THE REPUBLIC OF UGANDA

TRAINIG MANUAL FOR THE MANAGEMENT OF OPPORTUNISTIC INFECTIONS IN HIV/AIDS FOR OPERATIONAL LEVEL HEALTH WORKERS

2005

Table of Contents

Acronyms

AIM	AIDS /HIV Integrated Model District Programme
AIDS	acquired immune-deficiency syndrome
HIV	human immune-deficiency syndrome
CNS	central nervous system
GUS	genital-urinary system
ENT	ear nose throat
PLWHA	people living with HIV/AIDS
CCR	chemo-chine receptor
DNA	deoxyribonucleic acid
RNA	ribonucleic acid
MHC	major histo-compatibilty complex
HAART	highly active antiretroviral therapy
CD	cluster of differentiation
PJP	pneumocysytis jiroveci pneumonia (formerly PCP)
HSV	herpes simplex virus
CMV	cytomegalo virus
HZV	herpes zoster virus
CSF	cerebral spinal fluid
VDRL	venereal disease research laboratory
PML	progressive multifocal leuco-encephalopathy
ADC	AIDS dementia complex
CT	computerized tomogram
MRI	magnetic resonace imaging
KS	Kaposi's sarcoma
OI	opportunistic infections
PMTCT	Prevention mother-child transmission.
MOH	Ministry of Health

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Foreword

While Uganda is justifiably heralded worldwide as a "success story" with its unique multisectoral approach and subsequent success in reducing the prevalence of HIV infection, the numbers of people living with HIV/AIDS (PLWHAs) continue to increase as do the demands on health care services and consequently on health care workers at every level.

The provision of appropriate care and social support by health care workers is an integral and key component of the response to HIV/AIDS. Improvement in the quality as well as the prolonging of life of PLWHAs is a proven consequence and is the backbone of HIV/AIDS chronic care. For those who are not taking ARVs, as is the case for the majority of those infected the prompt diagnosis and effective management of opportunistic infections and HIV related conditions can make a significant difference in the quality and length of life they live.

The challenge is to ensure that health workers, in particular at the district and lower levels, are adequately equipped with the knowledge and skills to provide such care. This training manual has been developed in response to this need and in particular to standardize the training and management of opportunistic infections and HIV care and support in Uganda.

This manual will fill a void, as well as complement existing training programmes by providing a comprehensive and practical tool for health care workers in the effective and prompt diagnosis and treatment of opportunistic infections.

Dr. Elizabeth Madraa
Programme Manager
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Preface

As we enter the third decade of the pandemic, the urgency to provide adequate care and support for people living with HIV/AIDS (PLWHAs) remains a priority. It is true that prevalence rates here in Uganda have declined. For example, among 15-19 year olds and pregnant women attending antenatal clinics, the rate has declined from 30% in the 1990s to the present rate of 6.2%. This rate is however is still unacceptably high.

Antiretroviral drug therapies (ARVs), where available and accessible, have reduced morbidity (the incidence of opportunistic infections) and mortality as well as improving the quality of life and immune function of PLWHAs. It is estimated that in Uganda approximately 70,000 people have access to ARVs . The overwhelming majority of Ugandans living with HIV/AIDS, conservatively estimated at 1.1 million, still need proper management of opportunistic infections.

We have certainly made progress in combating HIV/AIDS in Uganda, but our efforts need to be continuously renewed and reinforced. We need to ensure that our health care workers, at every level, have the tools they need to provide appropriate care and support to people living with HIV/AIDS (PLWHAs), and in particular in the management of opportunistic infections (OIs). This is particularly crucial in the absence of universal access to antiretroviral therapies and the availability of sophisticated diagnostic techniques and facilities.

Given this situation and the realization that no standardized training manual for the management of opportunistic infections for health workers existed, MOH, with the support and cooperation of AIM, sought to remedy this with the development of this manual.

This manual has been developed in the spirit of cooperation and collaboration through consensus building. A committed and dedicated group of health care providers, recognized and respected by their peers for their excellence within their respective fields in HIV/AIDS care, came together to produce this manual. (The complete list of contributors and their affiliations follows).

This training manual serves to provide a standardized in service training for health workers on the management of opportunistic infections. The manual is intended for: trainers of health service providers and health service providers.

The primary objectives of the manual are to:

- Streamline/standardize training of health workers in the management of opportunistic infections,
- Facilitate the training of health workers in the management of opportunistic infections.

Underlying the development of this manual is the premise that good care is possible with minimal diagnostic tools and limited treatment options.

The manual consists of 16 modules which can be used in sequence or separately. The first module comprises two parts. The first provides an overview of HIV/AIDS and the second part an overview of opportunistic infections within the context of HIV/AIDS. **The modules that follow correspond to the different body parts / systems affected. Pain management and nursing care are integral to all modules (with the exception of Diagnostics)**.

We do not claim the manual to be exhaustive. Our aim is to equip health workers in Uganda with the tools that will enable them to provide prompt and appropriate diagnosis, treatment and/or referral and follow-up to PLWHAs according to the ailments with which they present.

Each module consists of an introduction, goal, learning objectives, content outline, methodology, suggested teaching materials and trainer's notes. The trainer's notes broadly comprise the

following: topic, OI condition (s), causative agents (aetiology), epidemiology, pathogenesis, clinical presentation, diagnosis and differentials, treatment, complications and prevention. **Exceptions are those modules dealing with Common Mental Health Problems and Diagnostics. The trainer's notes within these modules** vary slightly. The former provides a background on the signs and symptoms of mental illness and those disorders common among PLWHAs with the expectation that the module will equip health workers with the means to recognise, diagnose, treat, refer and/or provide follow-up to PLWHAs. The module on Diagnostics is for Laboratory personnel and is intended to provide them with the appropriate knowledge and skills in Laboratory diagnosis of OIs among PLWHAs. In addition, it is expected that individual trainers will, as needed, supplement and adapt the materials to the particular setting in which they are working. Additional modules covering patient evaluation, post exposure prophylaxis and OI prophylaxis are included.
The manual can also be used as a reference tool.

The modules were written after a careful and thorough review of the literature together with the contributors' practical experiences in caring for PLWHAs in Uganda. We have taken great care to ensure the accuracy of the information in this manual, including treatment recommendations and dosage.

Change is a constant within the medical field. With this in mind the trainer should review, where possible, the information presented here with other information available and with their own practical experiences, for which there is no substitute.

Module 1A

OVERVIEW OF HIV/AIDS

Introduction:

Debate and theoretical speculation as to the origins of the human immunodeficiency virus (HIV-1 and HIV-2) responsible for what is known as acquired immune deficiency syndrome (AIDS) have been a constant since the discovery of the virus in 1985 by Gallo and Montagnier.
While one group of researchers in 1999 claimed to have discovered an indisputable link between a primitive virus from Central West Africa and HIV-1, others refuted it arguing that a version of HIV may have been prevalent in humans.

Trainer's Notes:

Global overview

As of December 2002 an estimated 42 million people are living with HIV/AIDS which includes 3.2 million children under 15 years of age and 19.2 million women.
Approximately 5 million people were newly infected with HIV during 2002. 800,000 were children under 15 years of age. 2 million of the 4.2 million new infections among adults were in women.
The total number of AIDS death in 2002 was 3.1 million. Adults accounted for 2.5 million and almost half (1.2 million) were women. 610,000 children under the age of 15 died as a result of AIDS in 2002.
There were approximately 14,000 new HIV infections a day in 2002, 95% of which were in the developing world. Of the 12,000 new infections occurring daily in people aged 15-49, 50% are in women and 50% are in people aged 15-24.
More than 21 million people have died as a result of AIDS since the beginning of the pandemic. (1)

Uganda

Since HIV/AIDS was first described in Kalisizo Health Centre, Rakai district, the Ministry of Health estimated that by the end of 2000 2 million people had been infected with HIV.
Conservative estimates suggest that 1.1 million people are living with the disease while close to 850,000 have died from it. The majority of those infected in Uganda are within the 15-49 age group with a disproportionate number of women affected, and in particular young women.
In Uganda HIV prevalence among 15-19 year olds and pregnant women has been dropping steadily. The prevalence rate among women attending antenatal clinics in the 90s was 30%; it is now at 6.5%. In spite of this considerable drop, the rate still remains at a level that is unacceptably high.
Provision for adequate treatment, care and support for people living with HIV/AIDS on a global scale is woefully insufficient. Fewer than 4% of people in need of antiretroviral treatment in low and middle income countries had access to treatment by the end of 2001. And less than 10% of people currently living with HIV/AIDS have access to palliative care and/or treatment for opportunistic infections.
In Uganda as of December 2005, the total number of patients in need of ARVs was 150,000 of which about 70,000 people are currently receiving treatment. The remaining one million or so Ugandans are either being treated for opportunistic infections or are without any form of treatment.
Given this situation it is vital that health care workers in Uganda are knowledgeable about the management of opportunistic infections. It is anticipated that this manual will fill a void and help attain this goal.

Life Cycle of HIV

HIV life cycle in CD4 lymphocyte

Human immunodeficiency virus (HIV) belongs to the class of viruses known as retroviruses. HIV is composed of a protective envelope and genetic material (viral RNA). When HIV is outside the host cell, it is called a virion.
For HIV to reproduce it needs an intact host cell. The life cycle of HIV has six stages.

1. Fusion:

Viruses often have a specific cell in the host (human, animal or plant) that they target. HIV infects those cells which carry a molecule known as CD4 on their surfaces, namely T-helper cells and macrophages (cytotoxic to [ability to kill/destroy] bacterial and other germs).
HIV binds to the CD4 receptor using a protein on its envelope called gp 120. This inactivates other proteins on the human cell i.e. CCRs and CXCR4 and in so doing completes the fusion on the host cell.

2. Reverse Transcription:

Following fusion the viral contents are released into the host cell. The viral enzymes reverse transcriptase carries out the process of translating viral RNA into DNA.

3. Integration:

The newly formed viral DNA is integrated into the human DNA by the action of the viral enzyme integrase. The human cell is now reprogrammed to make more HIV.

4. Transcription:

The DNA undergoes replication to form single strands of viral RNA (messenger RNA).

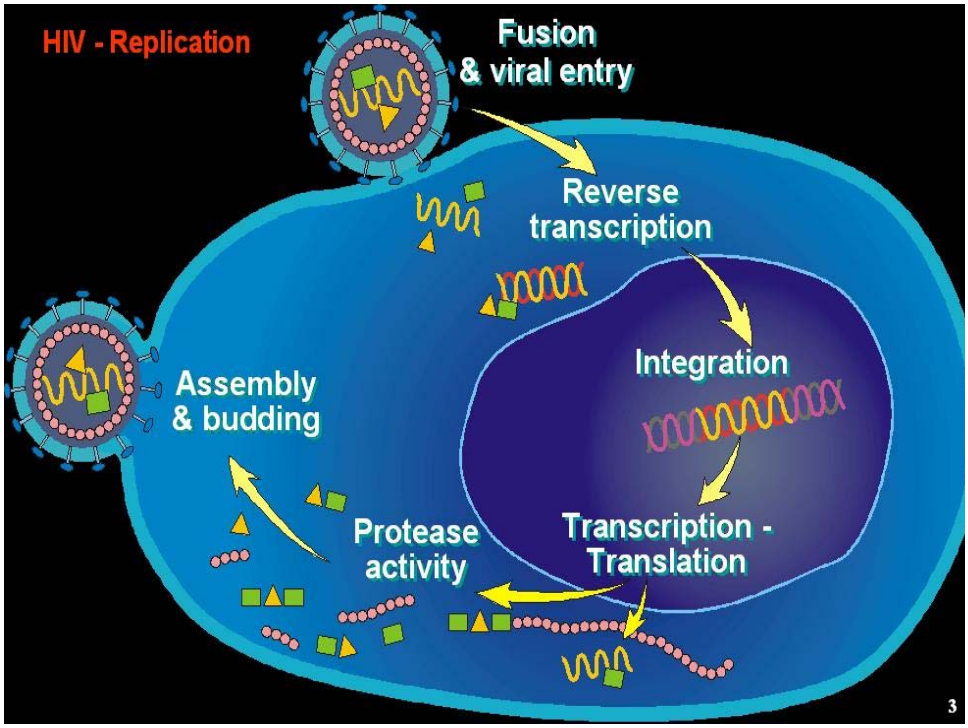
5. Translation:

Using the viral RNA protein building blocks are translated within the human cell to form a new HIV particle.

6. Viral assembly:

The viral enzyme protease helps to assemble the viral proteins and viral RNA to form new HIV particles. These are released into the blood stream and are able to infect other cells. Between 10.3 billion new virions are produced per day in people not on Highly Active Antiretroviral Therapy (HAART).

HIV life cycle in CD4 lymphocyte



Immunology

The human body has two forms of immunity: natural and acquired.
Immune responses conferring protection against disease can be induced by

a) Direct infection and b) artificial exposure of the individual to inactive forms of the infectious organism, for example, immunisation.

In terms of HIV/AIDS the focus is on acquired immunity. This includes:

- Humoral immunity involving antibody protection and complement, and
- Cell–mediated immunity

Humoral Immunity

Humoral immunity involves antigen–antibody reactions. Antigens are substances that elicit (bring out) an immune response in vertebrate animals. Antibodies are directed specific epitopes on the surface of the antigen. Lymphocytes and cells of the monocyte macrophage series play a major role in antibody production:

Macrophages trap the antigen and partially degrade it. This degraded antigen is carried on the surface of the macrophage as small highly immunogenic peptides in association with cell antigens and presented to T and B-lymphocytes. These lymphocytes undergo a "blast formation" to produce antibodies. Specific

lymphocytes arise by random mutation. Initial exposure to antigen results in the appearance of circulating antibodies within 3 days and maximal antibody production is within 7-10 days. This is the primary response in which IgM class antibodies are produced and also generated. Subsequent exposure to the same antigen results in proliferation of mainly B cells and a subsequent generation of:

- IG antibodies
- T- helper cells (T_H cells), which with the assistance of plasma cells produce certain antibodies
- T suppressor cells which regulate antibody synthesis

Cell mediated immunity

Cells involved include lymphocytes, macrophages, monocytes, eosinophils, mast cells and neutrophils and are produced in the marrow. Lymphocytes are distributed in all organs, tissues and intestinal fluids. However, in lymphoid organs they are more concentrated, i.e. bone marrow, spleen, thymus, lymph nodes and mucosal associated lymphoid tissue (MALT) e.g. breast, GUT, salivary glands.

The resting lymphoid tissue consists of 3 areas:

i) The cortex which contains B lymphocytes
ii) Para cortex which contains T lymphocytes
iii) The medulla which contains connective tissue

Following stimulation by an antigen, the following reactions occur:

- The cortex contains actively dividing cells
- The Para cortex contains blast-like cells and "germinal centres" containing actively dividing cells.
- The medulla contains plasma cells secreting antibodies.
- T cells are divided into T-helper, T suppressor, T cytotoxic and T delayed hypersensitivity cells. The surface phenotypes divide them into
  - CD8+ T cells recognise antigen with MHC class I molecules
  - CD4+ T cells recognise antigens when they are presented to them by the antigen-presenting cells in association with MHC class II molecules.

HIV and the Immune System

Whenever HIV replicates in a CD4+ cell it destroys it. HIV can "escape" the antibodies and other immune cells that normally control infection resulting in increased plasma levels of viral RNA.

The genotype of each generation of virus is slightly different. This means that memory T cells are unable to detect the new forms. HIV is then able to replicate within the memory cells which are eventually depleted (exhausted). As the CD4+ cells are depleted the risk of being attacked by opportunistic infection increases.

HIV Transmission:

A: Mode of Transmission

- Sexual (which accounts for 90% of transmission in developing countries)
- Parenteral (blood borne)
  - ✓ Use of infected blood, blood products and aseptic conditions in health facilities
  - ✓ Sharing non-sterile sharp-piercing instruments with an HIV-infected person
- Vertical/maternal to child transmission
  - ✓ In utero
  - ✓ During delivery

- ✓ Breast feeding

B: Factors facilitating transmission:

Transmission of HIV infection can be influenced by several factors including:

- Infectiousness of the host
- Susceptibility of the recipient
- Viral properties.

a) Infectiousness of the host

The infected person is more likely to transmit the infection when viral replication is high. This occurs during the initial stage of HIV disease and more advanced stage of the HIV disease. Factors that decrease viral titers, including the use of antiretrovirals, may decrease infectivity, but does not eliminate the risk of transmission. Factors that increase the risk of exposure to blood, for example, genital ulcer diseases, trauma during sexual contact and menstruation of an infected woman during sexual contact may all increase risk of transmission. Unprotected sex: correct and consistent use of latex condoms provides protection for both men and women against HIV.

b) Susceptibility of recipient

The characteristics of the uninfected individual may increase the likelihood of infection, for example:

- Inflammation or disruption of the genital or rectal mucosa
- Absence of circumcision in men may increase the risk of infection
- Sex during menstruation may increase a woman's risk of acquiring HIV infection
- Bleeding during sexual intercourse

c) Viral properties

Certain viral factors may play a role in HIV transmission and include:

- Phenotypes
- Genetic factors
- Quantity of the virus

Staging:

HIV can cause a wide range of symptoms and clinical conditions that reflects varying levels of immunological damage. Certain conditions tend to occur sometimes in association with each other and at specific CD4+ levels.

An HIV staging system is of particular significance and usefulness for the following:

- Clinical evaluation
- Planning a therapeutic intervention
- Determining the individual level of infirmity
- Providing prognostic information

World Health Organisation (WHO) Clinical Staging:

1. Clinical stage 1

- Asymptomatic infection
- Persistent generalised lymphadenopathy
- Acute retroviral syndrome
- Performance scale level at which patient can perform normal activities.

2. Clinical stage II (Mild disease)

- Unintentional weight loss less than 10% of body weight
- Minor mucutaneous manifestation
- Herpes zoster developing in the previous 5 years
- Recurrent upper respiratory tract infections (for example bacteria sinusitis)
- Performance scale level at which symptoms are present but patient are almost fully ambulatory.

3. Clinical stage III (moderate disease)

- Unintentional weight loss greater than 10% of body weight
- Chronic (lasting >1 month) diarrhoea
- Prolonged (lasting 1month) fever (intermittent or persistent)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis developing within the previous year.
- Severe bacterial infections (for example pneumonia or pyomyositis)
- Vulvovaginal candidiasis that is chronic (lasting more than 1 month) or does not respond to therapy
- Performance scale level at which patient remains in bed less than 50% of the daytime but more than normal.

4. Clinical stage IV (severe disease)

- HIV wasting syndrome, defined as unexplained weight loss greater than 10% and either chromic diarrhoea or chronic weakness and unexplained fever.
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea lasting longer than 1 month
- Isosporiasis with diarrhoea lasting longer than 1 month
- Extra pulmonary cryptococcosis
- Cytomegalovirus diseases affecting organs other than the liver sputum or lymph nodes
- Visceral or chronic (lasting > 1 month) mucocutaneous herpes simplex virus infection.
- Progressive multifocal leukoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of the oesophagus trachea, bronchi or lung
- Disseminated atypical mycobacterium infections
- Non-typhoidal salmonella septicemia
- Extra pulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV related encephalopathy
- Performance scale level at which patient remains in bed more than 50% of day time.

Natural History of HIV/AIDS without Highly Active Antiretroviral Therapy (HAART)

For most people who are not on HAART the natural history of HIV infection from the time of infection to death is 10-15 years. The sequence is as follows:

1. Primary Infection:

At the time of initial infection with HIV the body's immune system is healthy. $CD4^+$ cell counts are usually > 1000cell/mm^3. However, the virus begins to replicate rapidly destroying $CD4^+$ cell counts.

2. Primary and acute retroviral syndrome

This is a transient symptomatic illness that can be identified in 40-90% of new HIV infections and is characterised by:

- high rate of HIV replication
- high titers of viral RNA (up to 7 million copies of viral RNA per cubic millimeter of plasma)
- Initiation of HIV-specific immune response. Recovery occurs when the amount of viral RNA begins to fall after the appearance of cytotoxic (killer) lymphocytes which specifically react with HIV antigens (sero conversion). The vigour of this response varies among individuals and is associated with the subsequent rate of disease progression.
- Symptoms have been identified 5-30 days after a recognised exposure to HIV. The signs and symptoms of acute HIV infection are non specific, for example, fever, fatigue, rash, aseptic meningitis, oral ulcers, GUT upsets etc. Clinical diagnosis of acute HIV infection is often missed as these symptoms are seen in many other viral infections.

Established Infection/Asymptomatic chronic HIV infection:

The HIV specific immunological response begins to control the intensity of the viraemia hence forming a "viral set point". It forms a steady state between viral replication and elimination. This varies from individual to individual. Most patients established a relatively stable viral load after recovering from the acute infection. According to some studies focused mainly on men, this viral set point is highly predictive of the prognosis of the illness:

- In cases with a high viral set point (values ranging up from 40,000 copies/mm^3) the decline in $CD4^+$ cell counts and occurrence of clinical illness is very rapid
- Patients with low viral load set points (<500 copies/mm^3) have a better prognosis.
- In long-term progressors as the name suggests there is no evidence of disease progression (either $CD4^+$ cell depletion or opportunistic infections) seen for a long period of time.

The viral set point is likely to be influenced by several factors which include:

- Genetic characteristics, for example HIV binding receptors on lymphocytes
- Presence of other infections at the time of HIV exposure
- Viral characteristics
- Age
- Gender (see below)

During the period of clinical stability acute illnesses (for example TB) may stimulate the immune response resulting in increases in viral load. This is transient and usually resolves within 2 months. Determination of viral load for prognostic purposes should not be done either during or shortly after an acute illness. The level of viral RNA in tissues does not correlate with blood levels.

Long term Non Progressors

8-15% of people infected with HIV remain symptom free for longer periods of time (the average 8-10 years) and are referred to as long-term survivors (LTS).

They are divided into 2 groups:

a) Those with stable CD4+cell counts
b) Those with low CD4+ cell counts but no AIDS–defining condition

Factors associated with LTS are:

- Presence of specific anti-HIV cytotoxic lymphocytic responses
- Viral characteristics e.g. defective genes and gene products. LTS tend to have consistently lower viral RNA levels after the period of acute infection, suggesting a better control of viral replication.

Module 1B

OPPORTUNISTIC INFECTIONS: AN OVERVIEW

Introduction:

This module provides an overview of opportunistic infections and their implications in people living with HIV/AIDS (PLWHAs). Different types of opportunistic infections (OIs) encountered in the care of PLWHAs are outlined. This module will provide a background leading to a more detailed study in the modules that follow of the individual opportunistic infections and their management.

Goal:

This module aims to provide health workers with a solid background in the management of opportunistic infections for PLWHAs within the Ugandan setting. And, consequently to provide a platform that will facilitate the goals of each subsequent module in the manual.

Definition of OIs (2)

Opportunistic infections (OIs) are infections that take advantage of weakened immune system. Most OIs are caused by micro-organisms that are common and may have lived in the body for many years. When the immune system is undamaged and working properly these micro-organisms are prevented from growing or spreading within the body and causing disease. However, if the immune system is damaged by HIV (or other sources of immune suppression such as post-transplant treatment drugs) the micro-organisms are able to reactivate and grow.

HIV/AIDS, the Immune System and Ois

When HIV enters the body the immune system is gradually depleted. HIV kills cells (cytosis) in the lymph nodes (clusters of immune cells or T-cells that trap foreign organisms and in so doing are able to fight and prevent infection). The level of the virus in the blood and lymph nodes increases because HIV can "escape" the antibodies and other immune cells that normally control infection.

Each generation of viruses is slightly different. This constant evolution helps keep HIV one step ahead of the immune system. The immune cells are always looking for viruses that resemble the previous generation of HIV. Subsequently the virus "escapes" resulting in a progressive increase in viral load. The CD4+ lymphocytes, or T-cells, gradually decline in number because they are killed by the virus, and are killed more rapidly as the viral load increases. HIV destroys the immune system's memory (CD4+ cells that have been programmed to recognise infections) and eventually it will be depleted. Consequently as CD4+ cells decrease, organisms which are normally kept in check by an undamaged immune system begin to grow and spread causing disease (opportunistic infections).

Prevalence of OIs in PLWHAs

OIs are very common in PLWHAs. For example, almost every PLWHA will have at least one episode of candidiasis (thrush) during his/her illness. Approximately one in every ten PLWHAs gets infected with cryptococcal meningitis. About 36% or more of new cases of TB occur in PLWHAs.
Community acquired pneumonias are much more common in PLWHAs. Knowledge of the incidence and prevalence of OIs in PLWHAs in Uganda is limited by the general scarcity of diagnostic services and surveillance mechanisms.

Types of OIs commonly seen in PLWHAs

The depletion of CD4+ cells leads to the growth and dissemination of various types of OIs. The study of OIs in PLWHAs can be categorised either according to the organ or system of the body affected or by the biological groupings or aetiological causes. In this manual we have categorised the study by those systems of the body affected. The exception to this is Module 13 Diagnostics (Laboratory component) where infectious agents are reviewed organism by organism.

The biological or aetiological causes are:

- Bacterial
- Fungal
- Protozoal
- Viral
- Other (Kaposi's Sarcoma and lymphomas)

Almost any organ or system of the body can be affected by the different OIs. Those most commonly seen within the different organs or systems are:

The brain and its meninges which are usually affected by

- Cryptococcosis
- Toxoplasmosis
- Tuberculosis

The eyes and its appendages

- Cytomegalovirus
- Herpes zoster

The mouth, throat and oesophagus

- Candidiasis
- Oral hairy leukoplakia
- Kaposi's Sarcoma
- Aphthous ulcers

The lungs and pleural coverings

- Tuberculosis
- Pneumocystis jiroveci pneumonia (formerly known as PCP)
- Histoplasmosis
- Kaposi's Sarcoma

The gut and the liver

- Cytomegalovirus
- Hepatitis viruses
- Candidiasis
- Cryptosporidiosis
- Mycobacterium avium complex
- Kaposi's Sarcoma

Genito-urinary system

- Genital herpes
- Candidiasis
- Human papilloma virus
- Cervical cancer
- Syphilis

The skin

- Herpes simplex
- Herpes zoster
- Molloscum contagiosum
- Staphylococcal infection
- Tinea infections

Diagnosis

Diagnosis of OIs like all other clinical cases depends on the symptoms of presentation

- Signs on evaluation
- Specific laboratory tests in accordance with the suspected OI

Management

Management of OIs will depend on the specific OI diagnosis. Many opportunistic infections require acute, consolidation and maintenance phase treatments. When treating opportunistic infections the health care provider should be aware that the patient may be on other drugs and should be alert to potential side effects from drug interactions. Similarly when there is no response treatment failure should be considered. The health care provider must be attentive to when therapeutic management ends and palliative care takes over.

References:

1. AIDS Epidemic Update, December 2002, UNAIDS
2. Prophylaxis for Opportunistic Infections, Treatment Update, Project Inform, November 4, 2002

Module 2

OPPORTUNISTIC INFECTIONS OF THE CENTRAL NERVOUS SYSTEM (CNS) IN HIV/AIDS

Introduction:

HIV is classified within the lentivirus family of viruses which are characterized in part by their tendency to cause chronic neurologic disease in their animal hosts. It is not surprising then that neurologic complications of HIV infection are common and not confined to opportunistic infections. All levels of the neuraxis can be involved and include the brain, meninges, spinal cord, nerve and muscle. Neurologic disease is the first manifestation of symptomatic HIV infection in approximately 10 to 20% of people, while about 30 to 40% of patients with advanced HIV disease will have clinically evident neurologic dysfunction during the course of their illness. The incidence of subclinical neurologic disease is even higher. Autopsy studies of patients with advanced HIV disease have demonstrated pathologic abnormalities of the nervous system in 75 to 90% of cases.

Goal:

To enable a health worker in Uganda to recognise, treat and/or refer CNS opportunistic infections (OIs) in PLWHAs.

