria parasites or serological test for malaria; urine analysis and microscopy; culture of appropriate samples (blood, sputum); a CXR and arterial blood gas (often pulse oximetry, although arterial blood gas may be possible in some centres. Pulse oximetry, which is a non-invasive way of measuring oxygenation, may be the more accessible way of assessing blood oxygenation).
- b. **Laboratory tests should not delay starting treatment in severely ill patients; where they are not available, a presumptive diagnosis should be made and empirical treatment started.**
4. **Start appropriate treatment**
- a. Specific treatment for acute cough should be directed at the presumed cause and in many instances is fairly straightforward (Table 1.5).
- b. Non-specific treatment for cough:
- *Antipyretics* (paracetamol, non-steroidal anti-inflammatory drugs) and antitussives are often useful for symptomatic treatment of patients with viral

URTI. For lower respiratory tract infections (LRTI) these ancillary treatments are not as important as the specific treatment directed at the specific cause.

- Supportive treatment including oxygen for severely ill patients should be used as required.
- In addition to a chest infection, PLHA with no previous history of asthma or chronic obstructive lung disease, may present with a wheeze, which may require the use of β_2 agonists (e.g. salbutamol).

5. **Review:**

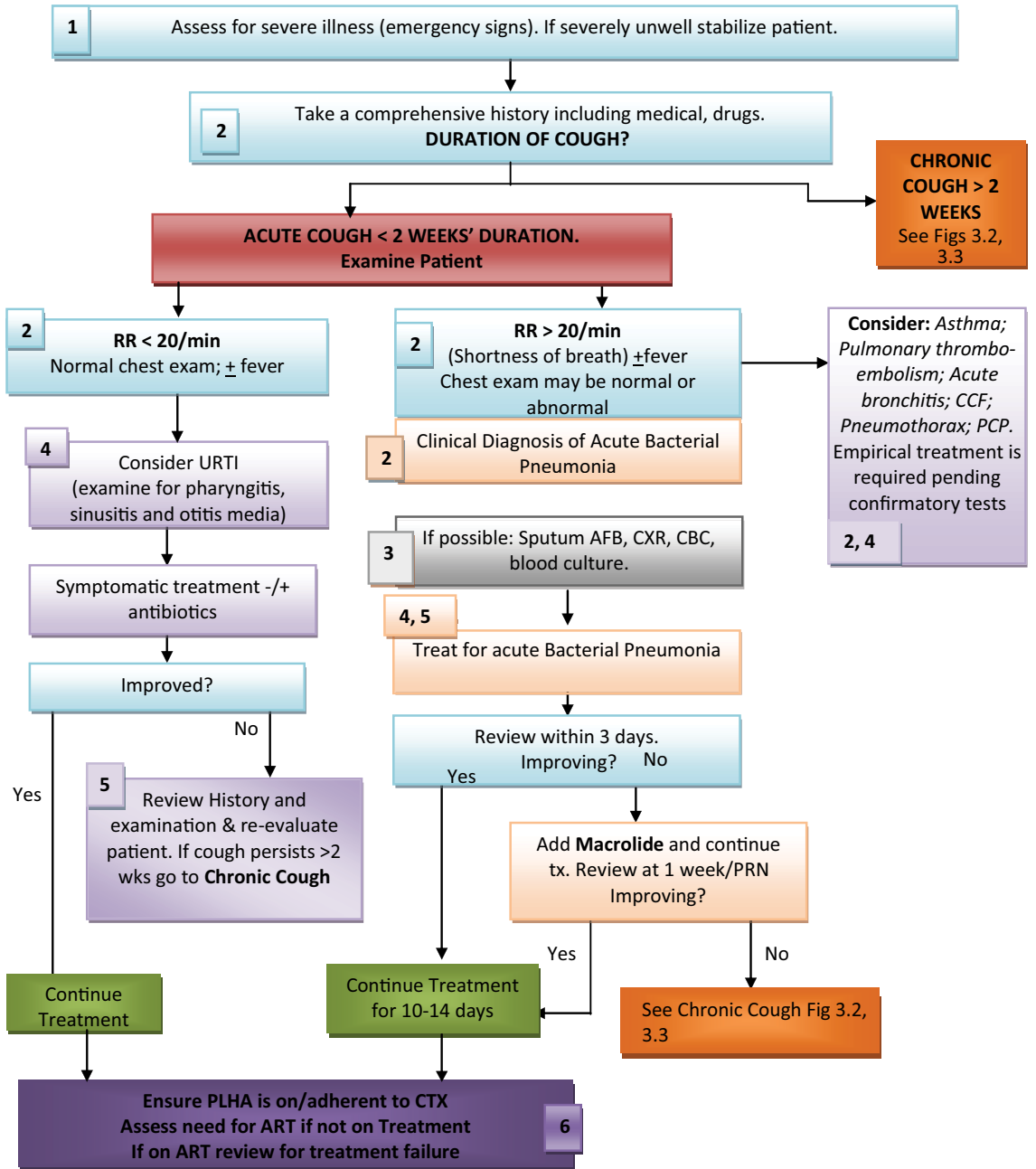
- a. Early review of patients with severe bacterial pneumonia is essential to identify patients who need a change in medication. Rapid improvement is expected in patients with bacterial pneumonia if appropriate treatment is given. If there is no improvement within 3 days a macrolide should be added to the initial treatment.
- b. Patients who have had antibiotics within the preceding 3 months and have presumed community acquired bacterial pneumonia should be given a combination of a macrolide and a broad spectrum penicillin at onset of treatment

6. **Is the patient on ART?**

- a. Bacterial pneumonia is classified as a severe bacterial infection and is a WHO Stage 3 disease or WHO stage 4 if recurrent or associated with bacteremia. As such all PLHA who are not on ART who present with acute bacterial pneumonia should be staged clinically and preparation for ART started as soon as possible (usually from the first visit) to the clinic.
- b. Recurrent URIs is an indicator of WHO stage 2 disease; PLHA who present with this history should be assessed fully for immunological status to help define their need for ART.
- c. PLHA who present with RTIs and are on ART should be assessed for ART failure.

The flow chart below summarizes the management approach of a patient with acute cough.

FIGURE 3.1: MANAGEMENT OF ACUTE COUGH



Indicators of severe illness requiring admission:
 Unable to walk unaided; unable to talk in complete sentences.
 Temp > 40/< 35.0C; PR > 120/min; RR > 30/min; SBP < 90mmHg; cyanosis, severe Hypoxemia (pulse oximetry)
 Co-morbidity (CCF, diabetes, severe renal or liver disease)

3.3.2 Bacterial Pneumonia

Bacterial pneumonia is a common cause of HIV related morbidity and occurs at a much higher rate in PLHA than in the non-infected population. Although bacterial pneumonia can occur at relatively high CD4 counts, disease is more likely to occur and recur the more severely damaged the immune system is. While recurrence of bacterial pneumonia is relatively unusual in the healthy adult, it is relatively common in PLHA; recurrent bacterial pneumonia is an indicator of severe HIV disease (WHO Stage 4). Where there is widespread use of HAART the epidemiology of bacterial pneumonia has changed significantly with a reduction in incidence reported.

The most common causes of community acquired bacterial pneumonia (CAP) are *Streptococcus pneumoniae* (50% of cases) and *Haemophilus influenzae*; less commonly atypical organisms such as *Mycoplasma* and *Legionella* species may be responsible. In more advanced HIV disease or in cases of hospital acquired pneumonia other pathogens such as *Staphylococcus aureus*, *Moraxella catarrhalis*, *Klebsiella*, and *Pseudomonas aeruginosa* become more common in PLHA. Infection with *S. pneumoniae* is many fold more common PLHA than in non-infected population and recurrence of pneumococcal disease is also very common. Knowledge of the likely cause of pneumonia is useful in choice of medication used for treatment even in the absence of an etiological diagnosis. Further, local patterns of antibiotic sensitivity should be considered in the choice of empirical antibiotic treatment.

Bacterial pneumonia in HIV patients has a higher rate of complications including intrapulmonary cavitations, abscess formation and empyema. The overall mortality, however, is similar to that of the non-HIV infected population.

Clinical Presentation

The clinical presentation of bacterial pneumonia in PLHA is the same as in non-infected people.

- Acute or abrupt onset of symptoms characterized by
 - High fever, chills, rigors
 - Cough which rapidly becomes productive of purulent sputum
 - SOB
 - Unilateral pleuritic chest pain
- Signs include fever, tachypnea (RR > 20/minute); chest signs of lung consolidation (localized crepitations, bronchial breath sounds on auscultation)
- Symptoms may develop very rapidly
- Inadequately treated pneumonia may have a sub-acute presentation.

Laboratory & Radiography

CXR typically shows lobar consolidation although unusual presentations such as diffuse pulmonary infiltrates may occur in PLHA. The CXR takes a little time to worsen and a long time to improve. Follow up films in patients who are improving should be repeated after at least 6 weeks.

Other investigations: sputum microscopy, AFB to exclude TB and culture; for hospitalized patients, blood cultures, urine Strep. pneumoniae antigen, CBC (shows neutrophilia) and biochemistry.



Rt lower lobe consolidation in a PA and lateral CXR

If pleural effusion present TB should be considered. A diagnostic tap can be done (for full biochemical and microbiological investigations including AFB) but has a poor yield.

Treatment of Bacterial Pneumonia

Whether patients are admitted into hospital or not for treatment depends on the severity of their

illness. Patients with emergency signs should have the initial antibiotic dose as IM/IV injection and then be transferred to a hospital for admission. Severely ill patients may require oxygen and/or ventilatory support.

Clinical improvement (reduction in fever, improvement in respiratory symptoms and signs) is expected within 48-72 hours of starting effective treatment. Failure of response to adequate antibiotic treatment (a lack of reduction in fever, RR remains high, persistent or worsening chest signs) should lead to consideration of atypical pneumonia (*Mycoplasma*, *Chlamydia*, *Legionella*) with addition of macrolides to the treatment. If response remains poor consideration should be given to and patient assessed for PCP and TB.

Out-patient Treatment

- **First line treatment:**
 - In patients with no history of antibiotic treatment in the preceding 3 months: **high dose amoxicillin at 1g TDS for 10-14 days**. Use in all patients including those taking CTX prophylaxis.
 - In patients with a history of antibiotic use in preceding 3 months use both high dose **amoxicillin 1g TDS + erythromycin at 500mg QID** for 10-14 days. Other macrolide may be used.
 - Review patients in 3 days or earlier if worsening. Add macrolide in patients who fail to improve on amoxicillin alone
- Alternative first line for outpatients:
 - Co-amoxiclav alone or with a macrolide
 - Doxycycline
 - Cephalosporins such as cefotaxime or ceftriaxone. (Of the 3rd generation cephalosporins, cefuroxime is the least effective against bacterial pneumonia)
- CTX is not recommended for treatment of RTIs in adults because of the high prevalence of bacterial resistance in this country and the widespread use of CTX prophylaxis in PLHA. *Cotrimoxazole prophylaxis has been shown to be an effective chemo-prophylactic despite this high level of pre-existing bacterial resistance.*
- Ciprofloxacin, norfloxacin and nalidixic acid are not recommended for pneumonia as they lack enhanced activity against the most common microorganisms.
- Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin) should probably not be used for CAP in this high TB-prevalence population because of their efficacy against TB, which may mask and delay diagnosis of TB.

In-patient Treatment

- First line treatment options
 - IV ceftriaxone + IV erythromycin or other macrolide OR
 - IV benzyl penicillin + IV erythromycin or other macrolide OR
 - IV co-amoxiclav + IV erythromycin or other macrolide
- Severely unwell (ICU)
 - IV ceftriaxone + IV erythromycin or other macrolide + IV gentamicin
 - For Aspiration pneumonia: clindamycin or co-amoxiclav should be used in addition to ceftriaxone.
 - Respiratory fluoroquinolone IV may be used in life-threatening pneumonia not responsive to the above treatments. In PLHA TB and PCP *must* be considered.

Prevention of Bacterial Pneumonia

Cotrimoxazole prophylaxis recommended for all PLHA may reduce the occurrence and recurrence of pneumococcal disease.

A polyvalent pneumococcal vaccine has been tried in PLHA in Africa with unexpectedly negative results and is therefore currently not recommended for routine use in HIV patients.

Management of Bacterial Pneumonia in Pregnancy

Bacterial pneumonia in pregnant women should be managed in the same way as it is in non-pregnant women. CXR may be done with shielding of the abdomen. Similar antibiotic treatment should be used, however fluoroquinolones and clarithromycin should be avoided because of potential for the development of arthropathy and birth defects in the foetus respectively.

3.4 MANAGEMENT OF CHRONIC COUGH

3.4.1 Introduction

In a setting of high tuberculosis (TB) prevalence chronic cough defined, as cough for more than 2 weeks' duration, in any patient regardless of HIV status, should always raise the possibility of TB as a cause. TB in any patient in high HIV-prevalence communities should likewise raise the possibility of HIV infection. Any patient presenting with a history of chronic cough whose HIV status is unknown should undergo HIV diagnostic testing and counselling.

Other causes of chronic cough in PLHA may include bacterial pneumonia (especially if inadequate treatment has been used) and *Pneumocystis jiroveci* (PCP), a common presentation in advanced HIV disease. Causes of chronic cough not discussed further in this section but for which patients should be assessed if indicated, include asthma and chronic obstructive lung disease such as bronchiectasis, which may occur after pulmonary TB.

3.4.2 Essential Steps in Management of Chronic Cough (See Figure 3.2)

1. Assess for emergency signs and stabilize the patient.
 - a. Always assess the sick patient for emergency symptoms and/or signs [patient short of breath (SOB) at rest, unable to walk or talk in complete sentences, RR > 30, temp > 40°C, SBP < 90mmHg]. Stabilize severely sick patients first before continuing with a more complete clinical assessment (see Tables 1.4)
 - b. **Does the patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs present and with the facilities available at the particular HCF. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
2. A clinical assessment as outlined in Table 1.5 will often elicit information and/or findings that direct the HCW to the likely diagnosis.
 - a. **Ask about:**
 - Duration of cough
 - SOB, its progression (sudden vs. gradual onset), whether on exertion or at rest.
 - Presence of wheeze (onset, duration, relation to activity, night or day etc)
 - Sputum production and whether there is blood in the sputum
 - Contact with patient with TB; treatment for TB, including adherence to TB and completion of TB treatment.
 - Weight loss, fever, night sweats; smoking status
 - Previous chest or heart disease
 - Previous recent and current medication as well as duration of these treatments.
 - a. **Look:** PR, RR, temperature, BP; cyanosis, pallor, lymphadenopathy; presence of wheeze, any abnormal chest signs; hepatosplenomegaly, as well as examination of other systems; weight.

3. **Shortness of breath (SOB)** is an important discriminating feature in patients with chronic cough; while SOB is *the* hallmark of PCP, patients with TB are unlikely to be severely SOB unless a large pleural effusion is present, they have TB pericarditis or very extensive lung involvement. Patients with partially treated bronchopneumonia, acute exacerbation of chronic obstructive pulmonary disease (AECPD), bronchiectasis, asthma, recurrent pulmonary thrombo-embolism (PTE), pulmonary hypertension, cardiac disease and pneumothorax may also be SOB. ***The diagnosis of these conditions depends on a thorough history and examination; a working (presumptive) diagnosis can be made clinically in the vast majority of patients with limited investigations. A clinician must review patients with SOB.***
4. **Investigations:** all patients with chronic cough *must* have a sputum examination for AFB where sputum is available; if sputum is not available sputum induction (with proper attention to infection control) should be considered where this is possible. CXR must also be done. Other investigations should be individualized according to symptoms and/or signs, but will generally include pulse oximetry, CBC, blood culture, biochemistry.

CD4 count is important in the differential diagnoses of cough with SOB in HIV-infected patients, thus the trend of previous CD4 counts should be reviewed and a test done if no previous CD4 counts available. ***Laboratory tests should not delay starting treatment in severely ill patients; where they are not available, a presumptive diagnosis should be made and empirical treatment started.***

- a. CXR findings: CXR is very important in patients with chronic cough; often times the CXR together with the history leads to a working diagnosis.
 - b. Although smear negative TB is more common in PLHA sputum examination is essential in patients with chronic cough. Where at least 1 sample is positive, anti-TB treatment (ATT) should be commenced without delay. Dual pathology may co-exist especially in severely immunocompromised patients.
 - c. As with all sick patients attending our HCFs including those with chronic cough should be offered diagnostic HIV testing if their status is unknown (PITC).
5. **Treatment**
- a. Specific treatment for chronic cough should be directed at the presumed cause. Where possible, investigations to support or confirm the diagnosis should be carried out as per the clinical findings.
 - b. Non-specific treatment for cough: For lower respiratory tract infections antitussives should be avoided; in any case expectoration of sputum is desirable to avoid accumulation of infected material. Supportive treatment including oxygen for severely ill patients, drainage of large pleural effusions, etc, should be used as required. PLHA with no previous history of asthma with LRTI may present with wheeze which may require the use of β_2 agonists (e.g. salbutamol)
 - c. Where smear positive TB has been diagnosed in a family member, patients with a LRTI should be assessed for TB. *Children less than 5 years of age, regardless of HIV status, living in such households should be assessed clinically and using CXR for TB; if TB is not found isoniazid preventive therapy (IPT) should be given as per the NTL guidelines.*
6. **Review:**
- a. Early review of patients with severe symptoms or with PCP is essential so as to identify patients who may need a change in or additional medication.
 - b. Patients who have presumed inadequately treated pneumonia should be given a combination of a macrolide (e.g. erythromycin) *plus* a broad spectrum penicillin or doxycycline or cephalosporin at onset of treatment
 - c. Patients with TB or PCP may have dual infection, thus at times treatment for concomitant bacterial pneumonia may be required. Patients may also occasionally have both PCP and TB together. Clinicians should be cautious when using high dose steroids in patients with PCP in whom a diagnosis of TB is a consideration; in such patients dual treatment of both

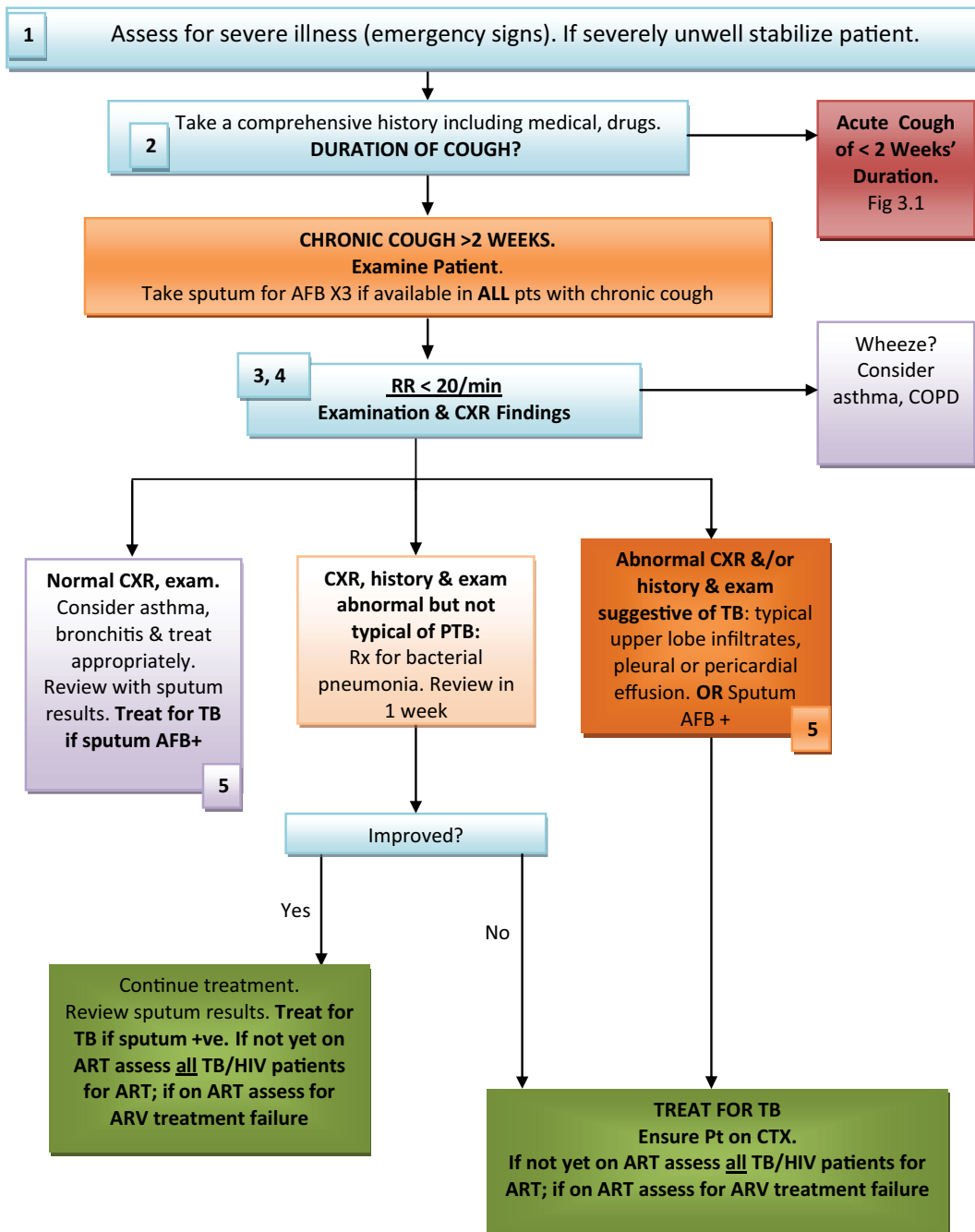
PCP and TB may be considered to avoid further steroid induced immunosuppression, which often results in death if TB is present and is not treated concomitantly.

7. Is the patient on ART?

- a. Lower respiratory tract infections associated with chronic cough such as TB or PCP are indicative of severe or advanced HIV disease (WHO Stage 3 or 4). As such all PLHA with these conditions should be staged clinically and preparation for ART started as soon as possible (usually from the first visit) to the clinic.
- b. Patients already on ART developing conditions associated with prolonged cough may be failing their ART and should be assessed for failure of their current regimen

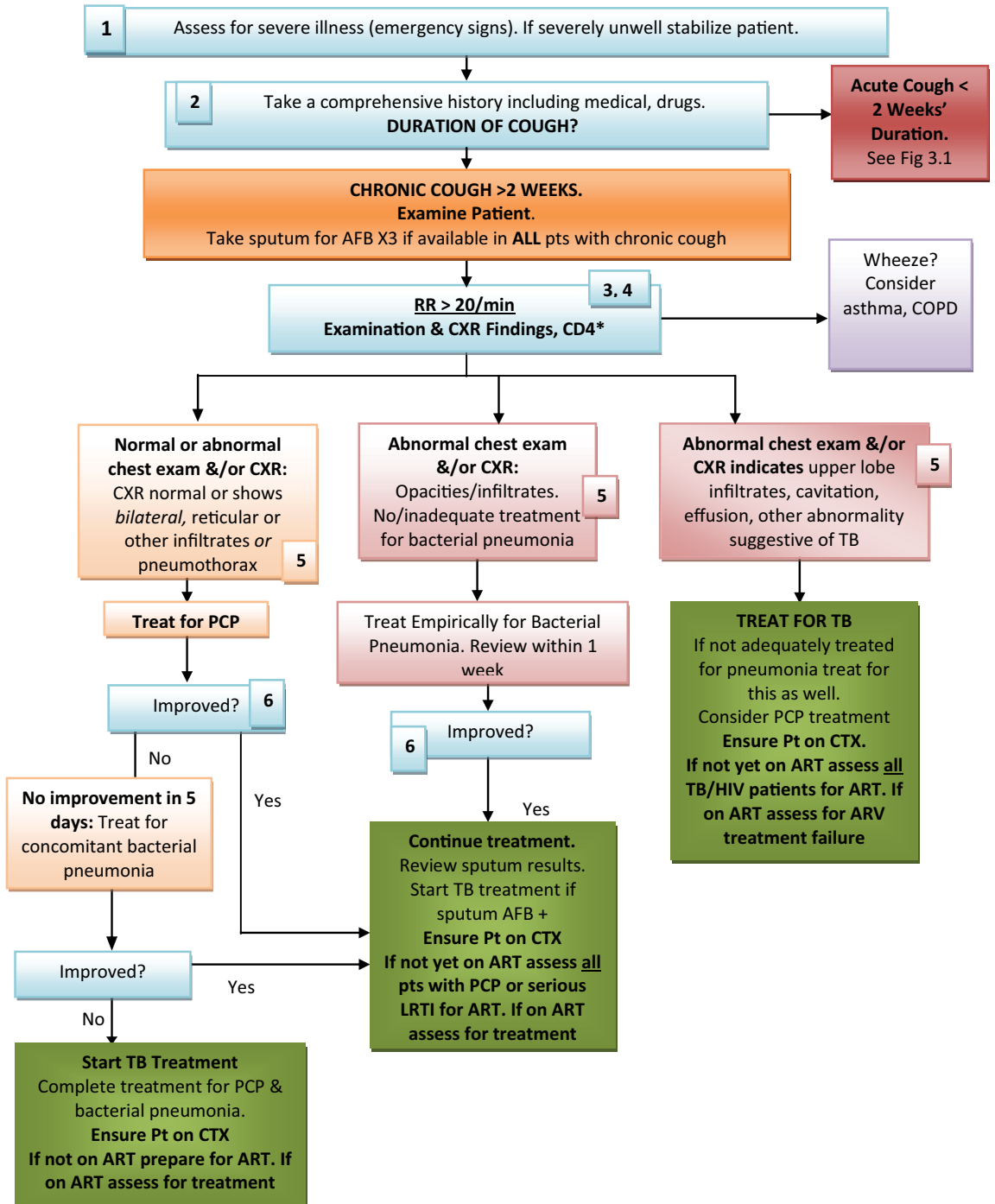
The flow charts below summarize the management approach of a patient with chronic cough with and without shortness of breath (SOB).

FIGURE 3.2: MANAGEMENT OF CHRONIC COUGH WITHOUT SHORTNESS OF BREATH



Indicators of severe illness requiring admission:
 Unable to walk unaided; unable to talk in complete sentences. Temp > 40/<35°C; PR >120/min; RR > 30/min; BP <90mmHg; Hypoxemia (pulse ox); Co-morbidity (CCF, diabetes, severe renal or liver disease)

FIGURE 3.3: MANAGEMENT OF CHRONIC COUGH WITH SHORTNESS OF BREATH



Indicators of severe illness requiring admission:

Unable to walk unaided; unable to talk in complete sentences. Temp > 40/<35°C; PR >120/min; RR > 30/min; BP <90mmHg; Hypoxemia (pulse ox); Co-morbidity (CCF, diabetes, severe renal or liver disease)

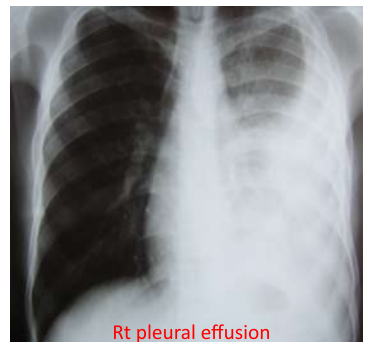
3.4.3 TUBERCULOSIS

3.4.3.1 Introduction

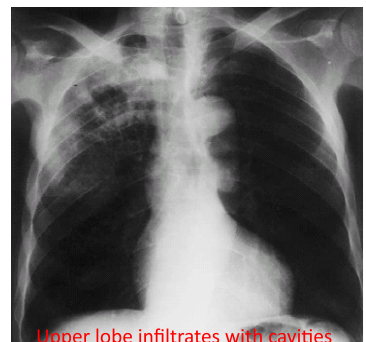
Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. The TB organism (bacillus) is transmitted from one person to another through droplets generated by coughing, sneezing, laughing and even talking. Primary infection may occur following exposure to the tubercle bacillus in a person not previously infected. Most primary infections (90%) do not result in clinical disease and a positive tuberculin (Mantoux) test may be the only evidence of infection. Primary infection may sometimes be associated with disease including hypersensitivity reactions, tuberculous pneumonia, pleural effusions or disseminated disease. Post primary or reactivation TB occurs after a period of months to years following the primary infection and is due to reactivation of dormant tubercle bacilli. Post primary TB may also occur following infection from another person in a patient with primary infection.



HIV is the most potent risk factor for the reactivation and progression of latent TB infection. This is because HIV damages the very cells (CD4 cells) needed to control TB. The lifetime risk of a PLHA developing TB is 50% compared to 5% in HIV-uninfected individuals. Consequently, the HIV epidemic has fuelled the TB epidemic with the result that the prevalence of TB in high HIV prevalence countries like Kenya has risen exponentially in the past 15 years or so. PLHA with TB have a higher viral load and faster disease progression when compared to PLHA without TB.



Other persons at higher risk of TB include those who live in overcrowded settings (such as urban slums) and those who live or work in congregate settings (e.g. prisons, hospitals). HCWs who are also HIV-infected should be advised to avoid working in areas where the risk of exposure to TB may be high (e.g. TB clinic, acute medical wards, overcrowded HIV care clinics if patients with cough are not segregated). This among other occupational reasons should encourage HCWs to know their status.



3.4.3.2 Clinical Presentation of TB in PLHA

The clinical presentation of TB in PLHA is largely influenced by the degree of immunosuppression. Thus the presentation of TB in patients with CD4 counts above 350 cells/mm³ may be similar to that seen in HIV-uninfected TB patients, with the majority of patients having disease in the lungs. With increasing severity of HIV disease, extrapulmonary TB (EPTB or TB in organs other than the lungs) with or without lung involvement becomes more common. Pulmonary TB (PTB) however remains the commonest form of TB in all HIV-infected individuals.



Patients with all forms of TB will commonly present with constitutional symptoms of

- Fever
- Anorexia and weight loss
- Night sweats.

In patients with severe HIV disease TB can be a severe illness with rapid

progression, high fevers and a “sepsis” syndrome.

3.4.3.3 Diagnosis of TB in PLHA

Because of the severity of TB disease in PLHA, early diagnosis is critical. The key to diagnosis of TB is a high index of clinical suspicion and an aggressive search for evidence to support the diagnosis. To help improve early diagnosis and case finding of TB (also known as intensive case finding – ICF), all PLHA enrolled in care should be routinely screened for TB (see Fig 3.5) at each clinical appointment or when symptomatic. The diagnostic work-up of patients suspected of having TB is as follows:

- Start with a **complete history** (which should include any history of cough > 2 weeks, weight loss, night sweats, fever)
- Carry out a thorough **physical examination** (assess for fever, anaemia, lymphadenopathy, chest abnormalities and hepatosplenomegaly) as well as examination of other systems as appropriate.
- Obtain **sputum** samples for AFB from all patients with chest symptoms or signs, cervical lymphadenopathy and/or abnormal CXR.
 - 3 sputum specimens should be collected, whenever possible, the first “on the spot”, another early the next morning and a third “on the spot” at the time the early morning sample is brought in.
 - Sputum smears for AFB should be prepared from all 3 samples and each examined. Sensitivity of smears is about 50%; sensitivity may be improved by induction of sputum.
 - More sensitive tests are in development but are as yet not available for clinical use in Kenya
- Carry out a **CXR** in symptomatic PLHA.
 - CXR findings in patients with severe immunosuppression are different from that in those with less severe HIV disease. In patients with mild HIV disease typical upper lobe opacities with cavitations is often seen, while in those with severe disease, lower and middle lobe involvement as well as miliary TB is more common.
- Carry out **needle aspiration** of relevant body fluids, nodes and bone marrow and examine for AFB. Needle aspiration preferable in patients with TB adenitis since healing after open biopsy may be slow and associated with scarring.
- Tissue **biopsy** of lymph nodes and other solid organs may be useful in patients with negative needle biopsy (low yield)
 - Histopathological findings of TB in HIV-infected patients is also affected by the degree of immunosuppression with granulomatous lesions prominent in early HIV disease and much less well formed or may even be absent in later disease.
- Mycobacterial **blood culture** although not widely available has a high yield in severely immunocompromised patients with systemic disease.
- Tuberculin skin test (Mantoux test) is less useful in PLHA suspected of TB because of false negative results especially in more severe HIV disease.

A positive smear result in any specimen should be treated as TB in symptomatic patients. Culture of the specimen and drug susceptibility testing should be performed on all patients who have previously been treated for TB or have had contact with a patient with drug resistant TB.

Table 3.1. Summary: Presentation and Diagnosis of TB in PLHA

Site	Presentation & Diagnosis
Pulmonary TB (PTB)	Early HIV disease: clinical symptoms & signs typical: cough > 2 wks (often productive); fever, night sweats; weight loss; chest pain. Tests: CXR typical upper lobe involvement, cavities. Sputum + for AFB. Severe HIV disease: mostly constitutional symptoms with fever, sweats, weight loss. Tests: sputum often negative; CXR mid & lower lobe infiltrates with no cavities; miliary pattern may be seen
Pleural effusion	Fever, cough, SOB; chest pain; night sweats; tracheal shift; ± stony dullness; Tests: CXR typical dense white opacification confirms unilateral effusion; loss of costo-phrenic angles, if small effusion. Diagnostic tap often not helpful.
TB adenitis	Asymmetrical, swollen, commonly non-tender lymph nodes; LN matted; may be fluctuant; eventually skin may break down & discharging sinuses develop. Neck commonest site. Tests: Aspirate and smear for AFBs & culture as well as histology. Results may be non-specific
TB meningitis	Chronic headache with gradual progression; impaired consciousness; cranial nerve palsies. Tests: LP - CSF examination often non-specific. Patients with pulmonary infiltrates on CXR & signs and symptoms of meningitis should be treated for TBM. CRAG test may be useful in excluding cryptococcal meningitis
Miliary TB	Common in advanced HIV disease and indicates disseminated disease; constitutional features, prolonged fever. Tests: CXR miliary picture; <i>Liver, bone marrow smears and culture</i> definitive. High index of suspicion required. Empiric anti-TB treatment should be used in severely immunocompromised patients with prolonged fever, night sweats, weight loss, hepatosplenomegaly, anaemia persisting despite conventional anti-infective treatment
TB pericarditis	TB is likely to be the commonest cause of pericarditis in our setting due to the high prevalence of TB (and HIV); pericarditis and effusion resolves spontaneously in about half of patients. Cardiac tamponade is a common presentation in patients with effusive/constrictive pericarditis. Fever; cough; SOB; orthopnea; central chest pain, shortness of breath; Signs consistent with right-sided cardiac failure (pitting oedema, tender hepatomegaly, hypotension with small pulse pressure; raised JVP with lack of fall with inspiration – Kussamaul’s sign; ascites if constriction occurs); pericardial rub; fall in blood pressure indicates cardiac tamponade. Tests: CXR may show enlarged globular heart; <i>ECG, echocardiogram; pericardiocentesis – exudate; low diagnostic yield on ZN stain; culture increases yield of M. tuberculosis.</i> AntiTB treatment reduces risk of death and development of constrictive pericarditis. Adjunctive steroid treatment and pericardial drainage are recommended. Pericardectomy should be performed in cases of recurrent effusion or constrictive pericarditis
TB peritonitis	Ascites in the absence of liver disease
TB spine	Pain in affected site. Focal lesion often causing deformity in the spine is a late presentation

3.4.3.4 Treatment of Tuberculosis

Treatment of HIV related TB should follow the general principles of TB treatment in the HIV-uninfected patient and should always conform to the National Guidelines on TB Therapy from the National Tuberculosis and Leprosy Program (NtLP). HIV patients with TB respond well to standard TB treatment and have cure rates and relapse rates similar to that of uninfected patients. Adherence to TB medication is important to ensure that TB is cured. Adherence in TB patients should follow the same principles as adherence in patients on ART; as such intense adherence support should be provided to all TB/HIV patients on TB treatment whether or not they are on concomitant ART.

Treatment of TB involves the use of multiple drugs taken in combination to prevent the emergence of drug resistance to any of them. The primary drugs used are Isoniazid (H, INH), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) as defined in the National TB treatment guidelines.

Anti-TB (ATT) medications may cause significant but largely tolerable adverse drug reactions (ADRs) or side effects. They include rash, anorexia, nausea, vomiting, peripheral neuropathy, hepatitis, auditory and vestibular damage and optic neuropathy. ADRs are more common in HIV positive TB patients than in HIV-uninfected TB patients. Because of the similarity of the ADRs caused by anti-TB drugs to those caused by ARV drugs, it is important that patients who need dual treatment for both conditions start TB treatment first, followed by ARV drugs, started a couple of weeks later.

Pyridoxine should be given to all HIV/TB patients to reduce the risk for INH-related peripheral neuropathy.

Figure 3.4: The Goals and Principles of Providing TB Treatment

Goals of TB Treatment
<p>The purpose of providing TB treatment is to:</p> <ul style="list-style-type: none"> • Cure the patient of TB. • Prevent death from TB. • Decrease TB transmission to other people. • Reduce TB relapse/recurrence. • Prevent drug resistance.
Principles of TB Treatment
<p>TB treatment is guided by the following principles:</p> <ul style="list-style-type: none"> • Never use single drugs. • Always use drugs in combinations – using Fixed Dose Combinations (FDCs) where possible. • Drug dosage to be based on weight. • Drug intake should as far as possible be directly observed. • Ensure that the entire 6-8 months treatment is taken.

Drug regimens for treating TB Patients

Table 3.2. Dosage Recommendations for the Treatment of TB in Adults

Drug	Daily dose in mg/kg (Maximum dosage in parentheses)
	Adults
Isoniazid (H)	5(300 mg)
Rifampicin (R)	10-20 (600 mg)
Pyrazinamide (Z)	15-30 (2 mg)
Ethambutol (E)	15-25
Streptomycin (S)	15 (1 mg)

Table 3.3. Anti-TB drug Regimens by Category

Category	Patient Type	Anti-TB Drug Regimen
I	TB patients who have Smear positive PTB/Severe forms of TB	2ERHZ/6HE (4RH*)
II	TB patients with relapse, treatment after default or treatment failure	2SRHZE/1RHZE/5RHE
III	TB patients who have smear negative/ Extra pulmonary TB	2RHZ/6HE (4RH*)

*The shorter 6-month rifampicin based regimen is being introduced in Kenya from January 2007

Adjunctive Corticosteroid use in TB patients

Steroids are indicated in the following patients with TB

- Tuberculous meningitis (start at the same time as TB treatment and continue for 4-6 weeks and taper over 2 weeks)

- TB pericarditis: For adult patients give prednisolone 60 mg/day for four weeks, 30 mg/day for four weeks, 15 mg/day for two weeks, then 5 mg/day for week eleven. For children, prednisone 1 mg/kg daily as the initial dose for four weeks, with a decreasing dose over time as described for adults.
- IRIS (severe symptoms such as pericarditis, severe respiratory distress, CNS manifestations, eye symptoms) in patients with TB/HIV on ART (duration of steroid treatment depends on patient presentation but usually a short course of 1-2 weeks is adequate). Dose: 1mg/kg/day of prednisolone.

Initiation of HIV Treatment in TB/HIV Co-infected Patients

All HIV/TB patients should be started on anti-TB drugs as a priority. CTX prophylaxis should also be commenced immediately if not previously used. PTB is a WHO Stage 3 defining condition while EPTB (except TB adenitis) is indicative of WHO Stage 4 disease; the majority (as high as $\geq 75\%$ where CD4 testing is available) of TB/HIV patients in our setting therefore qualify for ART. There is no clear evidence indicating when it is best to start ART in co-infected patients who qualify for ART; however the aim should be to start ART for patients who qualify after initiating, but *during the course* of TB treatment. To facilitate adherence, TB medication should ideally be collected at the same time and place as the ARV drugs; in other words TB and HIV care and treatment should be integrated as much as possible without compromising treatment of either condition.