Learning objectives:

By the end of this module the participants should be able to:

- List the common causes of CNS OIs in HIV/AIDS
- Know the risk factors for CNS OIs
- Recognise signs and symptoms of the common CNS infections
- Know how to make a definitive diagnosis of the different pathogenic organisms
- Manage the infections and associated complications including referral where necessary

Content outline:

1. Categories of CNS opportunistic infections

- Meningitides
  - ✓ Fungal (Cryptococcal)
  - ✓ Bacterial (TB, Syphilis)
  - ✓ Viral (Aseptic meningitis)
- Encephalitides
  - ✓ Viral (HSV, HZV, CMV)
  - ✓ Protozoa (Toxoplasmosis)
  - ✓ Fungal

Methodology:

1) Introduction

Steps

1. Trainer gives a general definition of the Central Nervous System

2. Trainer gives a brief overview of OIs in the CNS (see module 1)

2) Listing of OIs in the CNS and their causative agents

Steps

1. Brainstorming
2. Trainer clarifies and makes additions as needed
3. Trainer gives simple and easily remembered classification

3) For each OI the trainer will go through the following:

I. Clinical features of the individual OIs in the CNS

Steps

1. Brainstorming
2. Trainer summarises

II. Diagnosis of the OIs

Steps

1. Brainstorming.
2. Trainer summarises investigations done in the CNS

III. Management of the different OIs of the CNS

Steps

1. Brainstorming on principles of management
2. Trainer summarises

IV. Prevention of OIs of the CNS

Steps

1. Brainstorming on principles of prevention.
2. Trainer defines the principles of prevention.

Teaching materials:

- News print
- Markers (different colours)
- Flip chart
- Chalk board
- Over head projector
- Slide projector
- Transparencies
- Computer (Power point presentation)
- Pencils, pens
- Notebooks

Trainer's notes:

Cryptococcal Meningitis (CM)

Cryptococcal infection makes up 50% of all cases of meningitis seen in PLWHAs.

Causative organism: cryptococcus neoformans

Pathogenesis

The organism is a yeast-like fungus commonly found in soil contaminated by bird droppings. CM develops in people who are immune deficient. The fungus usually enters the body through the lungs. It does not appear to spread from person to person.

Cryptococcal infection often leads to cryptococcaemia and any organ can be infected. The most common clinical presentations are: meningeal, pulmonary or cutaneous. These can occur singly or in combination.

Risk factors for CM include:

- A CD4+ cell count of less than 50 cells/mm³
- A history of at least one previous episode of CM. A previous episode of CM means that there is about a 60% probability of recurrence unless this is prevented through secondary prophylaxis with fluconazole

Clinical presentation

The clinical features of CNS Cryptococcal disease are due to: subacute meningitis, encephalitis, and raised intracranial pressure and may include:

- Headache with fever and malaise usually lasting for days
- Lethargy, altered level of consciousness, irritability and personality changes
- Seizures, coma or specific symptoms and signs of raised intra-cranial pressure (such as visual disturbances or vomiting)
- Neck stiffness or photophobia can be found in about 25% of cases
- In a third of patients more classic signs of meningitis occur at the time of diagnosis such as meningismus (papilloedema may be part of the clinical features of raised intra-cranial pressure on fundoscopy). If this is the case, it raises questions about the safety of performing a lumbar puncture (LP).
- Localizing signs such as unilateral cranial nerve palsies can occur
- Associated chest symptoms are also common, resulting from an atypical pneumonia caused by Cryptococcus that presents with chest pain and cough. The chest x-ray could show one or more infiltrates, which are often well circumscribed.
- Associated skin lesions are sometimes present in the form of asymptomatic small popular lesions that slowly enlarge. These have a tendency toward central softening that may lead to ulceration (sometimes mistaken for molluscum contagiosum). The diagnosis is confirmed on skin biopsy.

The onset of CM may occur over days or weeks. Initial symptoms are frequently more subtle and may just include fever and headache. It does not present with obvious meningismus. Many patients present at an advanced stage of infection and their prognosis is usually poor.

Since CM occurs late in the progression of HIV disease, it may be associated with other co-morbid conditions which will make the signs and symptoms of its presentation less apparent, in some cases CM may co-exist with bacterial or TB meningitis. In this instance an invasive procedure, such as a diagnostic lumbar puncture is necessary.

Laboratory investigations

These include examination of cerebrospinal fluid (CSF) obtained at lumbar puncture. CSF results in CM can be normal in some cases, but usually show the following features:

- A mildly elevated serum protein, normal or slightly low glucose, a few lymphocytes and numerous organisms
- A wet preparation smear of the centrifuged CSF sediment with Gram staining will often show a large number of cryptococcal organisms

- India ink smear will show the encapsulated yeast in over 70% of cases, although artifacts can cause confusion
- Cryptococcal antigen is almost always (99%) detectable on CSF latex agglutination testing and can also be detected in the serum in 98% of cases (Crag test)
- Culture for Cryptococcus in the CSF is usually positive within 48 to 72 hours

Prognosis

Untreated CM is fatal within 2 weeks of diagnosis. This statement has particular resonance in our environment where a diagnosis of CM may be made when the patient is on the point of death or at autopsy. About 50% of all successfully treated patients survive from between 8 months to a year.
Poor prognostic factors include:

- Altered level of consciousness and localizing signs at presentation
- Raised manometric pressure (CSF)
- Significant co-morbidity (sepsis, pneumonia, TB, etc)
- Recurrence
- Lack of cellular response in CSF
- Poor response to Amphotericin B

Treatment

The treatment of CM is divided into three phases: acute, consolidation and maintenance.

Acute treatment:

The goal of acute treatment is to reduce the number of organisms by use of effective therapy and the management of complications.

- Effective therapy should be used in accordance with best practice guidelines. This is vital in order to prevent further deterioration of the patient's clinical condition.
- During the acute treatment phase of CM the aim is to reduce the number of organisms in CSF within a 2 week period.
- It is essential to manage complications of CM such as pain (especially headache) that can be severe. Complications such as raised intracranial pressure may be fatal at this stage if not managed.

Consolidation treatment:

The goal is to eliminate all organisms from the CSF and produce a "sterile" CSF. This is done by administering a higher dose of Fluconazole (Diflucan) for 8 weeks.

Maintenance treatment:

Ongoing maintenance is required to prevent recurrence: a lower dose (200 mg/day) of Fluconazole is administered as a secondary prophylaxis for life.

Drug Regimen

1. Acute treatment phase

Amphotericin B

The recommended dose is 0.7 to 1.4 mg/kg daily (administered as 50 mg vials, reconstituted in 200ml to 500ml of 5% dextrose water because it precipitates in other solutions) for 2 weeks.
Strongly recommended:

- Amphotericin B intravenous infusion (IVI) is considered the gold standard of treatment. It should be given as initial therapy whenever possible, especially in patients with severe infections (such as patients with depressed levels of consciousness).
    - ✓ It should be administered with a central line or long line as the IV solution causes severe phlebitis. If this is not possible, cycle drip sites should be used repeatedly and 1000 units heparin added to the infusion.
    - ✓ Amphotericin B is nephrotoxic therefore it is essential to ensure adequate rehydration of the patient during its administration.
    - ✓ Monitor serum urea/cretinine and increase fluid intake if there is deterioration. Avoid NSAIDS and other nephrotoxics if possible. Give antiemetics if vomiting occurs.

2. Consolidation phase

Fluconazole

Following Amphotericin B, Fluconazole 400 mg/day is given for 8 weeks. Although Fluconazole is generally well tolerated even in high doses (800 mg/day), it has the following side effects:

- Mild GIT disturbances
- Alopecia
- Rash
- Increase in liver enzymes
- Dizziness
- Headache
- Hypokalaemia

All these side effects are rarely significant and are usually reversible. Treatment should be stopped if there are signs of liver dysfunction or AST/ALT>10 times normal.

Comments: Amphotericin B is preferred for initial treatment but total dose prior to Fluconazole maintenance is arbitrary. Earlier changes to Fluconazole are recommended if there is intolerance or if IV Amphotericin administration becomes impossible. Some clinicians advocate a test dose of 1mg in 50 ml of 5% dextrose given IV over an hour with monitoring of vital signs. Then 0.3 mg/kg body weight over 4 hours, before the recommended dose when starting therapy. An alternative is a high dose of Diflucan given orally. This has been found to be effective as a primary treatment for patients who are at a lower risk of death from CM because of less advanced infection. Fluconazole is accepted as initial treatment only for patients with normal mental status.

3. Maintenance therapy

This is started immediately after the 8 weeks of consolidation therapy. Since maintenance therapy (secondary prophylaxis) is a life-long treatment, it is important that patients be educated to encourage adherence to treatment.

- The drug of choice is Fluconazole 200 mg/day.
- Primary prophylaxis is not recommended.
- Secondary prophylaxis is given to all patients who have documented previous cryptococcal meningitis, even if therapy was interrupted.

4. Management of CSF pressure

Individuals who remain symptomatic of raised intracranial pressure (without focal neurological signs) should be considered for therapeutic LP. This consists of serial LP, preferably with manometer.

- Measure initial opening pressure by manometry
- Remove ± 20 ml CSF if intracranial pressure is raised.
- Repeat daily until the opening pressure is normal.

5. Adjuvant Therapy

For the management of pain

- Pethidine 50 mg IM or paracetamol 1 g 6 hourly.

For the control of seizures

- Conventional agents like diazepam or Phenytoin are used.

Generally serial LPs will improve headaches as well. The Phenytoin dose should be adjusted when given in combination with Amphotericin B.

Follow-up:

This intervention will fail unless there is regular follow-up, regular treatment supply and good patient adherence. It is important for the health care professional to ensure that the patient has access to the following:

- Secondary prophylaxis with a regular supply of Fluconazole. This should be given to all individuals who have previously had CM even if therapy was interrupted and needs to be started again.
- Contraception for women. This is important for women taking Fluconazole as it is a potentially teratogenic drug.
- Adherence support: The needs and ability of the patient to cope should be continuously reassessed whenever possible and barriers to adherence identified and actively managed.
- Psychosocial support: This requires not so much quantity as quality of time spent with the patient/family to listen to their concerns, to ensure that they fully understand the nature of illness and are coping under the circumstance.

Treatment failure or Progression of symptoms:

Fluconazole resistance in Cryptococcus is rare but best practices recommend the following:

- Assess compliance
- Ensure the correct dose is being given
- Assess the availability of tablets in the clinic
- Consider another diagnosis

Special considerations:

Patients who are on antiretroviral therapy, or who begin this therapy after an episode of CM, may require some secondary prophylaxis. Caution should be exercised in prescribing Fluconazole to patients who are taking Rifampicin, Protease inhibitors, warfarin, oral contraceptives, oral sulphonyl ureas or Phenytoin because of the potential side effects and/or toxicity.

Tuberculous meningitis

Causative agent: mycobacterium tuberculosis

Pathogenesis

Scattered tuberculi foci (tubercles) are established in the brain, menninges or adjacent bone during the bacillemia that follows primary infection or late reactivation of TB elsewhere in the body.

Clinical presentation

- A prodromal (initial) phase lasting two to three weeks characterized by malaise, lassitude, headache, low grade fever and personality change.
- Menningitic phase follows with more pronounced neurologic symptoms such as meningismus, lingering headache and confusion, varying degrees of cranial nerve and long tract signs
- The paralytic phase. This is the stage during which the pace of illness may accelerate rapidly. Confusion gives way to stupor and coma, seizures and at times hemiparesis.

Diagnosis

Diagnosis can be difficult. Maintaining a high degree of suspicion is vital to initiate therapy

- CSF examination
- Elevated protein
- Lowered glucose concentration
- Mononuclear pleocytosis
- AAFB examination
- PCR (Polymerase chain reaction)
- Neuroradiology (computed tomography) Can show lesions like basilar arachinoditis, cerebral edema and infarction, and presence and cause of hydrocephalus

Treatment

(Uganda Clinical Guidelines 2003)

The treatment is in two phases (see doses in table)

1) **Intensive Phase:**
   2 months with a daily course of Streptomycin, Isoniazid, Rifampicin, and Pyrazinamide. In case of a reaction with Streptomycin, Ethambutol can be used instead.
2) **Continuation Phase**
   7 months with a daily course of Rifampicin and Isoniazid

Treatment of TB meningitis: Drug doses (mg) for different body weight ranges (Kg)

Drug	5-10	11-20	21-30	30-50	>50kg
Streptomycin	200	500	500	750	1,000
Isoniazid	100	100	200	300	300
Rifampicin	150	150	300	450	600
Pyrazinamide	500	500	1,000	1,500	2,000
Ethambutol	-	-		800	1,200

Streptomycin: The maximum dose in patients > 50 yrs is 750mg because of danger of deafness. It should also be avoided in pregnancy because of danger of deafness in neonates.

Adjuvant therapy

- Corticosteroids e.g. prednisone
  - ✓ Adults 60 mg/day
  - ✓ Paediatrics 1-3mg /kg

Complications

Hydrocephalus: This is corrected by surgical decompression of the ventricular system.

Neurosyphilis

Causative agent: Treponema pallidum.

It is unclear whether infection with HIV is an independent risk factor for the development of neurosyphilis. While some authors have suggested that neurosyphilis is both more fulminant and more difficult to eradicate in the setting of HIV disease, neurologic disease has always encompassed a broad spectrum of presentations and clinical courses, and clinical evidence does not support the theory that HIV alters the natural history of Treponema pallidum infection.

Clinical Presentation

Manifestations of neurosyphilis include meningitis, cerebral arteritis, and cerebritis, as well as optic neuropathy and deafness. Any HIV-infected patient with a positive serum FTA-ABS or MHATP should undergo lumbar puncture, regardless of presence or absence of neurologic disease.

Diagnosis and Treatment

In the absence of neurologic signs or symptoms, a positive CSF VDRL in the setting of abnormal spinal fluid establishes the diagnosis of latent neurosyphilis. Unfortunately, the sensitivity of the CSF VDRL in the setting of HIV disease is unknown but estimated at only 70% at best. A negative CSF VDRL does not exclude the diagnosis. A CSF pleocytosis (usually 10 to 400 cells/mm^3) and mildly elevated protein (46 to 200 mg/dl) with or without a positive CSF VDRL may be the only findings. One should probably err on the side of caution, and AIDS patients with abnormal CSF and a positive peripheral syphilis serology—even with negative CSF VDRL—should receive a course of at least 10 days of intravenous aqueous penicillin G, 4 million units every 4 hours. Repeat lumbar puncture with normalization of CSF is evidence of the efficacy of treatment. However, CSF abnormalities due to HIV infection alone can complicate interpretation. In contrast, a positive CSF VDRL in the setting of normal CSF poses another interpretive dilemma, particularly in a severely lymphopenic patient with advanced HIV disease. T. Pallidum has been recovered from CSF of patients with otherwise normal spinal fluid. In patients already treated for primary or secondary syphilis, either empiric therapy for neurosyphilis or careful interval neurologic and CSF evaluations are reasonable in such cases.

Aseptic Meningitis

Aseptic meningitis is a febrile meningeal inflammation characterised by CSF mononuclear pleocytosis, normal glucose, mild elevations in protein, and an absence of bacteria on examination and culture.

Clinical presentation and Diagnosis

Patients with aseptic meningitis often present initially with headache, occasionally in association with altered mental status or cranial neuropathies. Many patients with this syndrome probably have primary HIV meningoencephalitis. The meningitis can manifest at the time of seroconversion and can recur

spontaneously or become chronic. Because of the extremely high incidence of CSF abnormalities in HIV-infected patients, regardless of symptoms (see in this module under Diagnostic Procedures and Tests: Lumbar Puncture), interpretation of CSF in this population can be difficult. In investigating symptoms such as headache, altered mental status, and cranial neuropathy, aseptic meningitis must be a diagnosis of exclusion.

Prognosis and Treatment

The mortality rate varies with the cause. Permanent cerebral sequelae are more likely to occur in infants, but young children show improvement for a longer period of time than adults with similar infections. Patients will benefit from supportive therapy, this may involve correction of:

- Dehydration
- Electrolyte disorders and
- Fever
    - ✓ Patients with cerebral oedema must not be over-hydrated.
    - ✓ Anticonvulsants should be administered to control convulsions.
    - ✓ For cerebral oedema severe enough to produce central or trans-tentorial herniation, controlled hyperventilation, mannitol (0.25 to 0.50g/kg IV) and dexamethasone (4mg IV q 4hrs).

Viral Encephalitis

Overview

Viral encephalitis is an acute inflammatory disorder of the brain due to direct viral invasion or hypersensitivity initiated by a virus or other foreign protein. Encephalitis is distinguished from aseptic meningitis by the extent and severity of cerebral dysfunction, independent of signs of meningeal inflammation. Among the opportunistic viral infections of the CNS, the most important are the herpes viruses: herpes simplex 1 and 2 (HSV-1 and -2), herpes zoster (HZV), and cytomegalovirus (CMV). Each can cause a meningoencephalitis with mental status changes and focal neurologic findings. Diagnosis can be difficult, especially because of the low yield of CSF viral cultures in this setting. Sensitive CSF PCR assays have been developed for each of these conditions, however, and, where available, can greatly aid diagnosis.

Herpes Simplex Virus

In general, the onset of headache, fever, and seizures should, in the absence of other clear causes, prompt empiric treatment for herpes simplex encephalitis with acyclovir (10.0 to 12.5 mg/kg intravenously every 8 hours). Interestingly, HSV encephalitis is rarely reported among AIDS patients. Also, in contrast to its extremely severe course in immunocompetent persons, HSV infection in patients with advanced HIV disease is often insidious in onset and chronic in duration. Skin or mucosal lesions are absent in the majority of patients.

- CT or MRI scans may reveal edema, focal hemorrhage, or contrast enhancement in the characteristic locations: medial temporal lobes and inferior frontal lobes especially are affected if coronal images are obtained.
- However, diffuse lesions also occur. CSF often shows a lymphocytic pleocytosis and elevated protein.
- In addition, red blood cells may be a prominent, although nonspecific, finding.

- Glucose levels are usually normal.
- Electroencephalogram may show diffuse slowing, common to all encephalitides, or periodic lateralized epileptiform discharges or other focal abnormalities.
- Definitive diagnosis often requires brain biopsy, but CSF PCR may reduce the need for tissue diagnosis in the near future.
    - ✓ When herpes simplex encephalitis cannot be ruled out, acyclovir 10mg/kg IV q 8hrs must be started promptly (before patient lapses into coma) and continued at 10 days for maximal benefit. Acyclovir is relatively nontoxic but can cause abnormal liver function, bone marrow suppression and transient renal failure.

Herpes Zoster Virus

Herpes zoster infection of the CNS is associated with meningoencephalitis, cranial nerve palsies, myelitis, leuko-encephalopathy, ependymitis, or cerebral vasculitis leading to strokes and transient ischemic attacks (TIAs). Zoster encephalitis is probably underdiagnosed among AIDS patients. Clinical suspicion should be high in AIDS patients with stroke or TIAs.

Clinical presentation and Diagnosis

Neurologic signs and symptoms can precede or follow the rash, or be unassociated with a rash, present or past. CSF usually reveals only nonspecific, mild pleocytosis and protein elevation. HZV viral cultures of CSF and CSF PCR for HZV should be performed, where available. Positive PCR or culture results justify high dose intravenous acyclovir treatment. CT or MRI scans may demonstrate cerebral ischemia or combined hemorrhagic and ischemic changes.

Treatment

If skin lesions are present, immunofluorescence of biopsied tissue should be performed. Acyclovir (10.0 to 12.5 mg/kg intravenously every 8 hours) for 14 to 21 days has, in our experience, resulted in excellent recovery in zoster vasculitis.

Cytomegalovirus

Clinical presentation and diagnosis

Because CMV is ever-present in patients with advanced HIV disease, it can be difficult to determine what role, if any, CMV is playing in CNS disease.

Cells bearing CMV inclusion bodies are a common finding in the brains of patients with HIV disease at autopsy, regardless of presence or absence of neurologic symptoms. Occasionally, severe necrotizing CMV ependymitis or meningoencephalitis is seen on pathology, as well as necrotizing involvement of spinal roots. CT and MRI scans are usually normal or reveal only nonspecific changes, even in biopsy-proven CMV encephalitis. Occasionally, an ependymitis is evident on imaging but is not diagnostic for CMV infection. Similarly, CSF examination is nondiagnostic and cultures are usually negative, even in pathologically proven CMV encephalitis. CSF PCR, where available, should be performed. CMV PCR or bDNA is unlikely to be positive in the absence of real CNS disease. Because CMV involvement of the brain is usually patchy, even a brain biopsy can be falsely negative. Evidence of systemic CMV infection—retinal, gastrointestinal, or pulmonary—should be sought aggressively in any patient with HIV infection and signs and symptoms of acute meningoencephalitis for which no other convincing cause is found.

Treatment
Therapeutic response to ganciclovir has been documented in patients with spinal root involvement. A small clinical series of patients with CMV encephalitis described response to treatment with ganciclovir or foscarnet in 3 of 5 patients.

Toxoplasmosis (commonly known as toxo)
Causative agent: A protozoon called toxoplasma gondii.

Epidemiology
Incidence varies from region to region reflecting variations in exposure to the parasite. It is estimated that 28% of PLWHAs with antibodies to toxoplasma will develop toxoplasma encephalitis.

Pathogenesis
Toxoplasma gondii, an obligate intracellular protozoa, is recognized as a major cause of neurologic morbidity and mortality among patients with advanced HIV disease. Like other opportunistic pathogens, T. gondii causes asymptomatic or mildly symptomatic infections in normal hosts, but rapidly progressive, fatal disease in immunosuppressed patients.
Toxoplasmosis is a zoonosis with an infectious reservoir encompassing all animals. As the definitive host, the domestic cat and dog appear to be the major culprits in transmission to other animals. Excretion of oocysts has been documented in approximately one percent of cats. Invertebrates such as cockroaches and flies can also serve as transport hosts for oocysts.
Transmission to humans usually occurs by:

- Eating poorly cooked meat containing tissue cysts
- Eating food contaminated with soil containing oocysts
- Vertical transmission from mother to fetus during an acute infection
- Through infected organ transplantation
- Granulocyte transfusion

Risk factors involved in getting Toxoplasmosis include:

- CD4+ cell count below 100/mm³
- Past infection with T. gondii

The mean CD4+ cell count at the time of the initial diagnosis of toxoplasmosis is 44 and the median duration of survival after onset is 180 days if untreated.

Clinical presentation
Toxoplasmosis causes a multifocal cerebritis and the initial symptoms are often both diffuse and focal. The symptoms are often vague and nonspecific.

- Headache, usually dull and constant, it is present in 50% of patients presenting with toxoplasma encephalitis (TE). Severe headaches are more suggestive of cryptococcal meningitis.
- Fevers – occur in 40-50% of cases
- Confusion and lethargy are common
- Generalized or focal seizures occur in 15 to 30% of patients. Among all HIV related OIs, toxoplasmosis is the most common cause of seizures
- Frank meningisms occur in less than 5% of patients
- Hemiparesis, hemisensory loss or other focal neurological deficit also occur. At the time of physical examination up to 75% of toxoplasmosis patients are found to have focal neurological deficit.

Diagnostic procedures and tests

In almost all our centres a definitive diagnosis of toxoplasmosis is difficult to make.

- Computed tomographic (CT) scanning and magnetic resonance imaging (MRI) of the head are the key methods for identifying lesions suggestive of CNS toxoplasmosis. The head CT scan in patients with CNS toxoplasmosis typically appears abnormal; enhancing lesions are usually seen in 80 to 90% of patients. 60 to 70% of patients have multiple lesions shown by CT or MRI. Lesions are more common in the frontal lobes, basal ganglia, and parietal lobes and generally in cerebral white matter or subcortical grey matter.
- Lumbar Puncture (LP)

LP is a valuable diagnostic technique in this setting because it excludes other OIs as the cause of neurological signs and symptoms. For example, meningitides caused by Cryptococcus or Mycobacterium tuberculosis are common in this patient population and both have similar neurological presentations to CNS toxoplasmosis. Before LP is performed evidence of raised intracranial pressure should be ruled out via CT or MRI, where possible, otherwise simple fundoscopy can be used. Analysis of CSF in patients with toxoplasma encephalitis usually reveals normal glucose content,

- 50% show mildly raised CSF protein
- 15 to 50% show mild mononuclear pleocytosis
- Very high CSF proteins rarely occur in reactivated disease unlike congenital toxoplasmosis.
- Toxoplasmosis can be isolated by inoculating the clinical specimens into the peritoneal cavities of mice and subsequently examining peritoneal fluid and tissues for histopathologic evidence of infection.
- Serological tests: patients with active CNS toxoplasmosis tend to have higher titers than those with asymptomatic latent infection. However, this finding is not sufficiently reliable for diagnostic use. Positive IgM titers are unusual among HIV-infected patients with Toxoplasma encephalitis (TE). CSF anti-toxoplasma titers are positive in only 30-60% of HIV infected patients.

1. 1g titer should be measured for all HIV infected patients early in their disease (that is before HIV disease advances to significant immunocompromise) because a positive serologic finding, regardless of titer, indicates that the patient is at risk for reactivation of latent toxoplasmosis.

2. In patients who have signs and symptoms suggestive of reactivated toxoplasmosis, 1gG measurement alone cannot prove or disprove the diagnosis. Nevertheless a toxo titer should be determined if the patient has never had a titer measure in the past. Because a negative 1gG titer is uncommon in a patient with reactivated toxo and should prompt the clinician to consider an alternative diagnosis that will explain the clinical presentation.

3. Although 1gM anti-toxoplasma antibodies are not a routine part of the diagnostic work-up for toxoplasmosis in PLWHAs, who have reactivated disease, they should be considered when the clinical presentation is consistent with toxo but serum 1gG toxoplasma antibody titers are negative.

Treatment

Acute treatment: An HIV infected patient with TE should be treated initially with one of the following regimens for 8 weeks or until all CT evidence of toxo has resolved. Then a lower dose maintenance regimen should be initiated and continued for life.

Regimen of choice:

- Sulfadiazine and Pyrimethamine.
  - ✓ Dose of sulfadiazine 1.0 to 1.5 g orally every 6 hours
  - ✓ Dose of pyrimethamine 75-100mg loading dose followed by 50 - 100 mg orally per day.

Side effects of sulfadiazine include: neutropenia, nausea, vomiting, diarrhoea, rash, fever, interstitial nephritis, crystalluria and nephrolithiasis.

- To minimize nephrotoxic complications, it is recommended that urinalysis, serum creatinine, and blood urea nitrogen values be obtained before starting sulfadiazine treatment. Patients should be advised to drink 2 to 3 litres of water per day, becausedehydration increases the risk of crystallization of sulfadiazine in the urinary collecting system.

Side effects of pyrimethamine include: pancytopenia, headache and gastrointestinal upset. To decrease the incidence of pancytopenia 10 mg of folinic acid is administered orally with each dose of pyrimethamine. This addition does not negate the beneficial effect of the drug therapy because T. gondii is unable to use folinic acid.

Alternative regimen:

- Clindamycin and Pyrimethamine
  - ✓ Dosage of clindamycin: 450-600 mg orally, 600-1200 mg IV 4 times daily for 6 to 10 weeks followed by a maintenance regimen of 300 mg orally 4 times daily.
  - ✓ Dosage of Pyrimethamine as above

Side effects of clindamycin include: drug related non-infectious diarrhoea and other gastrointestinal tract (GIT) side effects. However, significant incidence of pseudomembraneous colitis is rare.

- Trimethoprim-Sulfamethoxazole:

This regimen is not recommended for primary or alternate therapy for toxo, but may be useful in treating patients who are comatose (because it can be given intravenously) or in patients who also have PJP. It may also be of some use in resource limited settings like ours where patients or relatives cannot afford the other regimens.

- ✓ Recommended dosage: Trimethoprim 10 mg/kg/day
- ✓ Sulfamethoxazole 50mg/kg/day

- Atovaquone:

Atovaquone, a hydroxynaphthoquinone, can be used as a salvage therapy in patients who cannot tolerate standard regimens or who have a relapse on such regimens.

- ✓ Recommended dosage: 750 mg orally 4 times per day for 18 weeks.

Other drugs:

Roxithromycin, Azithromycin and Clarithromycin are new macrolide agents under investigation for the treatment of TE. Whereas Spiramycin, the agent used to treat primary toxo during pregnancy, is not believed to be useful in treating CNS toxo in HIV infection.

Maintenance therapy for chronic suppression of Toxoplasmosis

HIV infected patients with TE require suppressive anti-toxoplasma therapy for life. Relapse after discontinuation of therapy is the rule rather than the exception, even if clinical and CT abnormalities have totally disappeared. This tendency to relapse is attributable to the inability of current therapy to eradicate the cyst form of the organism, which can subsequently rupture and release tachyzoites that reinitiate active

disease. Thus HIV infected patients with TE should receive full-strength therapy for 8 weeks or until all CT evidence of toxo has resolved, followed by lower dose chronic suppressive therapy.

Recommended drugs are:

- Co-trimoxazole 960 mg daily for life.

Unfortunately, as many as 60% of patients receiving daily sulfa diazine-pyrimethamine develop drug toxicity and in 40 to 50% of patients use of the drugs must be discontinued and alternative regimens as described above, given.

Adjuvant therapy

These may include:

- Steroids:Dexamethasone (Decadrom) for abscesses associated with severe mass effect (on a tapering dosage schedule, for example, starting with 2 mg given orally or intravenously every 6 hours)
- Anticonvulsants: For infection induced seizures (E.g. Epanutin (dilatin^{R}) 300 mg given orally at bedtime)

Prevention of Toxoplasmosis in HIV-infected persons

- Prevention of seroconversion:
- HIV infected persons who are sero-negative for toxo should avoid situations/practices that put them at risk
    - ✓ Avoid contact with longstanding cat feces
    - ✓ Cook meat thoroughly (internal temperature of 66ºC for at least 10 minutes to kill any tissue cysts) before being eaten by patients or pets
    - ✓ Wash hands after contact with soil that may be contaminated with cat feces.

- Prevention of reactivation of the disease in seropositives.
- There are no established guidelines for Primary TE chemoprophylaxis, but there are general recommendations for all HIV infected people who are seropositive for toxo and who have CD4+ cell counts below 100-200.
    - ✓ Oral sulfamethaxazole-trimethoprim (septrin) 960mg once a day
    - ✓ Oral dapsone and pyrimethamine (100 mg twice weekly dapsone and 25 mg twice weekly pyrimethamine).

Fungal Encephalitides

Candida albicans, which commonly infects the oral mucosa of patients with HIV disease, can cause a meningoencephalitis, usually in the setting of fungemia. Microabscesses are the usual pathologic findings in the brain. Mucormycosis, especially among injection drug users, and aspergillosis have been reported causes of meningoencephalitis in patients with advanced HIV disease, as have coccidioidomycosis and histoplasmosis in patients from endemic areas.

Diagnosis

Diagnosis usually requires demonstration of fungus from biopsied tissues and a high index of suspicion.

Treatment

Standard regimens for Candida meningitis have not been established.

- Amphotericin B IV has been successful in some patients, but intrathecal administration has been required in many cases.
- Fluconazole has also been reported to be effective. Usually, 400 to 800mg/day (po, or if necessary, IV) may be used.

Mucormycoses and Aspergillosis require aggressive management with IV Amphotericin B (usually 1.0 to 1.5mg/kg/day)
Histoplasmosis is due to Histoplasma capsulatum causing primary pulmonary lesions and hematogenous dissemination.

- Amphotericin B is the treatment of choice for disseminated histoplasmosis, itraconazole can be used to treat less severe cases. In AIDS patients indefinite chronic therapy with itraconazole is used to prevent relapse because the best duration is not known.

Progressive Multifocal Leukoencephalopathy (PML)

Clinical presentation and diagnosis

Progressive multifocal leuko-encephalopathy (PML) is caused by JC virus, an ever-present polyoma virus that affects approximately 4 to 8% of patients with advanced HIV disease. It is a subacute or chronic progressive illness most often characterized by focal neurologic findings, such as hemiparesis, gait abnormalities, and visual field cuts, and by mental status and personality changes. Dementia, encephalopathy, and coma can occur with fulminant disease. Seizures are uncommon, but not rare.

If focal deficits are not prominent, it can be difficult clinically to distinguish PML from AIDS Dementia Complex (ADC). CT or MRI usually reveals focal or diffuse lesions in the white matter, particularly in the parieto-occipital region. The brainstem or cerebellum may be solely involved in up to 15% of cases. Single lesions are not uncommon in PLWHAs however, making “multifocal leukoencephalopathy” something of a misnomer in this population, and grey-matter involvement is well described. With rare exceptions, the lesions do not enhance, nor do they cause tissue edema or mass effect. Routine CSF evaluation is nondiagnostic and is usually normal or reveals only nonspecific changes, such as mild pleocytosis or protein elevation. CSF PCR detection of JC virus DNA has become a useful tool in the diagnosis of PML, and is available in some commercial laboratories.

Treatment and Prognosis

In many cases, there is progressive decline over the course of 4 to 5 months leading to death. There appears to be, however, a spectrum of disease possibly related to the degree of immune competence in HIV-infected persons. Stabilization of symptoms, either without treatment or in the setting of antiretroviral therapy, occurs in some patients with relatively high CD4+ counts (> 200), for whom PML is the CDC AIDS-defining illness. A small group of patients with progressive disease have improved and stabilized for up to 2 years after therapy with intrathecal cytosine arabinoside (araC). A controlled clinical trial, however, showed no benefit of either IV or intrathecal araC when added to antiretroviral therapy (ACTG 243). The topoisomerase inhibitor Topecan, active against both HIV and JC virus, is in pilot clinical trials for PML. Early results look promising.

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Module 3
OPPORTUNISTIC INFECTIONS OF THE PULMONARY SYSTEM IN HIV/AIDS

Introduction:
Opportunistic infections affect all systems of the body. However, the lungs are the most common site for these diseases. They cause significant morbidity and mortality in PLWHAs.
They are classified as:

- Bacterial infections
- Fungal infections
- Viral infections
- Protozoal infections
- Non infectious opportunistic diseases

Goal:
To enable a health worker in Uganda to recognize, treat and/or refer respiratory tract OIs in PLWHAs.

Learning Objectives:
By the end of this module the participants should be able to:

- State the cause of respiratory opportunistic infection
- Explain the mode of transmission of the common causes
- Recognise clinical presentation
- Make a diagnosis and differentials
- Provide treatment and
- Prevention

Content Outline:
1. Categories of OIs in the respiratory system
    a) Bacterial
        i. Pneumonias
        ii. Tuberculosis
            Adult
            Pediatric
    b) Fungal
            Pneumocystis jiroveci (PJP)
            Other fungal pneumonias
    c) Viral
    d) Non infectious opportunistic diseases

2. Diagnosis of OIs of the respiratory tract
3. Management of OIs of the respiratory tract
4. Prevention of OIs of the respiratory tract

Methodology:

1) Definition

Steps

1. Brainstorming
2. Trainer summarises and clarifies as needed

2) Listing of OIs in the respiratory tract.

Steps

1. Brainstorming
2. Trainer clarifies and makes additions as needed
3. Trainer gives simple and easily remembered classification.

3) Manifestation of OIs in the respiratory tract

Steps

1. Brainstorming
2. Trainer summarises

4) Diagnosis of OIs

Steps

1. Brainstorming.
2. Trainer summarises investigations done in the respiratory tract

5) Management of OIs of the respiratory system

Steps

1. Brainstorming on principles of management
2. Trainer summarises

6) Prevention of OIs of the respiratory tract

Steps

1. Brainstorming on principles of prevention.
2. Trainer defines the principles of prevention.

7) Individual common respiratory infections

Steps

1. Lectures on the common respiratory tract infections
2. Questions + Answers

Teaching Materials:

- Flip Charts
- Markers (Different colours)
- Masking tape
- Posters
- Slides/transparencies
- Projector
- Notepads
- Pens, pencils

Trainer's Notes:
Bacterial Pneumonias

Causative agent: Streptococcal pneumonias

H. Influenza, staphylococcal aureus and pseudomonas aerogunosa.

Epidemiology

Incidence is 5.5-29 per 100 seropositive patients compared to 0.9 -10 per 100 in HIV -+seronegative patients

- More frequent in advanced HIV immunosuppressed patients.
- Other predisposing factors: Intravenous drug use (IDU), smokers and patients of low socio-economic status

Pathogenesis

The infection in immunosuppressive syndrome (ISS) involves encapsulated organisms mainly because of

- A deficiency of immunity
- Alveolar macrophage dysfunction.

Clinical presentation

The clinical presentation is similar to that in patients not infected with HIV. There is an abrupt onset of fever, chills, rigors, dry cough with sputum production later. Dyspnoea and pleuritic chest pain commonly occur.

Diagnosis

1) History suggestive of pneumonia
2) Sputum: G-stain culture of expectorated or induced sputum.
3) Blood cultures
4) Chest X-ray : Segmented, lobar Reticular nodular, or Rarely lobar infiltrates

Treatment

- In a mild disease oral Penicillin such as amoxicillin, ampicillin or penicillin.
- Cephalosporins: cefatorxime, cefuroxime and ceftriaxone are used
- Macrolides: used if a typical pneumonia is suspected or as an alternative to penicillins; this includes erythromycin, azithromycin plus clarithromycin.
- Fluoroquinolones: levofloxacin, moxifloxacin
- Others: gentamycins, meropenem, clindamycin

Commonly a combination of the above antibiotics is used depending on the suspected causative organisms.

Complications

- Pleural effusion
- Empyema
- Bronchiectasis

Prevention

- Avoid smoking
- Pneumovax (controversial)
- Use of septrin in severe immunosuppression (stage 4)

Tuberculosis in Adults

This section provides basic information that will enable a health worker in Uganda to recognise, refer and/or treat tuberculosis in a PLWHA. It also highlights the importance of TB as a health problem.

What is the cause?

Tuberculosis infection in the majority of cases is caused by a bacterium called mycobacterium tuberculosis. However, other forms of mycobacteria such as mycobacteria bovis and mycobacteria africanum also cause tuberculosis. The lungs are the usual target organ of infection, but the organisms can also enter the blood and spread to infect almost any part of the body. This includes the liver, kidneys, stomach and gut, bones, skin, breast, brain and spinal cord. Other mycobacterium include: Mycobacterium avium complex (MAC) and Mycobacterium avium intracellulare (MAI).

The importance of TB as a health problem

The following facts are provided to highlight the importance of TB as a health problem.

- In 1993 WHO declared TB a global emergency
- Worldwide:
    - ✓ 1.9 billion people are infected by the tubercle bacilli
    - ✓ 3 million deaths occur from TB every year
    - ✓ 95-98% of new infections, illness and deaths occur in the developing world
- Africa - out of a total population of 395 million
    - ✓ 200 million are infected by the tubercle bacilli
    - ✓ 0.6 million die of TB annually
    - ✓ 50%-70% of new TB cases are also infected with HIV
- Uganda
    - ✓ In 1991 there were 19,016 cases of TB but by 1996 it had risen to 27,122 cases

Mode of transmission

An infectious case of tuberculosis (sputum smear positive cases) is usually the source.

- A patient with pulmonary TB expels micro-organisms into the air in tiny droplets when coughing, sneezing or laughing. These droplets containing the micro-organisms may be inhaled by another person. The micro-organisms settle in the lungs of the person who has inhaled them and they begin to multiply, and so infection occurs.
- Exposure to the micro-organisms is greatest among those living in close proximity to the patient.

Other modes include

- A person who drinks unpasteurised milk from an infected animal can get TB.

Primary infection in TB

When a non-infected person inhales droplets, the organisms will lodge in the terminal airways. This leads to primary infection in the lungs, regional lymph nodes or pleural.
Primary infection can lead to either of the following situations:

- No clinical disease. The patient develops immunity which can be recognized by a positive tuberculin skin test. This is what occurs in 90% of cases. And is what is known as the *tuberculosis-infected* person. In such a person there are latent (dormant) tubercle bacilli in the body. The person is not sick from TB, nor is s/he infectious.
- In 10% or so of cases the primary infection progresses directly to disease. The form of tuberculosis which results from progression of the primary infection is called progressive primary disease.

Specifically such patients may develop tuberculosis meningitis, pericarditis and military tuberculosis.

Post Primary tuberculosis

When a person, who in the past has had primary infection, develops symptoms suggestive of active TB and is then found to have TB, s/he has Post Primary TB or Secondary TB.

Pathogenically therefore tuberculosis diseases are divided into two types.

- Primary tuberculosis – resulting directly from primary infection
- Post Primary tuberculosis – occurs years after primary infection

Tuberculosis may also be classified on clinical grounds as follows:

- Pulmonary tuberculosis (PTB) – TB of the lungs
- Extrapulmonary TB – TB occurring outside the lungs

Tuberculosis and HIV infection

As noted above, 90% of people who get primary infection retain the dormant (latent) bacilli in their body. In a person who has both HIV and TB infection, progression of HIV leads to further weakening of the immunity which facilities the reactivation of the dormant infection.

- How does TB interact with HIV?

TB accelerates HIV progression, and HIV increases the risk of developing active TB disease.

Diagnosis of TB in both HIV infected and non-infected

- Signs and Symptoms
  - ✓ Persistent cough for 3 or more weeks
  - ✓ Sputum production which may be blood-stained (haemoptysis)
  - ✓ Chest pain
  - ✓ Loss of weight, loss of appetite, evening fevers and night sweats
- Confirmation that a person has TB (a TB case) can be made by performing the following investigations:

1. **Sputum smear staining with Ziehl-Neelsen stain.**

   This stain detects Acid-Alcohol fast bacilli (AAFB), the bacteria that cause tuberculosis in the patient's sputum. The patient should produce 3 sputum specimens.

   - 1st specimen given the first time the patient is seen
   - 2nd specimen taken early the following morning (the patient takes the specimen bottle home)
   - 3rd specimen when she/he brings the early morning specimen (one early morning specimen and 2 spot specimens)

   - Chest X-ray

   This test is particularly useful in children who have been in contact with tuberculosis patients.

2. **Lymph node biopsy or tissue biopsy can be taken for diagnosis**

   Again this requires surgical procedures and machines to process the tissues and expert (pathologist) to read the results.

   1. Tuberculin test (mantoux).

2. Abdominal ultrasound examinations to identify enlarged lymph nodes are sometimes used as a means of diagnosing TB.

The Different "Cases of Tuberculosis"

Tuberculosis patients are not the same which leads to "case definition". Following are the different types of defined TB cases.

1. New patient: A patient who has never taken tuberculosis medication or has taken it for less than one month. The patient can have new pulmonary or extra pulmonary TB.
2. Treatment failure: A patient whose sputum smear turns or remains positive for tubercle bacilli when examined after 5 months of the recommended drug combination and dosage.
3. Default (Treatment after Interruption): A patient, who has taken tuberculosis drugs for more than one month, stops for more than two or more moths, then returns to the clinic with sputum smear positive for tubercle bacilli.
4. Relapse: A patient, who received a full course of drug treatment for TB, was declared cured and discharged, but later returns to the health unit with sputum smear (AAFB) positive upon examination.

It should be noted that in order to define cases 2, 3, and 4 a sputum smear of the patient must have been examined and found to be AAFB positive.

Treatment of tuberculosis

The five essential drugs used for the treatment of tuberculosis are:

- Rifampin ®
- Isoniazid (H)
- Ethambutol (E)
- Pyrazinamide (Z)
- Streptomycin (S)

In brackets are the standard abbreviations for these drugs.

- How TB drugs are given:
  - ✓ The drugs are given in combination (regimens)
  - ✓ Never give the drugs singly
  - ✓ Never give the drugs in unknown regimens
- The regimens:
  - ✓ Have been combined according to specific scientific guidelines
  - ✓ Have a specified duration
  - ✓ Specify how the drugs are to be given during treatment
  - ✓ Have a standardized short-hand that is easily read and understood internationally
- Treatment duration is always divided into two parts:
  - ✓ Intensive phase
  - ✓ Continuation phase

Intensive phase (in cases of 8 months duration) takes 2 months with 4 drugs being used. While the continuation phase takes 6 months with 2 drugs used.

Using the abbreviations above, a regimen can be written as: 2 EHRZ/6 EH

- This is usually used for "a new case of TB"
- For a default/return after treatment interruption a re-treatment regimen shown here is used:

2 EHRZS/1 EHRZ/ 5 HER

- For relapse a re-treatment regimen can be used whilst awaiting the results for a sputum culture and the drug sensitivity test
- For treatment failure drug sensitivity is required and alternative TB drugs are used
- Children with pulmonary or extra pulmonary TB:

2 RHZ/4 RH

Practices affecting proper treatment of TB

- In-patients' treatment is not supervised
- Patients are given intensive phase drug (rifampicin) without ensuring a DOT service
- Follow-up treatment services are not easily accessible and convenient to patients. They end up by defaulting before completing their full course of treatment.
- Patients feel better and stop taking drugs
- Family life is troubled by initial long admissions
- Economic activities are affected by frequent referral to health units for follow-up and collection of drug supply.

Community based directly observed treatment short course strategy

This strategy recommended by WHO in highly endemic countries has been adopted by the National TB and Leprosy Programme and has five pillars:

Political commitment – to District and Health Service District (HSD) TB control services integrated into Primary Health Care (PHC)

1. Case detection by microscopy – 3 sputum smear examination of self referred Tbpatients

2. Directly Observed Therapy (DOTs) – provided with recommended drug regimens that are free of charge. The daily direct observation is undertaken by a volunteer or a health worker to ensure proper case management and full patient adherence to treatment.

3. Regular supply of all anti-TB drugs - based on the number of registered patients and stock levels

4. Information systems – to monitor case detection and treatment outcomes. Recording of patient information on health unit, laboratory, sub county health workers, sub district health registers. Quarterly analysis and reporting of cohort of patients (see algorithm illustrating CB DOTs)

Prevention of TB

- Risk PPD> 5 mm induration without prior prophylaxis or treatment
- Recent TB contact
- History of inadequately treated TB that healed

Preferred: INH 300mg/day + pyridoxine 50mg/day >270 doses

9 months or up to 12 months with interruptions

or

INH 900mg + pyridoxine 100g twice weekly with directly observed therapy >76

doses 9 months or up to 12 months with interruptions

or

INH – resistant stain
Rifampicin plus PZA x 2 months

Tuberculosis in Children

Unlike adults, TB in children is difficult to diagnose. It is even harder in the HIV infected child where other opportunistic infections can present like TB.

Clinical features suggestive of TB

- Failure to thrive (FTT)
- Fever more than one month
- Persistent cough > 1 month with an abnormal CXR that does not improve despite adequate broad spectrum antibodies (>2 wks)
- Close contact with a TB infected adult

Diagnosis

(i) Mantoux test

A positive Mantoux test may be helpful in deciding if the child has TB; however, a negative Mantoux does not exclude TB.

False negative Mantoux in the presence of TB may be because of:

- Underlying immunosuppression
- Overwhelming TB disease
- Malnutrition
- Incorrectly done test
- Recent measles infection

(ii) Sputum

- should be examined for AAFBs in older children
- in children under 5 years of age early morning gastric aspirates should be examined instead of sputum

(iii) CXR

When in doubt after above work up, a trial anti-TB therapy can be given and response to treatment documented by weight gain and resolution of symptoms.

Treatment

- See adult treatment regimes but in paediatric doses.

Children with pulmonary or extra –pulmonary diseases:

- ✓ Initial phase 2RHZ
- ✓ Continuation phase 4RH

Prevention

It is recommended that children born to HIV infected mothers should get all their childhood immunisations on schedule as prescribed by MOH. However, when a child has symptoms of HIV disease, BCG and other live vaccines should be avoided. When a newborn is exposed to open TB in the mother, prophylactic isoniazid is to be given for the first six months. If Mantoux remains negative and the child is well, stop prophylaxis.

Fungal Pneumonia

Pneumocystis Jiroveci Pneumonia

Introduction

Causative agent

Although Pneumocystis Jiroveci has long been considered a protozoan, recent studies of ribosomal RNA from the organism have shown greater similarities with fungi. This would suggest that it should be re-classified. Such a re-classification has no immediate clinical importance, but it may suggest new therapeutic approaches. Because P. jiroveci has not yet been officially "re-classified", for the purposes of this discussion it is considered a protozoon.

Pneumocystis jiroveci pneumonia (PJP) is a common opportunistic infection that occurs almost exclusively in people who are severely immunosuppressed (CD4+ count below 200/mm³) In immunocompetent hosts infection probably occurs but the individual remains asymptomatic, presumably because of the organism's low virulence. Serological studies have shown that 65 to 100% of children have antibodies to P. jiroveci by 2-4 years of age.

How one gets PJP is not clear, since the organism's natural reservoir and life cycle is not known. The organism may reside in the lungs as a latent infection since seropositivity to P. jiroveci occurs early in life. Active PJP probably can occur as a result of re-activation of latent infection, de novo infection or re-infection.

The relationship between PJP and HIV hinges on the effect of HIV on CD4+ cell counts. HIV infection destroys CD4+ cells as it progresses in an individual leading to a fall in the number of CD4+ cells. A critical number (<200 cells/mm³) is reached, below which the body's immune system cannot maintain P. jiroveci in a latent state. At which point it begins to multiply and cause PJP disease.

The relationship between CD4+ cell count and incidence of PJP does not have significance in infants. One report cited CD4+ cell counts of 451 to 1,530 cells per microliter in 8 HIV-infected infants with PJP.(1)

Risk factors for PJP

According to guidelines published by the US Public Health Service, candidates for PJP prophylaxis include:

- A patient with a prior history of PJP
- A patient with CD4+ cell count of less than 200 cell/mm³
- An HIV infected person with thrush or persistent fevers
- Several studies have collected data suggesting that it may be appropriate to begin PJP prophylaxis in patients with other AIDS defining opportunistic infections, possibly even non PJP pneumonias (2)

Clinical Presentation

Because of the diverse presentation of PJP and the lack of pathognomonic physical findings for this disease, patients usually do not appear with a "classic" presentation.
Typically, however, patients present with:

- Fever

- Dry cough
- Shortness of breath on exertion
- Symptoms appear gradually over several weeks

Physical findings are sparse. Laboratory findings are non specific.

Physical findings

HIV-infected patients with PJP may initially exhibit minimal signs, but they often appear ill due to several weeks of fever and cough.

- Tachypnoea may be so pronounced, and patients may be so dyspnoeic that they are unable to talk without stopping to rest
- Circum-oral, acral, and mucous membrane cyanosis may be evident
- Chest findings are minimal despite advanced pneumonitis
- Rarely will hemoptysis be a presenting symptom

Prophylactic aerosolized pentamidine is reported to make patients have milder respiratory symptoms.

Laboratory findings

Blood chemistries: Complete blood count (CBC) and Erythrocytes sedimentation rates (ESR) show no characteristic pattern on PJP patients.

Serum chemistries are not particularly helpful. However, in many studies serum LDH concentration is frequently increased. (3, 4, 5)

Given these data the serum LDH concentration, although a non-specific indicator of lung parenchymal damage appears useful in predicting which patients will do well. Other investigations include: Arterial blood gases and serologies.

Pulmonary function tests: The most consistent abnormality of pulmonary function in a patient with PJP is a decrease in the single breath diffusing capacity for carbon monoxide (DLCD).

Radiographic presentation: The classic presentation for PJP in PLWHAs is a diffuse interstitial infiltrate, although all of the following presentations have occurred: abscesses, cavitations or cystic lesions, lobar consolidation, nodular lesions, effusions, pneumothorax, pneumo-mediastinum and a normal chest radiograph.

Treatment

PJP is treated by oral or intravenous (IV) medications given for up to 3 weeks.

- Patients who are very ill with PJP should be admitted to hospital, treated with IV medications and given oxygen to help them breathe better.
- Patients who are not so ill or those who recover quickly are treated as outpatients with oral therapy
- The most commonly prescribed medication for PJP is trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, and Septra). That is: TMP/SMX (2 double-strength tabs every 8 hours or 5 mg/kg TMP and 25 mg/kg SMX intravenously every 8 hours) x 3 weeks.

or

- IV pentamidine 3 mg/kg/day for 14-21 days. It is given intravenously once a day.

Alternative treatment:

- TMP 320 mg every 8 hours + Dapsone 100 mg every 8 hours
- Clindamycin 300-450 mg every 6 hours + Primaquine 15-30 mg once a day

- Atovaquine 750 mg once a day
- Pentamidine 300 mg daily

Additional alternative:

- TMP 45 mg/m² once a day IV + leucovorin 40 mg/m²/every 6 hours

Adjuvant therapy:

- Prednisone or another steroid is recommended if there is significant respiratory dysfunction. Prednisone 40 mg 12 hourly for 5 days, then 40 mg every 24 hours for 5 days, then 20 mg once a day for 11 days.
- Oxygen via Nasal prongs

Maintenance therapy

Everyone who has had PJP should be on maintenance therapy. The choices are the same as those for primary preventive therapy.

- Stopping maintenance: Although it may be possible to stop maintenance therapy if the CD4+ cell count stays above 200, there is still insufficient data available to be able to make a recommendation.

Primary Prophylaxis

Prophylaxis is indicated when CD4+ cell counts equal or are below 200 (some suggest <250); when the lowest ever (nadir) cell count is below 200 and/or if there is a history of candidiasis in the throat or unexplained persistent fever for over 2 weeks regardless of CD4+ cell count.

Preferred:

- TMP/SMX two single-strength tablets daily

or

- one double-strength tablet daily.

A gradual increase in TMP/SMX dosage may help reduce side effects.

Preferred alternatives: If unable to tolerate TMP/SMX then

- Dapsone (100 mg once a day) should be given

or

- Dapsone (50 mg once a day) + pyrimehthamine (50 mg once a week) + leucovorin (25 mg once a week).

Additional alternative:

- Aerosol pentamidine (300 mg once a month); atovaquine (1500 mg once a day)

or

- IV pentamidine (300 mg once a month).

Other Fungal Pneumonias

These fungal infections in the respiratory tract are rare. They include:

- Aspergillus
- Histoplasmosis
- Penicillosis
- Cocciodiomycosis

Aspergillosis

Introduction

This is a rare opportunistic fungal infection which has been reported in people with HIV infection.

The only species associated with disease in mankind is: Aspergillus fumigatus.
Target organs are: the lungs, sinuses, ears and vagina.

Clinical presentation

The disease presents in two forms in the lungs:

a) Superficial. An asthmatic type induced by an allergic reaction to the presence of aspergilli in the bronchial tree. The sputum contains the organism and mycelia may extend for a short distance into the bronchial epithelium.

b) Granulomatous: Cavitating granulomatous lesions occur occasionally, almost only in patients with chronic bronchitis, or previous tuberculosis cavity, or abscess. The lesions are commonly near the lung surface with bronchopleural fistula formation as a common sequel.

In the ear and vagina:

c) Superficial infections with aspergilli, particularly in chronic otitis externa and media are common. Superficial vaginal membranes can be infected where diagnosis becomes difficult to differentiate from candida.

Diagnosis

Sputum stain and culture is associated with a lot of false positives since Aspergillus fumigatus is a commonly occurring saprophyte.

Treatment

The recommended drugs are: Amphotericin B and Intraconazole.

Histoplasmosis

Causes

Histoplasmosis (also known as "histo") is an infection caused by the dimorphic fungus: Histoplasma capsulatum. In endemic areas (in the Mississippi and Obio River Valleys) the mycelial form can be found readily in the environment, and is particularly associated with bird roosts, chicken coops and caves with bats.
The two most important factors that appear to determine the outcome of infection are:

- The host immune status
- To a lesser extent the size of the innoculum.

Site of infection

Widespread dissemination occurs in most patients, most frequently in the lungs and less frequently on the skin and in the GI system.

Clinical presentation

Histoplasmosis in AIDS usually presents as a disseminated infection. The most common manifestation (and sometimes the only presentation) is fever and weight loss, which occurs in about 75% of patients. Respiratory complaints (cough and shortness of breath) occur in about 50% of patients.

Chest radiographs are normal in 30 to 40% of patients, while most of the remaining patients have diffuse nodular infiltrates. Local generalized lymphadenopathy, hepatosplenomegally, colonic lesions, skin lesions and oral ulcers also occur. The involvement of GIT is usually in the form of ulcers which may make the patient present with abdominal pain and GIT bleeding. Between 5 and 10% of patients present with acute septic shock-like syndrome that includes hypotension and evidence of disseminated coagulopathy. Such a presentation carries a very poor prognosis. CNS involvement with meningitis or cerebral mass lesions is a rare but important complication.

Diagnosis

Apart from chest radiographs as mentioned above, laboratory tests can be done.
The major differential diagnosis of disseminated histoplasmosis is mycobacterial infection.
The diagnosis is usually made by culturing the fungus from blood or another clinical specimen or by histopathologic examination of bone marrow aspirate or biopsy materials, lavage fluid, or biopsy material from a lung or skin lesion.
A peripheral blood smear may show intracellular organisms in white blood cells in up to 50% of patients.

Treatment
As with many fungal infections, treatment is for life as the risk of relapse is substantial if therapy is stopped.

- Amphotericin B (0.5 to 1.0 mg/kg/day for 7-14 days) is the drug of choice for patients with disseminated histoplasmosis and gives an 85 to 90% favourable response.
- Itraconazole is used for patients with mild to moderate disseminated histoplasmosis
- In suppression therapy after initial Amphotericin B, Itraconazole 200 to 400 mg daily is the drug of choice
- Fluconazole is regarded as a second line therapy for histoplasmosis.

Prevention

- People at risk for histoplasmosis who live in areas where H. capsulatum is found in soil should avoid environments such as construction sites or caves where they are likely to inhale dust infested with the fungus.
- Some experts recommend that HIV-infected people with a CD4+ cell count of less than 200/mm³ take Itraconazole preventively if they live in regions where Histoplasmosis is common.

Penicilliosis

Introduction
Penicilliosis is one of the opportunistic fungal infections, rarely seen prior to the HIV pandemic. The organism is endemic to South East Asia and the southern part of China.
The disease is not as yet a problem in our region.
This section can be mentioned in passing. If time and interest allow, the trainer may choose to include it so that participants are aware of the extent of opportunistic fungal infections related to HIV/AIDS.