Table 3.4: When to Start ART in TB Patients

CD4 Count	When to Start
CD4 Not Available	Start ART as soon as feasible
CD4 ≤ 200	Start ART as soon as feasible
CD4 201 - 350	Start ART in the continuation phase
CD4 > 351	ART is not indicated

Monitoring Patients on TB Treatment

Monitoring treatment response of HIV positive patients on TB treatment should be according to the NTLP recommendations and should include regular adherence assessment. Monitoring for adverse events is dependent largely on clinical assessment of patients. More frequent monitoring should be provided for patients with adverse events including liver disease and also in pregnant women. Patients who have positive sputum at any time from 2 months or more after starting ATT must have a sputum culture done.

TB Treatment in Patients with Liver Disease

Treatment options for patients with abnormal liver function (ALT $> 3x$ ULN) should be discussed and managed together with a senior clinician. Choice of treatment may be challenging and is likely to be individualized and may necessitate sourcing single drugs for the patient. Options may include:

- Standard therapy with frequent LFT monitoring (for mild liver enzyme derangement of Grade 1-3)
- If the liver ALT $> 10 x$ ULN treatment should be discontinued until liver function tests return to baseline. Thereafter the likely cause of the hepatotoxicity should be determined. For patients with sputum positive disease this may involve starting them on ethambutol plus streptomycin then adding the hepatotoxic drugs one at a time with monitoring of LFTs, starting with rifampicin, isoniazid followed by pyrazinamide. The drug that provokes a transaminitis should then be avoided in the final regimen, with possible options as
 - Rifampicin plus ethambutol plus pyrazinamide for 6 months (avoiding INH)
 - INH, rifampicin and ethambutol for 2 months and then INH and rifampicin for a further 7 months (avoiding pyrazinamide)

- For patients with **severe** liver disease
 - Only one hepatotoxic anti-TB drug could be used, thus a regimen of fluoroquinolone plus rifampicin and ethambutol for 2 months followed by rifampicin plus ethambutol for total of 12 months.
 - Alternatively, in patients unable to tolerate any hepatotoxic drugs a regimen of streptomycin, ethambutol and a FQ e.g. ofloxacin for 3 months followed by ofloxacin plus ethambutol for 9 months may be used (3SEO/9EO).

Whenever a non-standard TB treatment regimen is used patients should be monitored carefully for response to treatment and exit sputum cultures should be carried out.

TB Immune Reconstitution Inflammatory Syndrome

This is a paradoxical worsening of symptoms, signs or radiographic appearance of TB in patients on anti-TB treatment who start ART soon after initiation of ATT. Signs of IRIS in TB patients may include high fevers; increase in size and inflammation of lymph nodes or appearance of new enlarged nodes; worsening chest signs, infiltrations, pleural effusions; expanding CNS lesions. Although paradoxical reactions in TB patients on ATT were seen in the pre-HIV era they are more common and more severe in co-infected patients.

Mild IRIS can be managed symptomatically with NSAIDs while continuing anti-TB treatment (and ART if already started). *Severe and life-threatening* reactions require the addition of steroids (prednisolone at 1mg/kg/day reduced over a 1-2 week period); ART may on occasion need to be discontinued if already started in patients unable to continue both treatments.

3.4.3.5 TB and Pregnancy

- Pregnant HIV infected women should be screened for TB and where suspected investigated for TB as for non-pregnant patients, with special care taken if radiographic imaging is required.
- INH is safe in pregnancy, however hepatotoxicity may occur more frequently in pregnancy and the postpartum period; clinical monitoring should therefore be carried out monthly and appropriate lab tests performed as appropriate during pregnancy and the immediate postpartum period
- Rifampicin is associated with increased risk for rifampicin-related hemorrhagic disease among neonates born to women receiving anti-TB therapy during pregnancy; prophylactic vitamin K, 10 mg, should be administered to the neonate
- Streptomycin should be avoided in pregnancy because of the risk of VIII cranial nerve damage in the foetus. Similarly, fluoroquinolones should be avoided in pregnancy because of the association with arthropathy (animal studies)

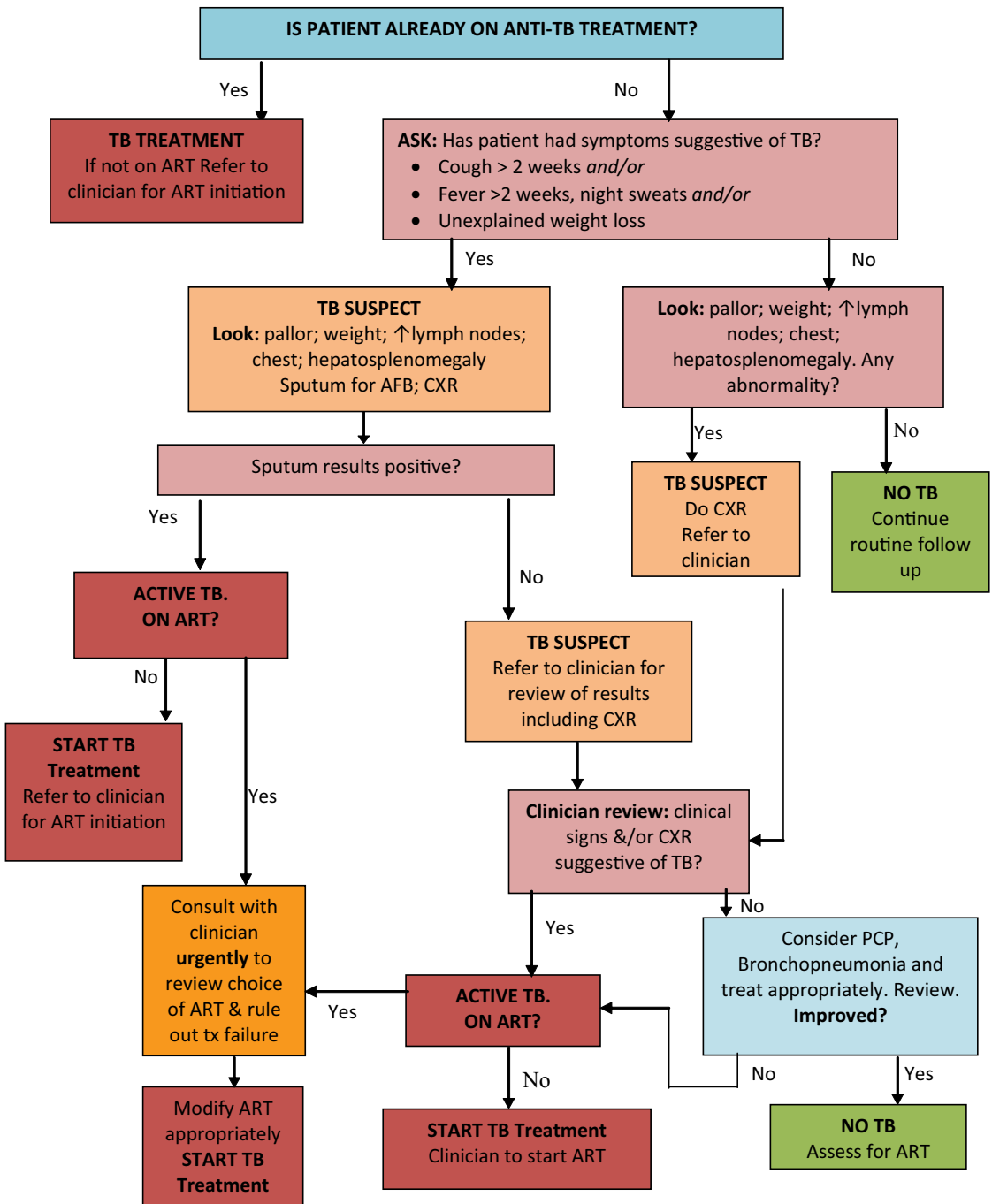
3.4.3.6 Prevention and Control of TB

- TB is the most common *serious* OI in PLHA in Kenya and is likely to be the most common cause of death in PLHA.
- It is an aggressive OI that may arise at higher CD4 counts than other serious OIs/conditions.
- Patients with HIV/TB co-infection are more likely to die than HIV-negative TB patients.
- ART reduces the incidence of TB, however, even PLHA on ART remain at a higher risk for development of TB than HIV uninfected individuals.
- *TB prevention and control depends on identification of patients with active disease and effective and complete treatment of cases.*
- Seamless **collaboration at the health facility level between HIV and TB treatment clinics** is essential in the effort to control the TB epidemic. To this end
 - **Active clinical screening for TB is essential in all PLHA** at entry into care, as well as during each routine follow-up clinical appointment. Symptomatic patients should have sputum examination for AFB and a CXR done. (See Fig 3.5)
 - **ALL TB patients should be screened for HIV infection** due to the high risk for HIV co-

- infection in these patients.
- HIV-infected patients exposed to open TB should also be identified for screening for active disease as part of intensive case finding.
- TB in HIV positive patients should be managed according to the national TB treatment guidelines.
- Other important aspects of TB control include
 - Public/patient education and awareness on the symptoms suggestive of TB and action to take if they occur
 - Basic cough hygiene/cough etiquette
 - Infection control within the work place including adequate ventilation patient flow that minimizes exposure of most patients to those with cough
 - Infection control and contact management in congregate settings such as prisons, schools (especially boarding)

FIGURE 3.5: SCREENING FOR TB IN HIV CARE CLINICS

All PLHA should be assessed for TB during each clinic visit and the result of the assessment recorded as either “active TB”, “TB treatment”, “TB suspect” or “no TB”.



3.4.4 PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

3.4.4.1 Introduction

PCP is caused by *Pneumocystis jiroveci*, a ubiquitous organism classified as a fungus but sharing biological characteristics with protozoa. Initial infection is usually asymptomatic and occurs in childhood. PCP in adults is most often the result of reactivation of a latent infection when the immune system fails, although occasionally new exposure to the organism results in disease.

PCP is one of the most serious OIs in late stage AIDS, usually occurring when CD4 counts fall below 100 cells/mm³ or when other Stage 4 illnesses are already present. It is rare when CD4 > 250 cells/mm³; more than 90% of patients develop disease with CD4 counts of less than 200 cells/mm³.



Untreated, PCP is almost always fatal and even when treated it is frequently fatal with mortality rates of up to 30 to 50% reported. The incidence of PCP is reduced dramatically by the use of CTX in PLHA as well as the use of effective ART. Thus, the well-trained HIV HCW must always be alert for early diagnosis of PCP in advanced AIDS patients, especially if the patient is not on CTX prophylaxis; PCP is rare while PLHA are taking CTX as recommended.

PCP interferes with the transfer of oxygen at the alveolar-capillary membrane throughout large sections of the lung tissue, which results in its cardinal manifestation, shortness of breath as a result of low blood oxygenation. Low blood oxygen saturation levels are a consistent finding even early in the disease. TB and bacterial pneumonia almost never give rise to these low oxygen saturation levels. Other common symptoms that distinguish PCP from bacterial pneumonias are gradual onset of symptoms (over several days to weeks) and the absence of shaking chills or *pleuritic* pain. TB and PCP share the gradual onset of cough and weakness. But with TB, weight loss and night sweats are prominent features while with PCP, shortness of breath is prominent. Clinicians should be aware that patients might have dual pathology.

3.4.4.2 Clinical Presentation

Symptoms are **gradual** in onset over several days to weeks (average 3 weeks) and include

- Shortness of breath (SOB or dyspnoea) initially on exertion but eventually at rest as disease worsens
- Cough, usually dry although scanty sputum may be present
- Fever
- Chest pain

The most consistent signs are

- Tachypnea (rapid breathing with respiratory rate 20-40 per minute or even more)
- Tachycardia (raised pulse rate - PR)
- Cyanosis in severe cases
- Chest examination is often normal or non-specific rales may be heard.

3.4.4.3 Investigations

The **diagnosis** of PCP in the local set up is based mainly on clinical symptoms and signs. Investigations that support the clinical diagnosis include:

- Low oxygen saturation:
 - Early in the disease process this needs to be measured after exertion (patient can climb up and down a step)
 - Simple point of care pulse oximetry is useful for identifying patients with impaired

oxygenation; it may be useful as a screening tool in HIV clinics to pick up early PCP disease. In mild disease, pulse oximetry may reveal oxygen (O₂) saturation levels below 90% on exercise while severe and clinically obvious disease is supported by O₂ desaturation at rest.

- Arterial blood gas where available will confirm low oxygen saturation and additional useful information beyond that obtained from pulse oximetry.
- CXR
 - Typically has diffuse bilateral symmetrical interstitial infiltrates starting at the hila and spreading out in a “butterfly” pattern
 - May be normal in early disease
 - Atypical, with nodular densities, blebs, and pneumothorax. Presence of cavities and pleural effusion suggests other pathology
- LDH characteristically high (non-specific)
- *Induced sputum, bronchoalveolar lavage for identifying cysts and trophozoites using different stains or immunofluorescence*
- *Transbronchial or open lung biopsy for histopathological identification of the organism*
- *Nucleic acid tests*
- *Thin section CT shows ground glass appearance*

3.4.4.4 Management

A high index of suspicion to enable early diagnosis, clinical diagnosis and empirical treatment of PCP is important to improve survival and reduce mortality.

First Line Treatment

- Cotrimoxazole (trimethoprim-suphamethoxazole fixed dose tablet in a ration of 1:5) is the drug of first choice. An attempt should be made to use CTX even if mild side effects occur.
- In patients with a history of allergy rapid desensitization (see Table 1.3) should be used to enable treatment to commence on the same day.
- Patients with a history of severe allergy (e.g. Stevens Johnson syndrome) should **NOT** be desensitized; an alternative (see 2nd line below) treatment should be used instead. Other side effects of CTX include hepatitis and bone marrow suppression. It is useful to monitor biochemistry and haematology regularly during treatment because of frequent biochemical abnormalities.
- Breakthrough PCP in those taking CTX prophylaxis is unusual, unless the patient has not been compliant with treatment. If it occurs CTX should still be the drug of first choice.
- CTX is the preferred treatment even in pregnant women.
- Although intravenous treatment may be desirable in the severely unwell patient IV cotrimoxazole is not easily available in most of our facilities. Thus all efforts (including the use of nasogastric tube) should be made to ensure oral treatment is given effectively.
- *There is no need for addition of leucovorin to prevent myelosuppression*

Calculating the dose of cotrimoxazole

CTX is given in high doses of 15-20 mg/kg/day (of the Trimethoprim component).

An easy way for calculating the number of **single strength (SS) tablets** of cotrimoxazole given per 24-hour period is **weight of the patient in kg divided by 4**. Divide this number of tablets into 3-4 doses and give every 6-8 hourly.

Example

A 48 kg patient needs:

$48/4 = 12$ SS tablets/day x 21 days

Give these as 3SS tablets every 6 hours OR 4 SS tablets every 8 hours with plenty of water.

Severe Disease

- Patients should be admitted and provided with supplemental oxygen. Where intensive care facilities are available ventilatory support should be provided as appropriate.
- Corticosteroids given with anti-PCP treatment reduce the incidence of mortality and respiratory failure due to PCP, which typically occur in the first few days of treatment. Thus in patients with severe illness (RR > 30/minute, oxygen saturation below 90% at rest on room air or an arterial blood gas showing a partial pressure of oxygen of < 70mmHg at rest on air), oral prednisone should be given concurrently with the CTX at the following doses:
 - Prednisone 40mg BD for 5 days, then
 - Prednisone 40mg OD for 5 days, then
 - Prednisone 20mg OD for the remaining 11 days.
- Corticosteroids may also be used in patients who have mild disease at the time of initiation of cotrimoxazole, but subsequently worsen during the course of treatment, if the diagnosis of PCP is highly probable. In such patients other co-morbidity should also be considered.

2nd Line PCP Treatment

Clindamycin 600-900 mg 8 hourly IV OR 300-450 mg 6 hourly PO **plus** Primaquine 15-30 mg/day PO for 21 days. Hematologic toxicity is more common with this regimen.

Pentamidine 4mg/kg/day IV/IM (may be available where leishmaniasis is still treated using this drug)

Monitoring

- Careful monitoring is necessary during treatment to review response and to assess for adverse drug reactions (ADRs). ADRs are generally dose related and include leucopenia, thrombocytopenia, and hepatitis; thus blood tests for CBC, LFTs, UE should be done at least weekly. Treatment should continue despite mild ADRs; CTX dose reduction may be considered if biochemical results are > 5x ULN. Hypersensitivity ADRs include rash and fever.
- Even with appropriate therapy, respiratory failure may develop. Mortality correlates with the degree of disease severity and is high in patients who develop respiratory failure especially where ventilatory support is unavailable.
- Pneumothorax is a relatively common complication of PCP in PLHA. Patients should be observed if they have mild symptoms associated with relatively small pneumothorax of less than 10-20% of lung volume. Symptomatic patients or those with large pneumothorax should be managed with a chest drain.
- Improvement of patients with PCP is slow but should be clear by the 5th to 8th day of treatment. If no improvement has occurred
 - Consider secondary bacterial pneumonia (review symptoms and CXR) and start empirical treatment
 - Consider changing PCP treatment to the second line option
 - Consider TB if patient has not recovered after the full course of treatment
- Cotrimoxazole prophylaxis should be started immediately after treatment is complete.

PCP in Pregnancy

Cotrimoxazole remains the drug of choice. If given in the 3rd trimester the risk of kernicterus in the neonate is increased.

Table 3.5: Summary of PCP Treatment

	Drugs	Dose
1st Line	Cotrimoxazole (Single strength, SS 400/80; double strength, DS 800/160) given for 21 days	20mg/kg of the trimethoprim component. (Alternatively, weight divided by 4 gives the number of SS tablets per 24 hr period)
2nd Line	Clindamycin <i>plus</i> Primaquine Pentamidine Given for 21 days	Clindamycin 600-900mg 8 hourly <i>plus</i> Primaquine 15-30mg/day Pentamidine 4mg/kg/day IV/IM
For the severely ill (O₂ saturation on air < 90%)	Add prednisolone from first day of treatment	40mg BD for 5 days, then 40mg daily for 5 days, then 20mg daily for the remaining 11 days

ART in patients with PCP

The potential problems associated with concomitant treatment for PCP and ART relate to pill burden, overlapping toxicities, drug interactions and the development of the immune reconstitution inflammatory syndrome (IRIS).

PCP is a WHO Stage 4 disease; thus patients who have started ART should continue treatment. For patients who have not started ART preparation for ART should begin as soon as practical and patient should generally be able to start ART towards the end of the PCP treatment when their illness is resolving, or soon after treatment is complete.

PCP IRIS has been reported where ART is introduced in patients with undiagnosed PCP, while patient is still on PCP treatment or soon after PCP treatment is complete. If IRIS develops after a full course of treatment for PCP has been completed then efforts should be directed at symptomatic management. Patients still on PCP treatment should continue. Patients who have not initiated PCP treatment should start this alongside the ART. Steroids may be used as described under severe PCP above or for severe symptoms of IRIS. Patients who develop worsening respiratory symptoms during or after treatment for PCP should always be evaluated for TB.

**CHAPTER 4:
GASTROINTESTINAL
MANIFESTATIONS OF
HIV INFECTION**

CHAPTER 4: GASTROINTESTINAL MANIFESTATIONS OF HIV INFECTION

4.1. Introduction

Gastrointestinal (GI) symptoms are some of the most frequent complaints that persons infected with HIV present with. Any part of the gut from the mouth to the anus can be affected by HIV-related conditions. Most GI disease in HIV infection can be attributed to infections. Other causes include malignancies (e.g. Kaposi's sarcoma, lymphoma), drugs (e.g. antibiotics, ARV drugs) and HIV itself.

4.2. Oral Manifestations of HIV Disease

Examination of the oral cavity is a routine part of the clinical assessment of all patients. Furthermore, many of the several conditions that involve the oral cavity in PLHA are useful in the clinical staging of HIV disease. It is therefore important to examine the mouth of every patient suspected of having or known to have HIV infection even in the absence of complaints. Oral lesions can be debilitating because they may interfere with adequate feeding. The common oral conditions seen in PLHA include candidiasis, aphthous ulcers, oral hairy leukoplakia (OHL), herpetic lesions, gingival hyperplasia and Kaposi's sarcoma (KS).

4.2.1 Oral Candidiasis (Thrush)

Candida albicans is the commonest causative agent of oral candidiasis. The presence of thrush in an adult whose HIV status is unknown should prompt HIV diagnostic testing. Oral thrush is a WHO Stage 3 condition; all patients with this condition should be prepared for and started on ART. If already on ART, assessment for possible treatment failure is mandatory.

Clinical Presentation

Painless creamy white curd-like (*maziwa lala*) patches or pseudomembrane on the tongue, inner surface of the cheeks and pharynx are characteristic of oropharyngeal candidiasis. The lesions can easily be scraped off, revealing raw red areas underneath that may bleed. Less commonly shiny red (erythematous) areas without white plaques are seen on the tongue and palate. Angular cheilosis may also be caused by candida. Symptoms include sore mouth and loss of taste. Oral thrush usually occurs if $CD4 < 200 \text{ cells/mm}^3$

Diagnosis of oropharyngeal candidiasis is clinical, based on the appearance of the lesions. The ability to scrape off the plaques associated with oral thrush differentiates it from oral hairy leukoplakia.

Treatment

1st Line Treatment

Nystatin mouth drops 500000 units (5 ml) 4x per day for 7-14 days

Miconazole gum patch

2nd Line Treatment (can be used in patients with extensive thrush or those failing above)

Fluconazole 100 mg/day for 7 days

Itraconazole 200mg/ day for 7 days (swished in mouth and swallowed on an empty stomach)

4.2.2 Aphthous Ulcers

These ulcers are well defined, have elevated margins, and are generally very painful. They may be minor (< 1cm diameter, shallow and self-limiting healing within 2 weeks) or major (deep, >1cm and persistent). The cause of aphthous ulcers is unknown. The differential diagnoses include herpes simplex virus, CMV and drug induced ulceration. Biopsy should be carried out if an ulcer fails to heal after about 4 weeks.

Treatment

- Antiseptic mouth washes (e.g. difflam)
- Local anaesthetic preparation prior to meals
- Corticosteroid preparations in oral gel
- Secondary infection of ulcers is common requiring metronidazole + penicillin OR co-amoxiclav
- For refractory cases:
 - Oral prednisolone (40 mg per day for 1-2 weeks before tapering)
 - Dapsone 100 mg /day

4.2.3 Kaposi's Sarcoma (KS)

Human Herpes 8 virus causes Kaposi's sarcoma (KS). Oral KS presents as part of this multicentric disease; often the patient will have other lesions elsewhere. Nodular lesions found on the roof of the mouth, gums or tongue, which do not hurt or itch characterize KS. The nodules vary in colour from dark red, to purple to brown. They start as patches then progress to thick bumps and may eventually grow to form large tumours. KS is a WHO Stage 4 condition; all patients with this condition should therefore be prepared for and started on ART. If already on ART, an assessment for treatment failure is mandatory.

For specific management of KS see Chapter 9.

4.2.4 Oral Hairy Leukoplakia (OHL)

OHL presents as unilateral or bilateral white patches or linear, vertical ridges along the sides of the tongue and sometimes on the other (dorsal and ventral) surfaces of the tongue. They are painless and cannot be scraped off. The main differential diagnosis is oral thrush.

Although caused by intense replication of Epstein-Barr virus, specific treatment (e.g. aciclovir) is not indicated, as they are rarely symptomatic. They are found almost exclusively in PLHA and are indicative of WHO Stage 3 disease. They respond to effective ART.

4.2.5 Salivary Gland Enlargement

Bilateral or unilateral non-tender parotid enlargement is seen commonly in PLHA, especially in children. Parotid enlargement is likely to be a result of lymphoid proliferation due to HIV. It may be associated with a dry mouth (xerostomia) or cosmetic concerns. If fluid-filled (cystic), decompression using needle aspiration may be attempted. Sugarless chewing gum is recommended for xerostomia.

Table 4.1. Summary: HIV Associated Oral Lesions

Clinical condition	Presentation	Management
Candidiasis	White curd like patches on the tongue and inner surface of cheeks; can be easily scraped off revealing redness underneath. May also present as shiny erythematous patches or angular cheilitis	Nystatin mouth drops 500000 units (5 ml) 4x per day for 7-14 days Miconazole gum patch Systemic therapy if above fails: Fluconazole 100 mg/day for 7 days Itraconazole 200mg/ day for 7 days (swished in mouth and swallowed on an empty stomach)
Apthous Ulcers	Ulcers in the mouth that are painful, are well defined with elevated margin and whitish floor	Antiseptic mouth washes (e.g. difflam) Local anaesthetic preparation prior to meals Corticosteroid preparations in oral gel 2° infection of ulcers is common requiring metronidazole + penicillin OR co-amoxiclav For refractory cases: Oral prednisolone (40mg per day for 1-2 weeks before tapering) Dapsone 100mg /day Resolves with ART.

Table 4.1. Summary: HIV Associated Oral Lesions cont.

Clinical condition	Presentation	Management
Kaposi's Sarcoma	Lesions usually found on the roof of mouth or gums and do not hurt or itch; vary in colour from dark red, purple to brown. They start as patches then progress to thick bumps, to may become large tumours.	ART together with specific treatment of KS. Should be managed by an experienced clinician.
Oral Hairy Leukoplakia	Oral mucosal disease, associated with EBV, non-painful white plaque along the lateral tongue borders. Diagnosis is clinical.	Treatment not required.
HSV - 1	Painful, progressive anogenital or orolabial ulceration; More likely to recur or persist in PLHA	Aciclovir 400mg 8 hourly for 7-10 days

4.3 HIV-Related Oesophageal Disease: Difficulty and Pain on Swallowing

4.3.1 Introduction

Difficulty swallowing (dysphagia), and pain on swallowing (odynophagia), are common GI complaints in PLHA and often indicates oesophageal disease. Dysphagia and odynophagia may be aggravated by certain medications or foods. Patients may also have associated symptoms, which may help the HCW arrive at a likely diagnosis. It is very important to address these complaints as they affect dietary intake; as part of the management of oesophageal disease a nutritional assessment of patients is important.

4.3.2 Causes of Oesophageal Disease

The most common causes of dysphagia/odynophagia in PLHA are **opportunistic infections** including:

- **Candidiasis:** oesophageal candidiasis is the most frequent cause of oesophagitis in PLHA.
 - **Presentation:** diffuse retrosternal (behind the breast bone) pain, dysphagia and odynophagia. Oral thrush is present in 50-70% of patients with oesophageal candidiasis. Fever is not often a sign associated with oesophageal candidiasis; the presence of fever suggests another cause of oesophagitis or additional pathology. Oesophageal candidiasis is a WHO Stage 4 condition; all patients with this condition should be prepared for and started on ART. If patient is already on treatment, assessment for possible treatment failure is mandatory. Other causes of oesophagitis are more difficult diagnose in our set up due to limited capacity.
- **Viral causes:** herpes simplex virus (HSV) and cytomegalovirus (CMV) may cause oesophagitis. Pain on swallowing is prominent and may be localized. Oral thrush is infrequent in these patients and often there are no oral ulcers. Fever is common in patients with CMV oesophagitis. Involvement of other systems or disseminated cytomegalovirus disease is not unusual. **These conditions are also indicative of severe HIV disease; patients with oesophagitis should therefore be assessed for ART.**
- **Non-infective** causes of dysphagia/odynophagia include:
 - Medication (AZT, Aspirin, NSAIDs, tetracyclines, ferrous sulphate (iron) tablets)
 - Foods – spicy foods, citrus, coffee etc.
 - Gastro-intestinal disorders – gastro-oesophageal reflux disease.
 - Aphthous ulcers of the esophagus

4.3.3 Diagnosis of HIV-related Oesophageal Disease

Diagnosis of the causes of oesophageal symptoms in PLHA in a resource-limited setting is largely clinical, based on the history and the examination findings. In a PLHA with dysphagia, the presence of oral candidiasis is highly suggestive of oesophageal candidiasis and the patient should be treated as such. If after a thorough history and examination the cause of oesophageal symptoms is not obvious then, empiric treatment with a systemic antifungal should be given.

Endoscopy is able to establish diagnosis in about 70% to 95 % and is indicated where adequate doses of empiric treatment for oesophageal candidiasis have failed. Brushing and biopsy samples should be examined for both fungal and viral pathogens.

4.3.4 Treatment of Oesophagitis in PLHA

Systemic therapy is required for effective treatment of oesophageal candidiasis. Patients improve fairly quickly, often within 2-3 days. Failure to improve after 7-14 days of fluconazole may be a result of fluconazole resistance or an alternative diagnosis; an alternative antifungal agent may be considered unless symptoms suggest HSV infection. Secondary prophylaxis is not necessary in the majority of patients treated for oesophageal candidiasis in the era of effective ART.

Systemic azole treatment may on occasion be associated with hepatotoxicity, especially if combined with other hepatotoxic drugs.

Pregnancy and fungal infections:

Treatment of fungal infections in pregnancy may be complicated by concerns of teratogenicity of antifungal medications. Although fluconazole is associated with teratogenicity in animal studies (at higher doses than would normally be used in humans) where alternative antifungal drugs (amphotericin B) are not available it should be used for invasive fungal disease at standard doses. Itraconazole should be avoided.

Table 4.2: Summary: Treatment of Oesophagitis in PLHA

Cause	Treatment
Oesophageal Candidiasis	Preferred: Fluconazole 200mg stat then 100mg OD PO x 14-21 days. IV if patient cannot swallow Failure to improve on Fluconazole: Increase dose to 400-800mg/day OR Itraconazole <i>solution</i> 200mg PO x 14-21 days OR Amphotericin B IV 0.3-0.7 mg/kg/day x 14-21 days If no response consider anti-HSV treatment
Herpes Simplex Virus (HSV) Oesophagitis	Aciclovir 800mg 6 hourly x 14-21 days Or Valaciclovir 1g PO TDS x 14-21 days
CMV Oesophagitis	Valganciclovir 900mg BD x 3 weeks
Aphthous Ulcers	Prednisolone 40mg/day x 7-14 days, then taper

4.3.5 Essential Steps in the Management of Oropharyngeal and Oesophageal Lesions

1. Assess for emergency signs and stabilize patient
 - a. Always assess the sick patient for emergency symptoms and/or signs (patient dehydrated [assess and classify – see Table 4.4], unable to walk, RR > 30, temp > 40°C, SBP < 90mmHg). Stabilize severely sick patients first (see Table 1.4) before continuing with a more complete clinical assessment. Patients with oropharyngeal or oesophageal disease may not be able

to take enough fluids or food and may therefore be dehydrated as well as malnourished. Further, oesophageal disease is associated with severe immunosuppression; for this reason other serious OIs may co-exist.

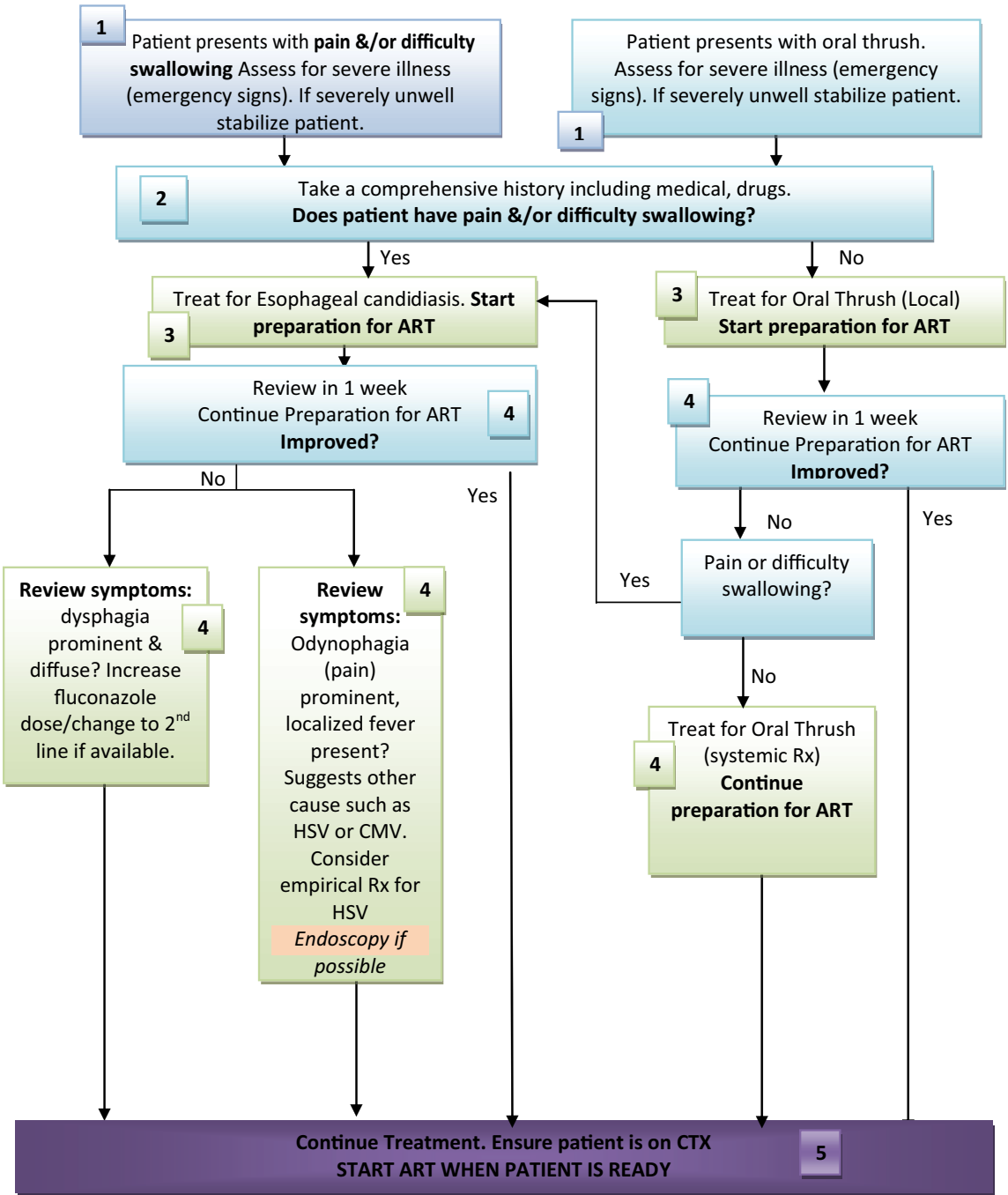
- b. **Does the patient need referral?** Always ascertain if the patient can be managed effectively by the cadre of HCWs present and with the facilities available at the particular HCF. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
2. Carry out a clinical assessment (see Table 4). A thorough clinical assessment will often elicit information and/or findings that direct the HCW to the likely diagnosis.
 - a. **Ask about:** duration of symptoms, whether pain or difficulty swallowing is the more prominent feature; whether pain is localized or diffuse; presence of any oral lesions; presence of vomiting, vomiting blood or history of black stools from altered blood; presence of fever and any other symptoms; previous and current medication as well as duration of these treatments.
 - b. **Look:** PR, RR, temperature, BP; skin fold return - hydration status; pallor, lymphadenopathy; weight. Oesophageal infections in PLHA are generally indicative of severe immunosuppression, thus it is important to perform a comprehensive examination of other symptoms.
 - c. The diagnosis of oropharyngeal and oesophageal lesions is largely clinical; following this empirical treatment should be started. Failure to respond to adequate treatment for the presumed condition indicates that the patient should be reviewed and assessed for possible alternative diagnosis.
 - d. **Investigations:** patients with oesophageal or oropharyngeal candidiasis have severe immunosuppression: they should be carefully assessed for other conditions. Investigations should be individualized according to symptoms and/or signs.
Endoscopy, where available, is recommended for patients who fail to respond to 2 weeks' worth of effective antifungal treatment for presumed oesophageal candidiasis.

3. Treatment

- i. Specific treatment is as per the tables 4.1 and 4.2 above or as per other findings. If the patient is unable to swallow compromising oral treatment, intravenous therapy should be considered
 - ii. Treatment of co-existing conditions and correction of hydration when necessary.
 - iii. Nutritional assessment and support as appropriate
4. **Review:** it is essential to review patients whose treatment is based on a clinical diagnosis to determine response to treatment, or whether an alternative diagnosis needs to be considered.
 5. **Is the patient on ART?**
 - c. Oesophageal candidiasis, KS, mucosal HSV and CMV are classified as WHO Stage 4 conditions, while oropharyngeal candidiasis is classified as WHO Stage 3 disease. As such PLHA with these conditions who are not yet on ART should be prepared for ART
 - d. Patients already on ART developing symptoms suggestive of oesophagitis or oral thrush may be failing their ART and should be assessed for failure of their current regimen

The flow chart below summarizes the approach to the management of a PLHA with oral and/or oesophageal symptoms.

FIGURE 4.1: MANAGEMENT OF ORAL AND ESOPHAGEAL CANDIDIASIS



4.4 DIARRHOEA IN THE HIV-INFECTED PATIENT

4.4.1 Introduction

Diarrhoea is a manifestation of a problem in the GI tract, which can be caused by different conditions. Diarrhoea is one of the most common reasons that PLHA seek medical attention and is also a leading cause of death in resource-limited settings. The definitions of diarrhoea vary; for practical purposes a patient can be said to have diarrhoea if they have unusually frequent and loose stools, often three or more loose stools a day. To facilitate patient management, diarrhoea can be classified as acute, when it is of less than 2 weeks' duration, or chronic, when it has lasted more than 2 weeks' duration.

4.4.2 Acute diarrhoea

For practical purposes acute diarrhoea can be defined as diarrhoea of not more than 2 weeks' duration. Like in HIV-uninfected patients infectious agents are responsible for most episodes of acute diarrhoea in PLHA. These agents cause diarrhoea by interfering with normal functioning of the intestines, resulting in either increased fluid secretion into and/or poor absorption of fluid from the intestines. Acute diarrhoea is only slightly more common in PLHA than in the uninfected population. In most of these cases, infection is acquired through eating contaminated food. Acute diarrhoea should always be addressed in the context of public health concerns. If the history suggests clustering of cases, efforts must be made to address a likely public health problem.

4.4.3 Chronic diarrhoea

The gastrointestinal (GI) tract is a common site for opportunistic infections and malignancies in patients with HIV infection, many of which may present with chronic diarrhoea. Chronic diarrhoea is defined as diarrhoea that has persisted for 2 or more weeks. Often patients with chronic diarrhoea will have had symptoms for much longer than this. Chronic diarrhoea is much more common in PLHA when compared to HIV-uninfected people.

4.4.4 Causes of Diarrhoea (See Table 4.3)

The exact hierarchy of the different infectious agents causing diarrhoea in Kenya is still largely undefined.