Causative agent: Penicilliosis is a disease caused by Penicillium marneffei.

Clinical presentation

- The most common presentation is fever and weight loss occurring in more than 75% of patients.
- Other common manifestations are:

- ✓ Skin lesions – present in about two-thirds of cases and be varied in appearance
- ✓ Generalized papular eruptions
- ✓ Central umbilicated papules resembling those of molluscum contagiosum
- ✓ Acne-like lesions and folliculitis

- Skin lesions commonly appear on the face, trunk and extremities. Pharyngeal and palatal lesions can also be seen. Occasionally, subcutaneous nodules will also be observed.
- Anaemia, lymphadenopathy and hepatomegally with or without splenomegally are also commonly seen
- Pulmonary symptoms (such as cough and dyspnoea) occur in 50% of cases

Therapy and Prevention

Patients with penicilliosis have a poor prognosis without treatment, but even with treatment the mortality rate is about 20%. Amphotericin B with or without flucytosine, or itraconazole is the treatment of choice, that is, Amphotericin B 0.6 mg/kg/day intravenously for 2 weeks followed by 10 weeks of itraconazole 400 mg/day has a good response. After completing initial treatment, patients with penicillium marneffei infection should receive secondary prophylaxis – itraconazole 200 mg/day can prevent occurrence of penicilliosis among PLWHAs and CD4 cell counts of less than 100 cells/cu mm (6)

Coccidioidomycosis

Introduction

This is another fungal infection which affects people with HIV/AIDS *but is of no clinical significance to our region.* The trainer can mention it in passing to complete the list of opportunistic fungal infections in HIV/AIDS.

Causative agent: coccidioidesimmitis.

Treatment

Treatment of disseminated coccidioidomycosis includes systemic antifungal therapy with Amphotericin B or azoles.

Fluconazole 400 mg daily or Itraconazole 200 mg daily may be used to treat non meningeal disease. Patients with coccidioidal meningitis are continued with high dose fluconazole for life except for those patients who fail to respond to treatment initially.

Viral pneumonias

Causative agents: Herpes simplex and cytomegalovirus. These are not common. They should be considered if there are co-pathogens that fail to respond to treatment.

Diagnosis

1. Pulmonary infiltrates.
2. Detection of CMV, herpes simplex with immunofluorescence technique.
3. Absence of another characteristic pathogen.

Treatment

- Ganciclovir 5mg/kg IV bid X 3weeks
- Acyclovir 30-36mg/kg/day IV for at least 7days.

The role of maintenance therapy is unclear.

Non Infectious Opportunistic Diseases

Non-infectious causes of lung disease include Kaposi's sarcoma (KS), non Hodgkin's lymphoma and interstitial pneumonitis. The malignancies (KS and NHL) are in other sites and just tend to involve the pulmonary system as a complication.

Non-specific pneumonistis may mimic pneumonia. In children this commonly presents as lymphocytic interstitial pneumonitis. Typically these patients present with several months of mild cough, dyspnoea and chest radiographs show interstitial infiltrates.

Treatment

Steroids are useful in this instance.

References:

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3. *Silver BA, Rubinstein A Serum lactate dehydrogenase levels and children with acquired immune deficiency syndrome (AIDS) and AIDS-related complex: possible indicator of B-cell lymphoproliferation and disease activity Am J Med 1985; 78: 728-36*
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Module 4

GASTROINTESTINAL INVOLVEMENT IN HIV INFECTION

Introduction:

The gastrointestinal tract (GIT) is a common site for OIs and neoplasms in HIV infection. Over 75% of PLWHAs experience GI symptoms such as dysphagia, abdominal pain, and diarrhoea and weight loss at some time during the course of their disease. In addition they may also have common gastrointestinal problems unrelated to the HIV infection. GIT manifestations are more likely to occur when the CD4+ counts fall below 300.

Side effects from other drugs being taken should be considered when evaluating a PLWHA who presents with GIT. Many of the antiretroviral drugs and antimicrobials used to treat HIV infection have serious GIT side effects, which are often overlooked in the differential diagnosis of GI problems in these patients.

Goal:

The goal of evaluation is to promptly identify treatable infections, ameliorate symptoms and preserve functional/nutritional status.

Learning objectives:

By the end of this module the participants should be able to:

- Describe the different conditions and causative agents of the GIT that affect PLWHAs
- Describe the signs, symptoms and problem approach of the common GIT conditions associated with HIV.
- Know how to evaluate and manage a patient with GIT conditions associated with HIV.

Contents outline

1. Different conditions of the GIT and their causative agents that affect PLWHAs.
2. Signs and symptoms of the common GIT condition associated with HIV.
3. Diagnosis, treatment and complications of GIT conditions associated with HIV.

Methodology

1. Different conditions of the GIT and causative agents that affect PLWHAs

Steps

1) Lecture
2) Questions + Answers

2. Signs and symptoms of the common GIT conditions associated with HIV

Steps

1) Brainstorming (and/or bedside teaching and/or case presentations where possible)
2) Trainer summarises and clarifies as needed
3) Small group discussions. Groups divided according to the conditions.
4) Report back
5) Trainer summarises and clarifies as needed

3. Diagnosis, treatment and complications of GIT conditions associated with HIV

Steps: Options can include brainstorming, small group discussions, case presentations and/or bedside teaching (or a combination of all). The setting will determine the appropriateness of the methodology.

Teaching materials:

- Markers (different colours)
- News print
- Flip chart or chalk board
- Over head projector
- Slide projector
- LCD projector and computer
- Pencils
- Pens
- Notebooks

Trainer's notes:

Bacterial Infections

Introduction

Typical enteric bacterial pathogens such as nontyphoidal strains of Salmonella, Shigella species and Campylobacter jejuni occur with only a slightly increased frequency in HIV-infected patients. When they do occur in immunocompromised patients the presentation is often atypical with a high incidence of bacteremia in addition to the typical symptoms of enteritis or colitis. PLWHAs also appear to be unable to effectively eradicate these organisms so that recurrent infection is common, often necessitating the use of chronic antibiotic suppression.

Diagnosis

Diagnosis is made with stool cultures. However, because of the high incidence of bacteremia, blood cultures should also be done in patients presenting with acute diarrhoea and fever.

Treatment

The principles of treatment for acute bacterial enteritis or colitis in HIV-infected patients are generally the same as for other patients, with supportive care and intravenous fluids as required. The infection will usually clear up and indications for antibiotic therapy are the same as for other patients. Immunocompromised patients and those with bacteremia should be treated with appropriate antibiotics (Table 1) Chronic suppressive therapy is often required as a result of the high incidence of recurrent infection.

TABLE 1. Treatment regimens for HIV-related gastrointestinal infections

ORGANISM	*DRUG OF FIRST CHOICE*	*ALTERNATIVE TREATMENTS*
Bacteria		
Salmonella	Ciprofloxacin 500mg PO/400mg IV × > 14 days	Ceftriaxone 2 g/day IV × > 14 days Trimethoprim/sulfamethoxazole 1 DS bid × > 14 days (5-10mg/kg/day)
Shigella	Ciprofloxacin 500 mg po bid for 10-14 days	Trimethoprim-sulfamethoxazole 160 mg/800 mg po bid Ceftriaxone 1-2 g IV q12-24h
Campylobacter	Ciprofloxacin 500 mg po bid or Erythromycin 500 mg po qid	Tetracycline 500 mg po qid
Mycobacteria		
Mycobacterium tuberculosis	Isoniazid 300 mg po qd + Rifampin 600 mg po qd + Pyrazinamide 15-25 mg/kg po qd + Ethambutol 15-25 mg/kg po qd	Depends upon sensitivity patterns
Mycobacterium avium-complex	Clarithromycin 500 mg PO bid + Ethambutol (EMB) 15mg/kg/day Azithromycin 600 mg/day + EMB 15mg/kg/day +/- RBT 300mg /day; adjust RBT dose for concurrent PI	Clarithromycin or Azithromycin + EMB+ Amikacin 15mg/kg/day or ciprofloxacin 500-750mg bid
Fungi		
Candida albicans (oral) (thrush)	Clotrimazole troches 100 mg po 1-3 times/day × 14 days Nystatin 500,000/mL units susp. 5 mL gargled or 200,000 units pastilles to suck 4-5×/day ×14 days Fluconazole 100 mg po/day × 14 days	Ketoconazole 200 mg po/day for 7-10 days Itraconazole 200 mg po/day or liquid solution to gargle
(esophageal)	Fluconazole 200mg/day × 2-3 weeks ± maintenance with 100mg /day (maintenance is optional)	Ketoconazole or itraconazole 200 mg po/day for 2-3 weeks + maintenance 200 mg daily

		Amphotericin B 0.3-0.5 mg/kg IV qd x 7 days
Histoplasmosis	*Initial therapy*: Amphotericin B 0.5-0.6 mg/kg IV qd for 4-8 weeks	Itraconazole 200 mg po bid
	Chronic suppression: Itraconazole 200 mg po bid	Amphotericin B 0.5-0.8 mg/kg IV weekly
Parasites		
Giardia lamblia	Metronidazole 250 mg po tid	Quinacrine hydrochloride 100 mg po tid
Entamoeba histolytica	Metronidazole 750 mg po tid x 10 d followed by Iodoquinol 650 mg po tid x 20 days	
Cryptosporidium	Paromomycin 500 mg PO tid with food × 2-4 weeks Paromomycin 1 gm PO bid with food + azithromycin 600 mg PO/day × 4 weeks , then paromomycin alone × > 8 weeks Misc. HAART, supportive fluid therapy, antiperistaltics eg Loperamide, food supplements	Paromomycin 500-750 mg po qid Octreotide 50-500 µg sq tid
Microsporidium	Albendazole 400-800mg Amphotericin PO bid × > 3wks (S. intestinalis only) Misc: HAART, Supportive fluid therapy, Nutritional supplements, Anti-peristaltic agents(Lomotil, Imodium, paregoric etc)	Metronidazole 500 mg PO tid Atovaquone 750 mg PO bid with Meals Thalidomide 100mg PO/day
Isospora belli	Trimethoprim-sulfamethoxazole 2 DS PO bid × 2-4 wks + maintenance 1-2 DS/day PO	Pyrimethamine 50-75 mg PO+ folinic acid 5-10 mg/day × 1 month + maintenance pyrimethamine 25 mg + folinic acid 5 mg/day
Viruses		
Herpes simplex virus	*For active lesions*: Acyclovir 200 mg po 5×/day or 400mg tid × 7-10 days Famciclovir 250mg PO tid × 7-10 days	Foscarnet 40 mg/kg IV q8h x 21 d

	Valacyclovir 1gm PO bid for 7-10 days	
	For maintenance therapy: Acyclovir 400 mg PO bid Famciclovir 250-500mg PO bid Valacyclovir 500mg PO bid	Foscarnet 40 mg/kg IV qd
Cytomegalovirus	*For active disease*: Ganciclovir 5 mg/kg IV bid × 2-3 weeks Valganciclovir 900mg PO/day with meals bid × 3 weeks Foscarnet 90 mg/kg IV q12h x 2-3 weeks	Cidofovir 5mg/kg/wk IV ×2, then 5mg/kg every 2 wks; each dose with Probenecid 2 gm PO 3 hours before each dose and 1 gm at 2 & 8 hours after.
	For maintenance therapy: Ganciclovir 5 mg/kg/day IV or 6 mg/kg IV qd 5 times/week Valganciclovir 900 mg PO/day with meals	Foscarnet 90-120 mg/kg IV qd

Mycobacterial Infections

Mycobacterium tuberculosis

Introduction

Pulmonary Mycobacterium tuberculosis (TB) is being seen with increased frequency in PLWHAs (see Module 3). In HIV infection the GI tract may be involved with extrapulmonary TB either as a direct extension from pulmonary lesions, where the esophagus is usually involved, or from systemic spread, where any part of the GI tract including the liver, pancreas and the peritoneum may be involved. Isolated involvement of the GI tract is unusual.

Diagnosis and Treatment

Diagnosis should be made with a biopsy with Ziehl Nielsen staining and culture of the most readily accessible lesions or peritoneal fluid. It is important to take a culture and do sensitivities on isolates of TB because of the rising incidence of multiple drug resistance. Initial therapy should include the four standard antituberculous drugs.

Mycobacterium avium complex (MAC)

Introduction
MAC is an atypical mycobacterium of environmental origin, which may occur in PLWHAs with CD4+ cell counts of less than 100.

Clinical presentation
It usually presents as a chronic systemic illness including fever, night sweats, weight loss and lymphadenopathy in addition to diarrhoea. The diarrhoea is often mild to moderate in severity and may have features to suggest malabsorption.

Diagnosis
Diagnosis can usually be made with blood and stool cultures. Blood cultures will usually be positive within 3-4 weeks, as this is a rapidly growing mycobacterium. Barium radiographs of the small bowel will often show dilation of the small bowel and irregular thickening of the small bowel folds. Ultrasound or CT scan of the abdomen will document hepatosplenomegaly, and there will often be enlarged intra-abdominal lymph nodes. Small bowel biopsy showing typical histology can also be used to establish a diagnosis. The appearance of Haematoxylin and Eosin (H&E) stains is strikingly similar to Whipple's disease. With mycobacterial stains the macrophages can be seen to be filled with acid-fast organisms.

Treatment
Therapy for MAC is difficult, requires multiple drugs (Table 1) and the results are generally poor. The organisms usually cannot be eradicated. The goal of therapy is chronic suppression. Drug side effects are common, and many patients are unable to tolerate full therapy. Despite treatment, many patients have progressive symptoms and wasting. Because of the difficulty in treating established MAC infection, prophylactic therapy is recommended, and recent studies have shown some benefit to using rifabutin 300 mg p.o. daily once the patient's CD4+ cell count falls below 100.

Fungal Infections

Candida albicans

Introduction
Candida albicans is one of the most common OIs in PLWHAs. Oropharyngeal candidiasis occurs frequently and is often one of the earliest clinical signs of immune damage.

Clinical presentation
When limited to the oropharynx it is often asymptomatic or associated with mild discomfort. Esophageal involvement is usually associated with difficulty in swallowing (dysphagia). However, many patients may have only vague epigastric discomfort during meals. Odynophagia (pain in swallowing) can occur with esophageal candidiasis, but severe pain with swallowing is unusual and suggests other infections such as cytomegalovirus (CMV), herpes simplex virus (HSV) or nonspecific HIV-associated esophageal ulceration. Patients with esophageal involvement usually have evidence for oropharyngeal Candida, commonly seen as whitish plaques on the buccal mucosa and posterior oropharynx. Esophageal involvement may occasionally occur in the absence of oral Candida, but this is unusual.

Diagnosis

The diagnosis is usually made on clinical grounds, and invasive investigations are only recommended where symptoms continue even after empirical anti-fungal treatment. Candidal esophagitis can be demonstrated with a barium swallow that shows abnormalities ranging from small filling defects on the mucosal surface representing mucosal plaques to thickening of the mucosal folds with a shaggy outline to the wall. Severe or deep ulcerations may be seen but are unusual. Endoscopy may show typical white adherent pseudomembranous plaques. In severe cases the entire esophageal mucosa may be covered with a confluent white membrane. Brush cytology or mucosal biopsy showing invasion of the candidal pseudohyphae into the squamous epithelium may confirm the diagnosis. Cultures are not routinely done, as these organisms are commonly present in normal individuals and tissue invasion should be demonstrated to confirm the diagnosis.

Treatment

Oropharyngeal candidiasis can be treated with a number of topical antifungal agents. (Refer to Table 1). Esophageal involvement should be treated with one of the systemic antifungal agents, as topical agents are generally not effective. Recurrence is common, and many patients require repeated therapy. Resistance to oral antifungal agents is starting to emerge. Disseminated infection with Candida may occur in HIV infection but is unusual, as the infection usually remains mucocutaneous. Disseminated infection has a poor prognosis and is often fatal.

Other Fungal Infections

Introduction

Other fungal infections seen in HIV infection include cryptococcosis, histoplasmosis and coccidioidosis. Disseminated infection of any of these fungi establishes a diagnosis of AIDS when present with a positive HIV antibody test. The incidence of these infections varies, and they are usually seen in patients who have lived in or have visited endemic areas.

Clinical presentation

Clinically, patients usually present with major systemic symptoms such as fevers, night sweats and weight loss. Neurologic involvement is usually seen with cryptococcosis. With histoplasmosis, the liver is often involved as part of a disseminated infection producing abnormalities of liver chemistry.

Diagnosis

Diagnosis of these infections generally depends on the demonstration of fungi through examination or culture of clinical specimens. Serologic tests are not dependable in the immunocompromised patient. Therapy usually requires intravenous amphotericin B in high doses. The response to therapy is generally poor, with a high rate of relapse and a poor overall prognosis.

Intestinal Parasitic Infections

Giardiasis

Introduction
Giardia lamblia is an intestinal parasitic infection in which transmission occurs via the oral-fecal route.

Clinical presentation
It usually infects the small bowel mucosa where it may be asymptomatic but usually causes diarrhoea with abdominal cramping, bloating and nausea. In severe cases it may produce malabsorption and steatorrhea.

Diagnosis
- Stool microscopy demonstrates Giardia ova and cysts. It may also be diagnosed on a duodenal aspirate or duodenal biopsy taken at the time of endoscopy.

Treatment
Refer to Table 1.

Entamoeba histolytica

Introduction
Entamoeba histolytica is an intestinal parasite transmitted by the oral-fecal route.

Clinical presentation
It usually causes colitis with bloody diarrhoea and abdominal cramps. Asymptomatic carriers are more frequent among PLWHAs than in patients with amebiasis who are HIV negative. Dissemination is rare and is not seen anymore frequently in HIV-infected patients than in other Entamoeba histolytica patients.

Diagnosis
Microscopy of fresh stool specimen demonstrates cysts and parasites. Sigmoidoscopy may show evidence of colitis, and typical punched-out “flask-shaped” ulcers.

Treatment
Refer to Table 1. Patients should have follow-up stool studies to confirm the eradication of the infection following treatment.

Cryptosporidium

Introduction
Cryptosporidium is a protozoal parasite that is now recognized as a cause of self-limited diarrhoea in immunocompetent persons. The infection is a cause of persistent diarrhoea in immunosuppressed persons and is an AIDS-defining illness.

Clinical presentation
In immunocompromised patients it causes chronic watery non-bloody diarrhoea that can be severe, leading to significant dehydration with electrolyte disturbances and death. Patients may have associated abdominal cramps and bloating, but these are not usually severe.

Diagnosis
The diagnosis of cryptosporidium infection is based upon the demonstration of cryptosporidial oocysts in stool by a modified ZN stain or on mucosal biopsy from the small intestine or colon. Involvement of the bowel may be patchy and involve the ileum, so intestinal biopsy from the duodenum or distal colon is not reliable and examination of the stool is the best diagnostic test. Stool concentration increases the yield.

Treatment
Therapy in immunocompromised patients usually is supportive with the use of intravenous fluids as necessary to correct volume depletion and antidiarrhoeal agents such as loperamide 2-24 mg per day to keep diarrhoea under control. In severe cases where diarrhoea cannot be controlled with antidiarrhoeal agents, the somatostatin analogue octreotide has been used successfully in doses ranging from 50 µg to 500 µg subcutaneously t.i.d. to control the diarrhoea.

To date, there is no proven therapy to specifically treat and eradicate Cryptosporidium. Trials using spiramycin and paromomycin have been reported, but the results have been disappointing.

Microsporidium

Introduction
Microsporidia are a group of intracellular protozoans .The commonest organisms of this group identified are Enterocytozoon bieneusi and Septata intestinalis. Asymptomatic carriage in HIV patients has been documented.

Clinical presentation
When symptomatic, infection with microsporidium resembles that of cryptosporidium, usually with watery non-bloody diarrhoea of variable severity, mild abdominal cramps and bloating.

Diagnosis
Electron microscopy of a small bowel biopsy is used to see the small intracellular parasites. Special stains have been developed to detect microsporidia in stool samples e.g. modified Giemsa, F.I.S.H test, PCR.

Treatment
Therapy of symptomatic microsporidial infection is similar to that of cryptosporidium, with the use of supportive therapy and antidiarrhoeal agents. Octreotide has also been used successfully for severe watery diarrhea. Metronidazole and albendazole have been used to try to eradicate microsporidium, but neither has been shown to be reliably effective.

Isosporiasis
Isospora belli is another intestinal protozoal parasite that is also an AIDS-defining illness.

Clinical presentation
Clinically it causes nonspecific non-bloody watery diarrhoea similar to that of Cryptosporidium.

Diagnosis
Diagnosis is usually easily made by examination of stool for ova and parasites.

Treatment
Unlike infection with cryptosporidium and microsporidium, isoporiasis can usually be treated successfully with trimethoprim-sulfamethoxazole 160 mg tmp/800 mg p.o. q.i.d. for 10 days, then b.i.d. for 3 weeks. Recurrence is common (approximately 50%), and some patients may need chronic therapy.

Strongyloides stercoralis

Introduction
Strongyloides stercoralis is a nematode endemic in tropical areas. It usually infects a host by penetrating the skin as filariform larvae. The larvae then travel via the bloodstream to the lungs where they leave the alveolar capillaries, and are coughed up and swallowed. Once they reach the small intestine they release eggs that develop into infective filariform larvae that burrow into the small bowel mucosa.

Clinical presentation
Pruritus, papillary rashes and oedema may occur at the site of skin entry. Intestinal involvement may result in fever, nausea, vomiting, diarrhoea, abdominal pain and weight loss.

Diagnosis
Diagnosis can best be made by examination of duodenal aspirate but can also be done by examination of concentrated stool specimens.

Treatment
Treatment is usually successful with thiabendazole 50 mg/kg/day in 2 doses for 2 days. Therapy in immuno-compromised individuals may need to be continued for at least 7 days, and some may require chronic therapy.

Viral Infections

Cytomegalovirus

Introduction
Cytomegalovirus is a common infection among PLWHAs. The two most common sites for CMV infection in HIV-infected patients are the retina and gastrointestinal tract. In immuno-competent patients the infection is latent and rarely causes clinical illness. Reactivation of latent infection is usually seen when the CD4+ lymphocyte count is below 50 x 10^6/mL.

Clinical presentation
The infection can involve any part of the GI tract, where it produces ulcerating lesions. The esophagus and colon are the most common sites of GI involvement. Oesophageal involvement usually presents with pain (odynophagia) and difficulty in swallowing (dysphagia). Involvement of the colon produces an acute colitis presenting with diarrhoea that may be bloody, often with severe abdominal pain.

Diagnosis
The diagnosis is based upon demonstrating the presence of intranuclear inclusion bodies in biopsy specimens. Endoscopy shows large shallow ulcerations that may be circumferential. Sigmoidoscopy or colonoscopy shows colitis with friable edematous mucosa and scattered ulcerations, a picture similar to Crohn's disease. Systemic infection can be confirmed by viral cultures of white blood cells from the buffy coat of a centrifuged specimen of blood.

Treatment
Therapy of symptomatic CMV requires ganciclovir 5 mg/kg IV q12h initially for 14-21 days. Foscarnet 60 mg/kg IV q8h for 14-21 days can be used as an alternative. These treatments usually result in clinical improvement and healing of mucosal lesions. Recurrence is high, and chronic suppressive therapy with ganciclovir or foscarnet after acute therapy is recommended.

Herpes simplex virus
Herpes simplex virus (HSV) most commonly infects the esophagus to produce multiple esophageal ulcerations.

Clinical presentation
Clinically herpetic esophagitis presents with extreme pain and difficulties in swallowing that are indistinguishable from symptoms of CMV esophagitis.

Diagnosis
Differentiation from other causes of esophagitis in these patients requires endoscopy. The ulcers produced by herpes simplex virus are usually multiple and small. Biopsies will show multinucleated giant cells and Cowdry type A intranuclear inclusion bodies. Viral culture of biopsy material should be positive for HSV.

Treatment
HSV esophagitis can usually be treated effectively with oral acyclovir 200 mg p.o. 5 times per day. In patients who are unable to take oral medications because of pain in swallowing can be given acyclovir intravenously in a dose of 5 mg/kg q8h. Initial therapy should continue for 10-14 days.

Recurrence is common, and many patients require chronic therapy with oral acyclovir. Foscarnet has been used as alternative therapy in those unable to take acyclovir or who fail therapy with acyclovir.

Human immunodeficiency virus

Introduction
It is not clear whether HIV itself causes gastrointestinal pathology. Two situations where direct pathologic effect of HIV in the GI tract is suspected are nonspecific esophageal ulcerations and HIV enteropathy. Ulcerations thought possibly to be directly due to the HIV occur as one of the seroconversion syndromes and as the idiopathic nonspecific esophageal ulcers seen in later stages of HIV infection.

Clinical presentation
Acute infection with HIV is usually associated with a nonspecific viral illness. As part of the seroconversion syndrome some patients develop severe pain on swallowing which may resolve spontaneously.

Later in the course of HIV infection, esophageal ulcerations may occur which are negative for the usual pathogens. These ulcers are usually deep with undermined edges and may be multiple. Although usually found in the esophagus, they can also occur in the posterior pharynx.

Diagnosis
Endoscopy, may show single or multiple superficial esophageal ulcers. Electron microscopy of these ulcers shows viral particles consistent with retroviruses.

Treatment
Dramatic response occurs with corticosteroids taken orally or injected intralesionally. Thalidomide may be used in resistant cases.

HIV enteropathy
HIV enteropathy is a term that has been applied to describe chronic diarrhoea and weight loss, where no identifiable pathogen can be found. It is unclear if this enteropathy is due to an unidentified pathogen or to a direct effect of the HIV on the gut. The HIV potentially could affect the gut directly by infecting enterocytes, or indirectly by inducing the local release of cytokines and other inflammatory mediators, which then may affect enterocyte function. Improvement in some patients has occurred with antiretroviral therapy. Otherwise, treatment is symptomatic only.

Neoplasms
Kaposi's Sarcoma

Introduction
Kaposi's sarcoma (KS) is the most common neoplasm seen in HIV-infected patients.etiologically associated with HHV-8. KS primarily involves the skin and oropharynx. Gastrointestinal involvement is seen in up to 40% of patients with skin involvement. Rare cases of visceral KS in the absence of skin lesions have been reported.

Clinical presentation
In most cases, GI involvement with KS is asymptomatic.

Mucosal lesions can occur throughout the GI tract and are usually incidentally found at endoscopy, where they appear as raised red to violaceous macules. Large lesions may be nodular and may ulcerate. Symptoms are usually the result of hemorrhage from ulceration or obstruction from bulky lesions. Diarrhoea and protein-losing enteropathy have also been reported. The exact presentation will depend upon the location of the lesions in the GI tract. Visceral KS should be suspected in any HIV patient with skin KS who has GI symptoms.

Diagnosis
The diagnosis is made by histologic examination of mucosal biopsies. A recently described infection, bacillary angiomatosis, has identical histology to KS; differentiation is made by demonstrating organisms on silver stains. Gastrointestinal involvement with bacillary angiomatosis has also recently been described.

Treatment
HIV-related KS can be treated by local or systemic therapy. Oral lesions are best treated with local radiation or laser excision. Symptomatic visceral involvement requires systemic therapy, usually with combination chemotherapy. Good responses to subcutaneous or intralesional interferon have also recently been reported.

Lymphoma

B-cell lymphomas represent the second most common neoplasm occurring in HIV-infected patients. These are usually high-grade lymphomas of the large cell type. However, patients with Burkitt's lymphoma and Hodgkin's disease have also been reported. The gastrointestinal tract represents the second most common site of involvement after the central nervous system. The lymphomas occurring in HIV infection are commonly extranodal.

Clinical presentation

Any part of the gastrointestinal tract can be involved, with the presentation and symptoms depending on the particular site. Systemic symptoms of fevers, night sweats and weight loss are commonly associated.

Diagnosis

The diagnosis is made by histologic examination of material obtained from endoscopy, or ultrasound- or CT-guided biopsy.

Treatment

Treatment requires combination chemotherapy similar to that for other high-grade lymphomas. Tolerance of therapy is generally poor, often as a result of the poor functional status of these patients when they develop lymphoma and the presence of other opportunistic infections. Full remissions can occur in patients who can tolerate combination chemotherapy, but the prognosis is generally poor.

Anal carcinoma

Introduction

Squamous cell carcinoma of the anal canal is seen with higher frequency in homosexual and bisexual men who practice anoreceptive intercourse. The increased risk is independent of HIV infection and, like cervical carcinoma in women, appears to be related to previous infection with human papilloma virus. Colorectal carcinoma is not seen with higher frequency in this risk group.

Clinical presentation

Anal carcinoma may present with a mass and associated fissure or fistula. Local pain is usually present and there may be bleeding.

Diagnosis

The differential diagnosis includes infections such as syphilis, lymphogranuloma venereum and condyloma acuminatum, and benign perianal conditions of fissure in ano and anal trauma from intercourse or instrumentation. Definitive diagnosis is made through biopsy of suspicious lesions, especially those that fail to heal after treatment of any secondary infections.

Treatment

Treatment modalities include surgical excision, but many may be treated with combined radiation and chemotherapy, which have had a good cure rate including preservation of the anorectal function.

Involvement of the liver and pancreas in HIV Infection

Introduction

The liver is commonly involved during the course of HIV infection, with hepatomegaly and/or abnormal liver chemistry being seen in approximately 60% of PLWHAs. Involvement of the biliary tree and gallbladder is much less common. Liver disease may occur as a result of opportunistic infections (HSV, CMV, MAC, fungi) or neoplasms (KS, lymphoma). In such cases the liver is usually involved as part of more diffuse systemic involvement and is rarely the sole site of infection.

Other infections such as hepatitis B and hepatitis C are common as a result of associated risk factors such as intravenous drug use and sexual transmission. Malnutrition, alcohol and hepatotoxicity of medications are other common factors that should be considered in the evaluation of hepatic abnormalities in these patients.

Co-infection of HIV with either hepatitis B or hepatitis C virus is often seen as a result of common risk factors. The effect of HIV-related immunosuppression on chronic hepatitis B often results in clinical improvement of the chronic hepatitis. Since it is the immune reaction to hepatitis B that causes the hepatic inflammation, biochemical parameters of hepatitis often improve, as does the activity on liver biopsy as the HIV-associated immunosuppression progresses. Despite the clinical improvement, hepatitis B viral replication increases. Hepatitis C, on the other hand, is directly hepatotoxic, and advancing immunosuppression is not uncommonly associated with worsening of the hepatitis and progressive liver disease. Treatment with interferon for either hepatitis B or C in this setting is generally associated with a poor response.

AIDS cholangiopathy

Introduction

Biliary involvement in HIV infection is commonly termed AIDS cholangiopathy and results from inflammation of the biliary tree and gallbladder. There can be a spectrum of involvement ranging from acute acalculous cholecystitis to papillary stenosis with bile duct obstruction or more diffuse involvement of the biliary tree producing a picture similar to sclerosing cholangitis. Cholangiopathy is most commonly due to CMV infection of the biliary tree but has also been reported to result from biliary infection with Cryptosporidium or Microsporidium.

Clinical presentation

Acute acalculous cholecystitis presents with RUQ pain, fever and tenderness on examination. Cholecystectomy is usually required. Cholangiopathy may present with less acute RUQ pain, fever and nausea, with cholestatic liver enzyme abnormalities.

Diagnosis and Treatment

Diagnosis of cholangiopathy is made by ERCP. Patients with dilated common bile ducts who presumably have papillary stenosis secondary to an acute papillitis have responded symptomatically to endoscopic sphincterotomy. Patients in whom CMV is proven or suspected as the cause may improve with specific treatment for CMV. Rarely Kaposi's sarcoma or lymphoma can involve the gallbladder or biliary tree.

Symptomatic pancreatic involvement in HIV infection

Clinical presentation and diagnosis

Symptomatic pancreatic involvement in HIV infection is not common, but clinically will usually present as acute pancreatitis. Asymptomatic elevations of serum amylase or lipase are common and are seen in up to 45% of patients. These are often related to medications but may also be due to asymptomatic involvement of the pancreas with opportunistic infection or neoplasm. Acute pancreatitis presents in a similar manner in patients with and without HIV infection. In addition to the commonly recognized causes of pancreatitis, other possibilities need to be considered in HIV patients. Drugs commonly used in HIV patients, including sulfonamides, pentamidine and the reverse transcriptase inhibitor dideoxyinosine (ddI), are common causes of pancreatitis. Pancreatic involvement with opportunistic infection and neoplasm, although usually asymptomatic, may cause pancreatitis.

Treatment

The principles of treatment of acute pancreatitis are the same for HIV-infected patients as for those without HIV infection. Drugs that may be involved should be stopped. Where no obvious cause is apparent, CT scan of the pancreas is useful to rule out focal lesions that might indicate infections or neoplasms involving the pancreas.

Nutritional Considerations and the Wasting Syndrome

Introduction

Weight loss is a common problem in HIV infection, especially in the more advanced stages of AIDS. Weight loss of greater than 40% of lean body mass is an independent predictor of mortality. Weight loss of greater than 10% of body weight with no obvious underlying opportunistic infection or neoplasm has been termed the HIV wasting syndrome and is an AIDS-defining illness. The cause of weight loss in HIV-infected patients is multifactorial and includes diminished intake, malabsorption and increased metabolic rate. The major cause for weight loss in most patients has been shown to be inadequate caloric intake.

Clinical presentation and diagnosis

Anorexia is a common result of systemic infection and drug side effects. Patients with pain and difficulties in swallowing have evident discomfort in eating and will decrease intake. The presence of gastrointestinal involvement is often associated with variable degrees of malabsorption so that the limited calories that are taken in are not assimilated efficiently. Increased basal metabolic rate as well as inefficient use of energy has been demonstrated in some cases. All of these contribute to weight loss.

Treatment

There is no reliably effective treatment for wasting. Underlying opportunistic infections should be treated if possible. Caloric intake should be optimized; assistance of a dietitian is invaluable in helping patients maximize caloric intake.

Intervention with oral or parenteral nutritional support has not been shown to be generally effective, but may be used successfully in selected cases. Appetite stimulants such as megestrol acetate have been shown to be effective, producing weight gain in patients with anorexia and limited intake. The weight gained appears to be predominantly fat, and whether this translates into an improved survival rate or quality of life has not been established. Metabolic agents such as anabolic steroids and growth hormone have been used with limited success but are not currently in widespread use.

Conclusions

Care of HIV-infected patients with gastrointestinal involvement represents a growing clinical challenge. Differential diagnosis and investigations should be guided by the degree of immunosuppression indicated by the CD4+ lymphocyte count. As curative therapies for most of the GI problems are not available,

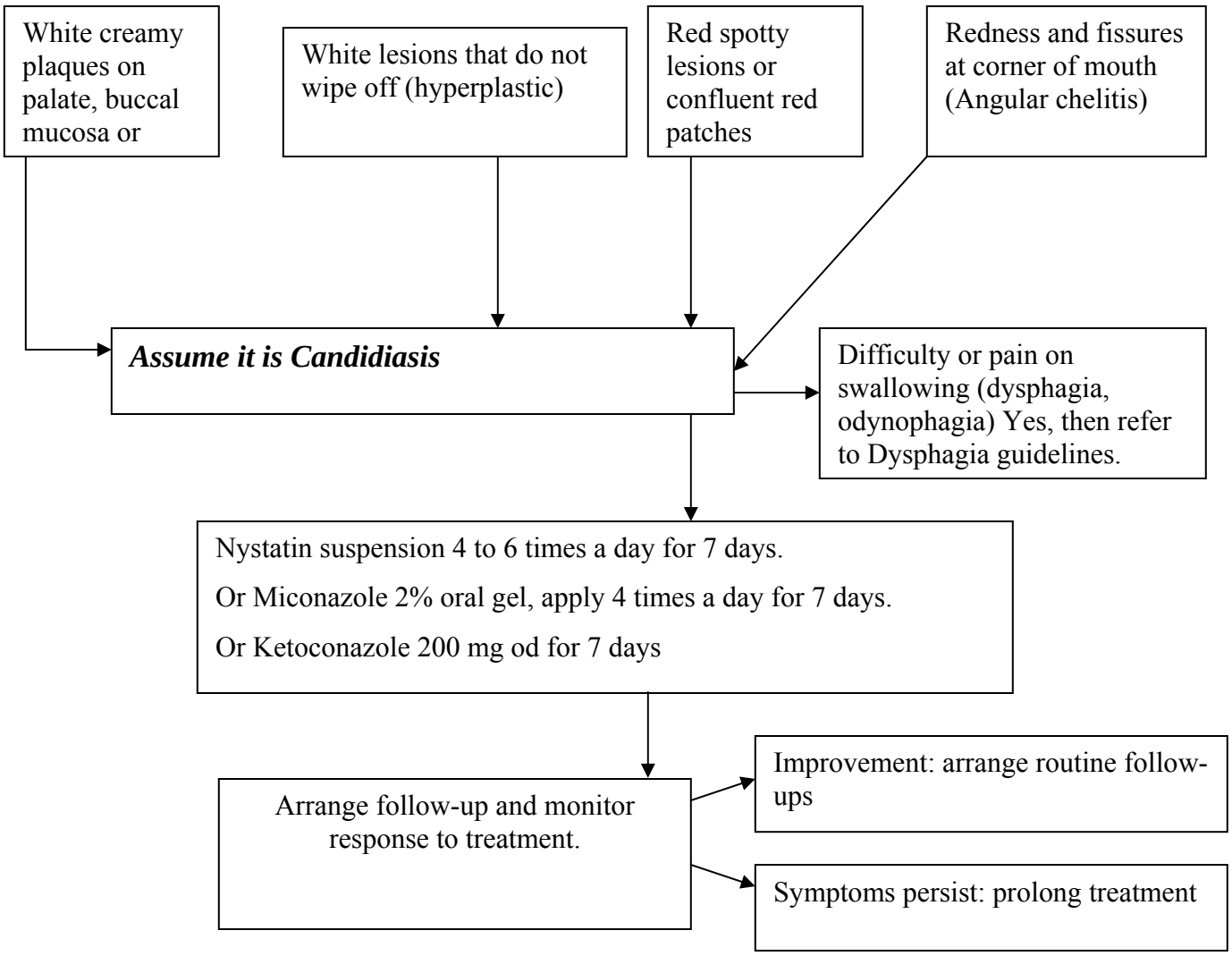
therapy is usually directed at symptom relief with the goal to improve the quality of life. Functional status and psychosocial issues need to be considered for the successful management of these patients.

Summary of Problem-based Approach

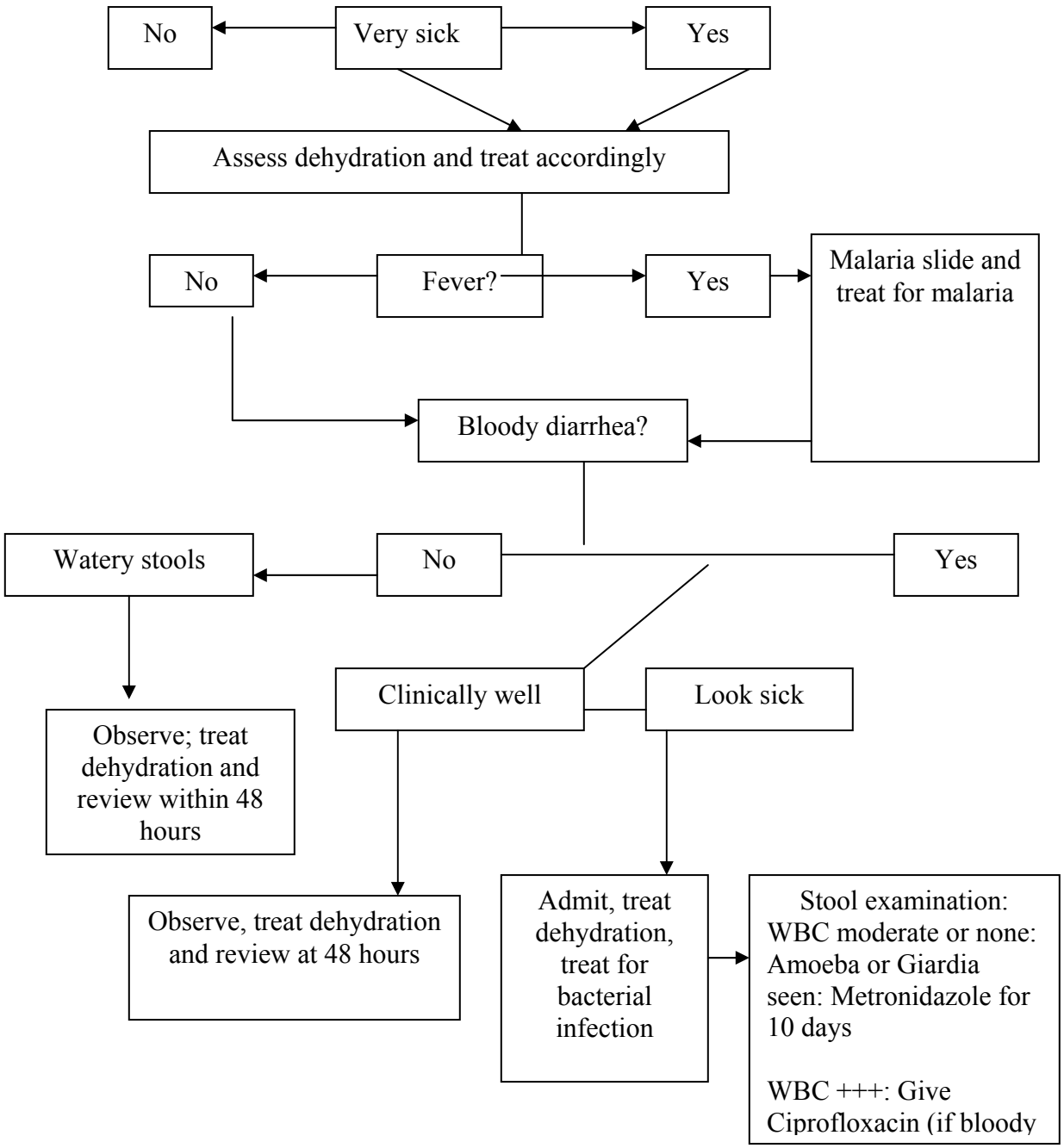
A Symptom Approach may be adopted in the Clinical Management of GIT Manifestations of HIV

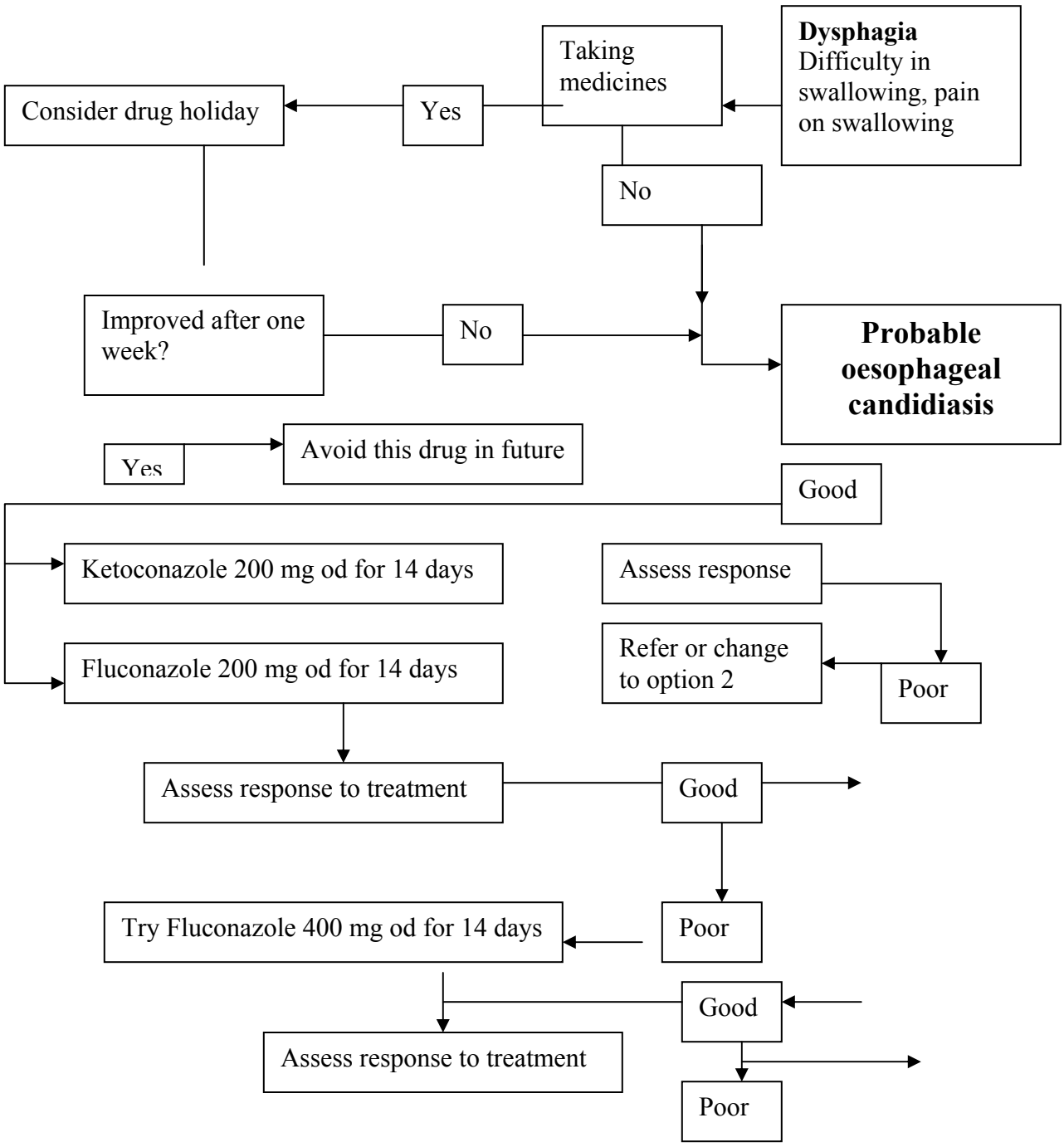
Symptom	Cause	Treatment
Oral Sores	Candida albicans	Nystatin, Ketoconazole Fluconazole, Amphotericin
	H.simplex	Acyclovir
	Bacterial gingivitis	Amoxycillin, metronidazole
	Kaposi's Sarcoma	Chemotherapy, HAART
	Lymphoma	Chemotherapy
Nausea and vomiting	Oral thrush	
	Gastrointestinal infections	Evaluate, treat cause
	CNS disease/depression	Evaluate, treat cause Metoclorpramide,
Abdominal pain		
Diarrhoea- Acute	Bacterial- salmonella Shigella Campylobacter Protozoa- E.histolytica Viral-Adenovirus Rota virus	Ciprofloxacin Amoxycillin
- Chronic	Bacterial- C.difficile M.tuberculosis MAC Protozoan- Cryptosporidium Isospora belli Microsporidia Giardia lamblia Viral-CMV HIV enteropathy	Metronidazole Vancomycin DOTS Ethambutol/clarithromycin Or Azithromycin Paramomycin/Azithromycin Septrin Albendazole for S.intestinalis Metronidazole,tinidazole Ganciclovir, Foscarnet HAART

Mouth lesions I



Acute diarrhoea





Trainer: Please include management of diarrhoea for paediatric patients

Module 5

ORAL OPPORTUNISTIC INFECTIONS IN HIV/AIDS

Introduction:

Oral opportunistic infections pre-date the era of HIV/AIDS. However, with the advent of HIV/AIDS there has been a marked increase in their prevalence. They tend to present with exaggerated clinical features and their management poses a challenge. Oral lesions are usually the first indicators of HIV/AIDS infection and have shown to be of use in diagnosis in areas where diagnostic equipment is lacking. (1, 2, 3) They are of great importance because they compromise the normal nutrition route of patients.

Goal:

By the end of this module the participants should be able to recognise and manage oral opportunistic infections.

Learning Objectives:

By the end of this module the participants should be able to:

- Name and define oral opportunistic infections in HIV/AIDS
- Identify and correlate oral opportunistic infections with the stages of HIV/AIDS infection
- Categorize the various oral opportunistic infections based on the causative agent
- Explain the common sites of occurrence of the different infections
- Describe the management of the oral lesions
- Explain the prevention of oral opportunistic infections

Content Outline:

1. Fungal:
   a. Candidiasis:
      - Pseudo membranous Candidiasis
      - Erythematous Candidiasis
      - Angular Chelitis
      - Hyper plastic Candidiasis

2. Viral
   a) Herpes Simplex
      - Primary
      - Recurrent
   b) Herpes Zoster
   c) Human Papilloma Virus Lesions
   d) Hairy Oral Leucoplakia

3. Bacterial:
   a) HIV-Associated Gingivitis
   b) HIV-Associated Periodontitis

4. Oral Malignancies:
   a) Lymphomas
   b) Kaposi's sarcoma

c) Carcinomas

5. Other Lesions:
   a) Salivary Gland Disease
      - Oral Ulcers
      - Xeroslomia

Methodology:

For each content item the trainer should use a combination of lectures with questions and answers; brainstorming followed by a summary and clarification as needed; and where possible the inclusion of case demonstrations. Good visuals, whether as posters or slides are crucial.

Teaching Materials:

- Lecture Notes
- Flip Charts
- Markers
- Slides and Slide Projectors
- Posters
- Demonstration patients

Trainer's Notes:

Candidiasis

Causative agent: Candida Albicans

Candida Albicans is frequently part of the normal oral flora. A number of factors predispose patients to candidiasis: Infancy, old age, antibiotic therapy, steroid and other immune suppressive drugs, xerostomia, endocrine disorders, anaemia as well as primary and acquired immune deficiency. Candidiasis is commonly found in people with HIV, but occurs mostly in patients with a falling CD4+ count in the middle and late stages of HIV disease (4,5,6). Candida albicans, as noted above, is part of normal flora in the mouth and causes diseases in conditions of primary or secondary immune deficiency hence its classification as an opportunistic infection. (7,8,9)

Clinical presentation

The clinical presentation of oral candidiasis varies.
Four major types have been recognized:-

1. Pseudomembranous
2. Hyperplastic
3. Erythematous / atrophic
4. Angular chelitis

These lesions may all present with burning mouth, changes in taste and difficulty in eating spicy foods.

Pseudomembranous candidiasis (oral thrush):

This is the most common presentation and is popularly referred to as oral thrush. The patient presents with characteristic creamy white removable plaques on the oral mucosa. Plaques are due to an overgrowth of fungal hyphae mixed with desquamated epithelium and inflammatory cells. Removal of the plaques reveals a red inflamed mucosa which may bleed. This type of candidiasis may involve any part of the oral mucosa and pharynx.

Erythematous (atrophic) Candidiasis:

Erythematous candidiasis appears as flat, red patches of varying size. It commonly occurs on the palate and dorsal surface of the tongue.

Angular Chelitis:

Angular Chelitis presents as redness, ulceration and fissuring either unilaterally or bilaterally at the corners of the mouth.

Hyper plastic Candidiasis:

This variation of candidiasis is rarely encountered in HIV/AIDS patients. The lesions appear as white plaques which cannot be removed on scraping. The plaques are due to hyper-keratosis. If encountered, the most common location is the buccal mucosa.

Differential Diagnosis

Erythematous Candidiasis should be differentiated from other red lesions in the oral cavity such as Kaposi's sarcoma or erythroplakia.

Diagnosis

Diagnosis is made by clinical presentation and by detection of organisms on smears. Culture may be useful for establishing the Candida species but it may not be very useful for diagnosis.

Treatment

Oral candidiasis can be treated topically or systemically.

Topical Treatment:

- 0.5% Gentian Violet aqueous solution painted in the mouth 3 times daily. Best for angular chelitis.
- Nystatin suspension oral 100,000 iu/ml 2.5ml 5 times daily.
- Nystatin oral lozenges sucked 6 hourly for 10 days.

In cases of use of sweetened preparations use of topical fluoride is encouraged to prevent tooth decay.

Topical cream:

- Miconazole gel applied twice daily for 10 days.
- Ketoconazole helpful in angular chelitis.

Systemic:

In severe cases or if topical treatment fails, systemic treatment can be adopted.

- Ketoconazole (Nizoral) 200-400 mg once daily taken with food for 10 days.
- Fluconazole 50-100 mg oral once daily for 7 days.
- Intraconazole 200 mg once daily for 7 days.

Dry or cracked lips can be kept moist with Vaseline, glycerin or liquid paraffin.

Complications

- Progression to esophageal and GIT candidiasis.
- Poor nutrition leading to patient emaciation.

Prevention
Minimize contributory factors like mouth appliances e.g. dentures, poor oral hygiene, smoking and xerostomia (dry mouth). There are other fungal opportunistic infections in the oral cavity, for example, histoplasmiosis and cryptococcus neoformans which are uncommon.

Herpes Simplex
Caused by herpes simplex virus causes both primary gingivo-stomatitis and recurrent disease. (Herpes labialis)

Primary herpetic gingivo-stomatitis commonly occurs in children and young adults which may be followed by frequent recurrences.

Clinical presentation
Recurrent herpes labilalis occurs on the vermilion border of the lips. Patients report history of itching or pain followed by appearance of small vesicles. Vesicles rupture and form crusts. Recurrent intra oral herpes usually occurs on the keratinized mucosa such as hard palate and gingival and appear as clusters of painful small vesicles that rupture and ulcerate and usually heal within 7-10 days. Recurrent Intra-Oral herpes appears more frequently in HIV/AIDS patients and are very slow to heal.

No definite differentials.

Treatment
- Acyclovir only shortens the healing time of individual episodes.
- Acyclovir 400-800 mg oral 8 hourly for 5-10 days.
- 1% Topical Povidone Iodine prevents supra bacterial infection, hence faster healing.
- 2% viscous lidocane gel every 3-4 hours for pain.
- Paracetamol 500 mg 4-6 hourly for pain.

Complications
Interferes with nutrition.

Herpes Zoster:
Caused by Varicella Zoster virus. Reactivation of the varicella zoster virus causes herpes zoster (shingles).

Clinical presentation
Oral herpes zoster generally causes skin lesions. Following a prodrome (initial phase) of pain, multiple vesicles appear on the facial skin, lips and oral mucosa. Lesions are frequently unilateral and follow distribution of the maxillary and or mandibular branches of the trigeminal nerve. Skin lesions form crusts while oral lesions join together to form large ulcers.

Differential Diagnosis
The appearance and distribution are characteristic.

Treatment
Acyclovir limits the duration of the lesions.
- Acyclovir oral 800 mg five times daily for 14 days.
- 0.2% chlorhexidine digluconate mouth rinse or oral lesions as an adjunct.

Complications
Post herpetic neuralgia.

Human Papilloma Virus Lesions
Oral warts and papillomas are caused by human papilloma virus. Oral warts are common in patients with HIV/AIDS.

Clinical presentation
Lesions may appear as solitary or multiple nodules with small papilliferous or cauliflower-like projections. May be sessile or pedunculated with a broad or narrow base.

Diagnosis
A biopsy is necessary for histology.

Treatment
Oral lesions can be removed surgically under local anesthesia if the lesion is solitary. Multiple flat warts can be removed using carbon dioxide laser surgery but recurrences are common.

Oral Hairy Leukoplakia
Associated with Epstein Barr Virus but actual cause is still unknown. Hairy Leukoplakia may occur in a symptomatic HIV infected people but becomes more common as CD4+cell count falls.

Clinical presentation
Lesions occur commonly on the lateral margins of the tongue and may be bilateral or unilateral. They appear as whitish-grey corrugations which cannot be scraped off, sometimes markedly resembling hairs. Hairy Leukoplakia lesions may also occur on the buccal mucosa as flat lesions.
No associated symptoms.

Differential Diagnosis
Other white lesions such as lichen palms, idiopathic leukoplakia, dysplasia and white sponge naevus should also be differentiated from hyperplastic candidiasis.

Diagnosis
Mainly clinical though definitive diagnosis can be made by biopsy.

Treatment
Hairy leukoplakia is asymptomatic and does not require treatment. It is almost always a manifestation of HIV infection so HIV evaluation is always necessary. Treatment with antifungals may be indicated in case of supra infection with candida albicans.

Bacterial Lesions

Periodontal Disease (Gum Conditions)
Periodontal disease in HIV/AIDS patients is caused by a variety of bacteria some of which are B-gingivitis, B-Inttermedius, Actinomyces actinomycetemcomitans (a. a) F-nucleatum. The disease takes two forms –

necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis (10). Periodontal disease is fairly common in both asymptomatic and symptomatic HIV/AIDS patients.

Clinical presentation

Necrotizing (ulcerative) gingivitis normally occurs in clean mouths where there is no plague or calculus to account for the gingivitis. It has a rapid onset with destruction of one or more inter-dental papillae, bleeding, ulceration necrosis and sloughing. Tissue destruction is limited to gingival tissues and does not involve the alveolar bone. Necrotizing ulcerative periodontitis presents with advanced necrotic destruction of the peridontium destruction or sequestration of bone and ultimately tooth mobility. There is associated severe pain and halitosis (bad breath).

Differential Diagnosis

It can be differentiated from non-HIV-related periodontal disease by its rapid onset, rapid destruction and occurrence in a clean mouth.