Table 4.3: Summary: Causes of Diarrhoea

Cause	Acute Diarrhoea	Chronic Diarrhoea
Bacterial Infections (watery diarrhoea, bloody, fever)	Non-typhi <i>Salmonella</i> species (NTS), <i>Shigella</i> , <i>Campylobacter jejuni</i> , <i>Yersinia enterocolitica</i> , <i>Escherichia coli</i> and <i>Vibrio cholera</i> , shigella, <i>Clostridium difficile</i> , <i>Vibrio cholera</i> ; Food borne toxigenic diarrhoea (staph aureus, B cereus)	<i>Salmonella typhi</i> ; <i>Mycobacteria avium</i> complex, <i>mycobacterium TB</i>
Protozoal Infections (watery diarrhoea, bloating, flatulence)	<i>Giardia lamblia</i> , <i>Entamoeba coli</i>	<i>Cryptosporidium</i> , <i>Giardia lamblia</i> , <i>Isospora belli</i> , Ent. histolytica, microsporidia
Parasitic		<i>Strongyloides stercoralis</i>
Viruses	Enteric viruses	CMV
Medication	Antibiotics, ARV drugs – PIs, DDI	ARVs
Toxins	<i>Clostridium difficile</i> , staph aureus, bacillus cereus	
Malignancies		Lymphoma, endocrine tumours
Other	Ischemic colitis	Endocrine disorders, malabsorption, ulcerative colitis, radiation or chemotherapy, unknown

4.4.5 Clinical Presentation of Diarrhoea

The severity of the clinical presentation will vary according to whether the diarrhoea is associated with systemic manifestations (fever, septicaemia) or has been severe or protracted enough to cause dehydration. Additionally, patients with chronic diarrhoea may have evidence of malnutrition. A thorough history and physical examination is therefore essential to assess the general state of hydration and nutrition and to exclude extra-intestinal causes of diarrhoea. Often, the cause of diarrhoea cannot be determined based solely on the physical findings present, which in any case may be scarce.

In the absence of adequate laboratory diagnostic capacity, the history is extremely important in determining the course of action in the management of PLHA with diarrhoea.

The following should be determined in the history:

- History of travel
- Food history (eating outside the home), food preparation at home, home hygiene
- Contact with others with diarrhoea (clustering of cases is suggestive of an outbreak)
- Duration of diarrhoea and rapidity of onset of symptoms, for instance in relation to food eaten.
- Drug history including new medication, antibiotic use (increased risk of *Clostridium difficile*), recent change in medication
- Ask about the characteristics of the diarrhoea and presence of any associated symptoms.
- Characteristics of the diarrhoea may suggest the likely cause; for example bacterial infections are likely to cause watery diarrhoea that is often bloody and associated with fever; *Entamoeba histolytica* causes a colitis with bloody diarrhoea and abdominal cramps; *Giardia lamblia* causes a watery diarrhoea that is associated with bloating and flatulence. *Cryptosporidia* and *microsporidia* cause chronic watery diarrhoea, with large volume stools and abdominal pain.
 - Presence and character of abdominal pain if localized may suggest the site of disease (e.g. colonic disease may be associated with tenesmus and lower left quadrant or back pain; peri-umbilical pain suggests small intestinal disease. Ischemic bowels may cause severe pain)
 - Presence of other symptoms:
 - Fever suggests an invasive organism as a cause or the presence of a more systemic illness
 - Vomiting may suggest upper GI or proximal intestinal disease. Vomiting also occurs in intestinal obstruction. Vomiting without diarrhoea should suggest a problem other than gastroenteritis.
 - Ask about weight loss, night sweats
 - Presence of blood in the stool suggests colonic ulceration (bacterial infection, inflammatory or ischemic disease)
 - Volume – small bowel disease produces large volume stools compared to colonic disease. White bulky floating stools suggest small bowel disease with malabsorption. Copious “rice water” stools are characteristic of cholera.
- Men who have sex with other men are more prone to diarrhoea caused by infections acquired via the focal-oral route.

The physical examination should include the following:

- Hydration and nutritional status
 - Lethargy, changes in mental status, confusion, unconsciousness; diminished skin turgor; resting hypotension and tachycardia, dry mucus membranes, decreased frequency of urination, and orthostasis can be used to gauge dehydration. Weight loss should be documented.
 - In children, the absence of tears, poor capillary refill, sunken eyes, depressed fontanelles, increased axillary skin folds, and dry diapers all may reflect a dehydrated state.
 - Muscle wasting and signs of neural dysfunction due to nutritional depletion may be observed in patients with chronic diarrhoea.

- Abdominal examination
 - A careful abdominal examination is necessary to exclude causes of diarrhoea that may require surgical intervention, such as pelvic abscesses close to the recto-sigmoid that are causing tenesmus.
 - The HCW should look for signs of an acute abdomen, determining the location of any tenderness, palpating for masses or organomegaly and listening for bowel sounds. Appendicitis in children may manifest as diarrhoea.
- General examination should be carried out to determine if there are other signs indicative of HIV immunosuppression as well as non-GI signs of illness.

Complications of Infectious Diarrhoea

It is important to assess patients for the complications of diarrhoea during the clinical evaluation. They include:

- Dehydration
- Malabsorption (fatty stools that are bulky, smelly and float in western lavatories; anaemia)
- Systemic infection (meningitis, arthritis, pneumonia) especially with *Salmonella* infections
- Septicaemia (*Salmonella*, *Yersinia*, *Campylobacter* organisms; fever with signs of severe illness)
- Hemolytic-uremic syndrome (much more common in children especially with *E coli* O157:H7)
- Toxic megacolon
- Reactive arthritides (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Giardia* organisms)
- Thrombotic thrombocytopenic purpura or TTP (*E coli* O157:H7)
- Guillain-Barré syndrome (*Campylobacter* organisms).

4.4.6 Diagnostic Evaluation of Patients with Diarrhoea

The extent of the diagnostic work up depends on the severity of the patient's illness (dehydration, electrolyte imbalance, high fever, sepsis), the history as well as access to appropriate laboratory tests.

- Stool examination is a simple procedure and the most important investigation that should ideally be carried out in all patients with diarrhoea and will, in many cases, suggest a likely cause. Using simple stains stool samples can be examined for ova, cysts and leukocytes; performing an occult blood test is also very simple.
- For acute diarrhoea:
 - The presence of blood or leukocytes in stool is a strong indicator of inflammatory diarrhoea. Faecal leukocytes are present in 80-90% of all patients with *Salmonella* or *Shigella* infections but are less common with other infecting organisms such as *Campylobacter* and *Yersinia*. They may also be present in inflammatory bowel disease, but are usually absent in viral infections, *Giardia* infection, *Entamoeba histolytica*, enterotoxigenic *E coli* infection, and toxigenic bacterial food poisoning.
 - A stool culture is not necessary or cost-effective in all cases of diarrhoea unless a bacterial cause is suspected. **Fever, bloody stools, leukocytes in stool, pain resembling that associated with appendicitis (Yersinia), or for epidemiologic purposes, diarrhoea involving food handlers** are all indications for culture.
 - *Testing for other pathogens, such as Vibrio species, enterohemorrhagic E coli* O157:H7, *and other shigatoxin-producing bacteria require special media not routinely available in many HCFs.*
 - Stool assay for *C. difficile* toxin may be carried out if antibiotic associated diarrhoea is suspected
 - A modified ZN stain may be performed to identify Cryptosporidia, cyclospora, Isospora in patients with chronic diarrhoea
- Other tests that may be carried out where necessary include:
 - CBC
 - Blood slide for malaria parasites
 - Blood culture

- Urea & electrolytes, creatinine
- Abdominal X-ray where an acute abdomen or perforation is suspected
- *Sigmoidoscopy for biopsy, where inflammatory bowel disease or pseudomembranous colitis is suspected*
- MAC cultures
- *Endoscopy and biopsy: (CMV, Kaposi's sarcoma and lymphoma)*
- *CT scan-most helpful with CMV colitis and lymphoma*

In patients with chronic diarrhoea who have had exhaustive investigations and no definitive cause has been found, HIV enteropathy should be considered.

Note: In our setting more often than not it may not be possible to conduct exhaustive laboratory investigations for a patient with diarrhoea. Based on clinical presentation a presumptive diagnosis should be made and empiric treatment instituted.

4.4.7 Treatment of Diarrhoea

The goals of treatment of gastroenteritis are to reduce morbidity and mortality, prevent complications and decrease the duration of illness.

- Emergency treatment should involve aggressive management of dehydration where this is found (see below). At the same time patients should be assessed for any signs of complications. Public health issues if found should be addressed.
- Empiric specific treatment for infective acute or chronic diarrhoea may be deemed necessary; in this case the suspected or confirmed causative agent determines the specific treatment. Mild to moderate acute diarrhoea with no suggestions of inflammation (fever, blood and polymorphs in stool) does not require specific antibiotic treatment. On the other hand patients who are immunocompromised, have constitutional symptoms, abdominal pain, bloody motions and polymorphs on examination of the stools generally require specific antibiotic treatment. Empiric treatment must cover the likely pathogens in the clinical context.
- Where an external cause of diarrhoea is identified it should be discontinued if possible (e.g. an offending drug)
- Anti-emetics can be used in adult patients with vomiting, but should be avoided in children.
- In adults anti-diarrhoeal agents have a role in managing mild to moderate diarrhoea by reducing frequency of stools; they should not be used in patients with bloody diarrhoea (to avoid toxic megacolon) or in children.
- Advise patients on how to avoid contracting diarrhoea and how to avoid spreading it to other family members (basic hygiene, care around food preparation, proper cooking of foods especially poultry and eggs, avoiding unpasteurized milk, hand washing after going to the toilet and before meals.)
- Nutritional assessment, resuscitation and support in patients who need this

4.4.8 Essential Steps in the Management of Diarrhoea

1. Assess for emergency signs and stabilize the patient
 - a. Always assess the sick patient for emergency symptoms and/or signs (patient lethargic, confused, unconscious, sunken eyes, unable to drink, PR > 120, RR > 30, temp > 40°C, SBP < 90mmHg).
 - b. Determine degree of dehydration and classify (Table 4.4 below)
 - c. Start correcting dehydration at all levels of HCF (see below)
 - d. **Does the patient need referral?** Always ascertain if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. *If referral is required patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer. (See Table 3)*

Table 4.4. Classification of Dehydration in Patients with Diarrhoea

Hydration Status	Symptoms and Signs
Severe Dehydration	Lethargy, confusion or unconsciousness; not able to drink or drinking poorly; sunken eyes, skin pinch returns very slowly (> 2 seconds). Radial pulse weak or not palpable. PR > 110/min; SBP < 90 mmHg
Moderate dehydration	Sunken eyes, thirsty, drinks eagerly, skin pinch goes back slowly; PR > 90/min
Mild or no dehydration	Patient may be thirsty. Vital signs normal

2. Carry out a clinical assessment (see Table 1.5). A thorough clinical assessment will often elicit information and/or findings that direct the HCW to the likely cause of diarrhoea.
 - a. **Ask about:** (see section 4.4.5)
 - Duration of diarrhoea
 - History of travel, contact with patient with diarrhoea, clustering, medications.
 - Characteristics of stool: volume, watery or formed, any blood in the stool
 - Associated symptoms: fever, abdominal pain, Have you had any treatment
 - a. **Look:** PR, RR, temperature, BP; hydration status. Look for pallor, lymphadenopathy; measure weight. Carry out a careful abdominal examination (look for distension, tenderness, masses). Rectal examination should be performed (frank blood, occult blood). The rest of the examination depends on other symptoms.
 - b. **Investigations:** Investigations should be individualized according to symptoms and/or signs; however stool examination is the key diagnostic procedure. It should include microscopy for ova and cysts, culture (and examination for *C. difficile* toxin) where possible. Blood cultures are extremely useful in febrile patients. Other tests are as listed above.

3. Treatment

a. **Correct dehydration**

Mild or no obvious dehydration: (Home treatment)

1. Give 2 sachets ORS to take home.
2. Drink extra fluid (any fluid except sugary or alcoholic) as much as desired
3. Drink 1 cup (200-300ml) of fluid after every loose stool
4. If vomiting, continue to take small sips of fluid in between
5. Continue extra fluids until diarrhoea stops
6. Continue eating
7. Return to the HCF if
 - Patient becomes unable to drink at all
 - Patient becomes lethargic
 - Patient develops abdominal pain
 - Stool becomes bloody
 - Diarrhoea persists after 3 days

Moderate Dehydration (Clinic and Home)

- Determine amount of ORS required in the 1st 4 hours based on age or weight

Table 4.5. ORS required in first 4 hrs in patients with moderate dehydration

Age (Weight)	5-14 yrs (20-30 kg)	> 15 yrs (> 30 kg)
Amount of Fluids (ml)	1000-2200	2200-4000

- Give frequent small sips using a cup
- If patient wants more ORS than shown give as much as desired
- If vomiting, wait for a few minutes then give fluids more slowly
- Reassess after 4 hours; if able to continue at home then discharge with ORS (demonstrate how to mix) and to use as described above
- If severe large volume diarrhoea persists, patient vomiting or not able to take fluids above in the time shown or the patient develops signs of severe dehydration then manage as below.

Table 4.6. Correction of Severe Dehydration (Health Care Facility)

1. Can you give IV fluids?	Yes → No. Go to 2	Start IV fluids immediately as per Table 4.7
2. Is IV treatment available nearby (can patient get there in 30 minutes?)	Yes → No. Go to 3	Refer urgently for IV rehydration. If patient can drink give ORS for use on the way to hospital
3. Is there someone trained to use nasogastric tube for rehydration?	Yes → No. Go to 4	Start ORS by NG tube at 20 ml/kg/hour for 6 hours. Review hourly. If stomach distended slow down rate. If no improvement in 3 hours refer to hospital for IV rehydration. If improving continue and review in 6 hours to determine continuing care
4. Refer urgently to hospital for rehydration		Give ORS for use on the way to hospital if patient can drink

Table 4.7. Intravenous Fluid for Rehydration of Severely Dehydrated Patients

- Give 100 ml/kg of Ringer’s solution (or normal saline if Ringer’s not available) divided as follows:

Age	Give 30 ml/kg in first:	Then give 70 ml/kg in:
Infants < 12months	1 hour (repeat once if radial pulse undetectable)	5 hours
Children > 12 months, adults and adolescents	30 minutes (repeat once if radial pulse undetectable)	2.5 hours

- Review patient hourly and if not improving, give IV fluids more rapidly.
- Start ORS at 5ml/kg once patient able to drink (after 4 hours in infants and 1-2 hours in older patients)
- Reassess infants after 6 hours and older patients 3 hours after able to drink ORS and determine continuing care.

b. Specific Treatment

Empirical Treatment for Diarrhoea

Most PLHA with acute diarrhoea have a self-limited illness that does not require specific antibiotic treatment. Where empiric therapy is indicated by the severity of the diarrhoea, fluoroquinolones are the agents of choice. Because of the possibility of protozoal infections like giardia and amoebiasis, metronidazole may be added to this treatment.

Most PLHA with chronic diarrhoea will have had different medications, often including antibiotics. Very ill patients with prolonged diarrhoea and fever may have non-typhi salmonella gastroenteritis with septicaemia, which in advanced HIV infection requires prolonged antibiotic treatment (4-6 weeks). In many cases the specific cause of chronic diarrhoea is undetermined. A large number of PLHA with chronic diarrhoea may fail to improve because some of the causative agents do not respond to the empiric treatments commonly available and in use locally. Apart from this, patients with chronic diarrhoea may also have other illnesses such as disseminated TB. Patients with chronic diarrhoea should therefore be assessed thoroughly for the presence of other conditions as well as prepared to commence ART. There is evidence that patients with chronic diarrhoea may improve when given albendazole for 2 weeks where other treatments have failed.

Table 4.8. Summary: Empiric Treatment of Diarrhoea (Also see appendix B)

Duration of Diarrhoea	Cause	Treatment
Acute Diarrhoea	Not determined or due to medication (no other symptoms)	Loperamide 4 mg stat then 2 mg after every loose motion (up to 16mg/day)
	Not determined. Other symptoms present (fever, bloody diarrhoea, abdominal pain); PMNs in stool	Ciprofloxacin 500mg BD for 5-10 days (or until symptoms improve) ±Metronidazole 500mg TDS for 5-10 days
	Campylobacter	Erythromycin 500mg QDS X 5days. Or Ciprofloxacin, although resistance occurs
	Non-typhi salmonella	Ciprofloxacin x 10-14d. May be longer if symptoms persist. ART indicated
	Enterohemorrhagic E. coli	Antibiotics contraindicated
	Other E. Coli	Ciprofloxacin 500mg BD x 3 days
	Shigella	Ciprofloxacin 500mg BD x 3 days
Chronic Diarrhoea	Patient on CTX prophylaxis	Metronidazole + Albendazole. Add Ciprofloxacin if patient febrile
	Patient not on CTX	Metronidazole + Albendazole + CTX 960 mg BD x 10 days
	Isospora belli	CTX 960 mg BD x 10 days
	Entamoeba histolytica	Metronidazole 500mg TDS x 10 days
	Giardia lamblia	Metronidazole 250 mg TDS x 10 days
	Cryptosporidia	ART; nutritional support; anti-diarrhoeal agents

a. Supportive treatment

Anti-emetic and anti-diarrhoeal agents can be used in adult patients where appropriate. It is important that the nutritional status of patients with chronic diarrhoea is assessed and corrected where necessary.

- Review:** it is essential to review patients whose treatment is based on a clinical diagnosis to determine response to treatment, or whether an alternative diagnosis needs to be considered. Laboratory tests where available should be used to modify treatment if appropriate. Response is indicated by reduction in frequency of diarrhoea and volume as well as in improvement of systemic manifestations like fever. In patients with chronic diarrhoea and prolonged fever TB should be considered actively and searched for.
- Is the patient on ART?**

- a. Chronic diarrhoea with fever in PLHA is indicative of severe immunosuppression and is classed as a WHO Stage 4 condition. As such, these PLHA should be prepared for ART
- b. Patients already on ART developing chronic diarrhoea should be assessed for failure of their current regimen

The flow charts below summarize the management approach of a patient with diarrhoea.

FIGURE 4.2: MANAGEMENT OF ACUTE DIARRHOEA

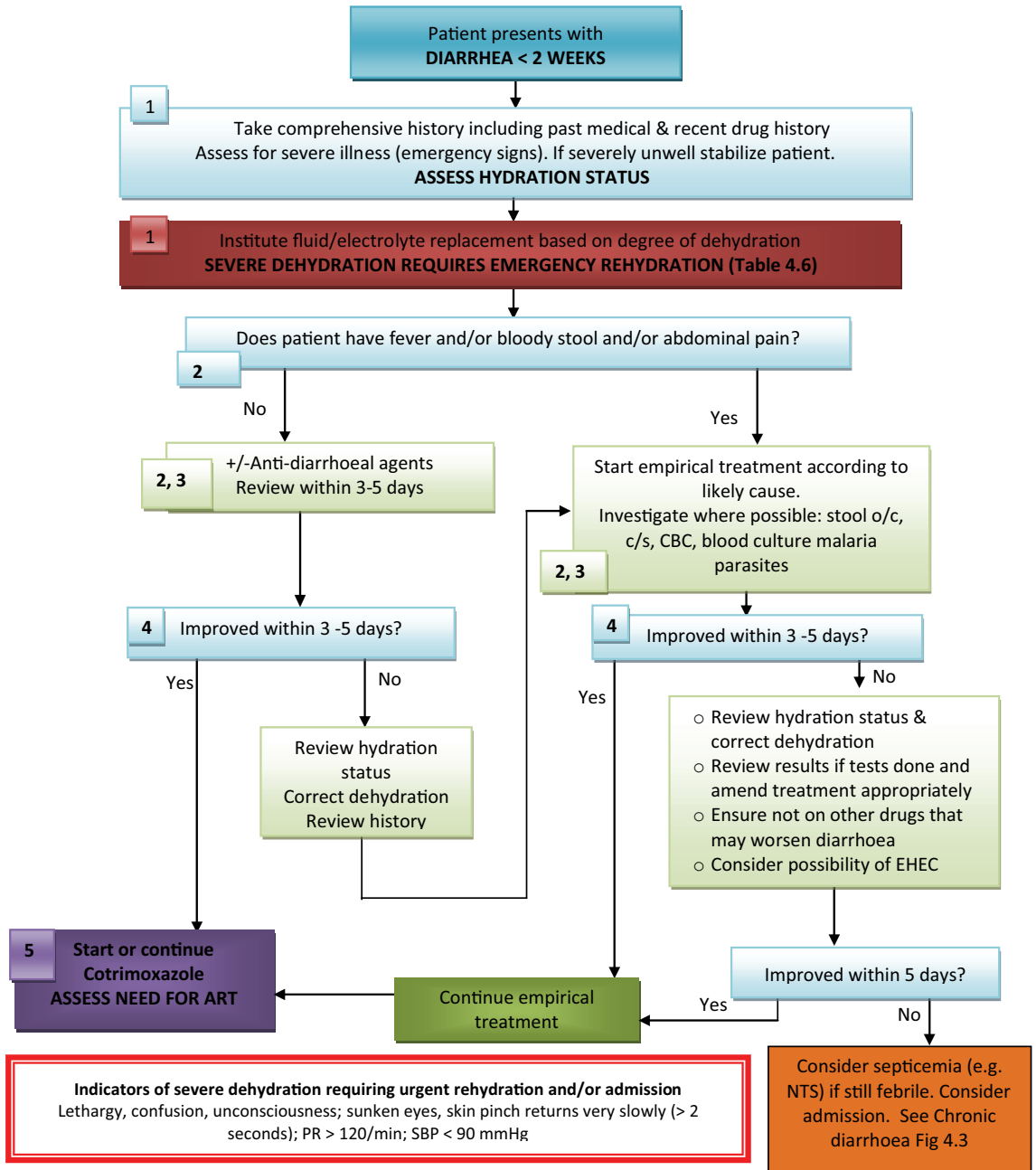
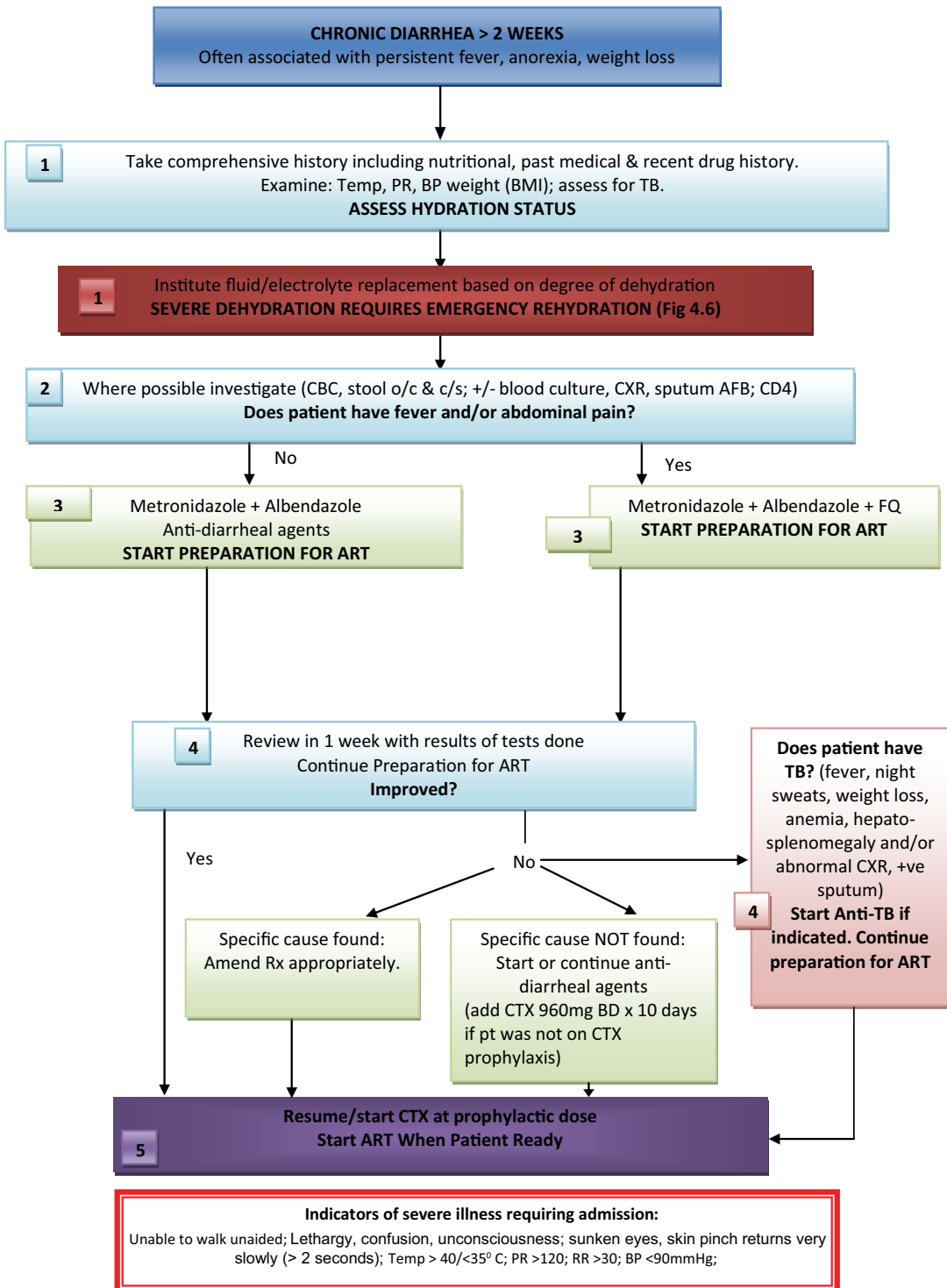


FIGURE 4.3: MANAGEMENT OF CHRONIC DIARRHEA



CHAPTER 5: DERMATOLOGICAL MANIFESTATIONS OF THE HIV DISEASE

CHAPTER 5: DERMATOLOGICAL MANIFESTATIONS OF THE HIV DISEASE

5.1 Introduction





Dermatological conditions are the most common manifestation of HIV infection and occur in about 90% of infected individuals. They can occur at any stage of the HIV infection. Some of the dermatoses are unique to HIV infection while others are common conditions, which also occur in HIV uninfected individuals. These common skin problems may present atypically, be more widespread, have a prolonged course and may cause diagnostic and treatment challenges in PLHA. It is important that HCWs be able to manage the common skin conditions because, apart from causing discomfort, they can be a source of stigma causing severe distress to patients, and occasionally be life-threatening. Many of these conditions are unusual in healthy HIV uninfected patients and should always raise the possibility of HIV infection and prompt provider-initiated testing and counseling (PITC) in affected patients.



Bullous lesion in patient on CTX

Like in HIV uninfected individuals, dermatological conditions in HIV are due to infections, infestations, inflammation or malignancies. To facilitate diagnosis in resource limited settings the commonest presentations of skin conditions are classified according to symptoms as shown in the table below:

Table 5.1: Symptom-based classification of skin lesions

Itchy skin	Blisters, sores or pustules	Skin rash with few or no symptoms	Nodular skin lesions
Scabies Pruritic Papular Eruption (PPE) Eosinophilic folliculitis Dermatophytes (ring worm, tinea) Dry Itchy Skin Eczema Contact dermatitis	Photo-dermatitis Herpes zoster Herpes simplex Drug reaction Impetigo Folliculitis	Seborrheic Dermatitis Psoriasis Acne	Kaposi's Sarcoma Molluscum Contagiosum
			

Chronic Eczema

Bullous lesion in patient on CTX

Seborrheic Dermatitis

Facial Molluscum Contagiosum

5.2 Itchy Skin Rash

Table 5.2: Itchy Skin: Clinical Presentation and Management

Clinical Condition	Presentation	Management
Scabies Caused by the mite, <i>sarcoptes scabiei</i>	Rash & excoriations on hands wrist, genital area, axillae & torso; burrows in finger webs & wrist; face spared. An eczematous rash due to hypersensitivity reaction to the mites may also occur. Intense scratching leads to secondary lesions (excoriations, lichen simplex, etc). Norwegian scabies is uncontrolled, extensive, crusted hyperkeratotic scabies, which may involve the entire body, face & scalp, associated with immunosuppression. The lesions in Norwegian scabies do not appear to be as itchy.	Diagnosis is clinical. Treat with <ul style="list-style-type: none"> ○ 25% Benzyl benzoate nocte for three nights or ○ Malathion 0.5% apply once and wash off after 24 hours or ○ Lindane 1% apply to whole body and wash after 8 hours or ○ Permethrin 5% apply and wash after 12 hours or ○ Ivermectine 200mg/kg stat especially for Norwegian scabies ○ It is important to treat the whole family, and to ensure clothing and bedding are washed in hot water and let to dry in sunlight. ○ For post scabies itch or eczematous dermatitis give antihistamines ○ Secondary bacterial infections should be treated with hygiene and appropriate antibiotics.
Papular Pruritic Eruptions (PPE)	Chronic, severely itchy rash with (hyperkeratotic & hyperpigmented) dark papules & nodules, scratch marks. Heal as dark spots/marks with pale centres or post inflammatory hypopigmentation. It occurs at CD4 counts of around 200 even though it is a WHO Stage 2 condition. Most lesions are above the nipple line on the torso and limbs.	<ul style="list-style-type: none"> ○ Rule out scabies; treat empirically where diagnosis unclear. ○ Treatment is usually symptomatic - give antihistamines for the itch (Chlorpheniramine – piriton, 4mg every 8 hours or Promethazine hydrochloride 25mg at night); if no improvement consider potent topical steroids ○ Consider ART for extensive intractable disease Treat itch with antihistamine. Antiseptic skin washes can be used when needed.
Eczema A non-infectious inflammation of the dermis, associated oedema giving rise to vesicles; usually in response to direct physical or chemical injury to the skin or certain allergens and can be acute, sub-acute or chronic	<p>Acute eczema characterized by wet swelling, oozing, blisters, sores and excoriations</p> <p>In the sub-acute and chronic phases, the lesions are thick (lichenified) and scaly.</p> <p>Seborrhoeic dermatitis/eczema is commonest form of eczema in PLHA & occurs in seborrhoeic areas of the skin (scalp behind the ears, eyebrows, nasolabial folds, chin, the sternum, middle of the back in between the shoulder blades, axilla, groin and perianal area). The lesions classically have scales that are oily</p>	<ul style="list-style-type: none"> ○ Sore oozing area should be washed with clean water (no soap) to remove crusts, and the skin dried gently. ○ Antihistamines should be prescribed for the itchiness ○ Short-term use of low potency steroid (1% hydrocortisone) cream instituted once or twice a day (but not on the face). ○ Where indicated (seborrhoeic dermatitis), antifungal cream BD or Ketoconazole 200mg OD for 1-3/52 can be used. Treat itch with antihistamines <i>(Rule of Thumb: when wet it is wet, when dry it is oily)</i>
Ringworm (Tinea)	Itchy pale, round bald scaling patches on scalp or round patches with a thick edge on body or web of feet; sometimes with elevated margins, and patchy hair loss (alopecia) with broken hair	Whitfield's ointment (or other antifungal cream) if few patches. If extensive, give systemic treatment: <ul style="list-style-type: none"> ○ Griseofulvin (10-15mg/kg) OD with fatty meal ○ Ketoconazole 200mg BD x 2/52 ○ Itraconazole 200 mg OD x 2/52 ○ If scalp involvement, use systemic treatment for at least 6/52. Shave hair if necessary. ○ Antibiotics should be administered if there is secondary bacterial infection. Treat itch with antihistamines
Dry Itchy Skin (Xerosis/ichthyosis)	Dry and rough skin, sometimes with fine cracks	Emollient lotion or Vaseline. Give Chlorpheniramine or Promethazine for itchiness.

5.3 Blisters, Sores or Pustules

Table 5.3: Blisters Sores and Pustules: Clinical Presentation and Management

Clinical Condition	Presentation	Management
<p>Herpes Zoster. Caused by reactivation of Varicella Zoster virus following previous chicken pox. The virus lies dormant in nerve ganglion after disease resolution and tends to recur in the immunocompromised.</p>	<p>Pain followed a few days later by grouped vesicles in a band like pattern involving one dermatome on one side of the body. More than 1 dermatome may be involved in PLHA. May come together to form blisters, which burst leaving superficial ulcers. Involvement of trigeminal (V cranial nerve) nerve especially the nasociliary branch (blisters on the side of the nose and forehead) may lead to corneal inflammation (keratitis) or iritis; blindness may occur if not treated aggressively. Involvement of the sacral nerves may cause urinary retention or constipation.</p>	<p>Treatment: Antiviral drugs shorten the clinical course, prevent complications, prevent the development of latency and/or subsequent recurrences.</p> <p>Acyclovir 800mg 5 times daily x 7 days OR Valaciclovir 1g TDS for 7 days, started as soon as possible after onset of symptoms or as long as new vesicles arise.</p> <p>Pain relief: – (NSAIDS, Codeine, dihydrocodeine - DF118)</p> <p>Lesions should be kept clean and dry; wash and soak lesions in potassium permanganate diluted to colour of nails (1:10,000) then apply 0.5% GV paint. Calamine lotion should not be used; it soothes but on drying breaks the blisters causing early ulceration with risk of bacterial infection.</p> <p>Follow up in 1 week if sores not fully healed.</p> <p>Post-herpetic neuralgia (PHN). A severe, sharp, stabbing pain along a nerve pathway that continues to be experienced long after healing of the lesions of herpes zoster. Most present within a few months of healing of lesions. It is difficult to treat</p> <p>Options for treatment of PHN</p> <ul style="list-style-type: none"> ○ Amitriptyline 25-50mg nocte ○ Carbamazepine 100mg BD (up to 200mg daily). Other anticonvulsants such as gabapentin may be used. Exact mechanism of action unclear but they have a central effect in pain modulation <p>Pts should be warned it takes weeks of treatment before any benefit is noticed</p>
<p>Herpes Simplex Types 1 and 2. HIV transmission is greatly facilitated by the presence of genital herpes. PLHA are more likely to have recurrent disease or chronic ulcers (considered WHO Stage 4 if they last more than 30 days).</p>	<p>Mucocutaneous vesicular lesions, which coalesce to form painful sores involving lips/oral cavity or external genitalia, perianal area. HSV Type 1 more likely to cause extra-genital disease</p>	<p>If first ever episode of HSV or severe ulceration, or chronic ulcer give Aciclovir 400mg 5 times daily x 5 days or until no more new lesions. Chronic herpetic ulcers may require longer duration of treatment.</p> <p>0.5% GV paint and potassium permanganate baths are indicated to keep lesions clean and dry.</p> <p>Chronic HSV lesions indicate severe HIV disease thus patient should be prepared for ART.</p> <p>For disturbing and frequent (> 6 episodes per year) recurrences suppressive therapy should be discussed with a senior clinician (given as ACV 400mg BD or Valaciclovir 500mg OD).</p>

Table 5.3: Blisters Sores and Pustules: Clinical Presentation and Management Cont'd

Clinical Condition	Presentation	Management
<p>Impetigo / Folliculitis Impetigo is an acute, superficial infection of the skin caused by group A haemolytic streptococcal or <i>Staphylococcus aureus</i> infection.</p> <p>Folliculitis is infection of the hair follicle and is characterized by painful pustules around a hair follicle caused by <i>Staph. aureus</i>.</p>	<p>Impetigo: characterized by clustered pustules, which burst and form a honey coloured crust. Tense bulla (large blisters) may be associated with staphylococcal lesions. Painless</p> <p>Folliculitis: Blisters with pus around a hair follicle and usually painful</p>	<p>Treatment of Impetigo: Gentle debridement of lesions to remove crusts. Potassium permanganate baths and 0.5% GV paint can be used</p> <p>Oral penicillins with staphylococcal cover (co-amoxiclav; penicillin V + cloxacillin; erythromycin)</p> <p>If the infection spreads to the surrounding skin (cellulitis) parenteral antibiotic treatment is required.</p> <p>Patients should not share clothing or bedding because impetigo is highly contagious</p> <p>Folliculitis: Clean with soap and water and keep dry. Give Cloxacillin, flucloxacillin or erythromycin x1 wk.</p> <p>Stop vaseline use</p>
<p>Drug Reaction SJS caused by other drugs such as allopurinol sulfonamides, penicillins, cephalosporins, antiepileptics as well as ARVs. HIV patients at 3x the risk of developing drug reactions compared to HIV-negative.</p>	<p>Drug reactions are commonly manifested through the skin in different ways including</p> <ul style="list-style-type: none"> ○ General redness (erythema) which may be macular ○ Patches of dark skin especially for fixed drug reaction. ○ Widespread maculopapular rash ○ Erythema multiforme (blistering rash with target lesions) ○ Stevens Johnson syndrome (fever, oedematous skin with moist rash, vesiculation, ulceration, mucus membrane involvement in the eyes, mouth, genital mucosa epidermal necrolysis), which can be fatal if the drug responsible is not discontinued. Termed "toxic epidermal necrolysis" if extensive or > 30% of epidermal involvement. TEN associated with skin pain. 	<p>For severe reactions (extensive skin involvement, dehydration, patient unable to drink, SBP < 90mmg, PR>120/min, fever) STOP THE DRUG responsible for the reaction. Admission is required and management in a burns unit may be necessary. Prednisolone as 30-60mg OD may be commenced and rapidly tapered off in 5-7 days as patient improves. The data supporting the use of steroids is not strong.</p> <p>Give chlorpheniramine or promethazine hydrochloride for itchiness.</p> <p>For mild drug reactions (redness, itching, rash, dry scaling) give chlorpheniramine or Promethazine HCL and observe. If the condition worsens, stop all medication.</p>
<p>Photo-dermatitis May be precipitated by a drug</p>	<p>Limited to areas exposed to sun Early: blisters and may be oozing. Later: Dark, thickened and scaly.</p>	<p>Hydrocortisone 1% ointment or cream. If severe reaction with blisters, exudates or oedema, give oral Prednisone. Find and remove cause.</p>

5.4 Skin rash with no or few symptoms

The common conditions in this category include:

- Seborrhoeic dermatitis (see Management of Eczema in Table 5.2)
- Psoriasis

Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by the development of red, thickened patches covered with silvery white scales that may be very itchy. Psoriasis often occurs on knees and elbows, scalp, hairline and lower back. PHA may develop psoriasis for the first time following infection with HIV.

Treatment is with 5% Coal tar ointment in 2% Salicylic acid, Dithranol for stable psoriasis and exposure to sunlight for 30-60 minutes a day. If the condition is severe, the patient should be referred to a

dermatologist.

5.5 Nodular Skin Lesions

The common conditions include:

Kaposi's Sarcoma

Kaposi's sarcoma is a neoplasm of blood vessels caused by human herpes virus- 8, that is characterized by the presence of firm purple to brown/black macules, patches, papules, plaques or nodules. Lesions are usually not itchy and non painful. It is a WHO stage 4 disease. Prior to the HIV epidemic KS was seen rarely as an endemic disease affecting older men; the lesions were largely localized rather than extensive as is seen in PHA. Management of KS is discussed fully in Chapter 9.

Molluscum Contagiosum

Molluscum contagiosum is a poxvirus that causes nodular skin lesions mostly in the genital area, but may become more extensive in PLHA involving the face. The lesions are discrete, waxy and pale, cheesy dome shaped nodules with central umbilication.

Treatment

Treatment in HIV uninfected patients is cosmetic as the lesions are largely self-limiting. In PLHA molluscum lesions can be extensive and persist for long thus treatment should be offered where possible.

- Puncture nodules with a sterile needle and touch with 80% Phenol, 90% Trichloroacetic acid (TCA) or 20% Podophyllin (not recommended in pregnancy or breastfeeding)
- Cryotherapy of the lesions
- Widespread lesions in the HIV infected patients do not respond to the above and require ART.

Warts

These are painless growths caused by the human papilloma virus, and are common, occurring in any place on the skin especially the feet, hands and face, but also the genital and peri-anal region.

Treatment

- For warts on the face, apply 2-5% Salicylic acid ointment twice a day for 4-8 weeks or caustic pencil daily. If treatment is not successful, leave them alone.
- When they are on the feet, the patient should shave down the wart and have a HCW apply 50% Salicylic acid (if at home can self-apply 5-20% Salicylic acid or Silver nitrate pencil once a day).
- Genital or anal warts:
 - Apply 10 - 25% Podophyllin solution to the lesions, (the surrounding area should be protected with vaseline) and wash off after 4-6 hour
 - Imiquimod cream, an immune modulator that is applied locally to the growths
 - 50–88% Trichloroacetic acid can be applied in the clinic or cauterisation done.
 - Surgery may be required for bulky lesions
- A HPV vaccine is likely to be available locally as part of the EPI in the near future; as with some other viral STIs, HPV infection is not easily preventable especially using barrier methods, a vaccine will be essential in the efforts to prevent and control infection with HPV types that cause genital warts as well as cervical cancer.

**CHAPTER 6:
NEUROLOGICAL
MANIFESTATIONS OF
HIV INFECTION**

CHAPTER 6: NEUROLOGICAL MANIFESTATIONS OF HIV INFECTION

6.1 Introduction

Neurological complications of HIV disease occur in a significant number of PLHA; in post mortem studies features of neurological abnormalities have been reported in about 80% of patients. Neurological manifestations are associated with considerable morbidity and mortality and in many cases are the presenting problems at initial diagnosis of often-late HIV disease. Many of the common neurological conditions can be managed successfully using a diagnostic approach based on the clinical presentation. Toward this end a thorough clinical assessment is essential to arrive at a working diagnosis that allows institution of empirical and sometimes life-saving treatment. Many of the investigations that may help confirm the diagnosis of these conditions are unfortunately often inaccessible particularly at the district hospital level and below; HCWs taking care of PLHA should therefore be able to perform an adequate neurological assessment in patients with neurological complaints to determine the most appropriate level of care as well as to facilitate a syndrome-based approach to care especially where capacity to carry out tests is limited.

Apart from the neurological diseases seen in HIV uninfected individuals, PLHA are also susceptible to several neurological conditions, most due primarily to opportunistic infections, neoplasms, HIV infection per se, autoimmune conditions or complications of drugs including antiretroviral therapy. The most prevalent HIV-related conditions include cryptococcal and tuberculous meningitis (TBM); cerebral toxoplasmosis; bacterial and tuberculous brain abscesses; progressive multifocal leucoencephalopathy (PML); bacterial and viral meningitis. Neurological manifestations directly related to HIV infection include HIV associated dementia (HAD) or the AIDS dementia complex (ADC), peripheral neuropathy, myelopathies and myopathy. Peripheral neuropathy is very common in the HIV infected and can occur at any stage of the disease. A variety of drugs including some antiretroviral drugs (e.g. stavudine) and anti-TB drugs (isoniazid) may also cause peripheral neuropathy. Amongst the neoplasms affecting PLHA, primary central nervous system (CNS) lymphoma is the commonest.

The manifestations of neurological complications of HIV differ in children, whose immune and nervous systems are infected at an immature stage, whether in utero, during delivery, or postpartum. CNS complications tend to progress more rapidly in children, probably because of the inability of their immune systems to mount an appropriate immune response to the infection. Neurological involvement in HIV infection is more frequent in children than in adults. It may take the form of a loss of previously acquired intellectual and motor milestones or of developmental delay. Opportunistic infections due to reactivation of dormant organisms are unusual, as children may not have been exposed yet to the responsible organisms.

6.1.2 Pathophysiology

When immune defences are impaired, opportunistic infections arise, often from reactivation of previously acquired organisms. This mechanism applies to agents such as *Toxoplasma gondii* and Epstein-Barr virus (EBV). Other organisms, such as the JC or SV40 viruses that cause PML, may be activated directly by HIV gene products.

The likelihood of a particular neurological syndrome correlates with the clinical stage of HIV infection as reflected by viral load, immune response, and CD4⁺ lymphocyte counts. This, in turn, is related to the severity of immunodeficiency and autoimmunity.

Manifestations at seroconversion (primary HIV infection) are often sub-clinical but may include meningitis, acute encephalopathy with seizures, confusion, and delirium. HIV enters the CNS soon after initial infection. Early peripheral nerve manifestations include isolated acute cranial nerve palsies and Guillain-Barré syndrome.

6.1.3 Clinical Presentation

The clinical presentations of neurological illnesses are varied, depending on the specific cause and include headache, fever, confusion, seizures, dizziness and visual changes and involuntary movements, gait disturbances and cranial neuropathy, loss of body function/focal deficits as well as cognitive and behaviour changes. A thorough clinical history and examination should be carried out in all patients who present with any neurological symptoms or signs.

6.2 Essential Steps in Management of Neurological Disease (See Figure 6.1)

1. Assess for emergency signs and stabilize the patient

- a. Always assess the sick patient for emergency symptoms and/or signs and stabilize the patient first, by instituting the appropriate emergency response, before continuing with a more complete clinical assessment. **In a patient with neurological complaints the following emergency signs indicate a severe illness requiring admission:**
 - History of recent convulsions
 - Recent loss of body function (weakness or paralysis)
 - Patient has impaired consciousness, is confused or agitated
 - Patient has a stiff neck
 - Temperature > 40°C; SBP < 90mmHg; DBP >110 mmHg
- a. Stabilize severely sick patients first before continuing with a more complete clinical assessment (see Tables 1.4 & 1.5)
- b. **Does the patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer. Patients with acute bacterial meningitis may die or develop complications if transferred before the initial parenteral antibiotic dose is given.*

2. Carry out a clinical assessment as shown in Table 1.5. The initial assessment should determine whether the patient has an acute emergency such as bacterial meningitis for which treatment *must* start immediately and also whether a patient needs referral to another facility for further assessment and management. The family member or friend accompanying a patient with neurological problems should be involved, to enable the full history and sequence of events to be obtained.

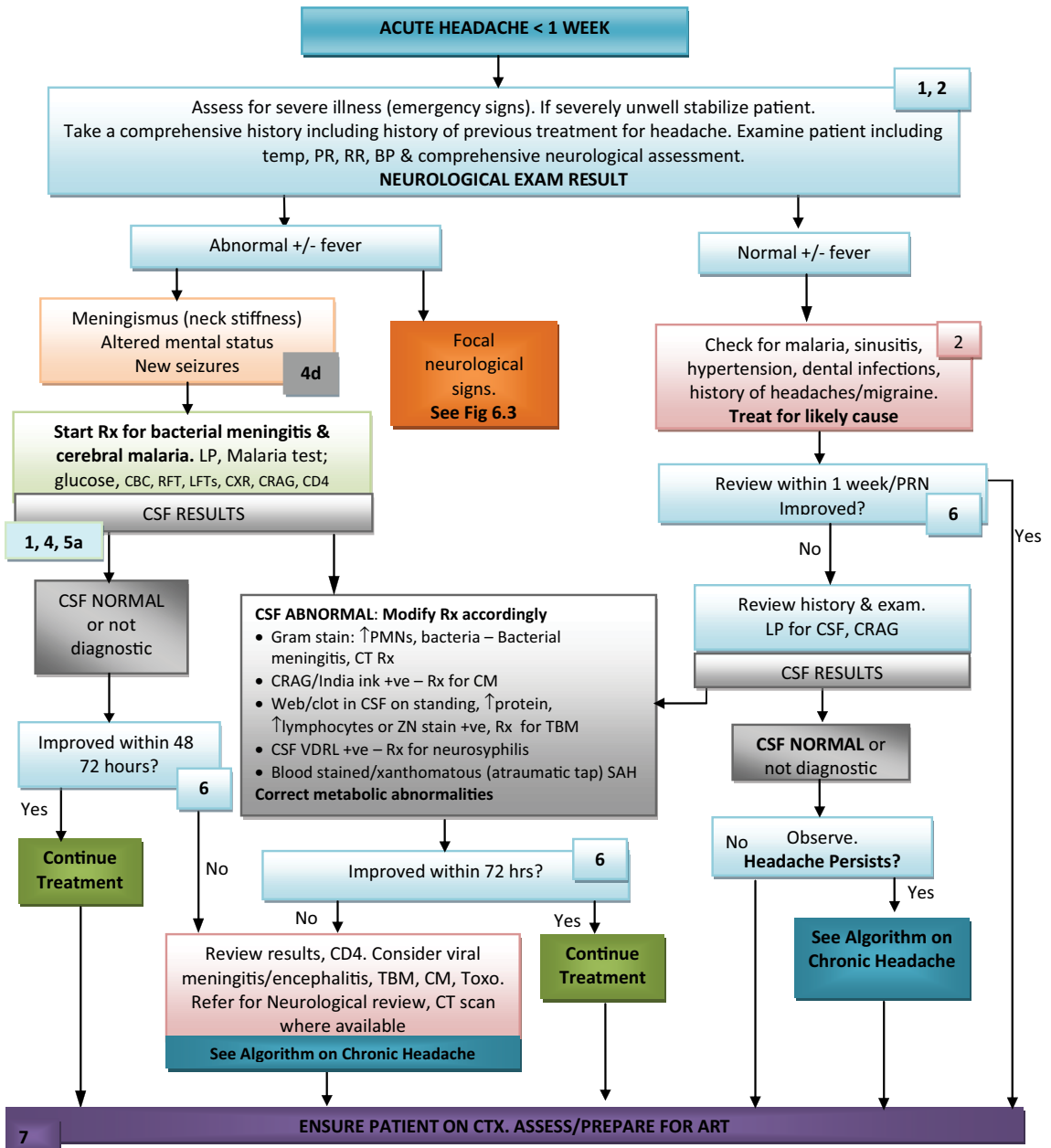
- a. **Ask** about and determine the following:
 - Duration of symptoms
 - History of headache – onset sudden or gradual? Previous headaches? Visual problems? Vomiting? Headache unilateral? History of discharge from ears or nose?
 - Presence of fever, neck pain/stiffness, photophobia?
 - Presence of convulsions and onset including whether previously known to be epileptic
 - Loss of consciousness?
 - Loss of function (weakness or paralysis)
 - Previous head injury?
 - Has family noticed any change in behaviour? Is the patient more forgetful? Is the patient confused? (Assess orientation and memory)
 - History of exposure to someone with meningitis
 - Recent antibiotic use
 - Alcohol or other recreational drug use?
 - Any other symptoms? Assess the patient as shown in Table 1.5 to exclude other conditions. PLHA with serious OIs affecting the CNS are likely to be severely immunocompromised and may have multiple OIs.
 - Any previous medical problem e.g. hypertension, diabetes, kidney or liver disease?

- a. **Look** and examine: PR, RR, temperature, BP; pallor, jaundice, lymphadenopathy; assess for focal neurological deficit (look at face and note any asymmetry; problem moving eyes, drooling? problems talking? Problem walking? Test facial muscle movement and muscle strength in all limbs); assess for confusion; check for neck stiffness; assess sinus tenderness if patient has headache. Chest signs may be found in patients with tuberculous meningitis. Clinicians should examine the fundi of patients with neurological complaints.
3. **Duration of symptoms** is very useful in grouping the likely diagnoses in patients with neurological complaints. Acute onset headache with fever may mean acute bacterial meningitis or malaria while chronic headache with fever is more suggestive of the chronic meningitides such as cryptococcal or tuberculous meningitis, both of which have a more insidious onset. ***The diagnosis of neurological problems depends on a thorough history and examination. A working diagnosis can be made clinically in the majority of patients, with limited investigations providing supportive evidence.***
4. **Investigations:**
 - a. Investigations should be individualized according to symptoms and/or signs, but should generally include malaria test; CBC; metabolic screen including random blood sugar, urea & electrolytes, LFTs especially in patients with altered mentation; blood and urine culture should be done if patient has fever if possible at the same time antibiotics are started for meningitis. First dose of antibiotics for patients with suspected bacterial meningitis should not be delayed while waiting to take samples for laboratory tests.
 - b. A CXR may be appropriate in febrile patients, patients with hypertension or in those being evaluated for tuberculous meningitis (TBM) or altered mentation.
 - c. Where meningitis is suspected and no focal neurological signs exist, a lumbar puncture should be performed as early as possible. The CSF should be evaluated according to the clinical picture, but evaluation should include microscopy for blood cells, protein, glucose, and bacterial culture in acute meningitis. Other tests like India ink staining, CRAG, AFB, RPR, should be done if deemed appropriate. **CD4 count** is important in the differential diagnosis in HIV-infected patients with neurological symptoms. Previous CD4 trends should be reviewed and a test done if no recent result available (preceding 6 months).
 - d. Syphilis should be ruled out in all PLHA with neurological complaints
 - e. ***Imaging while essential for assessing patients with focal neurological signs, new seizures and those with altered mental status, is of very limited availability. Where possible a brain scan (CT or MRI) is indicated for all patients presenting with altered mental status and seizures (unless a cause is identified e.g. metabolic abnormalities, known epilepsy) or focal neurological signs. While MRI is clearly the superior technique it is virtually inaccessible.***
 - i. *If this initial imaging study is normal, or shows atrophy or focal signal abnormalities but no mass lesion, diagnostic consideration should be given to the meningitides, PML, or HAD. A lumbar puncture should be done.*
 - ii. *In cases of multiple mass lesions, treatment for toxoplasmosis should be given.*
 - iii. *In cases of single mass lesion treatment for toxoplasmosis should begin while assessment for CNS lymphoma begins.*
 - f. ***Lab tests should not delay starting treatment in severely ill patients; where they are not available, a presumptive diagnosis should be made and empirical treatment started.***
5. **Treatment**
 - a. Specific treatment should be directed to the presumed cause. Where possible, investigations to support or confirm the diagnosis should be carried out as guided by the clinical findings. ***Treatment for acute bacterial meningitis and cerebral malaria should be commenced as part of the emergency response (see Table 1.4) in patients with suggestive symptoms without waiting for confirmatory results. Beyond this emergency response, which should be delivered from Level 2 HCFs upwards, a clinician must assess patients with significant neurological complaints or signs.***

- b. Non-specific or supportive treatment should be provided as necessary. Seizures should be controlled as part of the emergency response (see Table 1.4). Patients with focal neurological lesions who present with seizures require ongoing anticonvulsant therapy. Attention should be given to maintaining a clear airway and ensuring adequate circulation in the unconscious patient. Temperature control is important especially in children with recent onset seizures. High fever (temperature > 40°C) *requires* management with tepid sponging and antipyretics (regular paracetamol; non-steroidal NSAIDs only where there is an inflammatory component such as inflammatory joint disease. Avoid NSAIDs in children.)
 - c. Cotrimoxazole prophylaxis should be commenced if the patient is not on it already.
- 6. Review:**
- Many patients with neurological complaints will require hospitalization. It is essential to review the patient regularly to ensure they are improving; this is especially important where a presumptive diagnosis has been used as a basis for initiating treatment. Any laboratory results should be incorporated in the treatment plan as appropriate. For any patient with a neurological problem who fails to improve on treatment, the history should be reviewed, the patient re-examined, since disease progression may result in new findings. Where possible, the help of a senior clinician or a neurologist should also be sought.
- 7. Is patient on ART?**
- a. Cryptococcal meningitis, TBM, cerebral toxoplasmosis and lymphoma are classified as WHO Stage 4 diseases. As such all PLHA with these conditions should be prepared for ART and treatment started as soon as possible.
 - b. Some of these conditions take several months to treat; as such ART needs to be started some time during the course of treatment, usually once patient is stabilized and drugs can be administered reliably. Supervision of treatment, drug interactions, high pill burden and IRIS may be considerations in the decision as to when to start ART treatment in PLHA with these co-infections.
 - c. Patients already on ART developing OIs involving the CNS may be failing ART and should be assessed for failure of their current regimen.

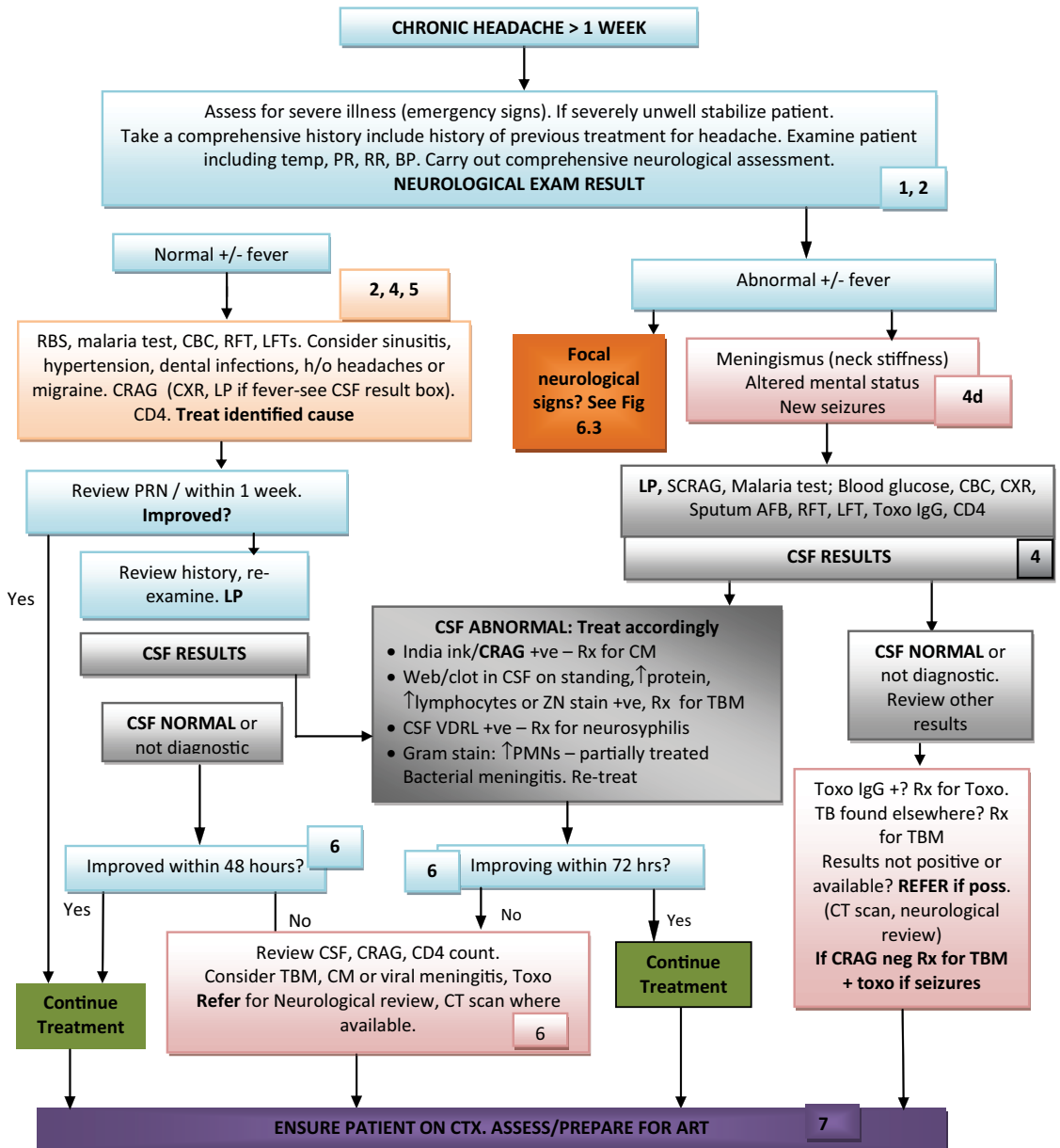
The flow charts below summarize the management approach to patients with different neurological presentations.

FIGURE 6.1: MANAGEMENT OF ACUTE HEADACHE



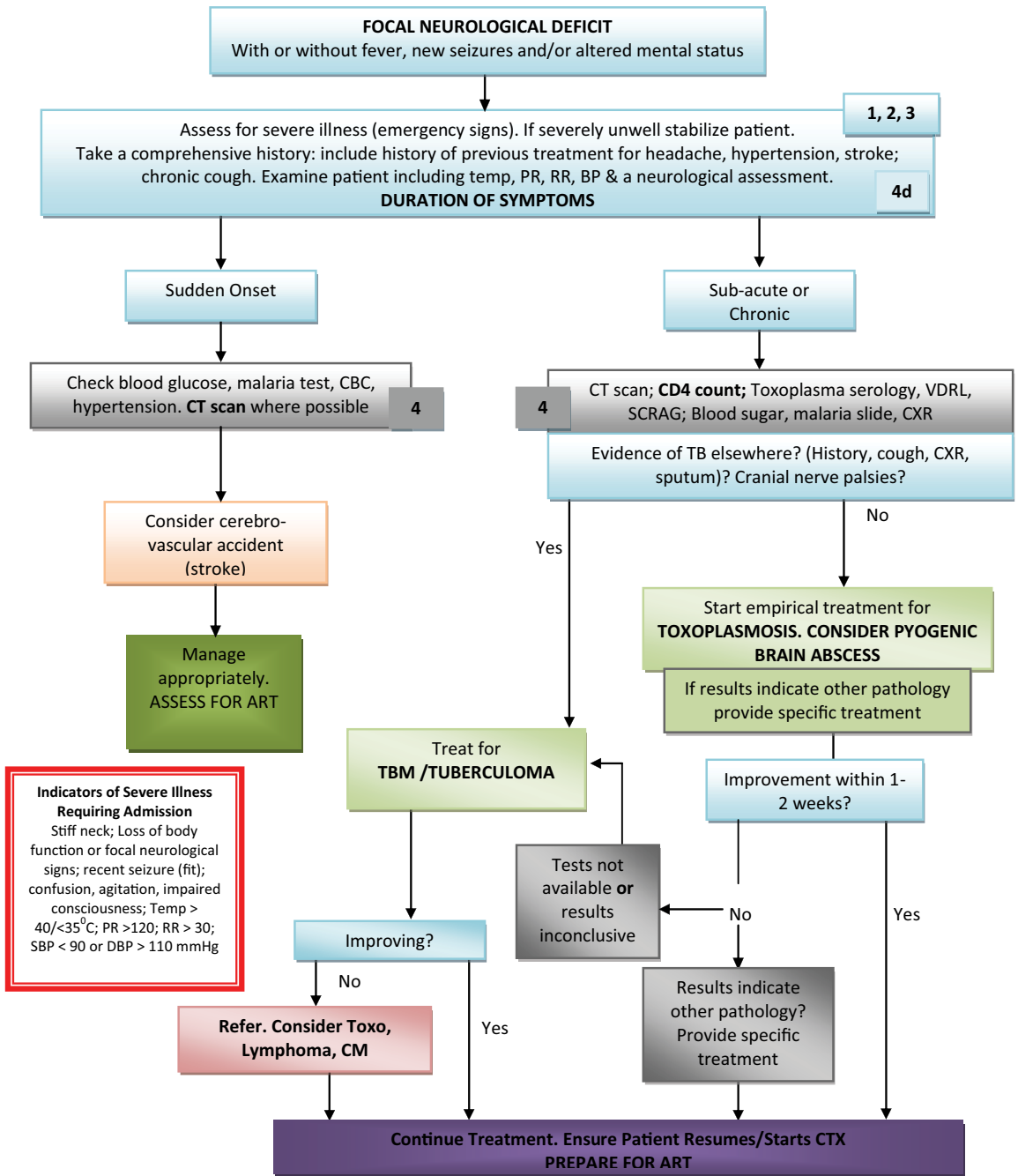
Indicators of Severe Illness Requiring Admission
 Stiff neck; Loss of body function or focal neurological signs; recent seizure (fit); confusion, agitation, impaired consciousness; Temp > 40/<35°C; PR >120; RR > 30; SBP < 90 or DBP > 110 mmHg

FIGURE 6.2: MANAGEMENT OF CHRONIC HEADACHE



CM-cryptococcal meningitis; CRAG-cryptococcal antigen; LP-lumbar puncture RBS-random blood sugar; TBM-Tuberculos meningitis; Toxo-toxoplasma;

FIGURE 6.3: MANAGEMENT OF PATIENTS WITH FOCAL NEUROLOGICAL DEFICITS

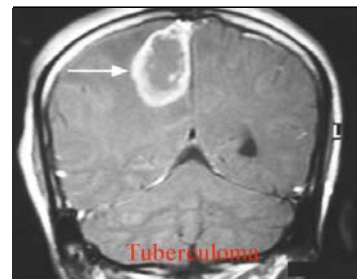


6.3 TUBERCULOUS MENINGITIS (See section 3.4.3)

Many of the symptoms, signs and complications of tuberculous meningitis (TBM) are a result of an immunologically mediated inflammatory reaction to the organism. As with other forms of EPTB, TBM occurs in severely immunocompromised patients with CD4 count often < 100 cells/mm³. The weakened immune system allows mycobacteremia to develop, with dissemination of the tubercle bacilli into the meninges and brain parenchyma. These bacilli multiply forming caseous lesions, which may rupture into the subarachnoid space causing meningitis. A thick gelatinous exudate is characteristic of the TB-associated inflammatory process; as the meningitis often involves the base of the brain cranial nerve dysfunction (VI, III, IV, VII) may result. Obstruction of the basilar cisterns may lead to an obstructive hydrocephalus. Tubercles in the brain tissue may expand and coalesce to form an abscess or a tuberculoma. Contiguous spread of meningitis to the spine may also occur; vertebral involvement is also seen. Vasculitis of vessels that traverse the base of the brain or are contiguous to the abscesses may, with resulting thrombosis and hemorrhagic infarction may result in loss of body function. Prior to the HIV epidemic TBM was largely a disease of children or adults not given the BCG vaccine; like with other forms of severe TB, BCG reduces the likelihood of children developing TBM. Adult TBM has become more common largely as a result of the HIV epidemic. Thus **all** patients with altered mental status or focal deficits should be assessed for other symptoms and signs suggestive of TB elsewhere.

Symptoms include:

- Chronic gradually worsening headache, personality change
- Fever as well as other constitutional symptoms, as with other forms of TB.
- Nausea and vomiting
- Seizures
- Visual impairment or blindness
- TBM may be associated with disseminated disease thus symptoms of pulmonary and other forms of EPTB may be present



Signs include

- Altered mental status or confusion; as it progresses patients may develop coma
- Papilloedema is the most consistently observed sign of TBM. Progression to optic atrophy and blindness may occur
- Cranial nerve palsies (especially VI, III & IV and VII)
- Other focal deficits (weakness of part of the body, including monoplegia, tetraparesis, hemiparesis),
- Clinical signs of meningeal irritation (neck stiffness, photophobia)
- Other signs of TB elsewhere (adenitis, pallor, chest signs, hepatosplenomegaly)
- Abnormal movements – e.g. tremor
- Syndrome of inappropriate ADH secretion (poor prognostic indicator)

Investigations

The diagnosis of TBM is difficult and relies on several clinical and lab parameters which lack sensitivity. The following tests should be carried out where possible to aid in diagnosis and exclude other conditions:

- Malaria test
- Random blood sugar
- CBC; U&E – hyponatremia indicating SIADH secretion occurs in almost half of patients
- SCRAG to rule out cryptococcal meningitis.
- LP should be performed if there are no focal deficits. CSF may clot on standing due to high protein; glucose is reduced; white cell count is raised with predominant lymphocytosis; gram stain and ZN stain should be done; mycobacterial culture; HSV serology; VDRL. In

- PLHA CSF may be acellular
- CT scan if possible (MRI) may reveal basilar meningeal thickening, hydrocephalous, abscesses, and tubercles. Scans are not diagnostic, but may be useful in detecting complications amenable to surgery
- CXR

Treatment

Once a diagnosis of TBM is suspected, ATT should be initiated as per the national TB treatment guidelines. Patients with features of TB elsewhere in the body *and* focal deficits or seizures should be treated for toxoplasmosis as well, since tests to support either diagnosis are often not available. The duration of treatment for TBM is unclear, but ATT continuation drugs should probably be continued for 9 months if the short course rifampicin-based treatment is used. Adjunctive treatment with steroids may be of benefit in adult patients with TBM and should be given at treatment initiation (Thwaite et al, NEJM, 2004). Supportive care should be provided for the unconscious patient or for the patient with seizures.

Prognosis

It is difficult to determine the prognosis of an individual patient with this protracted illness. Death is common if the diagnosis is delayed and if the patient already has altered mental status or is comatose at the time treatment is commenced. Children, patients with hydrocephalous, cranial nerve palsies and other focal deficits, SIADH secretion This is further complicated by the fact that the diagnosis of TBM is difficult and relies on several clinical and lab parameters which lack sensitivity. Permanent sequelae occur even when treatment is given in a timely way. IRIS may occur if ART is introduced during treatment of TBM, further increasing the challenges management of patients with TBM presents.

6.4 CEREBRAL TOXOPLASMOSIS

Toxoplasmosis is caused by *Toxoplasma gondii*, a small intracellular protozoan. Cats are the definitive host for this organism; transmission to humans is through ingestion of oocysts excreted in the faeces of infected cats or ingestion of tissue cysts in undercooked meat. Acute toxoplasmosis infection is asymptomatic in most immune-competent individuals. Congenital toxoplasmosis may result from transmission from a mother with acute toxoplasma infection to her foetus.

In PLHA and in other immunocompromised individuals, toxoplasmosis *disease* is almost always (> 95%) a result of reactivation of old central nervous system (CNS) lesions or spread through the bloodstream of previously acquired infection. The exact prevalence of cerebral toxoplasmosis in PLHA in Kenya is yet to be defined; it is however seen less commonly than TBM and cryptococcal meningitis. Toxoplasmosis is however the leading cause of *focal* CNS disease in PLHA. The incidence of toxoplasmosis is likely to fall as a result of widespread use of cotrimoxazole prophylaxis and ART by HIV positive individuals in Kenya.

Clinical Presentation of Cerebral Toxoplasmosis

Cerebral toxoplasmosis commonly presents with sub-acute onset of headache and constitutional symptoms. Later, confusion and drowsiness, seizures, focal weakness, and language disturbances may occur. Without treatment, progression to coma occurs in days to weeks.

Symptoms:

- Headache
- Fever
- Confusion, impaired consciousness (Altered mental status)
- Seizures

Signs

- Fever
- Focal neurological deficits (hemiparesis, hemianopia, aphasia, ataxia, and cranial nerve palsies may be found). Occasionally spinal cord lesions may cause a myelopathy.
- CD4 usually < 100 cells/mm³. The greatest risk of disease is in those with CD4 < 50 cells/mm³ while clinical disease is rare in patients with CD4 count > 200 cells/mm³.

HIV infected patient with cerebral toxoplasmosis may also present with disease outside the CNS including pneumonitis or chorioretinitis (white cotton wool spots on the retina). Hepatosplenomegaly and generalized lymphadenopathy may also occur.

Diagnosis of Cerebral Toxoplasmosis

- A **presumptive** diagnosis of cerebral toxoplasmosis should be considered in patients who are severely immunocompromised ($CD4 < 100 \text{ cells/mm}^3$) with features of a focal encephalitis with headache, fever, seizures, altered mental status and focal neurological deficit.
- A lumbar puncture is generally **contraindicated** in patients with focal neurological signs because of the possibility of raised intracranial pressure with the risk of brainstem herniation; CSF findings are non-specific in patients with cerebral toxoplasmosis
- Almost all patients with toxoplasmic encephalitis in Western cohorts are positive for toxoplasma antibody; a *rising* anti-toxoplasma IgG serology in patients with the above symptoms is useful to support the diagnosis. Serological tests can be falsely negative or non-contributory if levels do not rise from baseline. Thus in a patient with suggestive clinical presentation and single or multiple CNS lesions, treatment for toxoplasmosis should be given regardless of the serology result. Seroprevalence in Kenya is unknown.
- CT scan
 - Ring-enhancing (with contrast, indicating mass effect) single or multiple lesions, often in the basal ganglia or cortico-medullary junction. Diffuse encephalitis may occur in severely immunocompromised patients with normal imaging studies
 - CNS lymphomas may be difficult to differentiate from cerebral toxoplasmosis on imaging although single lesions more likely in CNS lymphoma. If there is no improvement to adequate anti-toxoplasma treatment a diagnosis of CNS lymphoma should be considered.
- *T. gondii* PCR of CSF is not very useful due to low sensitivity.
- ***CXR should be done as part of consideration of a diagnosis of TBM. Differentiation of toxoplasmic from tuberculous meningo-encephalitis may be impossible on clinical and radiological findings alone; treatment of both conditions may therefore be considered***

Treatment of Toxoplasmosis

The Preferred regimen:

Pyrimethamine 200 mg loading dose, then 50 mg –75 mg/day

+

Sulfadiazine 1000 mg to 1500mg P.O. 6 hourly

+

Folinic acid (leucovorin) 10-20mg/day PO

Folate is not a substitute for Folinic acid. The dose of Folinic acid can be increased to >50 mg/day to reduce Pyrimethamine-associated haematological toxicity

Alternative regimen:

Cotrimoxazole: 5mg/kg of Trimethoprim or 25mg/kg of CTX BD per day for 6 weeks (e.g. for 60kg man, 4 SS tablets per day). This is the regimen of first choice locally in the absence of key constituents of the preferred choice above. An advantage of this regimen over the above one is that it can also be given IV in patients unable to take oral treatment.

Progress

Clinical improvement is usually expected within 1 week and improvement demonstrated by CT scan or

MRI within 2 weeks. If a patient does not improve within this time, an alternative diagnosis should be considered, especially primary CNS lymphoma or tuberculous brain abscess. Patients should also be monitored for adverse drug reactions and interactions (for instance between the anticonvulsants and ARV drugs)

If intracerebral oedema is suspected or confirmed (suspected clinically, papilloedema on fundoscopy, or on CT scan), Dexamethasone 4-mg PO or IV q6h should be given (*note if steroids used in patients with CNS lymphomas they are likely to improve; this may cause confusion in the differential diagnosis of these 2 conditions*). If steroids are used, patients should be watched carefully for the development of other OIs such as TB. Steroid treatment should be discontinued as soon as feasible.

Anticonvulsants should be used in patients presenting with seizures and continued at least during the period of acute illness. Prophylactic anticonvulsant therapy is not necessary.

Toxoplasma antibody levels are not useful for monitoring response to treatment.

Maintenance Therapy

Treatment should last for 6 weeks, after which maintenance therapy should be given until documented sustained immune reconstitution. Preferred regimen: Pyrimethamine 25-50 mg/day PO+ Sulfadiazine 500-750 mg PO q6h + Folinic acid 5 mg/day or **Cotrimoxazole** in the standard prophylactic dose of 960mg OD.

Immune Reconstitution

If using the sulfadiazine/pyrimethamine maintenance regimen, the drugs should be discontinued following sustained immune reconstitution (CD4 count >200 cells/mm for > 6 months) **and** initial therapy completed **and** the patient is asymptomatic. **Cotrimoxazole should be continued indefinitely regardless of immune status of the patient.**

Primary prophylaxis

Cotrimoxazole 960 mg/day.

Pregnancy

The same criteria for diagnosis apply in pregnant women as in other patients. Children exposed to active disease in their mothers should be assessed for congenital toxoplasmosis. Treatment is the same as in non-pregnant patients. Additional intermittent malaria prophylaxis is not required in women on cotrimoxazole.

6.5 CRYPTOCOCCAL MENINGITIS

Introduction

Cryptococcal disease in HIV infected patients is caused by *Cryptococcus neoformans*, a yeast-like fungus. It is a relatively common life-threatening infection in severely immunocompromised PLHA, with the most common manifestation being meningo-encephalitis, although disseminated disease including cryptococcal pneumonia and skin involvement also occurs. *Cryptococcus* grows readily in soils contaminated with avian excreta, particularly those of pigeons. Initial cryptococcal infection most likely occurs via inhalation of the fungus leading to colonization of the airways. The incidence of cryptococcal meningitis increases as the CD4 count falls below 100 cells/ml, and most cases occurs when the CD4 count falls below 50 cells/ml.

Clinical Presentation

Cryptococcal disease in PLHA most commonly presents as a sub-acute meningitis or meningo-encephalitis with the following symptoms:

- Fever
- Malaise
- Headache
- Neck stiffness and photophobia (i.e. meningeal symptoms in 25-30%)
- Altered mental status, personality changes, memory loss (encephalopathic symptoms)

Signs include

- Fever
- Confusion, impaired consciousness and coma
- Focal signs – cranial nerve palsies

Disseminated disease associated with more frequent pulmonary involvement than CNS disease. Skin disease with nodular lesions similar to *Molluscum contagiosum* lesions also occurs.

Laboratory Diagnosis

Laboratory evaluation for cryptococcal meningo-encephalitis should be carried out in patients with advanced immunosuppression with a history of persistent headache and/or clinical features of meningitis, altered mental status or focal neurological deficits. This evaluation should include the following:

- Where possible a lumbar puncture should be performed; a raised CSF opening pressure is common often exceeding 200mm H₂O in more than 75% of patients. Patients with focal neurological signs should have CT scan before a LP is considered.
 - CSF examination – India ink stain (outlines the polysaccharide capsule) is positive on direct examination of the CSF in approximately 60-80% of patients; this is a simple test that all hospitals should be able to perform. Other findings on examination of the CSF include non-specific changes such as mildly elevated protein, a normal or slightly low glucose and a few lymphocytes.
- Evaluation of symptomatic patients for cryptococcal antigen is extremely useful, but may not be available in all care settings. Cryptococcal antigenaemia when identified in the serum is usually indicative of systemic disease and correlates with fungal burden. CSF CRAG is positive in > 95%; serum CRAG is positive in > 95%. *CRAG should not be used to monitor response to treatment.*
- Blood fungal culture positive in 75% and indicative of disseminated disease

Treatment and Secondary Prophylaxis

Untreated cryptococcal disease is fatal.

Preferred Treatment Regimen (See Appendix H for protocols)

- **Induction:** initial treatment is with Amphotericin B (0.7 - 1.0 mg/kg/d) for 2 weeks or until the patient is clinically stable. Amphotericin B therapy should be administered in qualified health facilities capable of close clinical and laboratory patient monitoring. In facilities incapable of administering Amphotericin B sole, treatment with Fluconazole (400-800 mg/d for 12 weeks) may be an alternative, although treatment failure and mortality are high.
- **Consolidation** phase: Fluconazole 400-800 mg/d for 8 weeks; the higher dose must be used in patients on concomitant rifampicin
- **Maintenance/suppressive** phase: Fluconazole 200 mg/d
- **Discontinuation of Fluconazole:** Fluconazole can be stopped in patients who have been on ART and have documented immune reconstitution as shown by CD4 consistently above 100 cells/mm³ for at least 6 months.

Alternative Treatment Regimen

- Induction: Fluconazole 400-800 mg per day for 2 weeks

- Consolidation: Fluconazole 400-800mg OD for 8 weeks
- Maintenance/suppressive phase: Fluconazole 200 mg/d

There appears to be no difference in outcome between using the lower dose or the higher dose of fluconazole during the induction phase. The dose of fluconazole should be increased to at least 800mg OD in patients on concomitant rifampicin.

Supportive care

- Management of the unconscious patient should be as per standard guidelines with attention to airways, nursing care and nutrition.
- Patients with worsening headache or those with a deteriorating consciousness should be assessed for increased intracranial pressure (ICP). Raised ICP causes most deaths (>90% in the first 2 weeks) in PLHA with CM and is likely to be a problem in patients with opening CSF pressure > 250 cm H₂O. The principle intervention in patients with symptomatic raised ICP is repeated daily LP until CSF pressure falls below 200 cm H₂O.
- CSF shunting may be considered for patients in whom daily lumbar punctures are no longer being tolerated or whose signs and symptoms of cerebral oedema are not being relieved; this is however unlikely to be accessible to most patients. There is no role for use of acetazolamide in relieving raised ICP in patients with CM.

Monitoring

Repeat LP to confirm clearance of infection is not necessary in patients with clinical improvement by 2 weeks of treatment. A repeat LP may be necessary if new symptoms develop in patients after 2 weeks of treatment; ICP should be assessed and India ink stain repeated on the CSF. Patients failing fluconazole therapy should be treated with amphotericin.

ART Initiation in Patients with CM.

Patients with CM should be prepared for ART. The best time to start ART in patients with CM, while reducing the likelihood of IRIS, is not known. ART should probably be started after the patient stabilizes to avoid severe IRIS, usually after about 8 weeks of anti fungal treatment.