Treatment

- Refer to oral health worker for scaling and debridement with topical 1% povidone iodine irrigation.
- Thorough oral hygiene instructions
- Antibiotic treatment
    - ✓ Amoxicillin 250 mg 8 hourly for 5 days or Erythromycin 250 mg oral 6 hourly for 5 days with Metronidazole 200 mg oral 8 hourly for 5 days.
    - ✓ Mouth rinse with 0.2% chlorhexidine gluconate 2-4 times daily.

Complications

Rapid tooth loss and osteomyelitis.

Neoplastic lesions

Kaposi's Sarcoma is an angiosarcoma and is associated with Herpes Simplex virus type 8. Kaposi's Sarcoma lesions may occur intra-orally only, or in association with skin and disseminated lesions. Intra-oral lesions may be the first manifestation of late-stage HIV disease (11,12). Kaposi's Sarcoma has been noted to be more prevalent in men than women.

Clinical presentation

Intra-oral Kaposi's Sarcoma can appear as a red, blue, or purplish lesion, may be flat or raised solitary or multiple. The most common oral site is the palate but lesions can occur on any part of the oral mucosa and oral pharynx. Oral Kaposi's Sarcoma lesions may enlarge, ulcerate and become infected.

Differential Diagnosis

Kaposi's Sarcoma must be differentiated from other oral vascular lesions such as hematomas, hemangiomas, pyogenic granulomas, and pigmented lesions such as oral melanotic macules.

Diagnosis

Diagnosis is made from histological examinations of biopsy specimens.

Treatment

Treatment is dependent on the number, size and distribution of the lesions. Small well-circumscribed lesions on the tongue and gingiva can be surgically removed.

- Local application of sclerozing agents may reduce the size of large oral lesions that interfere with eating.
- Intralesional vinblastin can be used for treating small lesions.
- Radiation therapy may be indicated for large multiple lesions.
- Systemic chemotherapy may be indicated.

Complications

- Progression into disseminated Kaposi's Sarcoma.

Lymphomas

Diffuse. Undifferentiated non-Hodgkin's lymphoma is a frequent HIV-associated malignancy. Oral lesions may appear as solitary lesions with no evidence of disseminated disease. Most are B-cell origin and Epstein Barr virus occurs in cells from several cases.

Clinical presentation

Lesions can occur anywhere in the oral cavity and there may be soft tissue involvement with or without involvement of the underlying bone. Lesions may present as firm, painless swelling that may be ulcerated. There may be associated tooth mobility if there is bone involvement.

Different Diagnosis

Oral non Hodgkin's lymphoma should be differentiated from major apthous ulcers and rarely as a pericoronitis associated with an erupting third molar.

Diagnosis

The diagnosis must be made by histological examination of biopsy specimens.

Treatment

- Chemotherapy

Other Oral lesions associated with HIV disease

Oral ulceration

Oral ulcers resembling recurrent apthous ulcers in HIV/AIDS patients are reported with increasing frequency. The cause is largely unknown but is associated with stress and unidentified infectious agents

Clinical presentation

Ulcers are well circumscribed with erythematous margins. They may appear as solitary lesions $\cong 0.5 - 1.0$ cm similar to minor RAU. Herpetic form type appears as clusters of small ulcers (1-2 mm) usually on the soft palate and orophargnx. The major RAU type appears as an extremely large 2-4 cm necrotic ulcer.

Different Diagnosis

- Rule out neoplasms in case of major RAU e.g. lymphomas
- Herpes simplex (primary gingivo-stomatitis)

Diagnosis

- Mainly clinical

Treatment

- Topical steroids such as fluocinonide 0.5% ointment mixed with equal parts of orabase applied six times daily
- Dexamethasone elixir 0.5 mg/5m used as a mouth rinse three times daily
- Systemic steroid therapy prednisolone 40-60 mg/day for 7–10 days, in severe cases
- 0.2% chlorhexidine digluconate mouth rinse 2-4 times daily
- Use of thalidomide 50-200 mg is still under clinical trials
- Local anaesthetic gel or spray for pain relief e.g 2% viscous lignocaine gel 3-4 times daily

Salivary gland disease and Xerostomia (dry mouth):

The cause is unknown. Salivary gland enlargement has been reported in both children and adults with HIV infection (13, 14).

Clinical presentation

There is unilateral or bilateral salivary gland enlargement usually of the parotid glands. The enlarged glands are soft but not fluctuant and may be accompanied by pain. Normally there is associated xerostomia and associated rampant caries mainly in the cervical areas of teeth. Xerostamia may exist without salivary gland enlargement.

Differential Diagnosis

Rule out other causes of xerostomia (dry mouth) such as Sjogren's syndrome, drugs like antidepressants, anti anxiety drugs, salivary gland neoplasms and duct obstructions. Diagnosis is mainly clinical but biopsy and sialography can be done to rule out other causes of salivary gland enlargement and xerostomia.

Treatment

Xerostomia (dry mouth) can be treated with salivary stimulants, for example, sugarless gum.

- Artificial saliva containing methyl cellulose or mucin based can be used
- Topical fluoride should be used daily to prevent tooth decay
- Moistening the mouth frequently with water

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Module 6

SKIN INFECTIONS IN HIV/AIDS

Introduction:

The skin is the largest and most visible organ of the body, comprising all the outer covering of the body, nails, hair and the genital mucosal membrane. Approximately 90% of people living with HIV develop skin changes and symptoms at some stage during the course of their illness. (1, 2, 3)
There are four main causes of skin problems in people with HIV:

- Interaction between the immune system and HIV
- Side effects of drugs either for OI treatment or ARVs.
- Infections, many of which are due to opportunistic agents
- Opportunistic malignancies

PLWHAs often have several skin conditions that appear at the same time or follow one after the other. In this module the participants will learn about opportunistic infections and neoplasms of the skin.

Goal:

To enable health workers in Uganda to recognise, treat, and/or refer PLWHAs with skin infections.

Learning objectives:

By the end of this module participants should be able to:

- Understand the scope of the skin.
- Appreciate the range of dermatological disorders in HIV/AIDS with specific emphasis on opportunistic infections.
- List these opportunistic conditions
- Mention the causative agents where known
- Know the clinical signs and symptoms of the condition
- Outline methods of diagnosis
- Discuss the treatment or remedy of the condition
- Recognise complications of the conditions
- Discuss preventive measures

Content outline:

1) Opportunistic Skin infections and Neoplasms.
   Opportunistic infections:
   - Bacterial (Staph. Aureus, Bartonella infection (bacillary angiomatosis), Pseudomonas aeruginosa).
   - Viral (Herpes simplex, varicella zoster virus (vzv), Human papilloma virus (HPV), and molluscum contagiosum).
   - Fungal (candida, Tinea, Crypotococcal, histoplasma, coccidioidomycosis, and penicillinosis).
   - Neoplasms.
   - Kaposi's sarcoma
   - Other cutaneous neoplasms
2) Diagnosis of the specific condition
3) Management of the condition
4) Outline of prevention

Methodology:

1. Define the particular infections/neoplasms

Steps

1) Brainstorming
2) Clarification and additions as needed
3) Trainer summarises and presents simple, easily remembered definition

2. Skin manifestations of the condition under consideration

Steps

1) Brainstorming
2) Trainer discusses the signs and symptoms of the disease condition allowing time for questions and answers
3) Summary of important symptoms and signs

3. Diagnosis of the condition.

Steps

1) Brainstorm on steps taken to arrive at a diagnosis.
2) Facilitator summarises main points
3) Questions and answers

4. Management of the skin condition

Steps

1) Brainstorm on the principles of management.
2) Clarification and additions as needed
3) Summary of the management principles

5. Prevention of the skin condition

Steps

1) Brainstorm on methods of prevention
2) Trainer summarise.
3) Trainer leads discussion on preventive procedures

Teaching materials:

- Flip charts
- Masking tape
- Markers (different colours)
- Posters
- Slides/transparencies
- Projector
- Notebooks
- Pens, pencils

Trainer's Notes:

A. Infectious conditions

I. Bacterial causes:

(i) Staphylococcus aureus:

Staphylococcus aureus is one of the most common skin infections in PLWHAs. The clinical syndromes are:-

- Bullous impetigo
- Ecthyma
- Folliculitis
- Hindradenitistis – like plagues
- Abscesses
- Cellulitis
- Pyomyositis

About 50% of HIV infected persons are nasal carriers of Staph.aureus, thus the high infection rate. (4, 5) Infection with S. aureus may occur before any sign of HIV infection.

Bullous impetigo:

- Common in hot, and humid weather
- Presents as very superficial blisters or erosions in the groin or axilla
- Blisters are flaccid and short lived
- Often only erosions or yellow crusts are present
- Differential diagnosis is cutaneous candidiasis

Ecthyma:

- an eroded or superficially ulcerated lesion with adherent crust
- Under the crust is often a plane of purulent material full of S. aureus. (crust removal is necessary to enable topical treatment).

Folliculitis:

- S.aureus folliculitis occurs in hairy areas of the body
- Folliculitis related to HIV is usually very itchy. Differential diagnosis is itchy dermatosis, for example, scabies. (about 50% of HIV infected patients with scabies have folliculitis).

Abscesses:

- Follicular lesion may extend deeply forming abscesses (pyomyositis) or under the skin forming cellulites.
- Hidradenitis-like plaque
- Rarely - follicles across several centimetres are infected, forming a large, violaceous (reddish-mauve) hidradenitis –like plaque. The plaque may mimic Kaposi's Sarcoma.

Treatment

- Superficial lesions are treated with an appropriate anti-staphylococcol antibiotic Erythromycin 500mg three times a day for 7 to 10 days.

Or

- Flucloxacillin 500mg three times a day for one week
- Deep lesions require treatment lasting for months. Other alternative treatment include Augumentin 375mg tds for five days.

Adjunctive topical treatment includes:

- Washing the infected areas once daily or every other day with antibacterial agent (Hibiclens, betacline, or benzyl peroxide) helps remove the crust.
- Topical antibacterials
- Mupirocin (Bactroban) topically daily x 7 days
- Fusidic acid topically daily x 7 days
- Localised abscesses must be incised and drained to make antibiotics effective.
- In case of severe cellulitis or evidence of bacteraemia the patient should be admitted and given intravenous therapy.

Prevention

- Reduction of nasal carrier stage by use of antibiotics
- Avoid minor skin tears (as occurs in skin lesion in scratching itchy skin conditions)

(ii) Bartonella infection: Bacillary Angiomatosis

"A rare condition in our day to day clinics" the agent causing this infection, initially designated as Rochalimaea, has been reclassified as Bartonella subsequently the term bacillary angiomatosis is being replaced by bartonella infection. (6)

Causative agent: B henselae and B. Quintana

One epidemiological study has demonstrated cat exposure and cat scratches as risk factors for acquiring bacillary angiomatosis (7)

Clinical presentation

The most characteristic cutaneous lesions resemble pyogenic granuloma (fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily).

- Deep cellulitic plaques and subcutaneous nodules may occur
- Lesions can number a few to hundreds
- Differential diagnosis is Kaposi's Sarcoma

Symptoms include: fever, night sweats and anaemia.

- Bacillary angiomatosis also affects other parts of the bodies resulting in many symptoms.

Diagnosis

Diagnosis is confirmed by biopsy which will give typical histopathological findings.

Treatment

- Erythromycin 500mg orally 4 times daily for 3 to 4 week for cutaneous lesions.

or

- Doxycycline 100mg orally twice daily. To prevent relapse treatment is continued for 8 weeks.

iii. Pseudomonas Aeruginosa:

Dermatological manifestation of P. aeruginosa have been reported in some centers (8, 9, 10) but not much is known about this condition.

II. Viral causes:

(i) Herpes Simplex virus infection:

Causative agents: Herpes simplex virus (HSV) type 1 & 2 (HSV1 & HSV2)

Epidemiology

The prevalence of HSV infection in the general population is high, but varies depending on the social and demographic characteristics of the particular population under study. Despite the close relationship of the two viruses, HSV -1 and HSV-2 display different epidemiologic patterns and the usual routes of transmissions are dissimilar. While the prevalence of HSV-1 in HIV infected persons is similar to that of the general population, studies show that HSV-2 is more prevalent in people with HIV infection (11). The virus is transmitted by close direct contact, during which the virus is inoculated on to a susceptible mucosal surface or through breaks in the skin. It requires a moist environment to survive. (12, 13)

During acute primary infection, the virus becomes permanently latent in the nerve root ganglia that correspond to the cutaneous or mucous membrane site of inoculation.

A variety of stimuli, such as ultraviolet light and trauma to the sensory nerve may reactivate latent HSV. During reactivation, virus replication occurs within the ganglia and progeny virons travel peripherally along sensory nerves to mucosal or epithelial surface innervated by the reactivated ganglion. Active virus replication at the cutaneous surface then produces clinical symptoms and lesions that are typical for recurrent HSV infection.

The clinical presentation of HSV infection in patients with HIV disease may be quite variable and may differ from that observed in an uninfected host. Lesions may appear as grouped blisters that rupture, crust and heal in 7 to 10 days. More commonly ulceration occurs without prior blister.
Severely immunosuppressed, HIV infected persons often experience chromic lesions that continue to expand and form large crusted lesions 2 to 10 cm or larger in diameter. Lesions may be very painful, especially if located perianally or perorally. Periungal infection is another characteristic manifestation of HSV-2 infection in the HIV infected patient.

A Tzanch smear taken from the edge of the ulcer stained with Giemsa or methelyne blue, when positive for multinucleated epithelial cells gives a rapid diagnosis. In case of a negative Tzanch smear, but where there is a strong suspicion of HSV, a biopsy of the skin from the edge of the ulcer should be done and tissue cultured for viruses. However, stains and cultures for other organism should also be done.

Treatment

- Oral Acyclovir 200 to 400mg 5 times daily till the ulcer heals (which may take several weeks); there after chronic suppressive therapy is given: oral Acyclovir 400mg twice daily.

Other drugs:

- Famciclovir 250mg 3 times daily
- Valiaciclovir 100mg daily

Complications

Untreated HSV lesions slowly enlarge and new lesions at distant sites may appear probably due to cross contamination rather than hematogenous spread. It is rare for HSV to disseminate even in those severely immuno suppressed HIV infected people. Large chronic perianal, perioral, or periungual ulcers that fail to heal with acyclovir treatment are often due to resistance. The treatment then is foscarnet and continuous – infusion of acyclovir.

(ii) Varicella Zoster virus (VZV) infections:

Causative agent: VZV a neurotropic member of the herpes virus family is the causative agent for both varicella ("Chicken pox") and zoster ("shingles"). Humans are the only known natural hosts of HZV. Transmission occurs through direct contact with infectious lesions or by inoculation of aerosolised infected droplets into a susceptible mucosal surface.

Primary infection occurs following inoculation of a previously uninfected individual. Initial virus replication occurs in the tonsillar and lymphoid tissue and is followed 4 to 7 days later by a primary viremia, a secondary or more prolonged viremic stage occurs 10 to 21 days after initial infection. Virus reaches the cutaneous surface during the secondary viremia and results in the characteristic rash of varicella.

Clinical presentation

Varicella:

The rash associated with primary VZV infection occurs about 14 days after infection. Prodromal symptoms often occur 1 to 2 days before the appearance of the rash. These include malaise, low grade fever, and myalgia. Skin lesion begin as small erythematous macules and progress over 12 to 36 hours to become papules and true vesicles.

Zoster:

Most HIV infected persons have had varicella previously, their initial manifestation of VZV infection is usually herpes zoster. (H-Z) in HIV infection precedes oral thrush and hairly leukoplakia by about one year.

In HIV infected person H-Z dermatomal eruption may be particularly bullous, haemorrhagic, necrotic and painful. Duration of the crust is usually 2 or 3 weeks or up to 6 weeks and pain may last 2 to 3 weeks. The necrotic lesions heal with severe dermatomal scarring suggestive of HIV infections. VZV dissemination in PLWHAs, though rare, occurs and gives rise to widespread blisters with or without an associated dermatomal eruption.

Chromic disseminated VZV may present as widespread ecthymatous ulcers or verrucous like lesions. A less common manifestation of VZV infection in HIV infected person is persistent, chromic localised herpes zoster. VZV is seven times more common in HIV infected than in non infected individuals.

Diagnosis

Diagnosis is based on the recognition of the vesicular eruptions and recurrences reported in up to 25% of African HIV infected persons. Lesion cultures can be done for identification of viruses for testing.

Treatment

- Oral Acyclovir 800mg 5 times daily for five days. (There is Acyclovir resistance.)
- Alternative treatment:-
  - ✓ Famciclovir 500mg 3 times daily
  - ✓ Valaciclovir 1000mg 3 times daily

Other treatment of VZV consists of topical care of skin lesions, with water and soap plus topical antibiotics. Analgesics are used to alleviate pain.

iii) Viral Warts:

Causative agents: Human papilloma virus (HPV)

Human papilloma virus (HPV) causes warts which are seen with increased frequency in people with HIV infection. Lesions may be extensive and resistant to therapy.

Clinical presentation

In most cases they appear as regular or flat warts but are often seen in multiple numbers in PLWHAs. Rarely, they may be very extensive lesions.
They are commonly found in the anogential area, but can be found anywhere on the body.
Diagnosis: Clinical features.

Human papilloma virus and sexually transmitted cancers

- Condylomata acuminata (viral warts) are of special significance in PLWHAs.
- Cervical dysplasia and carcinoma are clearly associated with HPV infection. (14)

The cervix and anorectal area have a transformation zone.

- Cervical dysplasia is extremely common in HIV infected women and should be looked for
- HPV type 16 is the potentially carcinogenic HPV.
- HPV may be the inducing agent and HIV the enhancing cofactor.

Female HIV infected patients must have regular gynaecological examinations and pap smears. Individuals who have had anal warts, should have regular rectal examinations.

Treatment: the goal is to eradicate all warts

i) Topical podophyllin (15-25%) once weekly for 6 – 10 weeks (Do not use it in pregnancy)
ii) Persistent lesions may be surgically debrided and bases cauterised
iii) Other methods include: Cryotherapy, excision or injections with alpha interferon in the lesion.

Note: Recurrence is almost universal.

iv) Molluscum Contagiosum:

Causative agent: Molluscum contagiosum virus:
Molluscum contagiosum occurs in approximately 10-20% of HIV infected person. Once CD4+ counts fall below 200, however, lesions tend to proliferate.

Clinical Presentation

Molluscum contagiosum presents as pearly, umbilicated papules. Severity correlates directly with the degree of immunosuppression. Extensive molluscum contagiosum is a cutaneous marker of advanced HIV disease. (CD4+ cells<50) They often number over 100 and may involve the face, axilla and groin. The preferred location is the eyelids.

Treatment

The objective of the treatment is primarily cosmetic and preventive.

i) Pricking the lesion with a large-gauge needle and removing the white core (molluscum body)
ii) Topical application of a tiny drop of cantharidin to each lesion for 3 to 6 hours will often induce sufficient inflammation to eradicate the lesions.

III. Fungal Infections

(i) Superficial Fungal Infections

Epidermal dematophytosis in HIV infected individuals tends to be extensive, recurrent and difficult to eradicate. The nails, feet, hands and trunk are the most common sites of infection. Nail infection due to tinea involves primarily the nail plate which appears opaque, thickened, discoloured and may split or crumble. Infection due to candida on the other hand affects the nail bed leading to an acute paronychia

with swelling and pus discharge from the space between the nail plate and the cuticle. Secondary bacterial infection is commonly due to Staph. aureus or pseudomonas aureginosa and results in discoloration and deformation of the nail plate.

Tinea of the palms and soles appears as dry scaly and powdery lesions but may occasionally form vesicles fused with straw coloured fluid. Toe web maceration may be due to either tinea or candida, while finger web space involvement is commonly due to candidiasis.

Causative agent: The most common is trichophyton rubrum.
Proximal white subungual onychomycosis, which is rare in non-HIV infected people is a common presentation of t.rubrum infection of the nail plate, and appears as chalky white discoloration of the proximal part of the nail, and should prompt HIV testing.

The prevalence of candida infection increases with immunosuppression. Mucosal candidiasis involves the upper aero digestive tract, vulvovagina, anorectal and other intertrigious areas. Invasive fungaemia may result in candidiasis of the oesophagus, trachea, bronchi or lungs and is an AIDS defining condition.

Clinical presentation
The majority of cases present with an altered sense of taste, stickiness or dryness in the mouth, dysphagia and/or recurrent vaginal discharge and genital itching. Physical examination reveals a white, curdle like discharge on the erythematous background which is adherent to the mucosa. Angular stomatitis may also be present.

Treatment
Tinea infections can be treated with

- Oral griseofulvin 500 – 750mg o.d for 6/52

or

- Fluconazole 100mg o.d for 6/52

or

- Itraconazole 200mg o.d for 6/52

or

- Terbinafine 250mg o.d. for 6/52

Used together with topical clotrimazole, miconazole or Ketoconazole cream.
Candida infections should be treated with:

- Oral ketoconazole 200mg B.D for 14 days

or

- Itraconazole 100g B.D for 14 days; Fluconazole 200mg stat & 100mg O.D x 14 days or
- I-V Amphotericin B 400 – 500 mg

(ii) Deep Mycoses

Cryptococcal infection, histoplasmosis, coccidioidimycosis and penicillinosis are deep fungal infections. They occasionally present as molluscum contagiosum like shiny papules on the head, neck or other parts of the body. Biopsy and appropriate staining will reveal the diagnosis.

B. Neoplasms:
Kaposi's Sarcoma (KS): KS is a neoplasm of endothelial cells involving the skin.

- Incidence in AIDS patients is about 34% and is occasionally aggressive. Death is usually due to lung involvement.

Clinical Presentation

KS may affect any portion of the cutaneous surface. Skin lesions are red and purple macules, nodules and plaques. Common sites include the tip of nose, hard palate and limbs. The lesions may number from one to hundreds and range in size from several millimetres to over 10 cm and may be widespread.

Diagnosis

Punch biopsy of the skin lesions. Select a palpable lesion, preferably one that has been present for at least several weeks, avoid a site of prior trauma.
Precautions:

1. Avoid foot and lower leg lesions
2. Inject Xylocain with epinephrine 1:100,000 at least 5 minutes before biopsy.
3. Extend the biopsy into the subcutaneous fat.
4. Suture all wounds

The sample should be taken to a pathologist for interpretation. This is the requirement for treatment.

Treatment

Therapy aims at controlling symptoms, reducing edema, eliminating pain and clearing lesions There is a role for chemotherapy using bleomycin and vincristine radiotherapy.

Other Neoplasms:
These include the following: Lymphomas, Basal cell carcinoma, Squamous cell carcinoma, Malignant melanoma and Intraepithelial carcinoma associated with warts in the anogenital area.

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Module 7

OPPORTUNISTIC INFECTIONS AND COMMON HIV-RELATED ILLNESSES IN THE GENITAL URINARY TRACT (GUT)

Introduction:

The Genitourinary System, like all other parts of the body, is a target for opportunistic infections (OIs) and opportunistic malignancies (OMs) in people with suppressed immunity. The incidence of opportunistic infections depends on the level of immunosuppression and the prevalence of the pathogens responsible for these infections in the environment. These opportunistic infections and malignancies are seen in immunocompetent people, but in PLWHAs they occur more frequently and in most cases are more severe.

Goal:

To assist health care providers in Uganda to recognise, treat and/or refer genitourinary OIs and OMs in HIV/AIDS patients.

Learning objectives:

By the end of this module the participants should be able to:

- List the common OIs and OMs that affect the genital urinary tract
- State the causes of OIs and OMs in the genital urinary tract
- State the mode of transmission of these OIs
- Outline the clinical symptoms and signs of these OIs and OMs
- Mention complications and differential diagnosis where available
- List some investigations used to confirm the diagnosis where possible
- Specify treatment or mention the syndromic type of treatment where available
- Discuss the preventive measures
- Identify referable cases where necessary

Content Outline*:*

1. Categories of OIs in the GUT
    a) Bacterial Infections
        - Syphilis
        - Tuberculosis
        - Bacterial Vaginosis
        - Non specific genital infections

    b) Fungal infection
        - Genital Candidiasis

    c) Viral infections
        - Genital Herpes
        - Genital warts (condylomata acuminata)

    d) Protozoal infections
        - Trichomonas vaginalis

    Malignancies
        - Cervical cancer
        - Penile cancer
2. Diagnosis of OIs and OMs in GUT
3. Management of OIs and OMs in GUT

4. Prevention of OIs and OMs in GUT

Methodology:

1) Defining and listing OIs and opportunistic malignancies in GUT

Steps

1. Brain storming
2. Trainer clarifies and makes additions as needed
3. Trainer provides simple and easily remembered definition

2) Clinical symptoms and signs of OIs and OMs in GUT

Steps

1. Brain storming
2. Trainer summarises stressing important points
3. Trainer demonstrates some lesions using pictures or slides where possible

3) Complications and differential diagnosis of OIs and OMs

Steps

1. Brainstorming
2. Trainer summarises with an emphasis on possible complications and differential diagnosis where available
3. Trainer may demonstrate some complications and differential diagnosis where possible.

4) Diagnosis of OIs and OMs in GUT

Steps

1. Brainstorming
2. Trainer summarises with an emphasis on available investigations in the diagnosis of OIs and OMs.

5) Treatment of OIs and OMs in GUT.

Steps

1. Brainstorming on the principles of treatment
   - following confirmatory diagnosis
   - syndromic type of treatment
2. Trainer summarises and highlights important points

6) Prevention of OIs and OMs in GUT.

Steps

1. Brainstorm on principles of prevention
2. Trainer summarises the principles of prevention.

7) Identification of referable cases

Steps

1. Brainstorming on criteria for referral of OIs and OMs
2. Trainer summarises the principles of cases for referral

8) Individual OIs and OMs in GUT.

Steps

1. Lectures on the common GUT OIs and OMs
2. Questions and Answers

Teaching Materials:

- Flip charts
- Notepads
- Pens, pencils
- Markers (different colours)
- Masking tape
- Slides
- Projector
- Posters

Trainer's Notes:

A. Bacterial

All bacterial infections of the GUT seen in people with normal immune systems (undamaged) are also found in people with immunosuppressed systems. Bacterial opportunistic infections commonly seen in PLWHAs are: syphilis, tuberculosis and bacterial vaginosis.

1. Bacterial vaginosis

Causative organism: Gardnerella vaginalis

Mode of transmission

This is a sexually transmitted infection. The change in PH (alkaline) of the vagina may facilitate proliferation of the organisms.

Clinical presentation

The vaginal epithelium looks pink but with an abundant, gray-white, thin and frothy discharge (exudates) that smells "fishy".

Complications

Genital infections during pregnancy can lead to the premature rupture of membranes.

Differential diagnosis

Trichomonas vaginalis

Diagnosis

Using a Cusco's speculum a specimen should be taken from the vaginal walls with a sterile swab.
A wet smear will show "clue" cells (Gardnerella).

Treatment

Metronidazole tablets 400mg PO BID for 7days

Prevention

- Personal hygiene
- Protected sex
- Treatment of the contact or partner

2. Tuberculosis

Tuberculosis is a common opportunistic infection in PLWHAs. All parts of the body including GUT can be affected. (for example: kidneys, uterus, fallopian tubes, ovaries, urinary bladder, testes, urethra etc).

Causative organism: Mycobacterium tuberculosis

Mode of transmission

- Haematogenous/ dissemination
- Direct sexual contact

Clinical presentation

Signs and symptoms include:

- Lower abdominal pain with or without swelling
- Ammenorrhoea or irregular periods
- Endometritis
- Infertility
- Grossly distorted tubes
- Tubo-ovarian abscesses
- Tuberculous epididymorchitis

Diagnosis

If there is associated chest infection

- Sputum Z-N stain for AAFBs
- Tuberculin skin test (mantoux/PPD).
- Biopsy of draining lymphnodes
- CXR
- Diagnostic dilatation and curettage
- Centrifuging urine and Z-N stain the sentiment (decant)
- Biopsy at laparotomy or laparoscopy

Treatment

National treatment guidelines should be followed as for TB in any other part of the body (see Module 3). Tubo-ovarian masses or abscesses require a surgical intervention. A consultation with the physician, as appropriate, should take place; and, for babies born to TB infected mother a consultation with the paediatrician.

Prevention

- Health education and information should be provided
- Household contact tracing should be undertaken
- Prophylaxis should be given to HIV positive mothers

3. Non specific genital infections

This is one of the most common infections affecting the genital urinary tract. However, it is very difficult and expensive to diagnose yet it continues destroying the tract silently.