Although nevirapine drug levels are increased markedly by fluconazole, patients appear to tolerate the two drugs well. Extra vigilance in monitoring patients on a nevirapine based ART regimen and fluconazole is however recommended.

Recurrence of CM is unlikely in patients who attain immune reconstitution on ART; maintenance or suppressive therapy should therefore be discontinued in patients who have achieved a CD4 count > 100 cells/mm³ for at least 6 months and have completed the consolidation phase of treatment. **Maintenance therapy should be recommenced** in patients who have had CM and who develop ARV treatment failure with CD4 < 200-100 cells/mm³.

Pregnancy

Patients with suspected CM should be investigated and managed in the same way as non-pregnant women. Fluconazole and itraconazole should be avoided in the first trimester because of teratogenicity; absent other options patients should be treated with fluconazole as per schedule above. The pregnancy should be monitored clinically as well as using ultrasonography where possible.

6.6 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML is a severe opportunistic infection of the CNS caused by reactivation of latent JC polyomavirus acquired in childhood. The JC virus destroys oligodendrocytes leading to multifocal areas of demyelination limited to the white matter, which causes neurologic dysfunction.

Symptoms

The symptoms are insidious in onset. The patient often presents with relatively rapidly progressive cognitive dysfunction, dementia, seizures, ataxia, cranial nerve deficits, hemi- or quadri-paresis and eventually lapse into coma, all ***in the absence of fever***.

In the absence of effective ART mortality is extremely high in patients with PML.

Diagnosis is clinical with, if possible compatible CT scan result (multifocal lesions in the white matter with no mass effect or enhancement with contrast). PCR for CSF JC virus is unlikely to be available in most of our facilities.

Treatment of PML

There is no specific treatment for PML. All patients must be prepared and started on ART as soon as practical. Patients may experience improvement in symptoms or just achieve stability. Progression of the disease may occur, sometimes as a consequence of the IRIS.

There is need to obtain the support of family or a CHW in the management of any patient with severe cognitive impairment.

6.7. PERIPHERAL NEUROPATHY

Introduction

This is a disorder of the peripheral nerves and presents with diverse symptoms depending on the cause, the nerves affected and the severity of the disease. Peripheral neuropathy can present as a mononeuropathy, which is the focal involvement of one nerve trunk usually due to a local cause; or polyneuropathy with many nerves affected and therefore with more widespread symptoms as occurs in metabolic disorders or following reactions to drugs and toxins.

Causes

Peripheral neuropathy can be caused by various conditions, which include:

- HIV infection,
- Diabetes mellitus,
- Vitamin B₁₂ deficiency,
- Drugs e.g. Nucleoside analogues (ddl, d4T), Dapsone, Metronidazole, Isoniazid, antineoplastic agents (vincristine, cisplatin)
- Toxins e.g. alcohol, diphtheria toxin

Presentation

- Peripheral neuropathy (PN) presents with pain or a burning sensation in the affected area, numbness, tingling sensation or even weakness. Symptoms usually start distally on the soles of the feet and progress proximally to the legs. The presentation may be symmetrical on both limbs or may progress faster in one limb. Peripheral neuropathy can also present in the upper limbs but is usually more common and worse in the lower limbs.
- PN is common in HIV infection and can occur at any stage of the infection.
 - The commonest presentation is the distal sensory polyneuropathy that can be a direct consequence of the HIV virus itself or a side effect of drugs like didanosine or stavudine.
- Presenting symptoms include burning sensation, numbness or pain of feet and lower extremities.
- Findings on examination may include sensory loss that begins distally and progresses proximally with loss of ankle reflexes. Muscle weakness is mild and limited to the smaller ones in the leg.

However gait can be compromised by loss of proprioception (position sense). If not managed early, PN can progress to a severe debilitating illness.

- Other presentations include: Acute inflammatory polyneuropathy (Guillain Barre Syndrome), chronic inflammatory polyneuropathy and mononeuritis multiplex, where a individual nerve(s) are affected.

Investigations

HIV test; FBC with PBF (macrocytosis); VDRL; random blood sugar; Schilling test.

Management or Peripheral Neuropathy

Careful history and examination of the patient is mandatory to determine the cause, rule out systemic diseases that may cause neuropathy as well as to determine the extent of nerve involvement. If the cause is identifiable it should be corrected.

- Withdraw the offending agent if known e.g. d4T
- If the MCV is high (in patients not on chronic AZT treatment) treat for B12 & folate deficiency
- If on INH: pyridoxine) 200mg orally OD, until TB treatment finished
- If on Stavudine and Grade 2 and above: change to Zidovudine (or Tenofovir if anemic);
- Diabetes mellitus: PN in diabetics is an indication of long standing disease and may be the presenting symptom.
- Pain control can be difficult: amitriptiline is normally used in the first instance for patients with symptoms that interfere with normal activities; carbamazepine may be added in addition to amitriptiline in adequate doses. Gabapentin is an alternative drug that may be used instead, on its own.

CHAPTER 7: HAEMATOLOGICAL COMPLICATIONS IN HIV INFECTION

CHAPTER 7: HAEMATOLOGICAL COMPLICATIONS IN HIV INFECTION

7.1 Introduction

Anaemia is a common presentation in HIV infected patients and may have serious implications, varying from impaired quality of life to an association to disease progression and poor survival. Anaemia should therefore not be ignored in PLHA and the HIV status of the patient should not preclude appropriate investigations and treatment of anaemia. At the same time individuals presenting with unexplained anaemia should have a diagnostic HIV test as part of their work up.

Definition

Anaemia is defined as a decrease in the circulating red blood cell mass; the usual criteria is a haemoglobin (HB) of less than 12 gm/dl [Haematocrit (HCT) <36%] in women and less than 14gm/dl (HCT<41%) in men. Anaemia can be graded in terms of severity as mild (8-10 g/dl); moderate (6.5-7.9g/dl); severe (< 6.5g/dl).

Anaemia can be classified depending on the cause as shown in Table 7.1 below:

Table 7.1: Classification of Anaemia

1. Anaemias Due to Decreased Production of Normal Red Blood Cells (RBC)	
Iron deficiency	<ul style="list-style-type: none"> ○ Infections and infestations (hook worm; schistosomiasis) ○ Nutritional deficiencies - diminished intake due to poor diet ○ Pregnancy and lactation with increased demand ○ Severe chronic blood loss - menorrhagia, GI bleeding ○ Others: - Malabsorption, Sideroblastic anaemia - failure of iron utilization rather than deficiency
Deficiency of Vitamin B₁₂ or Folate	<ul style="list-style-type: none"> ○ Nutritional - decreased intake due to poor diet, alcoholism. ○ Increased requirements - in pregnancy, infancy ○ Malabsorption ○ Drug induced - Trimethoprim, OCs; Sulfa drugs, Dapsone, Primaquine, Methotrexate, anticonvulsant
Bone marrow disease	<ul style="list-style-type: none"> ○ Leukaemia's ○ Aplastic anaemia and ○ Myelodysplastic syndromes ○ Infiltrative bone disease e.g. some cancers, ○ Infections that involve the bone marrow (disseminated TB, HIV) ○ Drugs that suppressive the bone marrow (CTX, AZT, ganciclovir)
Anaemia from chronic diseases	TB, HIV, rheumatoid arthritis, chronic renal insufficiency, liver disease and widespread malignant disease.
2: Anaemia Associated with Increased RBC Loss or Destruction	
Bleeding	<ul style="list-style-type: none"> ○ GI bleeding (due to peptic ulcer disease, Gastritis, hook worm infestation etc) ○ Menorrhagia (excessive menstrual blood loss)
Haemolytic conditions	<ul style="list-style-type: none"> ○ Inherited: sickle cell anaemia is the most common; others include thalassaemias (hereditary haemoglobinopathy), Glucose-6-phosphate dehydrogenase (G6PD) deficiency, ○ Acquired: drug related; autoimmune haemolytic anaemia, microangiopathic haemolytic anaemia.

7.2 HIV-associated Anaemia

Anaemia is common in PLHA occurring in 85% of patients with severe HIV disease. PLHA living with moderate to severe anaemia have reduced survival compared with those without anaemia. The causes of HIV-associated anaemia are as per Table 7.2 below.

Table 7.2: Causes of Anaemia in PLHA

Nutritional deficiency	Iron, folate, or B12 deficiency. Also associated with malabsorption and may be precipitated by OIs involving the gut
Drug induced – drugs that suppress the bone marrow	Cotrimoxazole, AZT, Amphotericin B, Pyremethamine (SP drugs for malaria), Rifampicin, Ethambutol, Lithium, etc.
Infections	TB, especially extrapulmonary TB (EPTB), Atypical Mycobacterial infections and non-typhi salmonella are relatively common causes of severe anaemia in PLHA who are severely immunosuppressed.
Malignancies	Lymphoma; Kaposi’s Sarcoma.
HIV infection per se.	<ul style="list-style-type: none"> • HIV infection can cause pancytopenia affecting all bone marrow cell lines. • Thrombocytopenia alone is also common, presenting as an idiopathic thrombocytopenia purpura. • Risk of anaemia in HIV associated with the following: severe HIV disease, CD4 < 200, female gender, older age, and use of AZT.

7.3 Clinical Features of Anaemia

Signs and symptoms of anaemia vary depending on the degree and rapidity of onset. Other underlying disorders such as cardiopulmonary disease may contribute to the severity of the symptoms. Severe anaemia may be well tolerated if it develops gradually. Generally, patients with moderate to severe anaemia will present with the following symptoms and signs.

Symptoms

Symptoms of anaemia may be non-specific and include fatigue; headache; breathlessness on exertion; light-headedness or dizziness due to tissue hypoxia; chest pain (angina pectoris) due to myocardial hypoxia, especially in older patients; palpitations and oedema (swelling) of feet/legs.

Signs

- Pallor of the skin and mucous membranes.
- Raised pulse rate (tachycardia), functional systolic murmurs.
- In severe cases, there may be signs of congestive cardiac failure (CCF) including oedema, basal crepitations
- Signs specific to the cause of the anaemia may be present, for example jaundice with haemolysis; melaena in GI bleeding; peripheral neuropathy with tingling and loss of sensation in the feet/legs with B₁₂ deficiency.

7.4 Laboratory investigations in Patients with Anaemia

Investigations ought to be guided by patient presentation but should always include a complete blood count (CBC), a peripheral blood film (PBF) and a reticulocyte count.

The suggested investigations include: -

- CBC, PBF, reticulocyte count
- Stool examination for the presence of frank blood, ova, cysts and a test for occult blood
- Bone marrow examination - should be done if
 - Pancytopenia is found
 - Common causes of anaemia have been excluded or addressed without improvement of patient.
- HIV test should be offered to all patients with anaemia of unknown origin

Other relevant investigations as indicated, where feasible include: -

- Serum B₁₂ and red cell Folate.
- Serum Iron, total Iron binding capacity (TIBC), serum Ferritin
- Anaemia is a common presentation in very ill patients and may be an important indicator of illnesses such as EPTB or NTS. Patients with anaemia should therefore be assessed for the presence of other systemic symptoms or signs and where indicated investigated with this in mind.

7.5 Management of Anaemia

- After initial assessment, patients should be stabilized prior to further investigations.
 - This includes stopping continued blood loss, managing hypovolaemic shock and managing heart failure.
 - Blood transfusion (preferably packed red cells) is indicated to alleviate acute symptoms only in patients with shock due to blood loss (radial pulse weak or absent, PR > 120/min, SBP < 90mmHg) or in those with haemodynamic compromise as a result of severe anaemia.
 - Transfusion may not always be necessary in some patients with severe **chronic** anaemia if they are haemodynamically stable *and* specific treatment can be given.
- Address underlying correctable cause. Treatment of the underlying cause is of utmost importance. Providing haematinics without finding and addressing the cause may delay appropriate treatment.
 - Specific treatment when cause is identified include: -
 - Nutritional assessment and advice to all patients targeting foods rich in iron, folate and B₁₂.
 - Antihelminthic treatment for worm infestation.
 - Iron and folate supplements are indicated for patients with increased demand or excessive blood loss.
 - Treatment with B₁₂, iron and folate is indicated for patients with these specific deficiencies. (Although AZT anaemia is associated with a macrocytic picture replacement folate and B12 are not indicated).
 - ART is associated with a reduction in the prevalence of all degrees of anaemia; however many patients on ART may have persistent anaemia. Where anaemia persists it is associated with disease progression and death

7.6 Essential Steps in the Management of Anaemia

1. Assess for emergency signs and stabilize the patient
 - a. Always assess the sick patient for emergency symptoms and/or signs
 - Patient bleeding
 - Patient short of breath (SOB) at rest, unable to walk or talk in complete sentences and has pale sweaty and clammy skin
 - PR > 120/min or radial pulse weak or absent
 - RR > 30, temp > 40°C/< 35°C, SBP < 90mmHg
 - b. Stabilize severely sick patients first before continuing with a more complete clinical assessment (see Table 1.4). Ensure adequate venous access and stop any bleeding if this is possible. Arrange for blood for transfusion if indicated
 - c. **Does patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
2. A clinical assessment as outlined in Table 1.5 will often elicit information and/or findings that direct the HCW to the likely diagnosis.
 - a. **Ask about:**
 - Any bleeding; ask about blood loss in stools, melaena (black faeces in patients not on iron tablets). For women this should include an assessment of the

menses including duration and volume lost; pregnancy should be excluded. Ask about non-steroidal anti-inflammatory drugs (NSAIDs) use.

- Symptoms suggestive of peptic ulcer disease.
 - SOB, its progression (sudden vs. gradual onset), whether on exertion or at rest.
 - Previous heart disease if signs of CCF present
 - Dietary history
 - Any other problems (weight loss, night sweats etc)
 - Previous recent and current medication as well as duration of these treatments.
- b **Look:** PR, RR, temperature, BP; cyanosis, jaundice, signs of bleeding problems, pallor, lymphadenopathy, oedema; hepatosplenomegaly; rectal examination should be done and stool examined for frank or occult blood. Other systems should be examined as well and the weight taken.
3. **Investigations:** all patients with anaemia should have a complete blood count, a peripheral blood film and stool examination. Information obtained from these tests is often useful in determining whether further tests are necessary or whether the patient can be given specific treatment to correct the anaemia. Other investigations should be individualized according to the initial tests above as well as the symptoms and/or signs. ***Laboratory tests should not delay starting treatment in severely ill patients with haemodynamic compromise; where tests are not available, a presumptive diagnosis should be made and empirical treatment started.***
4. **Treatment**
- a. Correct anaemia causing severe acute symptoms (heart failure, shock) using transfusion of (packed) red cells.
 - b. Specific treatment for anaemia should be directed to the presumed/confirmed cause. Chronic conditions are common in PLHA, thus efforts must be made to exclude OIs or malignancies that may cause anaemia. For instance patients with TB often have moderately severe anaemia. Where found chronic illnesses should be treated.
 - c. HIV associated anaemia of chronic illness responds to ART; where indicated patients should be started on ART and the Hb monitored to determine response.
 - d. Treatment may include discontinuing drugs associated with myelosuppression and replacement with suitable alternatives e.g. AZT may be substituted with TDF, ABC or d4T;
 - e. Treatment of other HIV-related blood abnormalities such as idiopathic thrombocytopenic purpura (ITP) may require other drugs (steroids, immunoglobulins - IVIG). However, ART is often required for a sustained response; management of these conditions should involve an experienced clinician or haematologist.
5. **Review:**
Patients should be reviewed regularly to determine progress on treatment.
6. **Is patient on ART?**
- a. Anaemia may be found in PLHA in the absence of other causes (anaemia of chronic disease). Patients with anaemia of unknown cause should be tested for HIV infection. All PLHA should be assessed for ART at initial enrolment and regularly thereafter.
 - b. Patients already on ART developing unexplained anaemia should be assessed for the presence of OIs and of failure of their current regimen

CHAPTER 8: SWOLLEN LYMPH NODES

CHAPTER 8: SWOLLEN LYMPH NODES

1.1 Introduction

In normal well people, lymph nodes cannot be felt. Whether a node that is palpable is of clinical significance depends on its location and the age of the patient. Children are more likely than adults to have enlarged nodes due to minor stimuli e.g. upper respiratory tract infections. In adults however, persistently enlarged lymph nodes are usually suggestive of serious disease. The site of an enlarged lymph node is indicative of an abnormal process taking place within the drainage area of the node e.g. skin infection on the lower limb may be associated with inguinal nodes.

When assessing a patient with enlarged lymph nodes, the following should be considered:

- **Location** – define the location of enlarged nodes and examine the drainage area of the particular nodes for any obvious infection or wound or other abnormalities. If this is not apparent, examine further for other characteristics.
- **Pain** – ask the patient about any pain experienced either in the nodes or in the drainage area. Assess the nodes for tenderness. Pain/tenderness of nodes usually denotes a localized infection; absence of pain may point to a generalized infection, especially if more than one lymph node group is involved.
- **Pattern** – determine the pattern of the lymph node enlargement? Is it only one group of nodes that is affected or are groups of nodes affected? For example, is it only the axillary nodes that are affected or are the inguinal and cervical also involved?
- **Nature** – what is the nature of the enlargement i.e., are the lymph nodes discrete or are they matted together? Are they tethered to surrounding tissues or are they mobile?

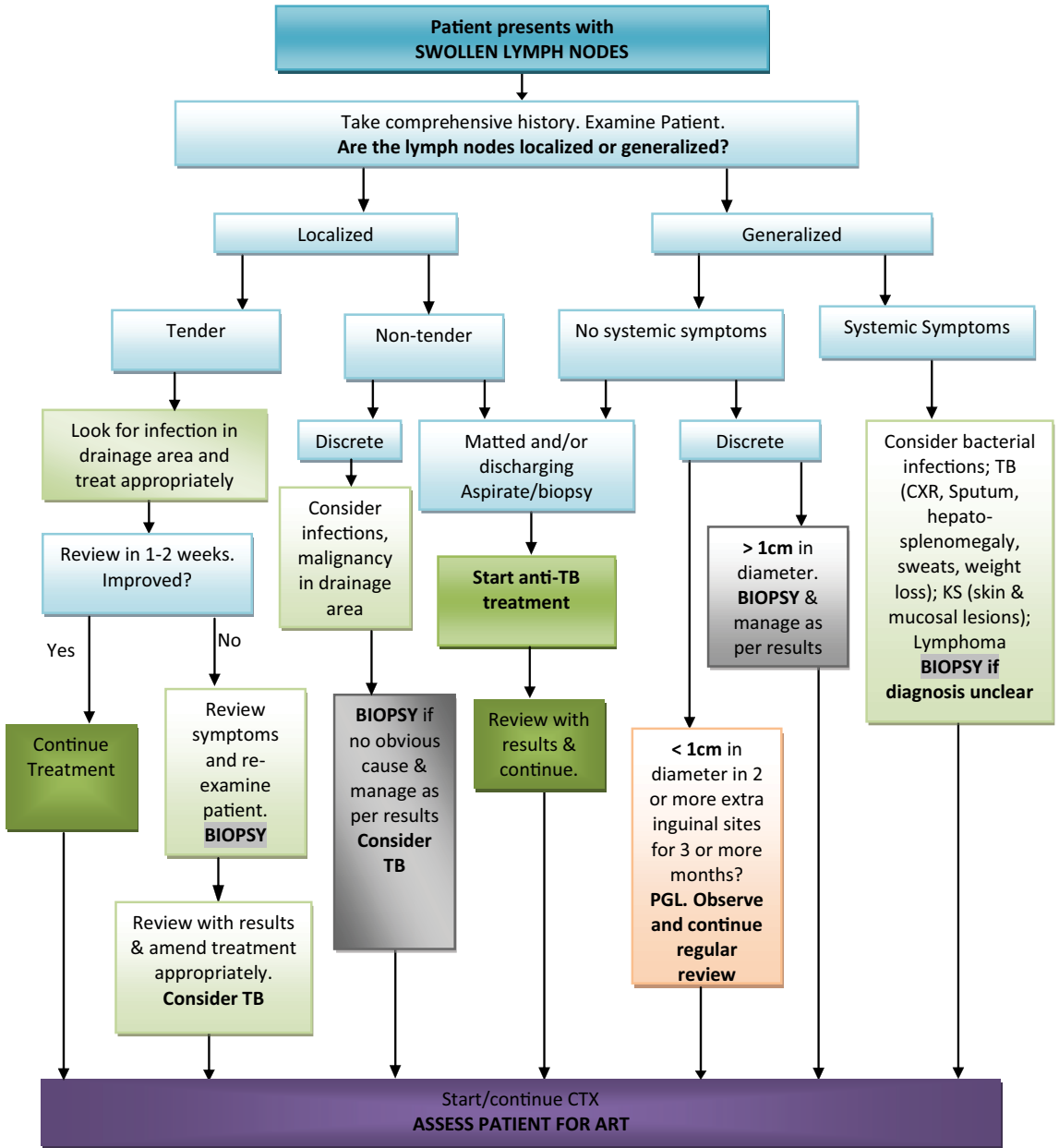
Various conditions can cause lymph node enlargement and in our setting these include: bacterial infections especially of the skin; tuberculosis; syphilis; infectious hepatitis; HIV infection; neoplasms (cancers); other inflammatory conditions and malaria. For patients with inguinal

It is worthwhile to note that HIV infection is associated with a generalized lymphadenopathy that persists and which cannot be attributed to any particular cause. This diagnosis, known as persistent generalized lymphadenopathy (PGL) is only arrived at after ruling out other causes of swollen nodes.

Treatment

Treatment depends on the presumed or the definitive diagnosis.

FIGURE 8.1 THE ASSESSMENT OF PATIENTS WITH SWOLLEN LYMPH NODES



CHAPTER 9: HIV ASSOCIATED MALIGNANCIES

CHAPTER 9: HIV ASSOCIATED MALIGNANCIES

9.1 Introduction

Patients with HIV disease are at an increased risk of developing malignancies. 25-30% of all human cancers are caused by infectious agents that are normally contained by the host immune system; it is therefore not surprising that cancers are more common HIV infection, a condition associated with a progressively failing immune system. Although defects in immune surveillance might be expected to contribute to risk of malignancies, some of this increased cancer risk might be due enhanced acquisition of exogenous oncogenic pathogens. The HIV-associated malignancies include Kaposi's sarcoma, HIV-associated lymphomas (non Hodgkin's and primary CNS lymphoma) and anogenital carcinoma (anal cancer and cancer of the uterine cervix). The clinical care of these patients requires a multidisciplinary approach drawing on the skills and experience of the different cadres of HCWs. To optimize the outcome of PLHA with malignancies, the close cooperation of HIV clinicians, oncologists, haematologists and palliative care groups is essential.

9.2 Kaposi's Sarcoma (KS)

9.2.1 Introduction

Kaposi's sarcoma is the most common HIV associated malignancy and was one of the first conditions recognized in 1981 as an opportunistic condition associated with HIV infection. Although KS is more common in immunocompromised patients it is 300 times more common in HIV-infected patients than in other immunocompromised patients such as organ transplant patients in whom KS forms 3% of tumors. The epidemiology of KS varies across regions and appears to be less common in HIV infected individuals in Asia. All types of KS are due to infection with human herpes virus-8 (HHV-8), a gamma-herpes virus that is widely prevalent in immunosuppressed populations and is associated with all the clinico-epidemiological forms of KS. The levels of HHV8 appear to be predictive of the development of KS. HHV8 is transmitted sexually or via blood or saliva.



KS is divided into several subtypes with varying clinical manifestations. Classic KS was first described in 1872 as a fatal, disseminated sarcoma of the skin. KS is endemic in parts of equatorial Africa where it is responsible for an estimated 1% of all adult tumours. In these regions, transmission of KSHV proceeds from mother to child before puberty and KS is often fatal by an early age. Widespread HIV-1 infection has now turned KS into an epidemic disease on the continent. Prevalence levels for KSHV antibodies reach 30% in black South African HIV patients and childhood KS has become the most common neoplasm in parts of Sub-Saharan Africa.

KS is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The most frequent manifestation of the disease is skin and mucous membrane lesions although the lungs, the gastrointestinal tract and the lymphatic system may be involved. In PLHA, KS is a WHO Stage 4 disease. While the disease course can be indolent in the immunocompetent individual with endemic KS aggressive forms of the disease have been seen in patients with severe immunodeficiency. With the introduction of HAART the incidence of KS in PLHA has fallen considerably while the prognosis of the disease has improved dramatically.

9.2.2 Clinical Presentation

The clinical presentation of KS varies depending on the particular part of the body that is affected. There is no pattern of localization of lesions in HIV patients with KS with any part of the skin being involved with or without mucosal and visceral organ involvement. Disease progression is also variable and lesions may remain unchanged for months or years, wax and wane or grow rapidly and disseminate.

Skin Lesions

Skin involvement is the most common presentation (95%) and ranges from firm pigmented macular (patches), papules to nodular skin lesions often along the tension lines of the skin. Subcutaneous nodules may occur without any skin discoloration. The lesions can range in size from a few millimetres to large confluent areas many centimetres in size. Skin lesions may become confluent and may be accompanied or preceded by local non-pitting lymphoedema. The colour of the lesions can also be variable, ranging from pink to red especially in early lesions, to purple or dark brown or black in the older lesions/darker skin. The lesions are often asymptomatic however rapid growth of skin lesions may lead to pain and necrosis with ulceration. The external genitalia may be involved.

Mucosal Lesions

Lesions of the oral cavity occur in about one third of patients with HIV-associated KS. Hard palate lesions are the most common. These flat, red or purple/black plaques, either focal or diffuse, may be completely asymptomatic and easily overlooked. In other patients, however, larger nodular lesions involving the hard or soft palate, or both may become large, may ulcerate or bleed. Other oral sites of KS involvement include the gingival, tongue, uvula, tonsils, pharynx, and tracheal area. These lesions may interfere with eating and speaking, cause tooth loss, or compromise the airways.

Visceral Disease

Visceral disease is the most aggressive form of KS and although it may initially be asymptomatic, KS lesions in viscera eventually lead to tissue destruction bleeding and ultimately death.

Pulmonary KS may involve any part of the airways or pleural surfaces of the lungs and occurs in 20-50% of patients. In general, patients with pulmonary KS have advanced HIV disease. Signs may include shortness of breath, cough, wheezing, or haemoptysis *without fever*, unless other OIs co-exist; features of respiratory failure may occur. Chest radiographs or CT scans often show ill-defined nodules, interstitial or alveolar infiltrates (which may be indistinguishable from infections such as *Pneumocystis*), or pleural effusions. Bronchoscopy may reveal endobronchial KS in the absence of radiographic findings. Pleural effusions associated with KS may be large requiring drainage and are often exudative with cytological findings that are non-specific. Untreated, pulmonary KS is rapidly fatal

GI disease is not uncommon (40%) often asymptomatic but may be associated with ulceration and bleeding. Although GI disease often occurs in patients with skin or mucosal lesions isolated GI disease may occur. Rectal examination should be part of the routine assessment of patients with anaemia since rectal KS may be palpated on digital examination. However the diagnosis of KS involving the GI tract generally requires endoscopy because most lesions may be sub-mucosal.

Lymph node involvement

As with other HIV-infected individuals, patients with AIDS-associated KS often have modestly enlarged lymph nodes. Lymph node biopsy as part of the assessment of patients with generalized lymphadenopathy may occasionally reveal focal KS involvement; however most patients with KS will be diagnosed on the basis of lesions elsewhere. Occasionally patients may present with nodal KS without obvious KS elsewhere. Because the causes of massive or asymmetric nodal enlargement include lymphoma or various HIV-associated infections, diagnostic biopsy is warranted in all such cases.

KS has been reported to involve many visceral organs, including liver, spleen, heart, pericardium, and bone marrow, but involvement of these sites is rarely diagnosed except at autopsy.

KS associated oedema

Lymphoedema is a frequent complication of AIDS-associated KS, and its severity may be disproportionate to the extent of cutaneous KS. The oedema is generally non-pitting. The feet and legs are most commonly affected, but other common sites include the groin, external genitalia, and the periorbital tissues. Less commonly, oedema may involve the upper extremities and trunk. The cause of KS-associated oedema is not entirely clear, but it may result from tumour involvement of dermal lymphatics or, perhaps, from the production by KS cells of growth factors that increase vascular permeability. Severe oedema, particularly of the legs, may be complicated by reduced mobility, contractures, and diffuse serous drainage with protein loss, skin ulceration and cellulitis, often caused by gram-negative bacteria. Lymphoedema is indicative of aggressive disease

9.2.3 Diagnosis of KS

- The diagnosis of KS involving the skin or mucous membranes is largely clinical, based on the presence of typical skin or mucosal lesions.
- Biopsy of atypical lesions or lymph nodes in patients with no obvious skin lesions may be indicated and may show characteristic histological features including
 - Intact epidermis
 - Slit-like spaces formed by new, thin-walled and partly aberrant blood vessels running alongside normal dermal vessels and adnexal structures.
 - Extravasated erythrocytes around the new vessels.
 - Hemosiderin deposits.
 - Lymphocytic inflammatory infiltrate.
 - An infiltrate of oval- or spindle-shaped cells (spindle cell KS).
- Visceral disease: presence of mucocutaneous lesions is helpful in diagnosis. Patients with pulmonary symptoms should have sputum examination and CXR; ideally bronchoscopy with direct visualization of lesions is very useful. A CT scan may also be beneficial. For GI disease patients with suggestive symptoms should undergo endoscopy where available.
- HHV-8 can be detected in lesions by PCR. HHV-8 antibodies are often detected months before the tumour becomes apparent; antibody levels are low in patients with KS.
- Patients with suspected KS should undergo a thorough cutaneous inspection (including genital and rectal examination). Lymph nodes should be assessed and a CXR carried out. If the HIV status is unknown PITC should be provided.

9.2.4 Prognosis and Staging of Kaposi's Sarcoma

Untreated KS in immunocompromised patients can result in rapidly progressive disease, which may eventually be fatal. ART has dramatically changed both the incidence and prognosis of KS in PLHA.

Staging of HIV-related KS is summarized in the table below and is based on the clinical presentation of the patient with particular regard to

- Whether disease is limited to the skin
- Whether there is mucosal or visceral involvement
- Whether there are associated systemic symptoms including unexplained fever, night sweats, diarrhoea for more than 1 month and unexplained weight loss.

Table 9.1: Staging of Kaposi's Sarcoma

Indicator	Early Disease	Late Disease
Lesions	T ₀ : Lesions confined to the skin and or lymph nodes and or minimal oral disease	T ₁ : Tumour associated oedema or ulceration present; extensive oral KS; gastrointestinal KS; KS outside nodal viscera
Constitutional Symptoms	S ₀ : No history of OI or oral thrush; no constitutional symptoms*. Patient well or ambulatory (functional status)	S ₁ : History of other OI and/or oral thrush; patient functional status affected (spends at least part of the day in bed); other HIV – related disease present; constitutional symptoms*
Immune status**	I ₀ : CD4 > 200 cells/mm ³	I ₁ : CD4 < 200 cells/mm ³

*Unexplained fever, night sweats or diarrhoea persisting for more than 1 month, involuntary weight loss of >10%

**CD4 count is of prognostic value in patients who have *not* been on ART

The disease stage generally determines the choice of treatment and also correlates well with the outcome of HIV related KS in the era of HAART. Thus early or relatively benign disease (T₀S₀I₀) can generally be treated with ART alone or with concomitant local cytotoxic therapy. Late or aggressive (T₁S₁I₁) disease on the other hand requires both ART as well as cytotoxic therapy with or without de-bulking radiotherapy.

9.2.5 Treatment

9.2.5.1 Antiretroviral therapy

In the absence of highly active antiretroviral therapy there is no cure for HIV-associated KS. Unlike ART no local or systemic cytotoxic therapy has been shown to increase survival. **ART is therefore the first line treatment and is indicated in all PLHA with KS.** The natural history of KS has changed dramatically in the era of effective ART with more patients experiencing complete resolution of tumour than was seen previously. The lower incidence and regression of KS observed with HAART may result from a variety of effects. These may include one or more of the following:

- Immune reconstitution following initiation of ART
- Inhibition of HIV-1 replication and the resultant decrease in its 'angiogenic' Tat protein, which induces the growth of KS cells
- Reduction in intracellular cytokine production, which triggers the production of angiogenic factors and KSHV reactivation, and, related to this, direct anti-angiogenic effects of ART on KS. Although the antiangiogenic effects of ARV drugs were demonstrated using PIs, NNRTIs have been shown to be equally effective in the treatment of HIV-associated KS.

Predictors of response to ART include early KS disease staging (see Table 9.1), baseline CD4 and increase in CD4 >150 cells/mm³ in the first 12 months of treatment. ART with viral suppression and immune reconstitution often results in tumour stabilization, regression or resolution. Occasionally, KS may sometimes progress even in patients whose HIV disease is well controlled by effective ART especially in patients with late or extensive disease.

9.2.5.2 Cytotoxic Drugs

Chemotherapy presents a challenge in immunocompromised patients; local side effects following extravasation of drug into tissues, drug induced myelosuppression, peripheral neuropathy, cardiotoxicity are all associated with cytotoxic drugs used in treating KS. Of particular concern is that myelosuppression can further worsen HIV-induced immunosuppression and may precipitate life-threatening OIs.

In addition to ART, chemotherapy may be indicated in some patients with KS. A wide variety of chemotherapeutic agents, individually and in combination, have been evaluated for the treatment of KS. Local chemotherapy may be used in patients with localized and small lesions. Systemic therapy is indicated

in patients with extensive or multiple lesions, mucosal lesions, symptoms suggestive of visceral involvement, extensive oedema, constitutional symptoms and in patients who fail local therapy.

a) Single agent chemotherapy.

The vinca alkaloids (Vincristine or Vinblastine) have been used as single agents on a weekly schedule. Lesion regression rates are however low at about 33%. In our settings vincristine is more readily available. It's given weekly for six weeks. Vincristine does not cause bone marrow suppression and can be used in patients with anaemia. Dose limiting toxicity includes vincristine-induced peripheral neuropathy (which limits its usefulness as a single agent and means that it should not be used in patients with pre-existing PN or concomitantly with stavudine, lamivudine or INH). Tissue necrosis can follow local extravasation of vincristine thus care should be taken when giving this drug IV.

Bleomycin may also be used as a single agent. Bleomycin is not myelosuppressive and has the added advantage of IM administration as well as a 2 weekly schedule. If after 12 weeks there is no or incomplete response a further course of 6 injections over 12 weeks can be given. Patients who fail to respond following a total of 12 injections of Bleomycin should be reviewed by a senior clinician/oncologist. Combination chemotherapy may be the best option for patients who still have significant disease at this point bearing in mind the dose limiting toxicity concerns with bleomycin: pulmonary fibrosis occurs if cumulative doses exceed 300mg or if single doses of 30mg are given.

b) Combination chemotherapy

Historically standard combination therapy of 3 drugs including vincristine, bleomycin and doxorubicin, given every 2 weeks, has been used to treat KS because they achieve higher remission rates than single drug therapy alone. Toxicity of this regimen includes bone marrow suppression (vinblastine, etoposide), mild nausea, moderate alopecia, and peripheral neuropathy and cardiotoxicity (doxorubicin). The new formulations of the anthracyclines (doxorubicin and daunorubicin) are however now the preferred treatment for KS because of the better treatment outcomes achieved with these drugs than with standard combination chemotherapy.

Unfortunately both standard combination chemotherapy and liposomal preparations of the anthracyclines are often not accessible to patients in resource-limited settings because of the high costs. In the RLS single or dual therapy of either vincristine or bleomycin, alone or in combination, can therefore be used instead of the preferred options.

Antiviral drugs

Although KS is caused by HHV8, specific antiviral therapy has not been shown to influence the prognosis of the disease. Chronic use of some of the specific antivirals like ganciclovir or foscarnet in patients without clinical disease has however been associated with lower incidence of KS.

9.2.5.3 Local versus systemic therapy

Local therapy may be indicated for the management of stable, limited localized KS lesions or early skin disease with no systemic manifestations. Local therapy may also be used for bulky tumour, in addition to systemic treatment. Local therapy has the advantages of being provided in the outpatient setting, well tolerated with minimal or no systemic effects, and less costly than systemic therapy. However in the era of HAART has limited place in the management of HIV-related KS because most lesions that qualify will resolve on ART alone. The following methods are used depending on the size and location of tumours:

- Cryosurgery
- Intra-lesional vinca alkaloids or bleomycin
- Radiation therapy for localized big (> 3cm) lesions (KS is very radiosensitive)

Radiation therapy is the most widely used local therapy for the treatment of KS. Radiation therapy provides effective palliation of cosmetically disturbing lesions or localized bulky symptomatic disease at any site.

Local and regional recurrences are common following local treatment; most irradiated lesions regress with treatment, but re-growth, often in 4-6 months, is common. Furthermore KS is a multifocal tumour thus lesions distant from the site of treatment may also occur.

Table 9.2: Summary: Adjunctive (non-ART) Therapy for HIV-associated KS (See appendix I & J for protocols)

Local Therapy	
Vincristine (0.1-0.2mg/ml)	0.1 ml/0.5cm ² every 3-4 weeks. Lesions regress but do not disappear
Radiation	Low dose radiation given weekly for 6 weeks
Systemic Therapy	
Conventional chemotherapy	<ol style="list-style-type: none"> 1. Doxorubicin (Adriamycin) <i>plus</i> bleomycin <i>plus</i> vincristine OR 2. Bleomycin 15mg IM <i>plus</i> vincristine 1mg IV every 2 weeks 6 times* OR 3. Bleomycin 15mg IM every 2 weeks x 6 OR 4. Vincristine 1-2mg IV weekly x 6 -12 times 5. In patients who fail bleomycin/vincristine, (absent the liposomal anthracyclines): Oral etoposide 50mg per week repeated every other week. Check CBC before each cycle
Liposomal anthracyclines	Liposomal daunorubicin or doxorubicin. Liposomal formulations of anthracyclines reduce the likelihood of cardiotoxicity and local tissue necrosis associated with the conventional formulation of these agents. Although they are preferred over the above regimens, the costs of these drugs currently make them inaccessible to most patients in RLS. This is unfortunate since they achieve much higher regression rates when compared to conventional chemotherapy.

*Preferred option in RLS

9.2.5.4 Monitoring Response to Treatment

As well as routine clinical assessment, reproducible measurements should be used to evaluate treatment response of patients with KS receiving ART with or without chemotherapy at 3 monthly intervals until resolution occurs. The following can be used to assess treatment response:

- Repeated counts of the lesions for patients with disease limited to the skin (if more than 25, a representative limb should be chosen and used consistently)
- Repeated measurement of 5-10 marker cutaneous lesions. Measurements should be in 2 directions, including the longest, at right angles to each other
- An assessment of the height of the marker lesions should be made and noted (nodule, plaque or macule). Presence of inflammation or ulceration should be noted and described
- Oedema where present should be noted and assessed by repeated measurement of leg circumference

Patients failing to respond to chosen treatment for KS:

- An experienced clinician or oncologist should review patients with KS who fail to respond to 6 months of ART *plus* single drug chemotherapy (e.g. 12 injections of bleomycin).
- Combination chemotherapy should be considered in patients with no dose limiting side effects of the vinca alkaloids *and* who have not exceeded cumulative bleomycin dose of 300mg.
- Alternative drugs may also be considered with the help of an oncologist where available, for patients who have failed to respond to combination chemotherapy and ART up to the cumulative maximum bleomycin dose.
- ART should always be reviewed in patients failing to respond to KS treatment and ART optimized where necessary.

Table 9.3 Summary: Response to Treatment of KS

Response	Definition
Complete response	No new lesions <i>and</i> absence of detectable lesions for > 1 month and
Partial response	No new lesions <i>and</i> reduction of tumour in number and or size by 50% for > 1month and No new lesions <i>and</i> flattening of nodular lesions
Stable	No new lesions <i>and</i> lesions persist with no obvious change
Progression*	Appearance of new lesions Increase in number and/or size of lesions by at least 25% Development of oedema

*Disease progression may be observed as part of the immune reconstitution syndrome; thus early in the course of ART KS lesions may appear, increase in number, size and inflammation

9.2.5.5 When to Start ART in Patients with KS

In general ART should not be started in patients with active OIs or conditions until they have been treated or stabilized because of reasons of toxicity, drug interactions, adherence to complex or multiple regimens and the immune reconstitution syndrome. HIV related KS is one of the exceptions to this rule.

- For patients with early KS ART should be started as soon as the patient is ready. Clinical response should be monitored; if the lesions fail to resolve or if they worsen after 6 months of ART, local or systemic adjunctive KS treatment may be used as appropriate.
- In patients with extensive KS, ART should be commenced as soon as the patient is ready *and* chemotherapy initiated at the same time. In practice, patients with severe KS including visceral disease will often and should start chemotherapy while they are being prepared for ART. If other OIs, such as TB, are also present their treatment should commence before ART is began.

Patients on ART who develop new or recurrent KS after at least 6 months of effective ART should be assessed for treatment failure. Since KS may develop at any CD4 count and may progress in patients with suppressed viral replication, ideally a viral load assay should be part of this assessment.

9.3 Anogenital Neoplasia

Anogenital neoplasia, which includes both cervical and anal cancer and their likely precursor lesions, cervical and anal squamous intraepithelial lesions (SIL), is an increasing problem among HIV-infected individuals. Human papillomavirus (HPV) infection is the cause of most anogenital neoplasia. In addition, both HIV and HPV are sexually transmitted diseases with similar risk factors for acquisition. The prevalence of HPV infection and anogenital neoplasia is increased in immunocompromised patients in general.

9.4 Cancer of the Uterine Cervix

9.4.1 Introduction

Human papilloma virus (HPV) is the causative agent of most cases of squamous cell carcinoma of the cervix. Risk factors for HPV acquisition include early sexual debut, multiple sexual partners, promiscuous male partner and a history of STIs.

The role of HIV in the development of cervical cancer is unclear. However,

- Immunosuppression is an important risk factor for the development of new HPV infection.
- HIV-infected women, even on highly active antiretroviral therapy, demonstrate a more aggressive clinical course of cervical HPV infections and fail to eradicate the disease more frequently than

HIV-negative women.

- Regression of pre-invasive disease is inversely related to the nadir CD4 at treatment initiation.
- Although ART results in regression of pre-invasive lesions, abnormalities persist in the majority of seropositive women on ARV drug treatment.
- Both pre-invasive disease and invasive cervical cancer have been reported to have a much poorer outcome in HIV-infected women than in the general population.
- Furthermore, HIV-seropositive patients present with invasive cervical cancer almost 10 years earlier than HIV-seronegative patients.
- The extent of disease at presentation in PLHA is associated with the degree of immunosuppression; patients with CD4 count of < 200 cells/mm³ are more likely to present with more advanced disease. World wide cervical cancer is the second most common cancer in women while in Kenya, cervical cancer is the number one cancer causing death in women. It is likely that the disease burden has increased as a result of the HIV epidemic. In Africa, perhaps because of the relatively poor survival of patients with invasive carcinoma of the cervix, HIV status does not appear to be a significant indicator of survival among women with this condition.

9.4.2 Clinical Presentation of Cervical Cancer

Symptoms

The presentation varies from early disease, which is largely asymptomatic to severe disease, which can present with a range of symptoms including

- Asymptomatic, diagnosed at cervical screening
- Abnormal vaginal bleeding (usually post-coital)
- Purulent discharge
- Mass in the vagina or the introitus
- Weight loss, incontinence of urine or stool, back pain, sciatica, oedema, hydronephrosis may indicate large lesion or spread beyond to the pelvic wall

Signs

- The physical examination varies according to the presentation. In early disease physical findings may be absent.
- As the disease progresses, the cervix may become abnormal in appearance, with gross erosion, ulcer, or mass. These abnormalities can extend to the vagina.
- Rectal examination may reveal an external mass or gross blood from tumour erosion.
- Bimanual examination findings often reveal pelvic metastasis.
- Leg oedema suggests lymphatic/vascular obstruction from tumour.
- If the disease involves the liver, some patients develop hepatomegaly or jaundice
- Pulmonary metastasis usually is difficult to detect upon physical examination unless pleural effusion or bronchial obstruction becomes apparent.

9.4.3 Diagnosis

- This is based on the clinical presentation and confirmatory tests. Clinical features plus digital vaginal examination and colposcopy may be suggestive
- Confirmation of the diagnosis is important and should involve a complete evaluation, which should include Papanicolaou test with cytobrush and endocervical and endometrial samplings. If the smear result is suggestive of adenocarcinoma in situ, a cone biopsy should be performed. If the pathology still is unclear after the above workup, the patient should have dilatation and curettage. The tumour should be graded by biopsy and histology.
- A complete physical examination and appropriate tests to assess extra-genital disease is important

9.4.4 Treatment

All patients with suspected uterine cancer should be referred to a gynaecologist for effective management. The treatment of cervical cancer varies with the stage of the disease. For early invasive cancer, surgery is the treatment of choice. In more advanced cases, radiation combined with chemotherapy is the current standard of care. In patients with disseminated disease, chemotherapy or radiation provides symptom palliation.

Management of Cervical Cancer in Pregnant Women

Pregnant women with cervical cancer should be referred to a gynaecologist.

9.4.5 Prognosis

Prognosis of cervical cancer depends on disease stage. In general, the 5-year survival rate for early (stage I) disease is higher than 90%, for stage II is 60-80%, for stage III is approximately 50%, and for advanced (stage IV) disease it is less than 30%.

9.4.6 ART in Patients with Cervical Cancer

Cervical cancer is classed as WHO Stage 4 disease and thus merits ART regardless of the CD4 count. Since cervical cancer is highly prevalent in Kenya, patients with cervical cancer may present early in the course of their HIV disease with a well-conserved immune status.

9.4.7 Prevention of Cervical Cancer

Cervical cancer is preventable to a large extent by

- Preventing the acquisition of HPV infection as part of prevention of STIs in general. Delaying sexual debut in young girls/women and reducing the number of sexual partners are particularly important in the prevention of acquisition of HPV.
- Screening women at risk for cervical cancer (all sexually active women including HIV infected women), according to an agreed national schedule, to enable early detection and treatment of mild abnormalities and pre-cancerous disease. Retrospective data have shown that screening with a Papanicolaou test reduces the incidence rate of cervical cancer by 60-90% and the death rate by 90%.
- Increasing use of new HPV vaccines, which are now available, will undoubtedly go a long way towards reducing the prevalence of HPV infection and the associated spectrum of condylomata accuminata (genital warts), pre-cancerous and cancerous cervical disease. A human papillomavirus (HPV) vaccine is now available for prevention of HPV-associated dysplasia and neoplasia, including cervical cancer, genital warts (condylomata accuminata), and precancerous genital lesions. The immunization series should be completed before sexual debut in girls and young women aged 9-26 years. The efficacy of these vaccines in HIV positive women is yet to be defined. Unfortunately HPV vaccines have as yet to be made available in RLS for use within the public sector under the expanded program of immunization.

Screening for Cervical Cancer

Screening for and management of precursor lesions of cervical cancer has been demonstrated to reduce morbidity and mortality due to cervical cancer. Kenya like many other developing or resource-limited countries has not been able to master the resources required for comprehensive cytological- (Papanicolaou smear) based screening program; at the moment less than 1% of the population at risk has a pap smear done for cervical cancer screening. Much simpler and inexpensive methods for screening women are needed to

enable RLS to provide a comprehensive service that prevents unnecessary deaths due to cervical cancer. To this end, visual inspection using either acetic acid (VIA), or lugol's iodine (VILI) to detect abnormal lesions of the cervix has been researched. Both VIA and VILI and have been shown to be much more sensitive than the standard Papanicolaou smear. Their main drawback is however, a low specificity compared to Pap smear, with false positive results and a tendency towards over treatment. Nonetheless this is a method of screening that would be relatively easy to adapt for use in countries like Kenya.

All sexually active HIV positive female patients should be screened for cervical cancer as a routine part of their care at baseline and, if normal, according to the national guidelines on cervical screening in HIV infected women. Treatment of pre-cancerous lesions should be made more accessible for the large number of patients likely to need it once widespread screening becomes standard. Referral of patients found to have cervical cancer should be made possible.

9.5 HIV-Associated Lymphoma

9.5.1 Introduction

Malignant lymphomas are neoplastic diseases of the lymphatic system that grow rapidly and aggressively, causing death within a few weeks or months if left untreated. Lymphomas occur much more frequently in patients with HIV disease than in the general population. While Hodgkin's disease (HD) and Burkett's lymphoma occur even in PLHA with a well-preserved immunity the non-Hodgkin's lymphomas (NHL) occur late in the course of HIV disease. Although described in HIV-infected Kenyan patients, the incidence of lymphomas in this population is yet to be defined. Among cohorts of PLHA in developed countries, the incidence of lymphoma may be rising; this may be a reflection of prolonged survival related to the increasing use of highly active antiretroviral therapy.

In the presence of severe immunosuppression (CD4 <100) Epstein Barr virus (EBV) is responsible for 50-80% of NHL. The commonest histological types of NHL seen in PLHA are the high-grade diffuse large cell or Burkett-like; a significant proportion remain unclassifiable. NHL, an AIDS-defining or Stage 4 condition, is more common in PLHA than HD; HD is not considered a WHO Stage 4 or AIDS defining condition.

9.5.2 Clinical Presentation

HD and NHL in HIV-infected patients have some characteristics in common including the usually aggressive growth, diagnosis in the advanced stages with frequent extra-nodal manifestations, poorer response to treatment, high relapse rates and an overall poor prognosis.

Enlarged lymph nodes, indistinguishable from TB, are the commonest presenting symptom/sign in HIV associated HD. However HD in PLHA tends to present with extra-nodal disease, "B" symptoms and advanced stages of disease.

The commonest presenting symptom of NHL is lymphadenopathy. However, patients with NHL tend to present with late disease sometimes associated with extra-nodal involvement and constitutional or "B" symptoms, including fever of unknown origin, night sweats, weight loss (not responding to TB treatment), hepatic dysfunction; marrow involvement with abnormal haematological indices; lung disease with effusions, multiple nodular infiltrates, consolidation, mass lesions, or local or diffuse interstitial infiltrates, hilar adenopathy; abdominal involvement with ileus, pain, haemorrhage, hepatosplenomegaly and diarrhoea; secondary CNS involvement with aseptic meningitis, mass lesions and cranial nerve palsies.

9.5.3 Diagnosis and Staging

A tissue diagnosis must be obtained, thus biopsy of lymph nodes where possible (biopsy preferred over fine needle aspirate) as well as bone marrow biopsy should be carried out. Other investigations should take in to account the potential treatment that the patient may undergo; where aggressive chemotherapy

is not indicated or is not possible investigations can be kept to a minimum. If chemotherapy is likely then patients should undergo the investigations listed in Table 9.4 below. Appropriate imaging should be carried out to support the staging of NHL and to confirm the presence of disease in the CNS, chest or abdomen.

Table 9.4: Baseline investigations for patients with lymphoma

Haematology:	FBC, ESR, group & X-match, unilateral bone marrow (BM) trephine & aspirate
Biochemistry	U&E, glucose, albumin, calcium, phosphate, liver function, uric acid
Virology	HbsAg, HbsAb, HepB core, anti HCV IgG, CMV IgG,
Lumbar puncture	CSF protein. CSF glucose, CSF cytology (intrathecal chemotherapy should be administered with the staging LP)
Scans etc	ECG; Neck-chest-abdomen-pelvis (NCAP) CT scan with contrast

Other investigations if clinically indicated

Table 9.5: Ann Arbor Classification/Cotswolds Modification

Stage I	Involvement of a single lymph node group or lymphoid structure
Stage II	Involvement of two or more lymph node groups on the same side of the diaphragm
Stage III	Involvement of lymph node groups on both sides of the diaphragm
Stage IV	Involvement of extra-nodal site(s) beyond those designated 'E'
X:	Bulky disease: > 10 cm or > 1/3 widening of the mediastinum at T5–6
E:	Extra-nodal extension contiguous or proximal to known nodal site of disease or single isolated site of extra-nodal disease
A/B:	Absence/presence of B symptoms (weight loss > 10%, fever, drenching night sweats)

9.5.4 Treatment

Management of lymphomas in HIV patients is complex; the drugs required are expensive, patient care during treatment challenging often complicated by serious OIs and will likely be out of reach of the ordinary patient in a RLS, like Kenya, for some time. Specific treatment should be discussed with an experienced HIV clinician *and* (where possible) an oncologist/haematologist. Chemotherapy with a curative intent is recommended and should be started as soon as possible because of the aggressive nature of lymphomas in HIV infection. Granulocyte colony stimulating factor (G-CSF) should be used to limit the period of neutropaenia associated with the cycles of chemotherapy. During chemo daily temperature, regular CBC, renal and liver function tests should be done. At the same time non-AZT based ART is required to allow the use of these regimens, which are associated with severe bone marrow suppression.

For NHL combination chemotherapy CHOP (Cyclophosphamide, doxorubicin, vincristine, prednisone) or M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) are possible options. At least 4 cycles should be given followed by 2 cycles after complete remission is achieved.

HD is treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) given in 4 cycles.

9.5.5 Prognosis

Even though the initial response rates of NHL may be relatively high at 50% to 60%, the long-term prognosis is poor with median survival of less than one year. Death is often a result of progressive lymphoma or progressive HIV disease with OIs. The use of concomitant ART appears to improve the prognosis markedly,

with a reported survival of one year at 84%.

While HD is highly treatable in the HIV-uninfected population, in HIV infection it has a very poor prognosis with a median survival of ~15-20 months in the absence of ART. Survival increases with the use of ART.

9.6 Primary Central Nervous System Lymphoma

HIV-associated primary CNS lymphoma (PCNSL) is a diffuse, large-cell non-Hodgkin's lymphoma that usually occurs in the brain and, rarely, in the spinal cord. It is a late complication of HIV infection and is the commonest lymphoma in PLHA, occurring up to 1000 times more commonly in PLHA than in the uninfected population (compared to NHL at 300-600 times and HD at 5-10 times). PCNSL is typically B cell in origin. Virtually all PCNSL are associated with EBV; EBV transformation of chronically activated B cells is probably responsible for lymphoma development. This opportunistic neoplasm is associated with severe immunodeficiency with CD4⁺ lymphocyte counts usually less than 50 cells/mm³.

The introduction of effective ART has resulted in a significant reduction in the incidence of PCNSL compared to systemic non-Hodgkin's lymphomas in developing countries; however the degree of reduction has been less dramatic when compared to the reduction in incidence seen with other opportunistic conditions, such as KS and the serious OIs, in the era of HAART.

9.6.1 Clinical Presentation

HIV-associated CNS lymphoma is the second most common mass lesion (after toxoplasmosis) in patients with severe HIV disease. The onset of CNS lymphoma is often more insidious (<3 months) than that of toxoplasmosis and fever is usually absent. Other differential diagnoses include tuberculous and bacterial abscesses, glioblastoma and cerebral metastasis of solid tumours.

Symptoms: may include

- Lethargy
- Confusion
- Impaired memory, personality changes
- Headache
- Seizures may be the first symptom
- Focal weakness

Fever is usually absent.

Signs: the following signs may be noted on physical examination

- Lethargy
- Confusion
- Impaired memory
- Focal neurologic deficits.
- Fundoscopy may reveal ocular involvement.

9.6.2 Diagnosis

The most important differential diagnosis is cerebral toxoplasmosis.

- CT scan is very useful in the assessment of patients with focal neurological deficits. Solitary lesions > 4 cm are more likely to be lymphoma than toxoplasmosis, although up to 2-4 lesions do occur; PCNSL is unlikely to present with more than 4 lesions. Therapeutic trial of anti-toxoplasmosis therapy should be given where there is doubt as to the likelihood of toxoplasmosis (e.g. multiple lesions in a toxoplasma antibody positive patient). Patients who fail to respond to toxoplasmosis treatment should be considered as possibly having PCNSL. In ideal settings a toxoplasma serology should be done; toxoplasmosis is unlikely in patients with negative serology. Such patients with focal CNS lesions should undergo brain biopsy to rule out the presence of lymphoma.
- In the absence of increased intracranial pressure a LP should be performed and an examination of the CSF for malignant cells carried out
- CD4 count is useful since PCNSL is unlikely in patients with a well-preserved immune function.

- CXR and abdominal ultrasound scan should be done to exclude the possibility of CNS disease being secondary.
- Fundoscopy should be done to exclude ocular involvement, which occurs in 20%.

9.6.3 Treatment

It is recommended that patients suspected of having lymphoma be referred to a senior clinician for assessment and are managed with the support of an oncologist.

Treatment consists of whole brain radiotherapy together with steroid therapy. The prognosis has been very poor with a median survival with this treatment in PLHA in the pre-ART era of only 2-4 months. With immune reconstitution following ART response rates have improved with more patients achieving remission; ART should therefore be commenced early in patients with PCNSL.

**CHAPTER 10:
OCULAR
MANIFESTATIONS OF
HIV INFECTION**

CHAPTER 10: OCCULAR MANIFESTATIONS OF HIV INFECTION

10.1 Introduction

HIV immunosuppression is associated with an increasing incidence of eye diseases with the majority of PLHA developing eye conditions during the course of their illness. The specific conditions are broadly related to the state of the patient's immune system, with the more serious eye problems occurring in advanced HIV disease. Thus ocular KS and TB may present in patients with CD4 counts above 350 cells/mm³ while toxoplasmosis of the eye usually occurs when CD4 counts are below 200 cells/mm³ and CMV in patients with CD4 count less than 100 cells/mm³.

Immune reconstitution inflammatory syndromes (IRIS) involving the eye can occur in patients with advanced HIV disease soon after initiation of effective ART, leading to exacerbation of a condition for which a patient is already undergoing treatment or the unmasking of pre-existing previously subclinical opportunistic infections. In the case of CMV, IRIS may present as retinitis, or less commonly as uveitis or vitritis. IRIS retinitis typically occurs in patients whose CD4 counts have increased from <50 cells/μL to >50-100 cells/μL on ART.

Drug-induced ocular toxicity may be caused by rifabutin, ethambutol, cidofovir, and less often with high-dose didanosine, intravenous ganciclovir and intravenous acyclovir.



Conjunctivitis

10.2 Principles of Managing Ocular Disease in HIV-infected Patients

- Due to the potentially devastating and rapid course of retinal OIs, all persons with HIV disease should undergo routine ophthalmologic evaluations at baseline
- Patients should be educated about ocular disease especially in relation to any drugs that may cause ocular toxicity. They should be encouraged to report any changes in vision to their health care provider as soon as possible.
- Any HIV-infected person who experiences ocular symptoms should receive prompt and competent ophthalmologic care. Referral to the nearest eye clinic should be arranged and communication between the HIV clinic and the eye clinic fostered to ensure the patient receives appropriate care.
- In patients with early-stage HIV disease (CD4 count >350 cells/μL), ocular syndromes associated with immunosuppression are uncommon. Nonetheless, eye infections associated with sexually transmitted infections (STIs) such as herpes simplex virus, gonorrhoea, and chlamydia may be more frequent in HIV-infected persons. Clinicians should therefore screen for HIV in the presence of these infections. Assess for emergency signs and stabilize patient
- Always assess the sick patient for emergency symptoms and/or signs. This is especially important because ocular disease may often be part of a systemic condition, many of which may be serious.
 - Patient short of breath (SOB) at rest, unable to walk or talk in complete sentences
 - PR > 120/min or radial pulse weak or absent
 - RR > 30, temp > 40°C/< 35°C, SBP < 90mmHg or DBP > 110mmHg
 - Stiff neck; Loss of body function or focal neurological signs; recent seizure (fit); confusion, agitation, impaired consciousness;
- Stabilize severely ill patients first before continuing with a more complete clinical assessment (see Table 1.4).
- **Does patient need referral?** Always determine if the patient can be managed effectively by the cadre of HCWs available and with the facilities available at the particular HCF. Most clinicians will have limited experience in the management of ocular disease, thus the opinion of an

- ophthalmologist should always be sought, particularly where serious ocular disease is suspected or a fundoscopic examination is necessary.
- a. *If referral is required the patient must first receive emergency response to any emergency signs to ensure they are stable enough for transfer.*
 - b. Patients complaining of flashes of light and/or sudden loss of vision in the absence of any systemic complaints should be referred immediately to an ophthalmologist due to possible imminent visual loss
- A clinical assessment as outlined in Table 1.5 will often elicit information and/or findings that direct the HCW to the likely diagnosis, or to which other system is involved.
 - a. **Ask about:**
 - Onset of symptoms, whether sudden or gradual
 - Duration of symptoms
 - Whether eye symptoms are unilateral or bilateral
 - Pain and where localized
 - Visual loss
 - Whether acute (haemorrhage, acute infections) or chronic (diabetes, glaucoma, cataract)
 - Whether complete or partial (central or peripheral; loss or distortion)
 - Scotomata (an area of lost or depressed vision within the visual field, surrounded by an area of less depressed or normal vision).
 - Occurs with reading, distance, or both?
 - Presence of associated symptoms (including fever, headache, neck stiffness, focal signs, seizures, altered mental status, cough, skin lesions, etc)
 - Recent or current herpes zoster
 - History of hypertension, diabetes, sickle cell disease
 - Previous or current medications used including local eye treatments
 - Use of corrective lenses
 - Date of last eye examination, if ever
 - b. **Look:** A complete examination of the eyes including the adnexa (eyelids, conjunctiva, cornea and lacrimal glands), the anterior and posterior structures. Where possible patients should be assessed by an ophthalmologist)
 - PR, RR, temp, BP should be measured.
 - Examine the eyelids for any lesions, inflammation, swelling, discharge
 - Examine external eye for oedema, ptosis, conjunctival injection or inflammation and corneal clarity.
 - Fundoscopic examination with pupillary dilatation should be performed. Note retinal appearance, lesions, condition of disc, vessels and macular
 - Test cranial nerves 2,3,4, and 6. If any abnormalities are elicited a full CNS examination should be carried out
 - Administer visual acuity using Snellen's chart.
 - Test ability to read small print, such as the classified ads in the local daily papers.
 - A targeted examination of other systems should be performed depending on any other complaints a patient may have, taking into account the fact that many eye conditions are a part of systemic conditions.
 - **Investigations:** patients with ocular symptoms should be investigated according to the particular complaint and whether or not systemic symptoms are present. Whatever ***laboratory tests are deemed necessary, they should not delay starting treatment in severely ill patients; where tests are not available, a presumptive diagnosis should be made and empirical treatment started.***
 - a. **CD4 count** is important in the differential diagnosis of eye disease in HIV-infected patients; thus toxoplasma or CMV are unlikely to be responsible for chorioretinitis if the CD4 count is > 200 thus every attempt should be made to get the most recent CD4 result

- **Treatment**
 - a. The likely diagnosis should be made based on patient presentation and treatment commenced as specified in Table 10.1. Where the ocular manifestation is part of a systemic condition treatment should be initially directed to the systemic condition e.g. hypertension, syphilis or TB.
 - b. Treatment may include discontinuing drugs associated with ocular toxicity and replacement with suitable alternatives
- **Review:** Patients should be reviewed regularly by the ophthalmologist if necessary, to determine progress on any treatment initiated.
- **Is patient on ART?**
 - a. Ocular disease can represent manifestations of HIV-associated diseases many of which are indications of severe immunodeficiency. For patients already on ART severe HIV associated ocular disease may be an indication of IRIS in patients recently initiated on ART. All PLHA should be assessed for ART at initial enrolment and regularly thereafter.
 - b. Patients already on ART developing unexplained anaemia should be assessed for the presence of OIs and of failure of their current regimen

Table 10.1: Common Ocular Manifestations of HIV

Condition	Causes	Presentation	Treatment
Infectious Blepharitis	Adenovirus is the most common cause of a red eye with a thin discharge. <i>Staphylococcus aureus</i> is common bacterial cause, associated with a thicker discharge.	The patient may complain of discharge and redness of the eyes or eyelids. Presents as inflammation of the eyelids often with conjunctival involvement.	Treatment includes strict hand washing, cleansing of eyelashes with warm water and mild shampoo, and application of a broad-spectrum topical antibiotic ointment if indicated.
Molluscum Contagiosum	Multiple, small, painless, umbilicated lesions characterize molluscum contagiosum. The lesions of MC tend to be larger, more numerous, and rapidly growing in HIV-positive patients than in HIV-negative patients. It is the most common condition affecting the adnexa of the eyes of HIV-infected patients, often accompanied with extensive lesions involving the face. MC in immunocompetent patients is a self-limiting disease with spontaneous resolution taking months to years.	MC may give rise to elevated, pearly, umbilicated nodules on the eyelids. The lesions are seen easily on the eyelids, but they sometimes may be missed with casual examination. Diagnosis is based on clinical findings of the characteristic fleshy umbilicated skin lesions.	Although a WHO Stage 2 condition, extensive MC is unlikely to respond to local treatments alone in HIV+ patients; ART is often indicated in patients with extensive disease
K a p o s i ' s sarcoma	About 20% of patients with KS have involvement of eyelids.	KS presents on the eyelid as a painless, violet-brown papule. It may involve the orbit with associated eyelid and conjunctival oedema. KS of the conjunctiva usually appears as reddish-blue, vascularized, subconjunctival lesions most frequently seen in the inferior fornix as nodular or diffuse lesion. Eyelid and conjunctival KS tend to mimic chalazion and localized subconjunctival haemorrhage, respectively.	Treatment always includes ART. Whether or not to use systemic chemotherapy depends on patient presentation and extent of the KS lesions. Single ocular lesions may be treated with local radiotherapy.

Table10.1: Common Ocular Manifestations of HIV cont.

Condition	Causes	Presentation	Treatment
Varicella Zoster	Reactivation of latent varicella (chicken pox) may affect any part of the eye. Most commonly involves 1 st division of trigeminal nerve. Predisposing factors include immunosuppression, age, and other malignancy. May involve the eyelids, conjunctiva or anterior (keratitis, uveitis and iridocyclitis). Acute retinal necrosis a fulminant retinal vaso-occlusive necrotizing retinitis may complicate VZV, HSV, or, rarely, CMV infections. Retinitis often results in rapidly progressive disease with blindness ensuing in the majority. PHN is the commonest neurological complication of ocular VZV; others are rare and include optic neuritis, encephalitis, and hemiplegia.	Patients may present with fever, malaise and painful vesicular rash involving the adnexae of the eyes. Involvement of the anterior or posterior segments may be acute or recurrent. When acute it presents after a few days from the onset of the vesicular rash. Diagnosis is clinical.	Treatment should start as early as possible to reduce the likelihood of visual loss. IV acyclovir 10mg/kg TDS for 14 days. (Oral acyclovir 800mg QDS can be substituted for the last 7 days if patient improving). If unresponsive, consider alternative antiviral e.g. foscarnet Patients with retinal necrosis should initial treatment with prednisolone and IV ACV and then have oral acyclovir continued treatment for at least 2 months. If intraocular inflammation is present, topical cycloplegic agent (scopolamine 0.25% TDS) and a topical steroid (prednisolone acetate 1% q1-2h) should be started.
Kerato-conjunctivitis Sicca	Dry eye is a common condition especially in advanced HIV infection as well as in patients with altered mental status.	Diagnosis of keratoconjunctivitis sicca usually is made with the aid of an abnormal Schirmer test and rose bengal stain, requiring an ophthalmologist therefore refer.	Artificial tears and long-acting lubricating ointments used in association with punctal plugs for symptomatic relief.
Infectious keratitis	VZV and HSV are the most common infectious causes of keratitis in PHLA. Other causes include bacteria, fungi, and other viruses. Bacterial and fungal keratitis occurs equally in HIV-uninfected and HIV-infected patients. Fungal infections are caused most frequently by the Candida species, especially in IV drug users.	The patient may complain of photophobia, eye pain, decreased vision, and irritation. In HIV-infected patients, keratitis may be more severe and may recur more frequently compared with HIV-uninfected persons. Evaluation should include slit-lamp exam by an ophthalmologist therefore refer. HSV and VZV serology may be useful	VZV is treated as above. HSV keratitis should be treated with topical acyclovir 3% 5 times daily for 14 days.

Table10.1: Common Ocular Manifestations of HIV cont.

Condition	Causes	Presentation	Treatment
Inflammation of the eye without infection	Presents as red eye associated with pain but no discharge. Associated with autoimmune diseases as well as some infectious conditions like syphilis. Acute angle closure glaucoma is a rare but important cause of a red painful eye associated with headache, nausea, and blurred vision.	Diagnosis requires a slit lamp examination therefore refer. (Episcleritis, scleritis, uveitis - iritis or iridocyclitis). Intraocular pressure should be measured if acute narrow angle glaucoma is suspected.	Treatment includes use of mydriatic agents, NSAIDS and topical steroids.
	Anterior chamber inflammation is fairly common in HIV and often is associated with CMV or HSV retinitis. Ocular bacterial infections, syphilis, toxoplasmosis, and tuberculosis can cause severe symptoms. Fungal retinitis rarely causes iridocyclitis. Other causes include other systemic conditions (e.g., reactive arthritis, sarcoidosis) and drug toxicity (e.g., rifabutin, cidofovir, ethambutol). Evaluation should include slit-lamp exam by an ophthalmologist.	The patient may complain of redness or watering of the eyes and blurred vision. On examination the pupils are constricted.	Treatment should be directed at the causative pathogen or illness. If drug toxicity is suspected, discontinuation or dosage reduction of the offending drug is indicated. Topical steroids may be indicated as an adjunctive measure. CMV IRD may present as posterior uveitis; for suspected IRD, consult an HIV-experienced ophthalmologist.
CMV Retinitis	In developed countries CMV retinitis is the most common intra-ocular infection of the eyes in patients with severe HIV disease. Most CMV retinitis is a result of reactivation of latent disease acquired in childhood or adolescence and early adulthood (perinatally, through close contact or through sexual contact). Primary infection is often asymptomatic, but may present with flu like symptoms. CMV causes a necrotizing retinitis and/or choroiditis. Untreated, it leads to significant visual loss. Progression is less fulminant than HSV or VZV retinitis. Retinal detachment is a common sequela of CMV retinitis. With the introduction of effective ART, the incidence of CMV retinitis has decreased substantially. Patients commencing ART with severe immunodeficiency may present with CMV retinitis as an IRIS.	Patient often has CD4 < 100. Patient may complain of floaters, flashing lights, visual field defect, and decreased visual acuity. Presence of an afferent pupillary defect strongly suggests significant retinal or optic nerve involvement. Diagnosis is clinical based on fundoscopic examination by an experienced clinician or ophthalmologist. Serum or urine CMV antigenaemia or IgG/IgM may be supportive.	Treatment will largely be out of the reach of the majority of patients. Oral valganciclovir is the drug most likely to be available is adequate for treatment at an induction dose of 900mg BD for 21 days followed by maintenance treatment of 900mg OD. Induction may be repeated if retinitis progresses. Valganciclovir causes myelosuppression and should not be used together with AZT.

Table10.1: Common Ocular Manifestations of HIV cont.

Condition	Causes	Presentation	Treatment
<p>Infectious retinitis and/or choroiditis</p>	<p>Common bacterial causes of retinitis in patients who are HIV positive include <i>Treponema pallidum</i> (syphilis) and <i>Mycobacterium tuberculosis</i>. Fungal causes of retinitis and/or choroiditis include <i>Pseudallescheria boydii</i>, <i>Cryptococcus neoformans</i>, <i>Histoplasma capsulatum</i>, as well as <i>Candida</i>, <i>Sporothrix</i>, and <i>Aspergillus</i> species. Parasitic causes include <i>Toxoplasma gondii</i> and <i>Pneumocystis jiroveci</i>.</p>	<p>Commonly patients have no ocular symptoms but may have evidence of the primary conditions elsewhere. Patient may complain of floaters, flashing lights, visual field defect, and decreased visual acuity. Conditions associated with raised intracranial pressure such as cryptococcal disease can be associated with papilloedema as well as chorioretinitis. The diagnostic work up should be consistent with patient presentation. Where ocular findings are present in isolation, all these possibilities should be considered during the history and physical examination. Most ocular manifestations of syphilis occur in the secondary stage; optic atrophy and the Argyll-Robertson pupil are however seen in the tertiary stage. TB if it involves the eye commonly presents with anterior uveitis and disseminated choroiditis. All patients with syphilis and eye symptoms should have a LP and/or managed as for neurosyphilis. Most patients with <i>P. jiroveci</i> retinitis are asymptomatic.</p>	<p>Treatment is generally of the primary condition and should be started immediately. Where retinitis is part of the IRIS, systemic steroid treatment should be considered to avoid extensive retinal damage that may otherwise occur.</p>
<p>HIV Retinopathy</p>	<p>This is the most common retinal pathology in patients who are HIV positive.</p>	<p>Patients are often asymptomatic. Manifests as cotton-wool spots seen on fundoscopy. A thorough assessment of the patient is necessary to exclude other systemic infections.</p>	<p>Treatment is not necessary.</p>

Table10.1: Common Ocular Manifestations of HIV cont.

Condition	Causes	Presentation	Treatment
<p>Ocular Drug Toxicity</p>	<p>Ethambutol-associated visual disturbances include loss of acuity, colour blindness, and restriction of visual fields. Toxicity more likely if excessive dosage is used or if there is renal impairment. The earliest features of ocular toxicity are subjective; patients should be advised to stop therapy immediately if they develop deterioration in vision and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. Ethambutol should be used with caution in children < 5 years old. Snellen chart should be used to test visual acuity before treatment with ethambutol. High-dose didanosine has been associated with retinal pigment epithelial abnormalities.</p> <p>As many as 33% of HIV-infected patients on high-dose rifabutin experience intraocular inflammation, especially when an antifungal azole is used concurrently. Corneal epithelial inclusions have been associated with intravenous ganciclovir and acyclovir, while atovaquone is associated with corneal sub-epithelial deposits</p>	<p>These adverse effects are dose related and resolve following discontinuation of the drug, with the exception of the abnormal retinal pigment epithelial changes.</p>	<p>Discontinuation of the offending drug is often adequate.</p>

**CHAPTER 11:
REPRODUCTIVE
HEALTHCARE FOR
PEOPLE LIVING WITH
HIV INFECTION**

CHAPTER 11: REPRODUCTIVE HEALTHCARE FOR PEOPLE LIVING WITH HIV INFECTION

11.1 Introduction

HIV/AIDS is a problem that profoundly affects most aspects of infected people's lives, including their reproductive health, their reproductive potential as well as their perceptions and understanding of the reproductive choices open to them. Studies have shown that HIV positive women in Western cohorts have lower live birth rates and higher rates of terminations and sterilization when compared to HIV negative women. Furthermore HIV has significant psychological as well as neuro-endocrine effects which may impact negatively on the sexual experience as well be associated with reduced libido and sexual dysfunction. Consequently it is essential that reproductive health services provided to PLHA are comprehensive encompassing the following:

- Preventive aspects such as
 - STIs prevention and management
 - Prevention of unwanted pregnancies/planning of pregnancies
 - Prevention of onward transmission of HIV
 - Prevention of cervical cancer and management of precancerous/cancerous cervical lesions
- Psychological aspects including management of sexual dysfunction and issues concerning sexuality.
- Support in and management of fertility problems

The fact that many of these services are as yet not available for PLHA in Kenya highlights the need for better understanding of reproductive issues in the local context.

11.2 Prevention Services for PLHA (“prevention with positives”)

Even in Kenya where widespread treatment has only recently become available, the impact of ART on the quality of life and longevity of PLHA is becoming evident. As the numbers of patients accessing life saving care and treatment increases, the cumulative number of patients living with HIV will likely rise with the *potential* that HIV incidence may go up beyond levels that may have occurred in the absence of ART. Additionally the availability of effective treatment may affect the perceptions about HIV among those who are not infected with the result that behaviour change gains may be lost. While evidence shows that people who know their status are likely to reduce risk to themselves and others, consistent safer sexual behaviour can be difficult to maintain over long periods of time. Further there is evidence from some African countries that have had successful prevention programs that risk reduction behaviour change in the population as a whole may not be sustained.

By the end of August 2007 over 400000 patients had been registered in HIV care clinics in Kenya, a figure that represents about one quarter of those estimated to have HIV infection in the country. Health care and paramedical workers regularly attend to this increasing “captive” group of people, with each patient attending a health facility at least 4 times a year for routine HIV clinical care, with or without ARV drug treatment. As such there is a unique opportunity to provide targeted prevention services among patients already identified to be HIV-infected.

Prevention programs that are participatory, involving patients in the decision making process through education and empowerment should be implemented in all HIV care centres. There is evidence that HIV risk behaviour and incident bacterial infections can be reduced in cohorts of HIV infected individuals over a period of time. Each HCF providing services for PLHA will therefore need to incorporate appropriate preventive interventions into the comprehensive package of care they offer. These should include

- Providing support for PLHA to disclose their status to any sexual contact but especially regular sexual partners; this should include assisted disclosure where appropriate.
- Testing of sexual contacts for HIV and assessment of contacts for other STIs should also be provided.
- Supportive management of discordant couples

- Education of PLHA to include information on the ability to transmit HIV despite ART and thus the need for use of condoms even in partnerships of HIV-concordant couples
- General safer sexual behaviour including limiting the number of sexual partners, use of latex condoms correctly during every act of sexual intercourse to reduce the risk for exposure to sexually transmitted pathogens.
- The sexual health of infected patients should be assessed regularly to help foster healthy sexual behaviour, facilitate treatment of any identified STIs and thus reduce the likelihood of onward HIV disease transmission. These services can be offered routinely at all levels of HCFs.
- PLHA/couples living with HIV in care should be encouraged to discuss their reproductive plans to allow opportunity for prevention of unwanted pregnancies through appropriate use of contraception. At the same time pregnancy should be anticipated to allow effective interventions to prevent mother child transmission to be implemented.
- Prevention services should include prevention, routine screening for and treatment of incident STIs.

11.3 Prevention and Control of Sexually Transmitted Infections

HIV is a sexually transmitted infection (STI) with the majority of adult HIV positive patients in Kenya acquiring the infection sexually. Further, STIs are important co-factors in the transmission of HIV infection; the presence of either inflammatory or ulcerative STIs facilitates both the acquisition (STIs increase susceptibility to HIV) and transmission (STIs increase infectiousness of individuals with HIV) of HIV infection. Additionally, HIV infection may alter the clinical course of STIs, often increasing the severity and duration of some. In resource-limited settings where routine screening for STIs is not possible, prevention and control of STIs is largely dependent on education and behaviour change to reduce the risk of acquiring STIs, treatment of symptomatic individuals and evaluation and treatment of contacts.

In the setting of high-prevalence HIV infection including HIV care clinics the following should be implemented for the prevention and management of STIs and reduction of onward transmission of HIV infection.