Causative agent: Chlamydia trachomatis

Mode of transmission

- This is a sexually transmitted infection

Clinical presentation

- There may be no symptoms
- Non gonococcal urethritis/ NGU
- A persistent abnormal vaginal discharge that does not respond to the usual antibiotics

Complications

- Chronic pelvic pain
- Infertility in men and women
- Urethral strictures in men
- Neonatal opthalmia leading to blindness

Differential diagnosis

- Gonorrhea
- Other gram positive and gram negative bacterial infections

Diagnosis

It is difficult to diagnose with simple labarotory tests. A PCR should be performed using endocervical swabs

Treatment

- Caps Doxycycline 100mg PO BID for 7-10 days
- Tabs Erythromycin 500mg PO QID for 7days
- Caps Tetracycline 500mg PO QID for 7days

Syphilis

Causative organism: Treponema pallidum

Mode of transmission

- This is a sexually transmitted infection.
- It is congenital

Syphilis appears to occur more frequently in HIV/AIDS. As an ulcerative lesion it enhances HIV infection. In PLWHAs, it runs a more severe course and does not respond easily to treatment.
However diagnosis, treatment and prevention are the same as for immunocompetent individuals.

Clinical presentation

- In women it may be symptomless or the lesions may be hidden in the cervix
- The primary lesion presents as a chancre
- The secondary lesion presents as erythematous macules and papules
- In men the sores are easily recognised on the prepuce and papules

Complications

- There may be dissemination to other parts of the body, especially the central nervous system

- Vertical transmission to the baby

Differential diagnosis

- Chancroid
- LGV
- Genital herpes

Diagnosis

- VDRL, RPR or TPHA should be performed
- These are virtually positive for secondary lesions in PLWHAs.

Treatment

- Benzathine penicillin 2.4mega I.M one dose
- Erythromycin 500mg PO QID for 28days

B. Fungal.

Candidiasis

Causative agent: Fungus candida albicans

Mode of transmission

This infection is sexually transmitted but not always. It can occur with a change in PH (alkaline) of the vagina, for example, after menses and during pregnancy. Some antiseptics or solutions used to clean the vagina may also change the PH. This is the most common OI in the GIT. It also occurs under other conditions such as pregnancy, diabetes mellitus and immune suppressive conditions that include prolonged antibiotic or steroid cover. Candida albicans is commonly found in the GIT. Up to one third of HIV negative women carry Candida albicans in the vagina.

Clinical presentation

Women commonly present with repeated:

- Vulvo vaginitis
- Pruritus and a
- Vaginal discharge that is thick milky/curd-like

Men present with:

- Balanitis
- Balanoposthitis
- Complaints of subpreputial discharge
- Itching of the penis and foreskin.

Complications

- Painful genital sores/ulcers
- Dissemination to other parts such as the lungs
- Blindness when it affects the eyes

Differential diagnosis

- Trichomonas vaginalis
- Gardnerella vaginosis
- Lichen plenus
- Other bacterial vaginosis

Diagnosis

Diagnosis is easily made from the history and clinical signs.

- Direct visualization
- Microscopic examination of material obtained from lesions and cultures
- Histological examination of tissue biopsies are used to confirm diagnosis

Treatment

- Localised disease can be treated with Nystatin, miconazole or clotrimazole creams or pessaries.
- Syndromic treatment should be used to cover the differential diagnosis.

In more extensive candidiasis or where local application has failed ketoconazole, itraconazole or fluconazole may be used.

- Fluconazole is given 100-150mg orally in a single dose for men
- Clotrimazole is given 500mg vaginally in a single dose for women

  or
- 200mg vaginally daily for six days for women
- Miconozole is given vaginally 200mg daily for 3 days
- Ketoconazole is given orally 200mg BID for 5 days
- or
- Daily 200mg OD for10 days especially in pregnancy.

In severely immunocompromised patients candidiasis can spread to other parts of the body like the lungs and eyes where it causes blindness.

C. Viral infection

Genital Herpes

Causative agent: Herpes simplex virus 1 or 11 (HSV1&11

Most adults have been exposed to herpes simplex virus. Herpes simplex virus I usually causes recurrent infection commonly known as "cold sores". While Herpes simplex virus II is the main causes of herpes sores on the genitals.

In HIV/AIDS, herpes simplex may recur more frequently, take longer to heal, be more severe and widespread, or occasionally cause longstanding painful ulcers.

Mode of transmission

- These are sexually transmitted infections
- Vertical transmission to the baby

Clinical presentation

The onset of herpes is usually preceded by a burning and stinging sensation, then little fluid filled 'blisters' appear, which break down and crust over before healing.

Complications of herpes simplex include:

- Spread of lesion to the surrounding skin.
- Presumed to be a causative factor in cervical and penile cancers
- Psychological stress due to pain

- Infected people with herpes simplex transmit HIV more readily
- Infection of newborns during delivery leads to encephalitis, blindness, meningitis, disseminated necrotic skin lesions
- Dissemination to the lungs, oesophagus and brain

Diagnosis

Based on clinical findings

Special laboratory tests that include:

- ✓ Viral culture
- ✓ Radio immuno assay
- ✓ Fluorescent and monoclonal antibody test.

- CT Scan can show typical changes for lesions in the brain

Treatment

First line treatment includes:

Acyclovir 400mg tds orally for 7 to 10 days

or

- Famiciclovir 250 mg tds orally for 7 to 10 days

or

Valacoclovir 1gm bid orally for 7 to 10 days

For recurrent disease:

Acyclovir 800mg bid orally for 7 to 10 days

or

Famicidovir 500mg bid orally for 7 to 10 day

or

Valacilovir 500mg bid orally for 7 t0 10 days

Genital warts

Causative agent: Human papilloma virus (HPV).

Mode of transmission

- These are sexually transmitted infections
- Vertical transmission at birth

Clinical presentation

Normally they are common, painless, flat growths that can occur in any part of the body including the genital and anal regions. About 75% of sexually active adults are infected with HPV. In HIV/AIDS they are large, more numerous and wide spread (condylomata acuminata). They usually start as a pin-head sized swelling which grows upwards and become pedunculated. They occur in clusters which ultimately give the lesion a cauliflower appearance. HPV type 16 is the leading causal agent in the development of premalignant and malignant lower genital tract disease including cervical cancer. The incidence of cervical dysplasia is increased in HIV-infected women. HPV may be the inducing agent and HIV the enhancing cofactor of cervical cancer.

Complications

- Psychological stress due to pain and foul smell

- Secondary infection
- Complicates vaginal delivery leading to PPH and tears
- Family disruption due to lack of coitus

Diagnosis

Diagnosis is made on clinical grounds:

- With gross morphology, in the case of exophytic warts
- With a hand lens or colposcopy following acetic acid staining in the case of condylomata.
- Histological examination of biopsy material if there is any suspicion about possible change in the malignancy.

It is important to differentiate condyloma acuminata from condyloma lata which is a manifestation of secondary syphilis by the use of dark field microscopy. HIV infected females should have regular gynaecological examination including papanicolao (pap) smears to detect early cervical cancer. HPV is also associated with the development of anal and rectal cancers.

Treatment

The goal is to eradicate all the warts**.**

- Topical podophyllin 15-25% for 10 weeks (not used in pregnancy)
- Surgical debridement and cauterization of the bases is done for persistent lesions

Other methods of treatment include

- Cryotherapy, excision or injection with alpha interferon in the lesions.
- All treatments involve complications.
- Recurrence is high and lesions respond very slowly to treatment

Prevention

- General hygiene
- Delivery by caeserian section
- Referral to theatre facilities
- Protected sex
- Early treatment of the partner

D Protozoa

Trichomonas vaginalis

Causative agent: A pear-shaped flagellate protozoan Trichomonas vaginalis.

Clinical presentation

In women:

- Vaginitis
- Cystitis
- Pruritus
- Foul smelling discharge In men:
  - ✓ Urethritis and balanitis are common
  - ✓ Prostitis and very rarely epididymo-orchitis.

Complications

- Batholinitis
- Rarely pyelitis
- Premature rupture of membranes

Diagnosis

- Using a Cusco's speculum, a specimen is taken from the posterior vaginal fornix
- Milking urethra for the discharge

These are examined by wet mount

Treatment

- ✓ Metronidazole or tinidazole 2g as a single dose by mouth.

or

- ✓ Metronidazole, 400mg, twice daily for 7 days orally

or

- ✓ Tinidazole, 500mg twice daily for seven days orally.

E Opportunistic GUT Neoplasms

- Cervical cancer
- Anorectal cancer
- Penile cancer

Human papilloma virus (HPV) infection is the leading causal agent in the development of premalignant and malignant lower genital tract, anorectal and cervical area. As mentioned previously, HPV may be the inducing factor while HIV is the enhancing factor in these malignancies. Refer to the section on malignancies in this manual (Module 12)

The clinical signs, diagnosis, management and prevention are as discussed in the specific module.

Of special note:

EMPHASIS SHOULD BE PUT ON ROUTINE SPECULUM EXAMINATIONS FOR ALL WOMEN WITH GYNAECOLOGICAL COMPLAINTS TO HELP IN EARLY DIAGNOSIS AND MANAGEMENT.

DURING PREGNANCY ALL WOMEN SHOULD HAVE A SPECULUM EXAMINATION ON THEIR FIRST VISIT.

Module 8

OPPORTUNISTIC INFECTIONS IN THE EAR, NOSE AND THROAT (ENT)

Introduction:

HIV infection is associated with a variety of problems in the head and neck region. As many as 70% of HIV infected patients eventually develop such conditions.

Goal:

To enable a health care worker in Uganda to recognise, diagnose, treat, prevent and/or refer ENT OIs in PLWHAs.

Learning objectives:

By the end of this module participants should be able to

- List those Ols and opportunistic malignancies seen in ENT care
- State the causative agent where identifiable
- Understand the mode of transmission and pathogenesis
- Recognise the symptoms and signs of these infections/conditions
- Diagnose and /or discuss a differential diagnosis
- Discuss treatments and where available administer the treatment.
- Outline preventive measures

Content outline:

1. Ears:
   - Opportunistic infections of the External Ear
   - Opportunistic infection of the Middle Ear
   - Kaposi's sarcoma of the External Ear

2. Nose:
   - Herpes zoster
   - Herpes simplex
   - Nasal and para-nasal sinuses
   - Bacterial sinusitis
   - Kaposi's sarcoma

3. Pharynx and larynx
   - Candidiasis
   - Herpes simplex
   - Cytomegalovirus
   - Kaposi's sarcoma and non-Hodgkins lymphoma

Methodology:

1) Define a particular infection/condition

Steps

1. Brainstorming
2. Trainer clarifies and completes as necessary
3. Trainer summarises providing a simple and easily remembered definition.

2) ENT: Manifestation of the condition
   1. Brainstorming
   2. Trainer discusses the signs and symptoms
   3. Questions + Answers (Q+A)
   4. Trainer summaries highlighting the major signs and symptoms

3) Diagnosis of the condition/infection.
   1. Brainstorming on the steps taken in a diagnosis.
   2. Trainer summarises the relevant investigations and expected results
   3. Q+A

4) Management of the condition.
   1. Brainstorming on the principles of management.
   2. Trainer clarifies and competes as needed
   3. Trainer summarises the management of the condition including possible side effects

5) Prevention of the ENT condition:
   1. Brainstorming on the methods of prevention.
   2. Trainer summarises
   3. General discussion
   4. Trainer provides final summary

Teaching materials:

- Models of the Ear, and Nose and related ENT structure.
- Slides/transparencies
- Projector
- Posters
- Flip charts
- Notepads
- Markers (different colours)
- Pens, pencils

Trainer's Notes

The External Ear

Introduction

The external ear includes the pinna and the external auditory canal (EAC). These two distinct parts of the ear have similar tissues and being close to one another, disease process occurring in one usually spreads to the other. The process most commonly reported includes seborrheic dermatitis, Kaposi's Sarcoma and bacterial infections.

Clinical presentation

Infection of the EAC with either pneumocystitis or mycobacterium tuberculosis separately can result in a tumor-like lesion in the EAC. Subcutaneous cysts due to pneumocystitis jiroveci can occur in the EAC and can grow to block the entire canal. (1)

Tuberculous infections of the middle ear can cause an aural polyp extending into EAC leading to conductive hearing loss with production of sparse, clear discharge (otorrhea).

Diagnosis
The diagnosis of these conditions can be made from a biopsy of the lesions.

Treatment
Treatment requires appropriate drugs for M- tuberculosis or pneumocystis jiroveci infection. (2)

Kaposi's Sarcoma (KS)
Kaposi's sarcoma (KS) can appear either on the pinna or in the EAC.

Clinical presentation
More severe symptoms, including conductive hearing loss, may arise if the tumor extends onto the tympanic membrane ™ or into the middle ear.

Treatment
Treatment requires carbon dioxide laser to excise canalicular KS. For TM KS the argon laser may spare the normal tissue and avoid perforation of the TM**.**

Please note: Laser surgery systems are not readily available in Uganda and KS lesions are controlled with chemotherapy and/or radiotherapy.

The Middle Ear
Introduction
The most common otologic (ear) problems reported in HIV infected patients are serous otitis media and recurrent acute otitis media. These conditions frequently affect pediatric patients with HIV infection because Eustachian tube dysfunction typical of this age group combined with depressed cell-mediated immunity markedly increases their susceptibility to middle ear infection. (3) Pneumocystis jiroveci, M-tuberculosis and candida have been cultured from the middle ear of HIV/AIDS patients.

Treatment
In these cases treatment depends on the organisms isolated.

The Nose and para-nasal sinuses
Recurrent acute sinusitis and chronic sinusitis are common in HIV/AIDS. The mucopus drainage streaming into the nasopharynx from infected sinuses can cause mucosal swelling around the Eustachian tube orifice. (4) Staphylococcus and pseudomonas infections are isolated more often in PLWHAs than in sero-negative patients with this type of infection.

Other causative agents: Either herpes simplex or herpes zoster may cause the giant herpetic nasal ulcer. (5) The lesions originate in the nasal vestibule and can extend to the facial skin and may be several centimeters large. Patients in advanced stages of HIV infection present with atypical opportunistic infections in the nose or para-nasal sinuses. Organisms like Aspergillus, crypotococcus and candida have been described. (6, 7, 8, 9)

Diagnosis and Treatment
The diagnosis and treatment of PLWHAs is in many ways similar to those who are sero-negative with the exception that a wider range and 'stronger' antibiotics are required for PLWHAs and for a longer period of time.

Kaposi's Sarcoma (KS)
Presenting symptoms of sinonasal KS include obstruction, intermittent epistaxis, and rhinorrhea. Although skin lesion can occur on the nose and face, sinus and intranasal lesions are less common.

Non-Hodgkin's lymphoma: (NHL)
NHL presents with nasal bleeding, obstruction, rhinorrhea, or a mass on the face. Needle aspiration or tissue biopsy confirms the diagnosis.

Pharynx and larynx
Because of the anatomic proximity and functional relationships, many conditions which occur in the oral cavity also occur in the pharynx and larynx.

Candidiasis
Candidal infection can occur in the oropharynx, larynx and usually results in severe odynophagia (pain in swallowing) and interferes with swallowing. When the larynx is affected there may be hoarseness and aspiration occasionally occurring due to impairment of laryngeal functions. Candidiasis of the pharynx, larynx and oesophagus is always associated with AIDS and requires systemic antifungal agents.

Herpes simplex and Cytomegalovirus
Herpes simplex lesions can occur in the pharynx and larynx and CMV lesions have also been seen.

Diagnosis
Diagnosis is made on biopsy.

Treatment
Treatment requires systemic antiviral drugs (for example, ganciclovir or foscarnet).

KS and NHL:
Note: KS and NHL occur in the pharynx and larynx. The ever present risk of airway obstruction and interference with swallowing makes early aggressive therapy vital.

Additional information:

Otits externa

This occurs in three clinical forms:
1. Circumscript or localized:

The skin elements of the outer 1/3 of the ear canal are affected and presents as a pimple or microabscess. The cause is always Staph aureas. Treatment is with drugs known to be effective, for example, cloxacillin or erythromycin are recommended. The patients must be given analgesics.

2. Diffuse:

The entire lining of the canal is affected. Early symptoms include itching and ear discharge. Blockage of the ear may follow due to accumulation of pus and dead skin and eventually pain.

3. Malignant or necrotising:

The ear canal is affected and spreads to the surrounding cartilage, bone and skin, causing necrosis and exposure of underlying tissues including dura if untreated. Patients prone to this condition are those debilitated by malnutrition, malignancy or HIV. Children are more susceptible than adults. The condition is associated with pseudomonas infection and must be treated vigorously with debridement and appropriate antipseudomonal drugs like gentamicin, ceftriaxone or quinolones.

Otitis media

Recurrent otitis media is common in PLWHAs. All age groups are affected, but especially children. The organisms in these patients are mixed bacteria and fungi including Candida albicans. Frequent aural toilet is recommended and the use of locally available ear drops. Bacteriological studies should be carried out where possible especially if the response is not satisfactory. Aminoglycoside ear drops should be avoided because they may damage the inner ear. Hearing loss may be corrected with a hearing aid. However, repair of the damaged ear drums may be attempted.

Adenoids and tonsils

These are usually enlarged and may be so big as to cause upper airway obstruction especially during sleep. Although adenoids disappear in adolescence, they reappear in PLWHAs. These tend to interfere with middle ear ventilation and predispose those affected to otitis media with effusion. Adenotonsillectomy to relieve airway obstruction should be considered

Nose and para-nasal sinuses

There is impaired ciliary clearance of mucus. This leads to accumulation of mucous in the nose and sinuses and predisposes those affected to recurrent sinusitis. A few patients present with chronic cough due to postnasal discharge. Antibiotic treatment, nasal decongestants and other supportive treatment should be given.

(Of note: most patients who get antiretroviral drugs experience relief in all these opportunistic infections**)**

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Module 9

THE EYES

Introduction:

Clinical and autopsy studies show that up to 75% of PLWHAs will have ocular (eye) problems. All parts of the visual system can be affected. There are numerous opportunistic eye infections found in PLWHAs. These infections are commonly due to bacteria, virus, fungus and protozoa. Tumours affecting the eye and its appendages are another common finding. Many eye afflictions associated with HIV/AIDS are responsible for chronic debilitation. The more severe afflictions like cytomegalovirus (CMV) and cryptococcal meningitis (CM) have the potential to cause extensive, if not total, loss of vision.

Goal:

To enable health workers to recognise, diagnose, treat and/or refer and offer preventive measures for common opportunistic infections/conditions of the eyes that affect PLWHAs.

Learning Objectives:

By the end of this module the participants should be able to:

- List the common opportunistic infections/conditions of the eyes associated with HIV/AIDS
- Discuss the causal agents where possible
- Recognise the signs and symptoms of the conditions
- Outline the approach to the diagnosis of these conditions
- Recognise and treat those conditions which are manageable at the health centre level
- Recognise and refer those conditions that cannot be managed at the health centre level
- Discuss preventive measures for these conditions

Content outline:

1. (a) Opportunistic Infections (OIs)
   (b) Other conditions.

Opportunistic infections (OIs).

- Bacterial infections
  - ✓ Syphilis, staphylococcus, streptococcus, pneumococcus and atypical bacteria.
- Virus infections Cytomegalovirus, Herpes Zoster & Herpes simplex, Molluscum contagiosum
- Fungus infections
  - ✓ Cryptococcosis, candidiasis and histoplamosis
- Protozoa
  - ✓ Toxoplasmosis, Pneumocystitis jiroveci

Other conditions:

- Tumours
  - ✓ Squamous cell carcinoma
  - ✓ Kaposi's Sarcoma
  - ✓ Non-Hodgkin's lymphoma
  - ✓ Burkitt's lymphoma
- Non-specific conjuctivitis
- Blepharitis

2. Management of the infection/condition
   - ✓ History taking, examination, investigation, treatment and follow-up.
3. Prevention of the infection/condition

Methodology:

1) Define the particular infection/condition

Steps
1. Brainstorming
2. Trainer clarifies and completes as needed
3. Trainer summarises in an easily remembered way

2) Eye manifestations of the infection/condition

Steps
1. Brainstorming
2. Trainer clarifies and leads a discussion on the signs and symptoms
3. Trainer gives a summary of the important signs

3) Diagnosis of the condition/infection

Steps
1. Brainstorm on steps taken in the diagnosis
2. Trainer summarizes and clarifies as needed
3. Questions and Answers

4) Management of the eye infection/condition

Steps
1. Brainstorm on the principles of management
2. Trainer clarifies and completes as needed
3. Trainer gives summary of the management principles.

5) Prevention of the eye condition

Steps
1. Brainstorm on methods of prevention
2. Trainer summarises
3. Trainer leads a discussion on preventive procedures

Teaching materials:

- Flip Charts
- Markers (different colours)
- Posters
- Slides
- Projector
- Pens, pencils
- Notebooks
- Eye Models
- Snellen chart (with literate and illiterate characters)

Trainer's Notes:

Of the many opportunistic infections and conditions in HIV infection that threaten loss of vision, the most common is CMV retinitis and is the one discussed in detail here.

CMV

Introduction

Cytomegalovirus (CMV) is a common virus that infects more than half of all adults. However, it rarely causes significant disease unless there is damage to the immune system. People usually become infected by CMV through close personal and sexual contact with others. In healthy people the immune system keeps the virus from spreading and causing disease, but it is never completely eliminated. Many people with HIV infection are also infected with CMV. When HIV has damaged the immune system, CMV starts to cause disease, this happens when the CD4+ cell count is between 50 and 75 cell/mm^3. In this instance CMV causes disease in the:

- Eyes - CMV Retinitis
- Gut - CMV oesphagitis, colitis.
- Liver and lungs (occasionally) - CMS

Epidemiology

The incidence of CMV retinitis in AIDS is very high, clinical and autopsy series indicate a prevalence of 17% to 34%. This is not the case in other immuno compromised states. One possible explanation of the high prevalence of CMV retinitis in PLWHAs is its interaction with other viruses, particularly HIV itself.

Clinical presentation

People with CMV retinitis may have blurred or lost vision, or they may see small moving spots called "floaters" or shadows. But early CMV retinitis has no symptoms.

Diagnosis

CMV retinitis is diagnosed through an examination with an ophthalmoscope. A typical lesion is a zone of white retinal infiltration with translucent, slightly irregular margins. Multiicentric origin and bilateral disease are frequently seen. As the lesions mature, they become more granular and ultimately become transparent. Faint pigment stippling is seen at the level of retinal pigment epithelium. Focal deposits of lipid, calcium and glial tissue may be seen within inactive lesions. The retinal vessels become markedly attenuated and secondary optic wasting develops. A zone of active necrotizing retinitis remains at the margin of the inactive lesions. In some cases, the eyes may look normal, but a thorough dilated retinal examination is needed to diagnose the retinal infection, seen as hemorrhagic retinal inflammation often following a vascular distribution. (This can spread throughout the retina and cause blindness). Retinal detachment is a late cause of vision loss and may develop in eyes with completely inactive infection.

Treatment

CMV retinitis is a progressive, bilateral and blinding disease if left untreated. Since all current drugs are virostatic, they must be given for the life of the patient. Current antiviral options include oral ganciclovir, intravenous therapy (ganciclovir, fascarnet, or cidofovir), and local therapy (ganciclovir implant, intraocular ganciclovir, foscarnet, cidofovir, or fomivirsen). All have their distinct advantages and disadvantages and none offer the perfect balance of quality of life, efficacy, safety and cost.

<u>Oral treatment</u>

For patients with active CMV retinitis, the recommended induction dose is:

- Valganciclovir (Vallcyte) is the oral prodrug of ganciclovir.

450mg tablets two, twice a day for 21 days followed by a maintenance dose of two 450mg tablets once daily.
- Patients with inactive CMV are given only a maintenance dose.

Intravenous treatment
- Intravenous ganciclovir or foscarnet are given in high doses for 2-3 weeks followed by a reduced daily dose once the infection is stabilized. Both drugs require daily infusion which takes 1 to 2 hours.

Intraocular (Local) anti CMV therapy
- Antiviral agents used for intraocular therapy include ganciclovir, foscarnet, cidofovir and formivirsen.

Of note: Systemic anti-HIV therapy with highly active antiretroviral therapy (HAART) restores immune system function and elevation of T-helper cells. Because it results in immunologic, virologic and clinical improvement, it is also an effective treatment for CMV.

Complications
Side effects of most of the antiviral drugs lead to bone marrow suppression.

Prevention
- Oral ganciclovir is effective in preventing CMV in patients at risk (CD4+ <100 cells/mm^3).
- Regular eye examination is useful in early detection of CMV in at risk patients (CD4+ <100 cells/mm^3).

The perfect drug to fight CMV retinitis has yet to be discovered. However, using the above screening and treatment strategies health care providers are almost always able to keep sight in at least one eye throughout a person's lifetime.
The most important points to remember are:
- CMV retinitis is often asymptomatic.
- Individuals with decreased T-helper cell counts (especially below 50 – 100) require dilated retinal examination every 3-6 months.
- Treatment usually controls the infection initially.
- Recurrent infection is common, particularly with patients who are not receiving (or who are resistant to) HAART and receiving intravenous anti-CMV therapy.

Other Opportunistic Infections
OIs other than CMV are much less common.

Viruses
Other viruses of the herpes group, including both herpes simplex and herpes zoster may cause necrotizing retinitis.

Protozoa
Toxoplasma gondii or pneumocystis jiroveci can both affect PLWHAs
- Toxoplasmosis may present with particularly fulminant retinochoroiditis resembling endophthalmitis.

- Pneumocysitis has been associated with cotton wool sports. Disseminated pneumocystis may cause a multifocal choroiditis that may remain asymptomatic for long periods of time. The characteristic changes in fundus are large, yellow, placoid lesions located in the choroids, without overlying retinal or vitreous involvement. The choroiditis will respond to specific systemic treatment.

Bacterial Infection

- Mycobacterial infection as a complication of systemic M.avium intracellulare has also been reported.
- Syphilis is usually a rare cause of ocular disease, but among this population syphilis is frequently seen, causing retinochoriditis.

Fungal Infection

Fungal infection with Candida, Histoplasma and Cryptococcus has been reported. Cryptococcus is a common OI in the CNS. Ocular involvement usually takes place secondary to meningeal infection extending along the optic nerve sheath.

Neoplasms

- Kaposi's Sarcoma is the most common neoplastic disease in PLWHAs. It presents in a very aggressive form in this population. It causes lesions on the face and ocular surface in addition to other parts of the body, lid dysfunction and orbital pain. The lesions usually require no treatment, but they can be locally excised or treated with radiation or chemotherapy.

- Non-Hodgkin's lymphoma is the second most common neoplasm.

- Burkitt's lymphoma. This lymphoma is frequently associated with AIDS and may involve the orbit in up to 50% of cases. The association of Burkitt's lymphoma with the Epstein – Barr virus (EBV) raises the possibility of viral interaction of EBV and HIV, which may explain the disseminated nature of the disease in the AIDS population.

Management of these conditions can follow the principles described in the respective modules.

Management of HIV/AIDS related conditions of the eye

Three factors: pain, discomfort and varying levels of loss of vision characterize HIV/AIDS related conditions of the eye and its appendages. The first two can be verified by taking a history and the latter can be accurately tested for by using dedicated testing methods.

History taking

History taking should clearly inquire for mucopurulent discharge which is often associated with bacterial and fungal infections and serous (clear) discharge which is associated with viral infections. Descriptions of the pain experienced should be asked for. Pins and needles on a hot surface is often associated with herpes zoster, burning and itching may be associated with Kaposi's Sarcoma, while sharp piercing pain on tight lid closure may be associated with acute lid infections like internal hordeolum.

Examination

An eye examination should be done systematically assessing the eye tissues with its appendages working from the front backwards. Natural light and a torch are desirable for good examination. New growths either on the eye or its appendages or protrusions of the eye need to be looked for. The colour of all tissues examined should be carefully and explicitly described especially redness and where possible noting where it is located. It is mandatory to record the visual acuity of the eyes. A Snellen chart, both with literate and

illiterate characters is used, and is mounted at 6 metres from the patient. Animal characters for testing children should also be available. The ophthalmoscope should be used to examine the fundus of the eye.

Diagnosis of specific conditions

Anterior segment of the eye and its appendages

Stye and chalazion

Causative agent: Bacteria usually staphylococcus

Clinical presentation

There is painful lid swelling, from which pus will collect. The sty forms on the lid margin, while the chalazion forms deep in the lid.

Treatment

In the acute painful stage an antibiotic to which staphylococci are likely to be sensitive, for example, ampiclox. Should be used.

If pus forms then surgical drainage should be done.

Prevention

Personal hygiene and early antibiotic use will help avoid the formation of pus.

Blepharitis

Clinical presentation

There are grey scales on the lid margin with or without ulceration of the lid margin.

Treatment

The lid margins should be washed and the scales removed with cotton buds. When ulceration is present oral antibiotics like ampiclox should be used.