- STI prevention outreach programs should promote voluntary HIV testing and educate communities about HIV management and linkages into care.
- All patients presenting with a suspected or confirmed diagnosis of STI should be tested for HIV, unless they decline testing (PITC). A repeat test should be carried out at 3 months if the initial HIV test is negative.
- All HIV service providers should be trained in taking a sexual history and should be able to make an appropriate sexual health assessment.
- A sexual health assessment including a sexual history should be documented at baseline and during each clinic visit for all HIV-positive people receiving long-term care. The assessment should be through review of recent sexual history as well as evaluation for symptoms suggestive of STIs.
- All sexually active PLHA should have syphilis serology test done at baseline followed by annual testing thereafter. All patients with neurological complaints or signs should also undergo syphilis testing. A positive non-treponemal test (NTT e.g. VDRL) should be followed by a treponemal test (e.g. TPHA) before treatment is considered. This will avoid inappropriate treatment since false non-treponemal tests may occur in association with medical conditions not related to syphilis. Non-treponemal tests correlate with the disease; a fourfold change in a test done in the same laboratory is required to indicate a clinically significant change in disease activity. In the majority of patients the NTT become negative after effective treatment; they may however persist at low titres in some patients. All HIV positive patients treated for syphilis should be followed up with a NTT for treatment response at 3, 6 and 12 months. Most patients with reactive treponemal tests remain reactive for life regardless of disease activity. HIV infected individuals may have unusual serological tests.
- All PLHA should be trained to be able to use condoms correctly. A supply of condoms should be made available to all patients at each clinic visit.

Treatment of STIs

Syndromic treatment of symptoms suggestive of a sexually transmitted infection is recommended as per the national guidelines. The objective of this is to provide rapid relief of symptoms, to treat all infections effectively and prevent onward transmission of STIs. Unfortunately not all STI syndromes are equally amenable to management by the syndromic approach with the result that over-treatment or less commonly, under-treatment may occur. This is especially true of vaginal discharge in women.

Failure to improve on recommended regimens should raise the questions of incorrect diagnosis, non-adherence to treatment or instructions or the disease having been altered by co-infection with HIV, in which case a longer course of treatment may be necessary.

Appropriate education about the risks and consequences of STIs to the individual and to others should be provided. Every attempt should be made to trace and treat the contact(s) as well; the index patient should be advised to avoid re-exposure until all contact(s) have been treated. The contact(s) should be offered HIV testing and counselling

Table 11.1: Summary: Syndromic Management of STIs

Syndrome	Comments	Treatment
Male urethral discharge (urethritis)	Discharge. Pain passing urine or dysuria. Treatment given for both gonorrhoea and chlamydia	Norfloxacin 800mg stat AND Doxycycline 100mg BD x 7 days (or Azithromycin 1 g stat instead of doxycycline) Alternative Rx: IM Spectinomycin 2g stat plus Doxycycline 100mg BD x 7 days
Vaginal discharge (suspected candidiasis)	Vaginal itchiness, thick curdy discharge	Clotrimazole 100mg pessary intravaginally daily x 6 days. Review in 7 days; if no improvement consider bacterial vaginosis/ trichomoniasis or cervicitis
Vaginal discharge (non-specific)	Vaginal discharge; may be smelly with or without itchiness. No risk of STIs or recently treated for cervicitis (bacterial vaginosis or trichomoniasis vaginalis)	Metronidazole 500mg BD x 7 days plus Clotrimazole 100mg nocte for 6 day
Suspected cervicitis	Intermenstrual bleeding; failure to respond to treatment for vaginal discharge. No abdominal pain or dyspareunia. Treatment given for both gonorrhoea and chlamydia	Norfloxacin 800mg stat plus Doxycycline 100mg BD x 7 days (or Azithromycin 1 g stat instead of doxycycline) If pregnant: IM Spectinomycin 2g stat plus Erythromycin 500mg QID x 7 days (or Azithromycin 1 g stat instead of erythromycin)
Pelvic pain	Abdominal pain, new dysmenorrhoea, dyspareunia. Tender pelvis on bimanual exam, cervical motion tenderness. Rule out masses or potential surgical causes*.	Norfloxacin 800mg stat plus Doxycycline 100mg BD x 14 days plus Metronidazole 400mg BD x 14 days OR Norfloxacin 400mg BD x 14 days plus Metronidazole 500mg BD x 14 days If pregnant: Refer to obstetric evaluation if PID is suspected Ceftriaxone 250mg IM stat (or Cefixime 400mg PO stat) plus Erythromycin 500mg QID x 14 days plus Metronidazole 500mg BD x 14 days

Syndrome	Comments	Treatment
Genital Ulcer Disease	<p>Multiple vesicles/coalescent superficial ulcers with history of recurrence suggest herpes genitalis. Clinical diagnosis of herpes genitalis is however non-specific and insensitive</p> <p>Chancroid also presents as multiple painful ulcers associated with painful often unilateral lymphadenitis. Syphilis commonly presents with single painless indurated ulcer although multiple or painful ulcers also occur. Co-infections of syphilis, herpes and chancroid have been reported in several African studies.</p> <p>Chronic ulcers that fail to respond to standard treatment including a trial of treatment for herpes genitalia should be biopsied.</p>	<p>If diagnosis suggestive of first clinical episode of genital herpes treat with acyclovir 400mg 3 times per day x 7 - 10 days. Start treatment as early as possible or as long as there are "new" vesicles</p> <p>For recurrent episodes of genital HSV Aciclovir 400mg TDS x 5-7 days</p> <p>Otherwise give the following: Erythromycin 500mg TID x 7 days plus Benzathine Penicillin 2.4MU IM weekly x 3 weeks</p> <p>If penicillin allergic: <i>desensitization recommended for pregnant women</i>; other patients can be given Doxycycline 100mg BD x 28 days.</p> <p>If donovanosis suspected: Erythromycin should be continued for at least 3 weeks or until the ulcers heal.</p> <p>Asymptomatic contacts: Doxycycline 100mg BD x 14 days</p>
Lymphogranuloma venereum	<p>Tender inguinal or femoral lymphadenopathy, usually unilateral. Rectal infection may present with mucoid or hemorrhagic rectal discharge, tenesmus and constipation. Fluctuant buboes may need aspiration or incision and drainage. Asymptomatic contacts should be treated as for male urethritis or female cervicitis.</p>	<p>Doxycycline 100mg BD x 21 days OR Erythromycin 500mg QID x 21 days.</p>
Genital Warts	<p>Multiple painless lumps in genital or perianal area.</p>	<p>Standard local or topical treatments should be used as would be the case in HIV uninfected patients Surgical treatment should be considered early in HIV infected patients with large warts</p>
Ophthalmia neonatorum	<p>Sticky eyes in the new born</p>	<p>Newborn: Procaine penicillin 300,000 IU IM AND 1% Tetracycline eye ointment TDS x 10 days.</p> <p>Review neonate in 24 hours; if no improvement: Erythromycin 100mg BD x 14 days AND 1% Tetracycline eye ointment TDS x 10 days OR Ceftriaxone 62.5mg IM stat AND 1% Tetracycline eye ointment TDS x 10 days</p> <p>Treat mother for cervicitis and father for urethritis</p>

*Surgical or gynaecological causes are suspected by the presence of rebound tenderness and/or guarding, last menstrual period overdue; recent abortion or delivery, menorrhagia or metrorrhagia

11.4 Contraception for Women and Couples Living with HIV

Ideally, contraception services should be integrated with HIV prevention, care and treatment services since the population in need of these services share the same risks and characteristics (young, sexually active, fertile).

PLHA have a right to access information and services for contraception. They should be informed and

educated about their reproductive options and they should be free to make their reproductive choices in the same way that other couples and women do. The advent of effective ART may make pregnancy more attractive for HIV infected women due to the improved longevity associated with ART. While pregnancy does not appear to accelerate HIV disease, it is associated with an increased risk of stillbirth and low birth weight. Further, unless effective preventive efforts are instituted, up to one third of HIV infected pregnant women will pass on the infection to their children during pregnancy, delivery or breastfeeding.

The choice of contraceptive methods in HIV infected couples and women are much the same as in HIV negative couples and women (see Table 11.2 below).

Effective use of contraceptives in HIV positive women plays an important role in the prevention of unwanted pregnancies and thus the prevention of mother to child transmission (PMCT) of HIV infection. HIV positive women not using effective contraception do not necessarily intend to become pregnant; they may lack sufficient power in their sexual relationship, be under pressure from partner or family to have children, may not have disclosed their HIV status to their partner, be unaware of their options concerning contraception or believe they cannot become pregnant. On the other hand an unplanned pregnancy in HIV positive women does not mean an unwanted pregnancy.

Therefore, HIV-infected women should be encouraged as much as possible to discuss their reproductive desires and options. Where pregnancy is not desired effective contraception should be offered and dual contraception (e.g. use of both hormonal contraception and condoms) encouraged. If a pregnancy is desired, the couple's status should be considered and where discordance exists, appropriate advice given. Where pregnancy has occurred in an infected woman, mother to child transmission (MCT) of HIV infection should be prevented using guidelines for the PMCT (see Chapter 3). Antenatal and postnatal care in HIV infected women should be as per national guidelines while taking into account their HIV specific needs.

Table 11.2: Contraceptive Methods for use Women and Couples Living with HIV

Method	Comments	Use in HIV Positive Patients
Condoms	<p>Both male and female condoms available</p> <p>Provide dual protection against STIs/HIV and pregnancy.</p> <p>Require attention and care for correct use each time.</p> <p>May require co-operation of the partner</p>	<p>Can be used at all stages of HIV infection</p> <p>Can be used by patients on ART</p> <p>Correct and consistent use by HIV infected patients recommended regardless of the use of other methods of contraception (dual contraception).</p>
Hormonal Methods	<p>Very effective and easy to use</p> <p>Suitable for short- or long-term use Reversible</p> <p>Non-contraceptive health benefits</p> <p>Serious complications extremely rare</p>	<p>Can be used without restriction in HIV-infected women who are not on ART</p> <p>Can be used without restriction in all HIV+ women for emergency contraception</p> <p>Some ARVs may reduce method effectiveness; avoid oral contraceptives and concomitant NNRTIs and PIs</p> <p>DMPA can however be used with ART; re-injection should be done at 10-12 weeks Implants may also be used in patients on ART.</p> <p>If hormonal method used condoms should still be used correctly and consistently</p>
Intrauterine Contraceptive Device	<p>Highly effective, long-term, reversible method</p> <p>Remains in place up to 12 years</p> <p>Almost 100 percent effective</p> <p>Has no effect on fertility when used by nulliparous women</p> <p>Should not be provided to women with high risk sexual lifestyle</p> <p>Bacterial STIs should be screened for and /or treated as a precaution prior to insertion</p>	<p>Attractive method for women with HIV who desire very reliable pregnancy protection</p> <p>Can be inserted in HIV+ women who do not have WHO Stage 4 disease</p> <p>For women with stage 4 disease IUD can be inserted once they are on ART and have controlled symptoms of severe illness</p>
Diaphragm	<p>Not as effective at reducing the transmission of STIs and pregnancy as condoms</p>	<p>Not recommended</p>
Sterilization	<p>Good very effective for couples who want no more children</p> <p>Safe, simple surgical procedure</p> <p>Considered permanent</p>	<p>No medical reasons to deny sterilization to clients with HIV</p> <p>Procedure may be delayed in event of acute HIV-related infection</p> <p>Encourage condom use</p>

APPENDIX

Appendix A: WHO Clinical Staging for Adults and Adolescents

Clinical stage	Selected symptoms
Primary HIV infection	<ol style="list-style-type: none"> 1. Unrecognized 2. Acute Retroviral syndrome
Stage I	<ol style="list-style-type: none"> 1. Asymptomatic 2. Persistent Generalized Lymphadenopathy (PGL)
Stage II	<ol style="list-style-type: none"> 1. Moderate weight loss (< 10% of presumed or measured body weight) 2. Minor skin and mucous membrane manifestations (Seborrheic dermatitis, PPE, fungal infection, recurrent oral ulcerations, Herpes Zoster in preceding 2 years) 3. Recurrent upper respiratory tract infections (bacterial sinusitis, bronchitis, otitis media, pharyngitis)
Stage III	<ol style="list-style-type: none"> 1. Severe weight loss (> 10% of presumed or measured body weight) 2. Unexplained chronic diarrhoea > 1 month 3. Unexplained prolonged fever > 1 month 4. Oral candidiasis (Thrush) 5. Oral Hairy Leukoplakia (OHL) 6. Pulmonary tuberculosis (PTB) in past 1 year 7. Severe bacterial infections (e.g. pneumonia, pyomyositis, empyema, bone or joint infections) 8. Unexplained anaemia (<8 g/dl), neutropaenia (< 500x10⁶/l) or thrombocytopenia (< 50x10⁹/l)
Stage IV	<p><i>Conditions where a confirmatory diagnostic test is required in italics</i></p> <ol style="list-style-type: none"> 1. Oesophageal candidiasis 2. <i>Pneumocystis jiroveci</i> pneumonia (PCP) 3. HIV wasting syndrome 4. Recurrent severe bacterial pneumonia (>/= 2 episodes within 1 year) 5. Cryptococcal meningitis 6. Toxoplasmosis of the brain 7. Chronic orolabial, genital or ano-rectal herpes simplex infection for > 1 month 8. Kaposi's sarcoma (KS) 9. HIV encephalopathy 10. Extra pulmonary tuberculosis (EPTB) 11. <i>Invasive cervical cancer</i> 12. <i>Chronic diarrhoea > 1month -Cryptosporidiosis, Isosporiasis</i> 13. <i>Lymphoma cerebral or B cell NHL</i> 14. <i>Visceral leishmaniasis</i> 15. <i>Cytomegalovirus (CMV) retinitis or disease of the organs</i>

APPENDIX B: FROMULARY TO SUPPORT THE MANAGEMENT OF COMMON OPPORTUNISTIC AND OTHER CONDITIONS SEEN IN HIV INFECTED PATIENTS

1. PATIENT ASSESSMENT

1.1. VITAL SIGNS

Normal Ranges in Adults and Children >13 years

VITAL SIGNS	NORMAL RANGES
Blood pressure: Systolic Diastolic Optimal BP: 120/80. Lifestyle interventions should be recommended for patients with BP > 120/80 but < 140/90 especially if they are diabetic.	< 140 60-89 (mm/Hg)
Temperature	36.6-37.2°C
Pulse	60-80 b/min
Respiration	14-19 breaths/min

Normal Ranges of Vital Signs in Children < 13yrs

Age	Neonatal	1- 6 month	7mo – 2 yrs	2yrs - 5yrs	5yrs - 12yrs
Respiratory Rate	30- 60	25- 50	18- 35	17- 27	16- 30?
Heart rate	100- 180	120- 160	80- 150	80- 110	70- 110
BP: Systolic	70- 100	87- 105	90- 106	94- 109	102- 117
Diastolic	50- 65	53- 66	65- 67	56- 69	62- 75

Respiratory rate = number of breaths per minute. Count the number of breaths in one full minute.

1.2. BODY MASS INDEX (BMI)

BMI= $\frac{\text{weight in kg}}{(\text{Height in meters})^2}$

BMI	Interpretation
< 18	Underweight
18- 24	Normal
25- 30	Overweight
30- 36	Obese
> 36	Morbidly obese

1.3. FUNCTIONAL ASSESSMENT

1.3.1. Karnofsky Score for Functional Status

100	Normal, no evidence of disease
90	Able to perform normal activity with only minor symptoms
80	Normal activity with effort, some symptoms
70	Able to care for self but unable to do normal activities
60	Requires occasional assistance, cares for most needs
50	Requires considerable assistance
40	Disabled, requires special assistance
30	Severely disabled
20	Very sick, requires active supportive treatment
10	Moribund

1.3.2. Simplified Assessment for Patient Functional Status (WAB)

Ask patient whether he is able to perform his normal activities without any impairment. If not find out if the patient is ambulatory and self-caring or is dependent, or spending time in bed during the day.

WORK (W) – Patient able to work as normal (household, farm, regular job)

AMBULATORY – (A) Patient unable to perform regular work but is otherwise independent in terms of self-care

BED (B) – Patient is dependent on others for their care and spends significant time during the day in bed

1.4. HIV DEMENTIA ASSESSMENT

A dementia assessment should only be carried out in conscious patients without any impairment of motor function that may interfere with the activities assessed.

Memory Registration Give patient 4 words to recall (dog, dress, sukuma, red) – 1 second to say each word. Then ask the patient all 4 words after you have said them. Repeat the words if the patient does not recall them all immediately. Tell the patient you will ask them to recall the words later.	
Assessment	Score
1. Motor Speed Have the patient tap the first 2 fingers of the non-dominant hand (left hand in a right-handed individual) as widely and as quickly as possible:	4 = 15 in 5 seconds 3 = 11-14 in 5 seconds 2 = 7-10 in 5 seconds 1 = 3-6 in 5 seconds 0 = 0-2 in 5 seconds
2. Psychomotor Speed Have the patient perform the following sequence of movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on the surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5 th digit. Demonstrate and have patient perform twice for practice.	4 = 4 sequences in 10s 3 = 3 sequences in 10s 2 = 2 sequences in 10s 1 = 1 sequence in 10s 0 = unable to perform
3. Memory Recall Ask the patient to recall the 4 words. For words not recalled, prompt with a clue as follows: animal (dog); piece of clothing (dress); vegetable (sukuma); color (red).	<ul style="list-style-type: none"> ○ Give 1 point for each word recalled without any prompting ○ Give 0.5 points for each correct answer after prompting Maximum – 4 points.
Total International HIV Dementia Scale Score:	This is the sum of scores 1-3. The maximum possible on this scale is 12 points. A patient with a score ≤ 10 should be evaluated for possible dementia.

1.5. GLASGOW COMA SCALE

Best Motor Response (in upper limbs)	Obeys simple commands	6
	Localizing - response to pain	5
	Withdraws – pulls limb away on painful stimulus	4
	Flexor response – abnormal flexion of limb to pain	3
	Extensor response – abnormal extension of limb to pain	2
	None	1
Best Verbal Response if Age > 1year	Oriented	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds, no words	2
	None	1
Best Verbal Response if < Age 1year:	Coos, smiles	5
	Crying, consolable	4
	Inappropriate crying, inconsolable	3
	Grunting	2
	None	1
Eye Opening	Spontaneous eye opening	4
	To speech - eye opening to any speech or sound	3
	To painful stimulus	2
	None	1
ASSESSMENT SUMMARY	GCS 3 COMATOSE; 3-7 SEMI-COMATOSE; 7-14 ALTERED CONSCIOUSNESS	

1.6. MUSCLE POWER

- 0 – No movement
- 1 – Flicker of muscle
- 2 – Movement with gravity
- 3 – Movement against gravity
- 4 – Movement against gravity with moderate resistant
- 5 – Normal

2. CENTRAL NERVOUS SYSTEM CONDITIONS AND TREATMENT

CXR must be done in all patients presenting with chronic neurological symptoms. Absent a CT scan and as long as there are no focal, deficits LP should be carried out in PLHA with altered mental status or other signs of neurological dysfunction.

2.1 TOXOPLASMOSIS

- **Cotrimoxazole** 5 mg/kg/day of the trimethoprim component (of which there is 80mg per SS tab)
- **Dose: patient < 50 kg** 3 SS tablets PO BD x 6 weeks then continue daily CTX prophylaxis. **Patient > 50 kg** 4 SS tablets PO BD x 6 weeks then continue CTX prophylaxis
- **Steroid treatment** may be required in patients with presumed or confirmed cerebral edema; it should be noted that patients with undiagnosed TB may worsen if steroid treatment is given, while those with PCNSL may improve.
- **Patients allergic to sulfa drugs: Desensitize** patients with mild/moderate reaction to sulfa drugs. For those with severe reaction/SJS give Doxycycline 200mg PO BD *with meals* plus Clarithromycin 500mg PO BD for 21 days

2.2 CRYPTOCOCCAL MENINGITIS

- Fluconazole 400mg OD x 8 weeks PO, then 200mg PO OD.
- **Pediatric:** 12mg/kg PO OD X 8 weeks then 6mg/kg OD.
- Fluconazole maintenance therapy may be discontinued after immune reconstitution occurs following treatment with ART *and* CD4 count that has been >> 100 cells/mm³ for > 6 months.

- Fluconazole prophylaxis should be **re-initiated** in patients who had CM and have new WHO stage 4 conditions and/or are failing ART with CD4 < 100 after a previously higher level. (Note serum CRAG not useful for evaluation of patients with suspected relapse of CM)
- *Patients on concomitant rifampicin should be given fluconazole 800mg OD (x 8 weeks) during the course of rifampicin treatment and for 2 weeks after discontinuation of rifampicin.*

2.3 BACTERIAL MENINGITIS

- Ceftriaxone 1g IV BD x 14 days (minimum) (pediatric: 50-75mg/kg)
OR Crystalline penicillin 4 MU (2.4g) every 4 hours & Chloramphenicol 1g IV QID for adults
OR Ampicillin 2g IV QID & Chloramphenicol 1g IV QID OD for adults
- **Pediatric:** Ampicillin 50-100mg/kg IV QID & Chloramphenicol 25mg /kg QID)
- **Note:** Chloramphenicol is contraindicated in pregnancy and breastfeeding
- Glucocorticoids have been shown to be beneficial in patients with meningitis due to *Streptococcus pneumoniae* especially if associated with impairment of consciousness, GCS < 11.
- Give dexamethasone 0.15mg/kg IV QID x 4 days.
 - First dose of dexamethasone just before or at the same time as the first dose antibiotics, but don't delay antibiotics if dexamethasone not immediately available
 - Prednisolone 1mg/kg/day for 4 days may be used as an alternative if dexamethasone is not available and acute bacterial meningitis suspected.
 - CSF gram stain should help in decision making as to whether or not steroids should be continued (presence of gram positive diplococci suggest *Strep. pneumoniae*)

2.4 TUBERCULOUS MENINGITIS (TBM)

- *Suspect in patients with headache, fever, altered mental status, papilloedema and cranial nerve dysfunction (VI, III, IV, VII).*
- *Concomitant treatment of cerebral toxoplasmosis must be given where these 2 conditions cannot be differentiated clinically and a CT scan cannot be carried out.*
- Treatment as recommended by the NLTP (see Chapter 6)

2.5 PERIPHERAL NEUROPATHY

Always assess new patients for PN before ART is started. Check baseline FBC and MCV results in case treatment is required.

- Ask about alcohol intake, diabetes, history of INH, d4T, or ddI
- Investigations include: Glucose, FBC (look at MCV), RPR, random blood glucose:
- **Treatment**
 - Diabetes Mellitus – start or optimize treatment
 - If MCV high and patient not on AZT treat for B12 & folate deficiency for 3 months then repeat FBC and review; most cases likely to be due to impaired absorption and poor diet, thus life long treatment is unlikely to be required. If recurs confirm diagnosis of B12 deficiency.
 - If on INH: B6 (pyridoxine) increase the dose to 200mg PO OD until TB treatment is finished
 - If on Stavudine and has PN Grade 2 and above: change to Zidovudine (or Tenofovir if anemic or Hb < 9.5g/dl)

2.6 HIV ASSOCIATED DEMENTIA (HAD)

Definition of Dementia in PLHA

- **Progressive** impairment of learning and memory *plus* impairment of at least one other cognitive function (impairment in handling complex tasks; impairment in reasoning ability –can't cope with unexpected events; impaired spatial ability and orientation – getting lost in familiar places; impaired language – e.g. word finding)
- Impairment in cognitive function must interfere with the individual's work performance and social activities

Treatment of HAD: HAD is a WHO Stage 4 condition. ART is therefore to be initiated expeditiously regardless of CD4 count.

2.7 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

- PML is a WHO Stage 4 OI of the CNS caused by reactivation of latent JC polyomavirus acquired in childhood. JC virus destroys oligodendrocytes leading to multifocal areas of demyelination limited to the white matter, causing neurologic dysfunction.
- **Symptoms** are insidious in onset presenting with relatively rapidly progressive cognitive dysfunction, dementia, seizures, ataxia, cranial nerve deficits, hemi- or quadriplegia and eventually coma.
- **Diagnosis** is clinical with, if possible compatible CT scan result.
- **Treatment for PML:** ART should be started expeditiously.

2.8 DEPRESSION

Diagnosis of a Major Depressive Episode

5 or more of the following symptoms lasting more than 2 weeks:

- Depressed mood
- Diminished interest or pleasure
- Significant change in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Inappropriate guilt or feelings of worthlessness
- Poor concentration
- Recurrent thoughts of suicide

At least 1 of the symptoms must be either depressed mood or loss of interest/pleasure.

Do not include symptoms that are due to medication side effects or drugs/alcohol. All symptoms must be present most of the day, almost every day, during the same 2-week period (but not within 2 months of losing a close relative). Symptoms should cause significant impairment in ability to function normally.

Management of Depression:

- Supportive counseling
- Close follow-up
- **Amitriptiline** is drug most likely to be available in our facilities
 - Starting dose: 75mg PO nocte.
 - Use lower dose in the > 60 yrs and adolescents; start at 20-50 mg PO nocte
 - Increase to 150-300mg per day in divided doses, with larger dose in evening e.g. 50mg am, 100mg nocte
 - Clinical response in 2-6 weeks
 - Continue for at least 4-6 months after symptoms have resolved
 - Most common side effects are drowsiness, dry mouth, blurred vision, constipation and difficulty passing urine.

Discontinuation of antidepressants: should be **gradual** over a period of 4-6 weeks or longer in patients who have been on treatment for > 12 weeks.

2.9 STATUS EPILEPTICUS (SE)

Definition: One continuous seizure lasting > 5 minutes or two or more seizures in between which there is incomplete recovery of consciousness. **Determine underlying cause:** consider non-adherence to antiepileptic drugs; new CNS infections; Cerebrovascular accident (CVA); metabolic conditions – hypo-/hyper-glycemia, hepatic encephalopathy, uremia, $\downarrow\text{Na}^+$, $\downarrow\text{K}^+$, $\downarrow\text{Mg}^+$, Ca^+ ; drug withdrawal – alcohol, barbiturates, benzodiazepines; first presentation of epilepsy.

Complications: SE is associated with a high mortality rate, depending on underlying cause. Complications include aspiration, respiratory failure, metabolic acidosis, rhabdomyolysis and death. *Treatment and assessment of patients in status epilepticus should proceed simultaneously.*

Table 4: Suggested Management Algorithm for Status Epilepticus

TIME	INTERVENTION
0 – 5 MINS	<ul style="list-style-type: none"> a) Position patient to avoid injury, aspiration b) Assess Airways, Breathing, and Circulation. Start O₂ c) Give <ul style="list-style-type: none"> • IV Lorazepam 4mg (0.1mg/kg at 2mg/min; pediatric 100mcg/kg max 4mg) • OR IV diazepam 10mg in 2 minutes • OR PR diazepam (20mg) 5microggram/kg, maximum 30mg. Hold buttocks together for a few minutes after PR dose. Pediatric: 0.3-0.5mg/kg. PR diazepam preferred d) Obtain quick history and do a rapid neurological, general exam e) Check finger stick glucose; give thiamine 100mg IV then give dextrose/glucose f) If fever, convulsions start IM/IV Quinine or artemisinin derivative <i>plus</i> give IV/IM ceftriaxone 1g stat or crystalline penicillin 2.4 MU IV or IM divided between the 2 buttocks. Pediatric: Ceftriaxone 50mg/kg g) Treat high temperature promptly with tepid sponging and antipyretics h) Start IV line and draw blood for electrolytes, glucose, FBC, renal and liver function test
5 -25 MINS	<p><i>If seizures continue patient should be transferred to a hospital, intubated and ventilated</i></p> <ul style="list-style-type: none"> • Repeat lorazepam once or diazepam after 10 minutes if seizures continue/recur (additional PR dose of diazepam at 10mg) • Start phenytoin loading dose at 20mg/kg in 50-100ml 0.9% saline at 50mg/min using a separate IV line to avoid precipitation when phenytoin and benzodiazepines are mixed • REFER PATIENT IF AT PRIMARY CARE LEVEL (per rectal diazepam can be repeated at 10mg every hour during transport OR IVI diazepam of 10ml in 150ml of dextrose/glucose or 0.9% saline over 6h) • Maximum total dose of diazepam should not exceed 50mg
25- 30 MINS	<p><i>If seizures continue</i></p> <ul style="list-style-type: none"> • Phenytoin additional 5-10mg/kg IV at 50mg/min • Provide hemodynamic support (IV crystalloids, dopamine if required) • Address underlying cause
30- 50 MINS	<p><i>If seizures continue</i></p> <ul style="list-style-type: none"> • Phenobarbital 20mg/kg IV at 50-75mg/min in hemodynamically stable patients OR • Consider proceeding directly to anesthesia with midazolam or if: i. patient already in ICU ii. Severe hemodynamic instability. iii. Seizures have continued for >60- 90 minutes
50- 60 MINS	<p><i>If seizures continue</i></p> <ul style="list-style-type: none"> • Phenobarbital additional 5-10mg/kg IV at 50-75mg/min
> 60 MINS	<p><i>If seizures continue</i></p> <p>Begin anesthesia in ICU with:</p> <ul style="list-style-type: none"> • Midazolam 0.2mg/kg IV followed by 75-100 ug/kg/hr OR propofol 1-2 mg/kg IV followed by 2-10mg/kg/hr • Adjust dosing to ECG response • Therapeutic levels may require intubation and pressor support

3) RESPIRATORY SYSTEM

3.1 URTI/ENT INFECTIONS

- i) **Presumed Viral URTI** – no antibiotic treatment necessary; give supportive treatment (analgesic, nasal decongestant)
- ii) **Presumed Bacterial URTI:** If patient is **unable to swallow or a pharyngeal abscess** is present give a stat dose of IM/IV co-amoxiclav (1g amoxicillin equivalent) or ceftriaxone 1 g and refer urgently to hospital. **Presumed bacterial pharyngitis:** Amoxicillin 250 mg TDS or Penicillin V 500 mg QID for 5-7 days. **Pediatric:** Amoxicillin 125-250mg TDS; Pen V 62.5mg in <1yr; 125mg in 1-5yr; 250mg in 6-12 yr all given QID.
- iii) **Gingivitis:** Metronidazole 400mg TDS or Co-amoxiclav (500mg amoxicillin equivalent TDS) for 7 days
- iv) **Acute Sinusitis**

Symptoms include headache, fever, sinus pain, obstruction, purulent nasal discharge and sinus tenderness

PLHA need antibiotics: either co-amoxiclav (500mg amoxicillin equivalent TDS) OR erythromycin 500mg QID OR Doxycycline 100mg BD for 7 days

Nasal decongestant sprays plus analgesia often sufficient in HIV negative patients

v) Otitis media: All children with fever should have their ears examined.

Amoxicillin 500mg PO TDS x 7 days OR Erythromycin 500mg QID x 7days. **Pediatric:** amoxicillin 30mg/kg TDS or 125 mg up to age 10 yrs, doubled in severe infections, x 7 days OR Erythromycin for child < 2yr 125; child 2-8 yr 250mg

vi) Otitis externa: Chloramphenicol eardrops: 3 drops TDS x 3 days

OR Ciprofloxacin eardrops: 3 drops TDS x 3 days

3.2 PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

- Cotrimoxazole 15-20mg/kg/day of the trimethoprim component in divided doses. **Simple formula: patient weight divided by 4 = Number of SS tablets/24 hour period.** E.g. Adults ~ 60kg – Cotrimoxazole SS 4 tabs TDS x 3 weeks (SS-single strength is 480mg tab).
- **Pediatrics** – Cotrimoxazole given at a dose of 20 mg/kg of Trimethoprim component PO in divided doses x 3 weeks
- **Add steroids if severe:** (RR > 30 or hypoxic, indicated by pulse oximetry < 90% on air at rest). Prednisolone- 40 mg PO BD x 5 days, then 40 mg PO OD X 5 days, then 20mg PO OD x 11 days, then stop)
- Continue standard prophylaxis: CTX 2 SS/1DS PO OD after treatment is complete

3.3 COMMUNITY-ACQUIRED PNEUMONIA

- **Outpatient** treatment (no recent antibiotics) – Amoxicillin 1g PO TDS x 7 days
- **If patient has had recent** antibiotic treatment (within the past 3 months) give Erythromycin 500mg PO QID x 10 days OR Doxycycline 100mg BD x 10 days
- **Pediatrics:** Amoxicillin 30mg/kg TDS or 250-500 mg up to age 10 yrs x 7 days OR Erythromycin for child < 2yr 250 mg; child 2-8 yr 500 mg QID x 7 days
- **Do not use fluoroquinolones to treat chest infections** to avoid partial treatment of TB; this may mask TB delaying the diagnosis or making diagnosis difficult.

3.4 BRONCHIAL ASTHMA

- Chronic asthma: aim to have patient free of symptoms. Step treatment up or down as needed
 - Mild intermittent: Occasional Salbutamol inhaler 2 puffs PRN; if use exceeds 1x per day then
 - Use salbutamol regularly plus add regular *inhaled* steroid (e.g. beclomethasone 200-400mcg/day or 1-2 puffs BD). If not controlled
 - Add inhaled long acting beta₂ agonist (e.g. salmeterol 50mcg BD) OR theophylline 125-250mg TDS *after meals* **plus** increase inhaled steroid dose to upper limit. If symptoms not controlled
 - Add oral Prednisolone 30-40mg per day for 5 days and stop. Treat any bacterial RTI if present. *Treatment should be downgraded once acute exacerbations are controlled until minimum treatment required to keep patient with minimum symptoms is used.*
 - Salbutamol tablets 4mg PO TDS/QID/PRN may be used where inhaler is not available (more side effects, less effective)

3.5 TUBERCULOSIS (TB)

- **All** patients are screened for TB through the routine patient follow up forms. Clinicians **must** respond to any symptoms suggestive of TB promptly.
- TB must be considered if a patient with a LRTI has had 2 weeks of **effective** antibiotic treatment at the correct dose without improvement. Once a diagnosis of TB is considered likely, start treatment ASAP, especially if no further *diagnostic* tests are pending.
- Remember to ask about family and to help patient arrange assessment of family members for TB.

Symptoms and Signs of TB:

Always consider other potential causes of these symptoms e.g. Pneumonia, PCP, bronchial asthma, CCF, COPD etc.

Symptoms	Signs
Cough > 2 weeks: ± sputum ± blood	Fever
Drenching night sweats; Intermittent or persistent fever	± Enlarged lymph nodes; hepatosplenomegaly
Weight loss (in children, unresponsive to nutritional interventions)	Sub-optimal weight
Chest pain	Moderate to severe anemia
History of contact with TB patient; especially important in children < 5yr	± Chest findings; CXR

Diagnosis of TB:

Adults and children > 7-8 years:

- Smear positive: minimum of one slide positive for AFBs in HIV positive patients (2 required in HIV negative patients)
- Smear negative: suggestive history +/- supportive CXR, extrapulmonary symptoms and/or signs
- Pneumonia unresponsive to adequate antibacterial treatment (at least 2 courses of effective antibiotics as per NTLP algorithm)

Table 5: Pediatric TB Score Chart for Children < 7 years

FEATURES	SCORE
Positive smear	7
Tubercle in biopsy	7
Contact with person suspected or confirmed TB	2
Tuberculin test results equal or more than 15mm	3
Enlarged painless lymph node +/- sinus present	3
Night sweats, unexplained fever, no response to anti-malarial	2
Abnormal CXR	2
Malnutrition not improving with 4 weeks of treatment	3
Angle deformity of the spine	4
Firm non fluid, non traumatic joint swelling	3
Unexplained abdominal swelling or ascites	3
Change in temperament, convulsions, or coma lasting more than 48hrs	3
Less than 2yrs	1
BCG vaccination given	-1

Table 6: Interpretation of Scores for TB Diagnosis in Children

Score	Interpretation
≥ 7	Definitely TB
5 – 6	Probable TB; may justify treatment
3 - 4	Possible TB; requires further investigations, observation and review of progress
≤ 2	Unlikely to be TB

TB Patient Follow up:

Repeat CXR

- If patient deteriorates while on anti-TB/±ARV treatment (may indicate IRIS or progressive disease due to failure of treatment)
- Patient with pre-treatment abnormal CXR fails to respond to TB treatment
- At treatment completion in patients with abnormal pre-treatment film; keep films safe to aid future patient management.

TB Treatment:

- **IS YOUR PATIENT ON ANY OTHER MEDICATION? Check Appendix G for drug interactions with rifampicin!**
- The short course TB treatment regimen of **2RHZE/4RH** is being rolled out in Kenya as of January 2007; where available it is the **preferred** regimen.
- All TB/HIV patients should receive pyridoxine to prevent INH related toxicity. **Adults:** Pyridoxine 50mg PO OD. **Pediatric:** 1.2-3 mg/kg max 50 mg per day.
- **Peripheral neuropathy associated with HIV/TB co-treatment INH.** Treat adults with 150-200mg per day until the end of TB treatment.

Table 7: TB Treatment Regimens

Category	Patient Type	Anti-TB Drug Regimen
I	TB patients with smear positive PTB/Severe forms of TB	2ERHZ/6HE (4RH*)
II	TB patients with relapse, treatment after default or treatment failure	2SRHZE/1RHZE/5RHE
III	TB patients who have smear negative/ Extra pulmonary TB	2RHZ/6HE (4RH*)
Children	Children with TB	2RHZ/4RH
	Children with TBM or re-treatment	2SRHZ/4RH

Table 8: Adult and Pediatric TB Drugs Dosing Chart

	5-9kg	10-19 kg	20-29kg	30-37 kg	38-54 kg	>55 kg
RHZE				2	3	4
RHZ	1/2	1	2	2	3	4
RH	½	1	2	2	3	3
RHE (combined pill)				3	3	3
EH				2	2	2
Streptomycin**				0.5gm	0.75gm	1gm

*RH+E =(3 tabs +2 tabs respectively); **Reduce streptomycin to 0.75gms if above 40 yrs

Undesirable TB Treatment Outcomes

TB Treatment failure: smear positive at initiation of treatment, still smear positive at 5 months of treatment

TB defaulter: any patient who discontinues medication regimen prior to completion for non-medical reasons

TB relapse: Recurrence of TB within one year of completing TB treatment

- *All TB relapse or failure cases should have sputum cultures taken prior to starting the re-treatment regimen; if positive repeat at 2 months. If sputum positive at 2 months send sputum for repeat culture.*

Management of defaulters/TB relapse or re-treatment

- If defaults for less than 2 weeks in the intensive phase or less than 2 months in the continuation phase, keep on current treatment but add the number of days missed at the end of that current phase of treatment
- If defaults for more than 2 weeks in the intensive phase or 2 months in the continuation phase, start re-treatment regimen (**2SRHZE/ 1RHZE/ 5RHE**)

Adjunctive Corticosteroid use in TB patients

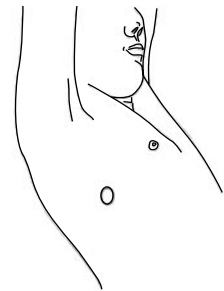
Steroids are indicated in the following patients with TB

- Tuberculous meningitis (start at the same time as TB treatment and continue for 4-6 weeks and taper over 2 weeks)
- TB pericarditis: For adult patients give prednisolone 60 mg/day for four weeks, 30 mg/day for two weeks, 15 mg/day for two weeks, then 5 mg/day for week eleven then stop. For children, prednisone 1 mg/kg daily as the initial dose for four weeks, with a decreasing dose over time as described for adults.
- For patients with TB/HIV on concomitant ART, if IRIS is associated with **severe** symptoms, e.g. pericarditis with hemodynamic compromise, severe respiratory distress, CNS manifestations and eye symptoms. Duration of steroid treatment depends on patient presentation but usually a short course of 1-2 weeks is adequate

Dose: prednisolone 1mg/kg/day.

3.6 THORACENTESIS

- Assemble all the equipment i.e. branula, giving set, urine bag, swabs, sterilizing solution
- Position the patient as per diagram (lateral approach)
- Select the entry site: safe triangle bordered by mid axillary line, anterior axillary fold and the 5th and 6th rib.
- Percuss area of dullness to determine the extent, select entry site 1st and 2nd highest intercostal space not the lowest
- Mark the entry point just above the superior aspect of the rib: Using the cap of a Bic pen or cap of a needle, apply pressure at the entry point for ~ 1 minute
- Use sterilizing solution to swab the area using circular motions starting at entry point and circling outwards (never swab back towards the entry point). Repeat 3 times. The entry point is now sterile and you can not touch it again, other than with the sterile needle tip
- Prick the superior aspect of the rib; direct needle laterally and inferiorly
- **NB:** Avoid pricking the inferior aspect of the rib: that is where the bundle of the nerve, artery, and vein is. Also avoid using puncture sites below the 8th intercostals space because of possibility of hepatic or splenic rupture
- Drain a maximum of 2 liters and monitor BP after the tap



4 LIFESTYLE DISEASES

4.1 HYPERTENSION

A single antihypertensive drug at an optimal dose may not be adequate and other antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently, an interval of at least 4 weeks should be allowed to determine response. For most of our patients' response to ACE inhibitors and angiotensin-II receptor antagonists is not as good as is desirable, thus a thiazide or a calcium-channel blocker should be chosen for initial treatment. Avoid beta-blockers, especially when combined with a thiazide diuretic for first line, especially in diabetics and PLHA on PI treatment.

ACE inhibitors are preferred in diabetic patients with microalbuminuria. Hypertension may cause renal impairment and many hypertensive drugs accumulate in renal impairment thus renal function should be assessed regularly in hypertensive patients.

Table 9: When to Start Hypertensive Drug Treatment

Treatment Indication	When to Start HT Treatment	Any other complications?
Accelerated hypertension (papilloedema, fundal exudates or impending cardiovascular complications admit for immediate treatment)	Admit patient and start treatment immediately. Recommend lifestyle changes once patient stable	N/A
Initial SBP is >220 or DBP>110-119 mmHg	Start immediately. Lifestyle changes should be encouraged once patient stable	N/A
Initial SBP is 200-219 or DBP 110-119 mmHg	Recommend lifestyle changes. Confirm over 1-2 weeks and treat if confirmed.	N/A
Initial SBP is 160-199 or DBP 100-109 mmHg	Recommend lifestyle changes and confirm. Review over 4-12 weeks and treat if BP unchanged	If patient has cardiovascular complications, diabetes or renal disease treat if confirmed over 3-4 weeks
Initial SBP is 140-159 or DBP is 90-99 mmHg	Recommend lifestyle changes. Review over 3-4 months and treat if BP remains unchanged	If patient has cardiovascular complications, diabetes or renal disease treat if confirmed in 4-12 weeks

Table 10: Choice of Drugs for Hypertension

Drug Class	Specific Drugs	Dose	Comment
Thiazide Diuretics	Bendroflumethiazide	2.5 mg OD	Preferred 1 st line drugs. <i>Higher doses increase ADRs without additional hypertensive effects. Loop diuretics should NOT be used for treatment of HT</i>
	Hydrochlorthiazide	25 mg OD	
Calcium Channel Antagonists	Amlodipine	5-10 mg OD	Add if above fails to control BP. <i>Can precipitate heart failure (other than nifedipine) and should not be used in patients with left ventricular dysfunction. The other drugs preferred to Nifedipine</i>
	Diltiazem	120mg BD	
	Nifedipine (long acting preparations)	10mg BD	
Angiotensin Converting Enzyme Inhibitors	Captopril	12.5mg OD increasing to 25-50mg BD	Use if calcium channel antagonist fail or are intolerable. They are indicated in hypertensive patients with diabetic nephropathy. <i>Monitor renal function while patients on ACE inhibitors. Also indicated in heart failure and LV dysfunction. Contraindicated in renal disease and pregnancy.</i>
	Enalapril	5mg OD increasing to 10-20mg OD. May be increased to max of 40mg OD in severe hypertension	
Angiotensin II Receptor Inhibitors	Losartan	50mg OD. Can be increased to 100mg OD	Recommended in patients who cannot tolerate ACE inhibitors due to persistent cough. <i>Monitor renal function while patients on All inhibitors</i>
	Candesartan	4mg OD increasing to 8-16mg OD	
Beta Blockers	Atenolol	50mg OD	Indicated in patients who fail to respond to the above class options. <i>Avoid in worsening or unstable heart failure, asthma, or COPD, diabetics with frequent hypoglycemic episodes</i>
	Propranolol	80mg BD increased up to 320mg in divided doses	
	Alpha Methyl dopa	250mg TDS increased over several days to maximum of 3g daily in divided doses	Preferred in pregnant women. Cheap alternative anti-hypertensive. <i>Avoid in hepatic disease.</i>

4.2 DIABETES MELLITUS

Diagnosis of Diabetes

The **diagnosis of diabetes should always be confirmed** by repeating an abnormal blood glucose test on another day unless patient has symptoms indicative of hyperglycemia.

The table below shows the cut off levels for fasting and casual (or random) blood glucose above which a diagnosis of diabetes is made.

Table 11: Diagnosis of Diabetes

Fasting blood glucose	>7 mmol/l
Casual (random) blood glucose	>11.1 mmol/l
Diabetes in pregnancy: fasting blood glucose	>7 mmol/l

Admit patients with acute symptoms of diabetes for assessment and initiation of appropriate treatment. Use the algorithm below for outpatient management of asymptomatic patient.

Table 12: Indications for Insulin in Patients with Type 2 Diabetes

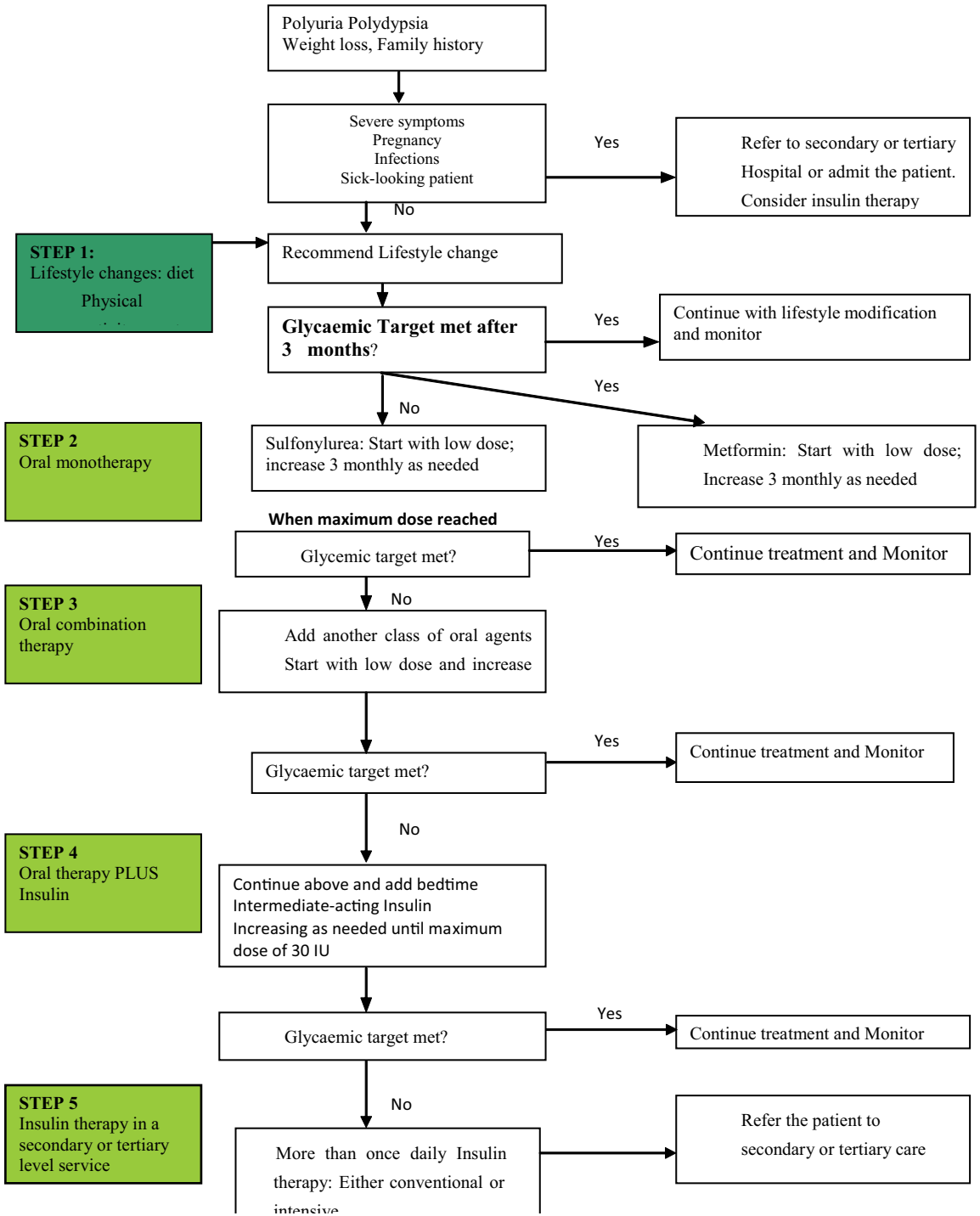
<ul style="list-style-type: none"> • Initial presentation with severe hyperglycemia • Presentation in hyperglycemic emergency • Peri-operative period especially major or emergency surgery • Other medical conditions requiring tight glycaemic control • Organ failure: Renal, liver, heart etc • Pregnancy • Contraindications to Oral Glucose Lowering Agents • Failure to meet glycaemic targets with OGLAs
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Management of Hypoglycemia in Diabetic Patients

Hypoglycemia in patients on OGLAs may be prolonged, thus patients need monitoring.

- **By mouth** (can be used at home)
 - **Child 2–18 years:** approx. 10–20 g (2 teaspoonfuls of sugar in a small cup) or 55–110 mL *Lucozade*® or 90–180 mL *Coca-Cola*®—both non-diet versions repeated after 10–15 minutes if necessary
 - **Adult** approx. 10–20 g (2–4 teaspoonfuls of sugar in a cup) or 55–110 mL *Lucozade*® or 90–180 mL *Coca-Cola*®—both non-diet versions repeated after 10–15 minutes if necessary
- **If hypoglycaemia unresponsive or if oral route cannot be used**
 - **Glucagon injection 1 mg/mL** subcutaneous, intramuscular, or intravenous injection
 - Child: body-weight under 25kg - 500 micrograms (0.5 mL); body-weight over 25kg 1 mg (1 mL)
 - Adult: 1 mg (1 mL)
- **If hypoglycaemia prolonged or unresponsive to glucagon after 10 minutes or glucagon not available**
 - **Pediatric** 1 month–18 years: **Glucose intravenous infusion 10%** into large vein: 2–5 mL/kg (glucose 200–500 mg/kg)
 - **Adult: Glucose** intravenous infusion 20% 50ml in large vein

Algorithm on the Management of Type 2 Diabetes



5) GASTROINTESTINAL SYSTEM

5.1 OROPHARYNGEAL CANDIDIASIS

- **Nystatin:** 500,000 IU swish in mouth for 1 minute then swallow, QID x 10 days or until symptoms resolve. **Pediatric:** 100,000 units/dose QID X 10 - 14 days
- OR Clotrimazole troches 1 PO QID until symptoms resolve
- OR Miconazole matt 1 buccal OD x 7 days
- Fluconazole should be given for intractable oropharyngeal candidiasis 50 -100mg OD x 7days
- Differentiate from Oral hairy leukoplakia (OHL) for which no specific treatment is required

ESOPHAGEAL CANDIDIASIS

- Fluconazole 200mg PO stat, then 100mg PO OD x 14 days.
Pediatric: 6mg/kg stat then 3mg/kg OD x 21 days)
- Treat each episode of esophageal candidiasis fully and start ART as soon as patient is ready

ANGULAR STOMATITIS

- Apply clotrimazole cream at the corners of the mouth and treat as for thrush

HERPES SIMPLEX (GINGIVOSTOMATITIS)

- Aciclovir 400 mg PO TDS x 7 days. **Pediatrics:** 20 mg/kg PO QID or 10 mg/kg IV TDS x 7 days
- Chronic ulcers (> 1month's duration) may require longer treatment and qualify for ART initiated

5.2 DIARRHEA

- Ideally perform stool for O&P and review empirical treatment based on result

Empirical treatment

- If diarrhea of short of duration and is not associated with fever or blood in motions and patient otherwise well give fluids, anti-diarrheal agent and observe. Frequently self-limiting.
- If acute diarrhea associated with fever and/or blood in motions give ciprofloxacin 500mg BD plus metronidazole 400mg TDS for 7 days. **Pediatrics:** *Ciprofloxacin is contraindicated in children < 16 years.* Ceftriaxone 20-50mg/kg/day plus Metronidazole 7.5mg/kg TDS for 1 week
- For chronic diarrhea: if associated with fever and no recent broad spectrum antibiotic treatment, treat with **Ciprofloxacin** 500mg BD plus **Metronidazole** 400mg TDS for plus **Albendazole** 400 mg OD all for 14 days. **Consider TB.**
- Patient with chronic diarrhea who do not respond to the above treatment should be rehydrated, given anti-motility agents (e.g. Loperamide 4mg stat followed by 2mg after every loose motion) and prepared for ART.

5.3 PARASITIC INFESTATIONS

- **Amoebiasis** – Metronidazole 800mg po TDS x 5 days (10 days if extraintestinal disease or liver abscess suspected) or Tinidazole 1g po BD x 3 days
- **Ascariasis** – Mebendazole 500mg stat **OR** Albendazole 400mg po stat **OR** Mebendazole 100mg po BD x 3 days
- **Cyclospora** – Cotrimoxazole 960mg po BD x 7 days
- **Giardia** – Metronidazole 250mg po TDS x 7 days
- **Isospora** – Cotrimoxazole 960mg po BD x 10 days
- **Schistosoma haematobium and mansoni** – Praziquantel 20mg/kg po stat
- **Taeniasis** – Praziquantel 5-10mg/kg po stat (for both paed and adults)
- **Trichuris** – Albendazole 400mg po OD x 3days

5.4 ENTERIC FEVER INCLUDING NON-TYPHI SEPTICEMIA, TYPHOID

- Unfortunately the much-used Widal test is not useful in acute infection due to false positive results in those with previous infection with salmonella typhi. Ideally, culture of blood, stool, bone marrow best for the diagnosis of enteric fevers.
- Ciprofloxacin 500-750mg PO BID x 14 days or more depending on response OR Ceftriaxone 1 g OD for 14 days

6 GENITOURINARY TRACT

6.1 URINARY TRACT INFECTIONS

i) Uncomplicated lower UTI

- Nitrofurantoin 50-100mg PO QID x 7 days. **Pediatric** 1.5 mg/kg QID 7days
- **OR** Cephalexin 250mg PO QID x 3 days. **Pediatric** mild-moderate infection 10 mg/kg PO QID; severe infections 25-40 mg/kg PO QID
- **OR** Norfloxacin 400mg PO BD x 7 days

i) Acute pyelonephritis is best treated with IV antibiotics; if pt is not severely ill

- Ciprofloxacin 500-750mg PO BD for 14 days
- **OR** Co-amoxiclav 1g BD or 625mg (amoxicillin equivalent) TDS x 14 days. **Pediatrics** 7 mg/kg TDS or 12 mg/kg BD
- **OR** Norfloxacin 400mg PO BD x 7days
- In hospitalized patients
 - IV Ceftriaxone 1g OD increased to 1-2g BD in severely ill. **Pediatric** 20-50mg/kg/day for 14 days (change to PO when pt stable)
 - **OR** IV Gentamicin 3-5mg/kg/day in 3 divided doses. **Pediatric** < 2wks: 3mg/kg BD; 2wks-12 yrs 2mg/kg TDS (change to above PO when pt stable)

6.2 SEXUALLY TRANSMITTED INFECTIONS (See Table 11.1 above)

- All patients with STIs should be screened for HIV and syphilis; PLHA should be screened for syphilis at enrolment and annually.
- **ALWAYS** carry out contact tracing and treatment of sexual partner(s)
- Advise patient not to have sexual contact with untreated partner.

7 OTHER CONDITIONS

7.1 ANEMIA

- **Good history important to determine the likely cause** blood loss; (through menses, stool or vomiting); other chronic illness e.g. TB, chronic renal disease. Examination should include a rectal examination.
- **Investigations:** FBC, peripheral blood film (PBF), malaria, Stool for occult blood, ova and parasites, (for all patients if available)

Treatment

- Consider transfusion at Hb < 5g/dl and/or if hemodynamically unstable
- **Suspected Iron deficiency anemia:** indicated by a microcytic hypochromic anemia – low MCV and the HB). Patients should undergo **presumptive de-worming** – Mebendazole 500mg PO stat or Albendazole 400mg PO stat or Mebendazole 100mg PO BD x 3 days. **Pediatric:**
 - Transfusion should be given to patients with Hb < 5 g/dl as well as in symptomatic patients (low Hb plus symptoms and signs of CCF or edema). Stable patients with low Hb may not require transfusion.
 - In addition patients should be given FeSO₄ 200mg PO BD or TDS x 3 months minimum and Folate 5mg PO OD x 3 months with a follow up Hb. Treatment should be continued until the HB is > 12g/dl and/or the peripheral blood film normalizes.
- **Macrocytic anemia:** Patients with a macrocytic anemia *who are not on AZT* should have a random blood glucose done. A trial of B 12 injections 1mg per month and folate 5mg PO pr day should be

given for 3 months. Repeat FBC and review. Maintenance dose of B12 may be considered where there is recurrence. Attempts to confirm diagnosis should be made.

7.2 EYE PROBLEMS

- **Suppurative conjunctivitis** – Chloramphenicol 0.5% eye drops 1-2 drops every 2 hours for 1st day and then every 4-8 hours till day 7 or 48 hours after symptoms resolve. **OR** Quinolone eye drops e.g. Ciprofloxacin 1-2 drops every 2 hours for 1st day and then every 4-8 hours till day 7
- **Suspected viral conjunctivitis**– usually unilateral pink eye – highly contagious – no treatment
- **For severe eye problems or patients complaining of visual loss refer to eye clinic.** Ideally a fundoscopy should be done in all PLHA with visual complaints.

7.3 MALARIA

Uncomplicated malaria

- Many PLHA are on cotrimoxazole and should be using ITNs, which are likely to reduce incidence of malaria; patients on cotrimoxazole should not be treated with sulfa-based anti-malarials alone.
- Confirm in the history whether effective and complete antimalarial treatment has been used recently to avoid unnecessary “presumptive” treatment. Carry out a blood slide when possible; if using an experienced and committed microscopist the slide result should be respected. Malaria is over-treated by clinicians in Kenya.
- Consider and look for other causes especially if fever is prolonged or antimalarial treatment has been used

Confirmed or suspected malaria

- **First Line Treatment: ACT e.g. Coartem** (artemether plus lumefrantine AL) 5-15 kg: 1 tab PO BD X 3 days; 15-25 kg: 2 tabs PO BD X 3 days; 25-35 kg: 3 tabs PO BD X 3 days; >35kgs: 4 tabs PO BD X 3 days **Dosing:** stat, after 8 hours, thereafter 12 hourly.
- **Second line treatment:** oral **Quinine** at 10mg/kg TDS for 7 days

Quinine 200mg tabs		Quinine 300mg tabs	
Weight Kg	No of Tabs	Weight Kg	No of Tabs
4-7	¼	6-11	¼
8-11	½	12-17	½
12-15	¾	18-23	¾
16-23	1	24-35	1
24-31	1 ½	36-47	1 ½
32-39	2	48 and above	2
40-47	2 ½		
48 and above	3		

Other treatment options for confirmed or suspected malaria:

- Cotexin 2 tabs PO stat then 1 PO OD x 6 days *plus* Metakelfin 2 PO stat
- If giving other Artemisinin derivative ensure that a second agent is present (some are combined pills -if not add Doxycycline 100mg po BID x 7 days, or Amodiaquine (see dose below)
- **Pregnant women:** 7-day therapy of oral quinine. Artemether-Lumefantrine (AL) can also be used in the 2nd and 3rd trimesters with dosage as above. *Do not withhold AL in the 1st trimester if quinine is not available*
- **Treatment failure** is failure to achieve the desired therapeutic response after the initiation of therapy; not equal to drug resistance. Failure is often due to poor adherence and wrong treatment. It should be suspected if patient gets worse or symptoms persist 3-14 days after initiation of drug therapy. If symptoms develop after 14 days or more where there has been clearance of symptoms, new infection should be considered and treated with first line drug. *Consider other causes of fever if symptoms persist despite effective treatment.*

Complicated malaria (cerebral malaria; malaria with hypoglycemia BS <2.2 mmol/l; malaria with severe anemia, Hb < 5g/dl or Hematocrit <15%; metabolic acidosis; hyperlactatemia [consider NRTIs as a cause in patients on ART]; pulmonary edema or black water fever).

- **Pre-referral management** at peripheral facility: IM quinine loading dose of 15mg /kg body weight in children (Quinine MUST be diluted to 60mg/ml using water for injection before IM injection preferably anterior thigh, 3ml per site). For adults loading dose of 20mg/kg maximum of 1200mg should be used.
- If quinine is not available, rectal artesunate at 10mg/kg or IM artemether at loading dose of 3.2mg/kg
- If referral delayed or not possible then continue IM treatment
- Management at referral hospital -Adults Quinine 20mg/kg in 10% dextrose (infusion to run over 2-4 hours) loading dose then 10mg/kg (max 600mg) TDS until can tolerate orally, making total of 7 days of treatment
 - **Always give IM quinine with glucose** (e.g. IV 25-50ml of 50% glucose diluted in 50ml of 0.9% saline) OR 4 level tablespoons of sugar dissolved in 200ml of clean water.
- Children quinine loading dose of 15mg/kg IV in 10mg/kg of 10% dextrose then 10mg/kg every 12hrs in 10% dextrose until can tolerate oral medication to complete a total of 7 days of treatment; same dose will be used for IM with directions as above

APPENDIX C INFANT FEEDING

a) Exclusive breastfeeding

The infant receives only breast milk with no additional fluids or solids apart from drops or syrups consisting of drugs, mineral supplements or vitamins from birth to the age of 4-6 months.

b) Weaning

The mother breastfeeds for 3.5-5.5 months then starts expressing breast milk into a cup for the next 2 weeks. Milk is given by cup and spoon without heating. After 2 weeks of giving breast milk by cup and spoon, full strength cow's milk is given. Other soft foods can also be introduced at this time.

c) Replacement Feeding

Cow's milk

- **Age < 2 months:** Milk:water ration of 1:1 i.e. 1 cup milk to 1 cup water (use same cup for measuring milk and water)
- **Age: > 2 months:** Full strength milk
- Encourage mother to use cup and spoon

Formula feeds

- Follow manufacturer's directions. Must use SAFE water: water should be boiled and cooled
- Encourage mother to use cup and spoon

APPENDIX D PAEDIATRICS REHYDRATION

a) Severe dehydration:

Any two of the following signs

- i. Lethargy or unconsciousness
- ii. Sunken eyes
- iii. Skin pinch goes back very slowly (2 or more secs)
- iv. Not able to drink or drinks poorly

Rx: Rapid IV fluids and oral hydration (ORS) if child can drink IV fluid 100ml/kg : ringers lactate solution OR Hartman's, or if not available: normal saline.

AGE	FIRST GIVE 30mls/kg in	THEN GIVE 70mls/kg in
<12 months old	1 hour	5 hours
> 12 months old	30 mins	2 ½ hours

Repeat again if the radial pulse is still very weak or not palpable

b) Some dehydration:

- i. Restlessness/ irritability
- ii. Thirsty and drinks eagerly
- iii. Sunken eyes
- iv. Skin pinch goes back slowly

Rx: In the first 4 hours give the child appropriate amount of ORS solution

WEIGHT	AGE	AMOUNT OF ORS IN FIRST 4 HRS
< 5 kg	< 4 months	200 – 400 mls
5 – 8 kg	4 – 12 months	400 – 600 mls
8 - < 11 kg	1 – 2yrs	600 – 800 mls
11 - < 16 kg	2 - < 5 yrs	800- 1200 mls
16 – 50 kg	5 – 15 yrs	1200 – 2200 mls

c) No dehydration:

- Present if child does not have more than two of the signs, which characterize some dehydration
- Treat the child as an outpatient
- Inform mother on three rules of home treatment:
 - **Give extra fluid:** For children < 2yrs give about 50 – 100mls of ORS after each loose stool. For children > 2yrs and above give about 100 – 200mls of ORS after every loose stool. (If you have weight replace 10mls/kg of ORS for each loose stool and 5 mls/kg after each bout of vomiting. ORS should be given slowly- approx 5mls/min especially in the child who is vomiting)
 - **Continue feeding**
 - **Advice on when to return.**

APPENDIX E: FOOD BY PRESCRIPTION

AGE	CRITERIA	PRESCRIPTION
6 - 24 months	Vulnerable	First Food
2 – 4 years	HIV positive, z score < 1.5	First Food
5- 10yrs	HIV positive, z score < 1.5	First Food
10-17 yrs	HIV positive, z score <1.5	Foundation Plus
≥ 18 yrs	HIV positive, BMI <18.5	Foundation Plus
Pregnant women and up to 6 months post partum	HIV positive with one other criteria listed below	Advantage Plus

Definitions for use in FBP:

1. Vulnerable child

- HIV+
- Mother HIV+
- Underweight
- Orphan (one or both parents)
- Other reason for vulnerability

2. Pregnant Women and up to 6 months Postpartum- Additional Criteria

- MUAC (mid upper arm circumference) <22cm

- Micro or macronutrient deficiency
- Slow or no weight gain during pregnancy (normal weight gain 0.5-1 kg per month- max 12 kgs during pregnancy)

3. BMI <18

NB: ALL patients on FBP are re-evaluated every 3 months for eligibility

APPENDIX F GRADING OF RENAL DYSFUNCTION

Grade of severity of renal failure	Glomerular filtration rate (ml/ minute)	Serum creatinine (umol/litre)
Mild	20- 50	150- 300
Moderate	10- 20	300- 700
Severe	<10	>700

Formula for calculating GFR

$$\text{GFR ml/min} = \frac{(140 - \text{age in yrs}) \times \text{ideal body weight in kg}}{72 \times \text{serum creatinine umol/l} \times 0.059}$$

* For **women** multiply result by 0.85

Ideal body weight - men 50.0 kg + 2.3kg for every 2.5cm above 152cm height

- women 45.5 kg + 2.3kg for every 2.5cm above 152cm height

GFR in children

Coefficient X height in cms

serum creatinine

Coefficient- preterms- 30

neonates- 35

< 2 yrs- 40

>2 yrs- 49

APPENDIX G: SOME COMMON DRUG INTERACTIONS

DRUG	INTERACTIONS
Rifampicin	<p>Antacids reduce absorption of rifampicin; avoid. Cimetidine conc reduced; use alternatives</p> <p>Antibiotics: Reduces plasma conc of Chloramphenicol</p> <p>Anticoagulant: Reduced anticoagulant effect of warfarin</p> <p>Anti-epileptics: Reduced plasma conc of phenytoin and carbamazepine: fits may recur</p> <p>Anti-fungals: Rifampicin reduces Fluconazole levels greatly: Avoid with Fluconazole; for CM give 800mg of Fluconazole OD. Ketoconazole reduces conc of rifampicin; avoid.</p> <p>Antiretrovirals: Don't use with PIs. Avoid when using NVP</p> <p>Cardiac drugs: Reduces antihypertensive effects of ACE Inhibitors, beta-blockers; antiarrhythmic effects of digoxin (reduced)</p> <p>Contraceptives: rifampicin reduces conc of both progestogen-only and COC. If using DMPA give at 10 weekly intervals. Avoid COC.</p> <p>Corticosteroids: rifampicin reduces conc of steroids. Reduced effect but use at recommended dose in TB patients</p> <p>Diabetes: reduced anti-diabetic effect of oral hypoglycemic agents; review diabetic control while on and for 2 weeks after discontinuation on rifampicin</p>
Fluconazole	Avoid when using NVP if possible, but if need be, monitor closely (it increases NVP by 100%)
Ketoconazole	Don't use with NVP and EFV
Oral contraceptives	When used with NVP, EFV, PIs needs alternative or additional method of contraception
Benzodiazepines	Avoid when patient is on NVP, EFV, or PIs Severe respiratory suppression may occur
Antihistamines	Avoid when patient is on NVP, EFV, PIs (cardiac arrhythmias)
D4T	Don't use with AZT (compete for same active site thus lower efficacy) Don't use with DDI Dose adjustment required in renal failure
3TC	Don't use together or sequentially with FTC (same single mutation causes resistance to both) Dose adjustment required in renal failure
TDF	Don't use with DDI Avoid in severe renal failure; ABC is an alternative for patients with impaired renal function since no adjustment necessary
PIs	Don't use with H2 blockers
Alcohol	Avoid when on ABC
NVP	Avoid if possible in women with baseline CD4 > 250 or in men with baseline CD4 > 400. Where NVP is used above these CD4 cut-offs clinical and lab monitoring is essential (ALT at baseline, 2 weeks, 6 weeks, and 3 months)
AZT	Don't use with D4T Dose adjustment required in renal failure

APPENDIX H: AMPHOTERICIN B PROTOCOL FOR TREATMENT OF CRYPTOCOCCAL MENINGITIS (CM)

- Parenteral use of amphotericin B is complicated by infusion related reactions, anaemia, electrolyte imbalance and renal failure.
- **Frequent side effects:** nephrotoxicity (renal tubular acidosis, hypokalemia); anemia; fever and chills. Use simultaneously with other nephrotoxic drugs may exacerbate the toxicity. Occasionally hypomagnesaemia and hypocalcaemia, hypotension and anaphylaxis may occur.
- Use of lipid formulations of amphotericin B is only recommended for patients with abnormal renal function indicated by creatinine level > 2.5 x ULN.
- In the absence of liposomal preparations patients with abnormal renal function should be given fluconazole alone for treatment of CM. [CID 2002; 35: 359].
- *The high rate of side effects associated with appropriate use of amphotericin B necessitates intensive laboratory and clinical monitoring of patients; consequently, amphotericin B should only be used in HCFs where the lab capacity and clinician supervision exists to meet the monitoring requirements. Facilities where this level of monitoring is not possible should use fluconazole alone for the treatment of CM.*

Indications

Parenteral amphotericin B is indicated for the treatment of cryptococcal meningitis, cryptococcosis outside the CNS and other deep mycoses such as aspergillosis.

Preparation

Available as 50mg vial

- Reconstitute each 50mg vial with 10 ml water for injection and shake immediately to produce a 5 mg/mL colloidal solution
- Dilute further in infusion fluid of 5% dextrose to a concentration of at most 100 micrograms/ml (consult product literature for details)
- Begin infusion immediately after dilution and protect from light; Infuse over 4 hours, or longer if not well tolerated
- Amphotericin B is incompatible with sodium chloride solutions; flush existing intravenous line with glucose 5% or use separate line for infusion; an in-line filter (pore size no less than 1 micron) may be used.

Administration

- Give paracetamol 1 g OR ibuprofen 400mg stat before each dose (plus promethazine 25 mg stat if patient vomiting)
- **Start pre-hydration of 500ml of normal saline to run in 2 hours to protect the kidneys before each dose.**
- Test dose of amphotericin should be given first: 1mg of the first dose in 100 mls of 5% glucose to run in 30 minutes. Observe patient for a further 30 minutes. If the patient is stable (no nausea, vomiting, fever, chills, headache) give the rest of the treatment dose slowly in 4 hours.
- **Dose should be escalated over the first 3 days**
 - Day 1: 0.3 mg/kg after the test dose
 - Day 2: 0.5 mg/kg
 - Day 3: 0.7 mg/kg to continue up to Day 14.
- **Give post hydration with normal saline 500ml over 2 hours after each dose.**
- Day 15: Start Fluconazole 400mg PO for 8 weeks then fluconazole 200mg OD until immune reconstitution has occurred (CD4 > 200 for at least 6 months)

Monitoring

- Clinical:
 - Vital signs and neurological condition should be monitored
 - Input-output chart maintained and balanced
- Lab
 - Initially daily renal function (serum urea and electrolytes including, potassium. Magnesium and calcium where possible) until patient stable on treatment
 - CBC at baseline and weekly

If patient needs to interrupt amphotericin for > 7 days, resume therapy at lowest level (e.g. 0.25 mg/kg)

APPENDIX I: BLEOMYCIN PROTOCOL FOR TREATMENT OF KS

- None of the chemotherapeutic agents in use can cure KS
- HAART in combination with chemotherapy increases the regression rate and achieves higher rates of remission of KS than chemotherapy alone; thus ART is the first line treatment of KS and **all patients with KS should be started on ART.**
- There are preferred chemotherapeutic drugs, the liposomal anthracyclines. The combination therapies of standard cytotoxic drugs previously used for treatment of KS have been succeeded

by the liposomal anthracyclines because they achieve much higher rates of remission than other previous drugs. These drugs are however currently inaccessible for patients in the public sector due to high costs.

- Chemotherapy (bleomycin and/or vincristine) is indicated in patients with extensive cutaneous or large mucosal KS lesions, those with rapidly progressive cutaneous disease causing pain, oedema, and ulceration and also in patients with visceral involvement. *Combination of bleomycin and vincristine is preferred if available.*
- Bleomycin is given intramuscularly or intravenously to treat Kaposi's sarcoma.

Side effects

- The principal problem associated with the use of bleomycin is progressive pulmonary fibrosis. This is dose-related, occurring more commonly at cumulative doses greater than 400 mg or if given at higher than recommended single doses; it is more likely in the elderly.
 - Basal lung crepitations or suspicious chest X-ray changes are an indication to stop therapy with this drug.
- It causes little bone-marrow suppression but dermatological toxicity is common and increased pigmentation particularly affecting the flexures and subcutaneous sclerotic plaques may occur.
- Mucositis is also relatively common and an association with Raynaud's phenomenon is reported.
- Hypersensitivity reactions manifested by chills and fevers commonly occur a few hours after drug administration and may be prevented by simultaneous administration of a corticosteroid, for example hydrocortisone intravenously.

Preparation

For IM administration add 1-5 ml of water for injection or normal saline to vial containing 15 units of bleomycin. (1unit = 1mg)

Dose

- Bleomycin is given as 15 mg IM every 2 weeks x 6. Patient should be reviewed after the 6 doses to determine whether further treatment is needed (See KS management Pg).
- Bleomycin may be combined with vincristine at a dose of Vincristine 1mg IV every 2 weeks if the latter is available.
- If vincristine is used, careful attention must be given to the IV site since extravasation is associated with severe tissue necrosis.

APPENDIX J: VINCRISTINE PROTOCOL FOR TREATMENT OF KS

Should be used either alone or in combination (with bleomycin) for the treatment of KS. Vincristine is administered intravenously.

Preparation

- It should be given in a drip with 5% glucose or normal saline. Dilute 1mg of vincristine in 250ml of either fluid and give in 1h.
- Alternatively vincristine may be diluted in 10-20ml of 5% glucose or normal saline and given directly IV slowly over about 15 minutes.
- Give weekly, if used alone, for 6-12 weeks and review.

Side Effects

- Severe local irritation with tissue necrosis may occur with extravasation of vincristine, thus care must be taken when inserting the IV line. Check that there is no extravasation before beginning the infusion.
- Peripheral or autonomic neuropathy occurs with vincristine and may be dose-limiting. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation. Motor weakness can also occur, and increasing motor weakness calls for

discontinuation of these drugs. Patients should be assessed for neuropathy before initiation of vincristine. Vincristine should not be used in patients with pre-existing peripheral neuropathy or those on stavudine, didanosine or INH. Vincristine-associated PN is reversible but recovery may take a long time.

- Ototoxicity has been reported with vincristine.
- Myelosuppression is uncommon and if present is relatively mild

APPENDIX K: INDICATIONS FOR SELECTIVE VIRAL LOAD TESTING (LIMITED AVAILABILITY)

CLINICAL INDICATIONS	<ul style="list-style-type: none"> ○ New or recurrent WHO stage 4 disease after at least 6 months of ART ○ New or recurrent WHO stage 3 disease after at least 6 months of ART ○ New or recurrent Papular Pruritic Eruptions after at least 6 months of ART ○ <i>Unexplained</i> weight loss > 10% (rule out TB) ○ Optimizing ART in women falling pregnant after at least 6 months of ART ○ Assessment of patients for treatment failure prior to single drug substitution after at least 6 months of ART <p>Additionally for children:</p> <ul style="list-style-type: none"> ○ Lack of or decline in growth response over a 6 month period, after treating for and excluding other causes, e.g. TB, malnutrition. ○ Failure to meet neuro-developmental milestones after 6 months of ART. ○ Recurrence of infections that are severe, persistent or refractory to treatment.
IMMUNOLOGICAL INDICATIONS	<ul style="list-style-type: none"> ○ CD4 (count or %) non-response ○ CD4 fall to baseline or below threshold levels for age ○ CD4 fall (CD4 % or absolute count) by > 30% of peak value

APPENDIX L: PAIN MANAGEMENT (AS PART OF PALLIATIVE CARE)

- *Providing pain relief as part of the care for patients with conditions for which curative treatment is not possible. Psychosocial and spiritual support should be part of palliative care.*
- *Give analgesics regularly to prevent pain rather than to relieve pain; they work better this way.*
- *For neuropathic pain amitriptyline is preferred; carbamazepine may be added or used instead.*

Non-opioid Analgesics

- Start with regular paracetamol at the full dose for non-inflammatory pain.
- NSAIDs in full doses are preferred for continuous pain or pain associated with inflammation and should be used for arthritides, back pain and soft tissue disorders.
 - Non-selective NSAIDs (e.g. ibuprofen) at higher doses may be associated with an increased risk of thrombotic effects (myocardial infarction and Cerebrovascular accidents); prolonged use should be reviewed regularly
 - Selective inhibitors of cyclo-oxygenase-2 (e.g. celecoxib) have similar potency to naproxen and diclofenac but with better GI tolerance; because of association with increase risk of MI and CVA they should only be considered for patients who can't tolerate non-selective NSAIDs
 - *Pain relief and anti-inflammatory effects take between 1-3 weeks to take full effect!* Therefore allow adequate time before changes are made.
 - Ibuprofen as first step as low incidence of ADRs
 - Naproxen or diclofenac can be used next (more ADRs than ibuprofen)
 - Indometacin may be more potent than naproxen and has a similar incidence of GI ADRs.
 - Celecoxib (Dose: 200mg/day in 2 divided doses)

Opioid analgesics

- Opioids such as codeine or dihydrocodeine can be used alone or added to a non-opioid drug from the above list. If these do not control pain, stronger opioids may be used (tramadol, morphine)

Dosing of Analgesics

DRUG	DOSE
Paracetamol	1g QID
Ibuprofen	1.6-2.4 g in 3 divided doses
Diclofenac	75-150mg in 2-3 divided doses. Can be given IM at 75mg OD or BD in severe pain or post-operatively
Naproxen	0.5-1g in 2 divided doses. Pediatric > 5y for arthritis: 10mg/kg/day in 2 divided doses
Indometacin	50-200mg/day in divided doses OR rectal suppository 100mg nocte
Codeine	30-60mg q4h (Max 240mg/day). Pediatric >1 year: 1-3mg/kg/day in 4 divided doses
Dihydrocodeine	30mg q4-6h. IM or deep subcutaneously 50mg
Pethidine	Acute pain: PO 50-150 mg q4h; IM 25-50mg q4h. Pediatrics: 0.5-2mg/kg 4hourly PO, s/c or IM
Morphine (preferred for severe pain)	Chronic pain: PO, IM or s/c 5-20mg q4h adjusted per response. Acute pain: s/c or IM 10mg q4h. Neonate 100mcg/kg q4h. Child > 1mo 100-200mcg/kg q4h.