The Cornea

Clinical presentation

The cornea is commonly affected by ulceration

Diagnosis

Diagnosis is made by application of fluorescein dye. The affected part stains green.

Treatment

Treatment with antibiotic eye drops like chrolmphenical should be used . Use of steroids should be avoided. Whenever in doubt about infections tetracycline eye ointment applied 3 times a day should be used as a first line treatment.

Vision loss, protrusion and growth

Any patient who has vision less than the standard vision of 6/6 should be referred to an ophthalmologist as should patients with eye protrusion and growths.

Module 10

COMMON MENTAL PROBLEMS AMONG PLWHAS WITH OPPORTUNISTIC INFECTIONS

Introduction:

Mental health problems are common among people living with HIV/AIDS (PLWHAs). It is estimated that 90% of PLWHAs suffer from acute psychiatric complications of HIV/AIDS such as acute stress reactions and adjustment disorders. Between one third to two thirds will eventually suffer from a chronic psychiatric complication, for example, AIDS associated dementia. These numbers make it vital that all health workers involved in the care of PLWHAs are able to recognise signs and symptoms of mental problems, to be able to make the relevant diagnosis and initiate the appropriate management. Psychiatric complications of HIV/AIDS can only be recognized by health workers if they know what to look for. A syndrome can be described by putting together commonly occurring signs and symptoms For example, depression is a syndrome characterised by persistently low mood, loss of interest in formerly pleasurable activities, reduced energy, poor sleep and loss of appetite and weight.

A common mistake is to conclude that a person has a mental disorder on the evidence of an individual symptom. For example, it is not uncommon for many people when falling asleep to experience very clear images of things that are not there. Perception of things that are not there is called hallucination and is one of the prominent symptoms of mental illness. However, experience of such a single symptom does not necessarily mean that someone has a mental illness. Symptoms are more likely to indicate mental illnesses if they occur together, are persistent and interfere with the daily functioning of the individual.

Immune suppression can lead to a variety of secondary complications that affect the brain in the following ways:

- Direct effects of HIV on the brain tissue.
- Opportunistic central nervous system infections, for example, Toxoplasmosis, Cryptococcus, etc.
- Malignant tumors (Neoplasms)
- General debilitation
- Side effects of the drugs including antiretroviral drugs (ARVs), anti- cancer drugs and anti-TB drugs
- Psychosocial stressors associated with living with HIV/AIDS

Goal:

This module aims to equip health workers with the ability to recognise, treat, refer and follow-up mental health problems as well as offer psychosocial support to PLWHAs.

Learning Objectives:

By the end of this module participants should be able to:

- Outline common symptoms and signs of mental disorders
- Describe the process of mental health assessment
- Discuss common mental health disorders in PLWHAs
- Discuss counseling skills in relation to mental health problems.
- Describe clinical management of mental health problems associated with HIV/AIDS.

Content outline:

1. Signs and symptoms of mental health disorders
2. Mental Health assessment
3. Common mental disorders in PLWHAs
4. Counseling skills in mental health problems
5. Clinical management of mental health problems.

Methodology:

1) Signs and symptoms of mental health disorders

Steps

1. Lecture combined with brainstorming
2. Questions and Answers/summary

2) Mental health assessment

Steps

1. Lecture combined with brainstorming
2. Questions and Answers/summary

For the topics listed under 3, 4 and 5 in the content outline above the trainer should use a combination of brainstorm, role-play and evaluation (questioning technique) as appropriate for the setting and participants.

Teaching Materials:

- Flip charts
- Markers (different colours)
- Notebooks
- Pens, pencils
- Case study materials
- Video sets and tapes

Trainers notes:

The signs and symptoms of mental health disorders

The signs and symptoms of mental illness are described according to the area of mind and behaviour they affect. These areas can broadly be divided into:

Speech: The way words are put together, their meaning and appropriateness.

Perception: The ability to become aware through the senses

Thinking: In both content and form/flow

Mood: The state of one's feelings or emotions

Motor function: Behaviour, facial expression and posture

Memory: The ability to recall past events and general knowledge.

Level of consciousness and orientation:

Relating: The way we relate to others our family and with society.

Speech

The rate and quality of speech should be assessed. Speech may be unusually fast as in mania or slow as in depressive disorders. Depressed or demented patients may pause for a long time before replying to questions and may then give short answers. The interviewer should consider the patient's utterances, which

could contain neologisms (strange words), invented by patients as seen in schizophrenia. Sometimes the speech is loud and angry and unusual for the patient's usual demeanor. This may occur in mania.

Disorders of Perception

Perception is the process of becoming aware of what is presented through the sense organs. Two common disorders of perception include illusions and hallucinations.

Illusion

An illusion can be defined as a misinterpretation of an external stimulus. Illusions can occur even in people without mental health problems when the level of sensory stimulation is low. For example, when it is dark and where an old tree stump may look like an assailant. It may also occur when an individual is in a strong effective state, for example, when walking alone through a known "dangerous spot" and the minor brushing of the vegetation may be interpreted as an attack by thieves or a snake. Illusions are common in mental illness when the level of consciousness is reduced, for example in acute brain disorder or delirium where the patient may mistake objects for people (attackers) particularly in a poorly lit room.

Hallucination

A hallucination is a sensation experienced in the absence of an external stimulus to the sense organs. A hallucination is experienced as originating in the outside world or from within one's own body but not from within one's mind. For example one may hear non existent voices, see snakes or experience a "Vision" of God. Hallucinations are named according to the sensory modality they occur in; for example visual hallucination (vision), auditory hallucination (if experienced as voices, sounds, music) olfactory hallucination (smells) tactile hallucination (movements under the skin) and others.

Thinking disorders

Disorders of thinking are recognized by listening to a patient's speech or looking at his/her writings. Disorders of thinking can broadly be classified into four categories:

- Disorders of the stream of thought
- Disorders of the form of thought
- Delusions (Disorders in belief)
- Pre – occupations and overvalued ideas

Disorders of the stream of thought

In disorders of the stream of thought both the amount and the speed of thoughts are changed. At one end there is pressure of thought and the patient has a wide variety of ideas coming on rapidly one after another. At the other end there is poverty of thought and the patient has only a few thoughts with little variety. The experience of pressure of thought occurs in a psychiatric disorder called mania, while poverty of thought occurs in depressive disorders.

Disorders of the form of thought

These can be divided into three sub groups:

- Flight of ideas
- Perseveration
- Loosening of association

Flight of Ideas: In flight of ideas the patient's thoughts and conversation move quickly from one topic to another, moving from one idea to another before completing the first. These rapidly changing topics however are related and his/her thought pattern is understandable, for example a patient who believes that he is the President of Uganda may talk about his riches but before enumerating them fully, may decide to switch to another topic of how many wives he has. The underlying idea between these two topics (though

the patient abandoned the first before expounding on it fully) is that the patient is a "great man". Flight of ideas is characteristic of the disorder called mania.

Perseveration: This is the persistent and inappropriate repetition of the same thought. A patient with this disorder will, in response to a series of simple questions, give the correct answer to the first but continue to give the same answer inappropriately to subsequent questions. Perseveration occurs commonly in dementia.

Loosening of associations: The normal structure of thinking is lost. Speech is muddled up and lacking in logic. Further questioning of the person with this disorder does not lead to any further clarity of the topic(s) under inquiry. Loosening of associations occurs most often in schizophrenia. Spoken and /or written ideas and thoughts do not form a comprehensive text nor do the ideas have any connection to each other.

Delusions

A delusion is a false belief that is firmly held by an individual contrary to their educational and cultural background and is not shared by people of the same background and experience.
There are different types of delusions, namely:

- Delusions of grandeur (person has a belief of exaggerated self importance, that s/he is very wealthy, is very wise etc)
- Delusions of guilt and worthlessness
- Religious delusions (delusion within a religious content),
- Delusions of jealousy and
- Paranoid delusions.

Preoccupations and overvalued ideas

This is a situation when a person presents him/herself with inappropriate concerns. For example, a person may feel that it is very important to appear clean and well dressed in public. S/he may even miss meals to save money to buy clothes and to appear smart. Any dirt on his/her clean clothes may be very distressing to him/her. Or another patient may have very strong views regarding his tribe, race, nation or religion and failure to observe any related rituals/practices by anyone else, especially a relative, may cause tremendous problems including much discontent or banishment.

Disorders of mood

The mood refers to the emotional state of a person. The mood may be elated (inappropriate happiness) as seen in mania or extreme sadness as may be seen in depression. The mood may be anxious or marked by anger (irritable). It may also be expressionless (blunt and flat).

Disorders of motor function

Abnormalities of behaviour, facial expression and posture may occur in mental illness. For example in depression the patient usually maintains a downward gaze, may have a frowned forehead and generally looking sad and stooped. On the other hand a manic patient may talk, laugh, sing, dance excessively or even undress in public.

Memory disorders

Failure of memory is called amnesia. Organic brain illness such as delirium and dementia affect memory to a great extent.

Disorders with level of consciousness

Consciousness is awareness of self and the environment. The level of consciousness can vary between the extremes of alertness and coma. Consciousness is usually impaired in organic brain illness, mainly delirium. Sometimes patients will not even be able to tell the time, place or who they are. These are said to be disoriented.

Assessment of a psychiatric patient

The assessment of a psychiatric patient involves the following:

- Taking a psychiatric history
- Conducting mental state examination
- Doing relevant investigations including getting collateral information.

Taking a psychiatric history

A psychiatric history from a patient should be supplemented by information from a close relative or another person who knows him/her well. A scheme that can be used to take a history is given below.
This scheme has the following components:

- Particulars of the patient including the presenting complaints
- History of present condition
- Past psychiatric history
- Past medical history
- Family history
- Personal and social history
- Drugs, alcohol, tobacco use

Particulars of the patient

These include the patients' name, age, occupation and address, name of any informants and their relation to the patient. The major complaints should be identified.

History of present condition

The symptoms a patient is presenting with together with their duration and mode of onset should be described. The affect of these symptoms on the patient's work, social functioning and relationship should be sought in addition to associated disturbances in the patient's sleep patterns, appetite and sexual drive. History of any treatment given by other doctors should be looked at including self – medication, alcohol and traditional herbs. Any behavioral changes are noted.

Family history

Father: Age now or at death (if dead give cause of death), health, occupation, personality, quality of relationship with patient. Any mental illness suffered.
Mother: Same items as above.
Siblings: Names, ages, marital status, occupation, personality, psychiatric illness and quality of relationship with patient.
Social position of family: Atmosphere at home, family history of mental illness, personality disorders, epilepsy, alcoholism, other medical disorder. Socio-economic status: profession, education, income level.

Personal history

Early development**:** Abnormalities during pregnancy and at birth, difficulties in habit training and delay in achieving milestones (walking, talking, sphincter control etc)
Present social situation: Housing, composition of household, financial problems
Previous medical history: Illness, operations and accidents.

Previous psychiatric illness**:** Nature and duration of illness; date, duration and nature of any treatment.

Forensic history**:** Arrests, convictions, imprisonment, nature of offences.

Personality before the present illness: Relationship – friendships, few or many, superficial or close with own or opposite sex, relations with workmates and superiors.

Use of Leisure: Hobbies and interest; membership of societies and clubs.

Predominant mood: Anxious, worrying, cheerful, optimistic, pessimistic, self depreciating, over-confident, stable, fluctuating, controlled, demonstrative character: sensitive, reserved, timid, shy, suspicious, jealous, resentful, quarrelsome, irritable, impulsive, selfish, shy, lacking in confidence, strict, fussy, rigid, meticulous, punctual, excessively tidy.

Attitude and standards: Moral and religious integrity.

Attitude towards health and the body: Habits, food, alcohol, tobacco drugs.

Health during childhood: Serious illness especially any affecting the brain including febrile convulsions.

Nervous problems in childhood: Fears, shyness, stammering, and bed-wetting, frequent nightmares.

School: Age of starting and finishing school, type of school, academic records, sporting achievements, relationships with teachers and pupils.

Higher education: Same enquiry as for school.

Occupations: List of jobs, reasons for changes, present financial circumstances, satisfaction in work.

Menstrual history: Age of menarche, attitude during period, regularity and amount dysmenorrhoea, age of menopause and any symptoms at the time, date of last menstrual period.

Sex history: Attitude to sex, experience of sexual abuse, current sexual practices, heterosexual and homosexual experiences, contraception, extra marital affairs.

Marital history: Age of patient at marriage, length of time spouse was known before marriage and length of engagement, previous relationships and engagements, present age, occupation, health and personality of spouse, quality of marital relationship. Is it polygamous or monogamous. Extra marital relationships. Any children from them.

Children: Names, sex and age of children, date of any abortions or still births, temperament, emotional development, mental and physical health of children.

Mental state examination

The mental state examination is concerned with symptoms and behaviour at the time of the interview. Mental state examination is sub-divided into the following:

- General appearance
- Behaviour
- Speech
- Mood

- Abnormal perceptions
- Thought disorders
- Cognitive function
- Insight and judgement

Appearance and behaviour

General Appearance

The patient's general appearance and clothing may show self–neglect as shown by a dirty unkempt look and crumpled clothing. This may suggest alcoholism, drug addiction, depression, dementia or schizophrenia or any psychotic disorder. The general state of health and nutrition is noted. Note of the patient's body build is taken.

Facial appearance

This provides information about the mood. In depression, for example, the most characteristic features are turning down of the corners of the mouth and vertical furrows on the forehead. An anxious patient on the other hand has horizontal creases of the forehead, raised eyebrows dilated pupils. A suspicious individual may appear indifferent, aloof and uninformative.

Posture and movement

This also reflects the mood. A depressed patient characteristically sits leaning forwards, with shoulders hunched, the head inclined downwards and gaze directed to the floor. An anxious patient usually sits upright with head erect, often on the edge of the chair with hands gripping its sides. Manic patients are over-active and restless and may walk about the room speaking loudly.

Social behaviour

Manic patients often break the social code with over familiarizing with people they do not know well. Demented patients sometimes respond inappropriately or may continue with their private preoccupations even in the middle of an interview. Depressed patients do not socialize, are difficult to engage in conversation and remain absorbed only in their own misery.

Disorders of motor behaviour

Interviewers should watch for abnormalities and repetitive movements (tics) or gestures (mannerisms) or assuming a peculiar posture, these are usually seen in schizophrenia. Repeated washing and checking are common in obsessive-compulsive disorders.

Speech

The rate and quality of speech should be assessed. Speech may be unusually fast as in mania or usually slow as in depressive disorders. Depressed or demented patients may pause for a long time before replying to questions and may then give short answers. The interviewer should consider the patient's utterances, which could contain words reflecting loss of self worth in depression, superiority of status, for example, very rich and important as in mania or strange words as in schizophrenia.

Mood

The mood is assessed by inquiring of the patient how s/he is feeling in his/her spirits. The response may be depressed, anxious, elated (extremely happy) or normal.

Abnormal perceptions
Any inquiry should be made to find out if the patient is currently experiencing illusions and/or hallucinations.

Thought disorders
This aspect of the assessment should take place at the same time as taking the history and other aspects of the mental state assessment. The interviewer should note the stream of thought – accelerated, slowed or normal speed; the thought form – loosening of association, flight of ideas or perseveration and content of the thoughts – presence of delusions, suicidal thoughts and intent, preoccupations, concerns and overvalued ideas.

Cognitive assessment
Assessment of the higher centres of functioning is made and is usually impaired in delirium and dementia. A general comment is made about the level of consciousness of the patient. The other aspects looked at include:

- Orientation
- Attention and concentration
- Memory
- Insight and judgement

Orientation
An assessment is made by asking about the patient's awareness of time, place and person.

Attention and concentration
Attention is the ability to focus on the matter at hand. Concentration, on the other hand, is the ability to sustain that focus. This can be assessed using the serial seven test, the patient is asked to subtract seven from 100 and then subtract seven from the remainder repeatedly until this is less than seven. The time taken is recorded together, with the number of errors, if poor performance is due to poor arithmetic, patients may be asked to do simpler calculation, for example, the days of months in a year in reverse order. For illiterate patients, common household or farm objects could be used such as the total number of legs 3 cows and 2 chicken have.

Memory
Memory may be subdivided into immediate recall, short –term memory and long term memory. *Immediate recall memory*: This may be assessed by giving the patient the interviewer's name and address after prior notification to him that he will be requested to memorize and recall it. The patient is then asked to repeat it at after 1 minute and 5 minutes. It is usually impaired in delirium.

***Short Term Memory*:** This is assessed by asking the patient to repeat a sequence of digits that have been spoken slowly. An easy short sequence is given first to make sure that the patient understands the task. Then five different digits are presented. If the patient can repeat them correctly, six are given and then seven. A normal response from a person of average intelligence is to repeat seven digits correctly.

For an illiterate patient a 24-hour food recall could be used whereby the patient is asked to say what s/he had for breakfast, super, lunch and breakfast the previous day. This can be verified by interviewing a close relative. Assessing short-term memory is dependent on an intact concentration. Therefore memory cannot be assessed if tests of concentration are abnormal. Short-term memory is impaired in delirium and dementia. In moderate to severe depression patients may have impaired concentration and may thus present with memory impairment, which is so called pseudo dementia of depression.

Long-term memory. This can be assessed by asking the patient to recall personal events or well-known public items for some years before, for example the birth dates of his/her children or the names of earlier political leaders. Awareness of the sequence of events is as important as the recall of the individual items. Long-term memory is usually impaired in the late stages of dementia long after the other aspects of memory have been impaired.

Insight. By the end of the mental state examination, the interviewer should have a provisional estimate of how far the patient is aware of the nature of his/her psychiatric illness or insight into his/her illness. Insight is usually reported on a continuum ranging from insight present through partial insight, to lack of insight.

Judgement. For example – the patient's ability in decision-making is assessed.
Formulation. A summary is then made of the salient features of the history, mental state examination, the provisional diagnosis and the suggested management plan.

Common Mental Disorders

They can be classified as:

- Anxiety disorders
- Substance use disorders
- Affective disorders
- Psychotic disorders
- Organic psychiatric disorders

1. Anxiety disorders:

Anxiety disorders affect between 20-40% of PLWHAs. Diagnosis of anxiety is important as the anxiety can affect the capacity of the person to take in information, plan ahead, or adhere to a treatment plan.

Forms of anxiety disorders:

- Generalised anxiety disorder (GAD)
- Panic attacks
- Obsessive-compulsive disorders
- Post-traumatic stress disorder

The essential feature of GAD is the difficulty or inability to control apprehension or worry. This is coupled with:

- Muscular tension
- Autonomic arousal, for example, sweating, shaking, heavy breathing, increased heart beat
- Diarrhoea and increased frequency of urination
- Sleeplessness
- Avoidance behaviour
- Difficulty in concentration

In panic disorder there are brief episodes of intense fear and discomfort accompanied by fear of dying, loss of control or other dreadful happenings, plus intense physical symptoms, for example, choking, palpitations, dizziness, breathlessness etc. In between attacks there is worry about future attacks and avoidance behaviour.

In obsessive- compulsive disorders there are recurrent unwanted thoughts or impulses which cause worry or distress. PLWHAs may obsess about CD4+ count, viral load, side effects of medication, physical

symptoms, weight loss and the like. These obsessions may lead to frequent requests for tests or intense concern about insignificant changes in physical health.

Management of anxiety disorders:

It involves:

- Pharmacotherapy
- Counselling and psychotherapy.
- Social support

For short-term treatment of anxiety disorders, benzodiazepines are used until the psychotherapy treatment takes effect. The benzodiazepines used are:

- lorazepam 0.5 – 1mg tds
- Diazepam 5 – 10mg tds
- Clonazepam 1 – 2 mg bd

The above should not be used for more than two weeks.
For longer/chronic anxiety maintenance treatment with antidepressants is used.

2. Substance use disorders

Substance use disorders complicate the psychiatric diagnosis and treatment of PLWHAs. People with a triple diagnosis of HIV, psychiatric disorder and substance use are at an increased risk for poor access to care, adherence to treatment, and increased psychological distress leading to increased morbidity and mortality. Screening for substance abuse should be routine in HIV/AIDS management

Management of HIV positive substance abusers:

The following approach is used:

- Look for and treat substance related physical complications and presenting emergencies.
- Detoxification
- Supportive counselling to maintain abstinence from substance abuse
- Mobilise social support

3. Affective disorders

- These are psychiatric disorders where the main disturbance is one of mood
- The clinical types are: Mania, depression, mixed picture (bipolar) and suicide.

Causes

Affective organic syndrome can be caused by

- Opportunistic infections within or out of the CNS
- Opportunistic tumors
- The medications used for treating the above conditions notably ARVs, anti cancer drugs, anti-TB drugs and steroids

a) Mania

Mania refers to a persistently elevated, expansive or irritable mood. Most cases occur in advanced HIV disease though it can occur at any stage of HIV infection. It is the most frequent reason for psychiatric hospitalization among PLWHAs. Mania is thought to be due to increased activities of certain brain chemicals called noradrenaline and serotonin neurotransmission.

Clinical presentation

Persistently elevated /expansive/irritable mood.

Associated features: over talkativeness, grandiosity, distractibility, diminished need for sleep, racing thoughts, unrealistic plans and disturbed social functions.

Management

- Identify and treat underlying disorder
- Treatment with neuroleptics for example, chlorpromazine 100mg-8 hourly or 1-2 mg haloperidol 8 hourly;
- If mania is recurrent
  - ✓ Lithium carbonate 400 mg twice daily is used for up to a period of six months

  or
  - ✓ Sodium valproate 4oo mg twice a day

  or
  - ✓ Carbamazepine, 400 mg twice daily.
- Usually need to be hospitalized
- Discontinue treatment after 3-6 months
- If condition recurs, prophylaxis with lithium carbonate
- Family therapy, follow up counselling is necessary.

b) Depression

- Depression often occurs in association with symptomatic HIV disease especially during the early stages of HIV dementia.
- Severe depression has been reported in about 15% of psychiatric referrals.
- It is thought to be due to reduced activity of certain brain chemicals called noradrenaline and serotonin neurotransmission.

Clinical presentation

- Persistent sadness, despair, dejection, and social isolation with themes of guilt, self-reproach and suicidal ideas. Others include somatic complaints, poor concentration and memory, sleep disturbance, poor appetite and weight loss.

Management

- Counselling and practical support in mild and moderate cases.
- In severe cases use of anti-depressants, for example,
  - ✓ amitryptiline or imipramine 50 to 100mg, nocte,

  or
  - ✓ fluoxetine 20mg o.d. Treatment is continued for 3-6 months from the time when the symptoms subside
- Psychosocial support, (and follow up) to patient, family and care givers

c) Mixed affective syndrome (mania + depression + anger)

In this condition one may see rapidly fluctuating or mixed mood states often accompanied by anger and sometimes accusatory (paranoid) phenomena.

These cases respond very well to treatment with a combination of antipsychotics, for example,

- ✓ Chlorpromazine or haloperidol with an antidepressant, such as amitryptiline, imipramine or fluoxetine. Prescribed as above.

If the condition is recurrent, prophylaxis with

- ✓ Lithium carbonate 300 to 500 mg b.d may be attempted. Alternative drugs are carmazepine and sodium valproate. Prescribed as above.
- Follow up counselling, family and caretaker support is very important.
- Safe sex practices must be emphasized.

d) Suicide

This is an ever-present danger in HIV diagnosed individuals and must always be looked for in all assessments of PLWHAs including those with opportunistic infections.

- ✓ It is more common during the symptomatic stage especially with deteriorating health. It is also common during the period of bereavement. The risk is increased when a patient has depression.

Management

- Look for risk factors e.g. single, widowed, unemployed, little social family support, previous suicidal attempt, substance abuse, depressive illness, financial problems etc.
- Suicide is a psychiatric emergency and the patient must be admitted
- Assess and address the precipitating factors
- Anti depressants if depression is the cause
- Counselling to address underlying conflicts
- Family social support
- Discharge only if patient is out of danger

4. Psychotic syndromes

In these psychiatric disorders, the patient loses touch with reality due to disturbances in thinking, relating, behaviour and speech. The disturbance shows itself by the presence of:

- Delusions (usually of a paranoid or persecutory nature)
- Hallucinations (these are usually in the form of visual and auditory hallucinations. They can also be tactile.
- Behavioural disturbance e.g. self-neglect, agitation, running away, hiding from enemies or accusing others. The patient may be withdrawn or self preoccupied.
- Mixed features: Any two or more of the above.
  - ✓ Opportunistic infections, tumors and their treatment can precipitate the above disorders.

Management

- Neuroleptic drugs at lower doses are recommended, because there is an increased risk of developing side effects.
- The most common drugs used are chlorpromazine 100mg 8 hourly or haloperidol 5 to 10 mg 8 hourly.
- After the psychosis abates, taper down the dose and stop after 3 months.
- Hospitalization is usually required
- Family therapy counselling and social support is necessary.

5. Organic mental syndromes

There are two types in this context: HIV associated delirium and HIV associated dementia (HAD)

a) HIV associated delirium

Delirium occurs when a patient experiences rapidly evolving cognitive decline especially in the area of attention, memory, orientation and alertness.

Causes

- Opportunistic infections both in the central nervous system and other organs
- Neoplasms
- Metabolic disorders, for example, hypoglycaemia, electrolyte imbalance, and hypoxia.
- Pharmacological toxicity
- Drugs of abuse including alcohol
- Epilepsy
- Delirium is one of the most frequent diagnoses made by psychiatric consultation services in patients who are admitted in general hospitals.

Clinical presentation

- Acute onset
- Fluctuating symptoms
- Disturbed behaviour e.g. restlessness, disturbed sleep
- Impaired level of alertness
- Cognitive impairment characterized by:
  - ✓ disorientation in time, place, and person
  - ✓ impaired memory especially short term
  - ✓ impaired attention and concentration
- Perceptual disorders:
  a. Hallucinations
  b. Especially visual and tactile: illusions
  c. Delusions

Management

- It is an emergency and the patient must be hospitalized.
- Identify and treat the cause
  - ✓ haloperidol 2 to 10 mg 2 to 3 times a day
  - ✓ Low doses of neuroleptics such as chlorpromazine 100-mg tds
- Nursing care: Well-lit room, nutrition, fluid and electrolyte balance plus nursing Observation.
- Follow-up with family and social support

HIV Associated Dementia (HAD)

HIV/AIDS associated dementia (HAD) is said to affect between one to two-thirds of all PLWHAs. Direct HIV infection of the brain is thought to be the cause. It typically occurs in association with advanced immune-suppression and is most often preceded or accompanied with other major clinical features of AIDS. However, there are also other causes of dementia in HIV including OIs such as PML, Toxoplasmosis and the like.

HAD is characterised by:

- A slow, progressive behaviour change.
- Associated cognitive dysfunction including memory decline.
- Motor disabilities.

Patients initially show a characteristic apathy or disinterest and slowness in both mental and motor function inappropriate for their age. The patient's general affect may be mistaken for depression at this stage. Cognitive dysfunction may easily be missed in the early stage, but becomes more apparent with disease progression. Later impairment in concentration, attention and memory may occur and patients may find difficulty with or fail simple bedside tests such as the short-term memory recall of names and events and tests for learned abilities such as the subtraction of serial 7s from 100. Orientation, personality, general

knowledge, language difficulties, judgement, abstraction and the like are often impaired as well as social and occupational functioning. The bedside clinical mini mental status test is always impaired. HAD progresses slowly and eventually leads to the patient becoming apathetic and withdrawn as well as having difficulties in carrying out the simple daily activities of living (ADL). Disorientation in person, place and time are generally late findings associated with advanced disease.

At the final stage the patient becomes bed-ridden and may become mute and incontinent. Death usually follows this stage within days or weeks. HAD may have complicating effective, delirious, psychotic or epileptic disorders.

Motor disabilities frequently accompany the progression of HAD. They include tremor, ataxia with impaired rapid alternating hand movements, hyper-reflexia and extensor plantar response. Although more common in the later stages of HAD, motor disabilities may be found in early HAD. In Uganda diagnosis of HAD is usually based on clinical grounds. In the early stages, for example, in the asymptomatic phase, HAD may present as minimal neurological damage (MND) only to be detected as decreased speed of information processing or new learning. On the other hand organic personality changes are seen in late HAD with disinhibitions and poor judgment.

Management:

The treatment of HAD in Uganda is mainly a supportive one with symptomatic patients discharged to their families for home–based care. Some clinical improvement in HAD from antiretroviral drugs has been reported in the West, but such treatments are yet still too expensive for most Ugandan patients.

Associated behavioural disturbances are correspondingly treated: irritability, psychosis and aggressiveness with neuroleptics; convulsions with anti-convulsants such as phenytoin and depression with antidepressants. Family and caretaker support is paramount. Safety and security of patients including physical restraint if necessary and care for ADL must be considered. HAD is usually terminal and the family and caretakers must be accordingly prepared in counselling.

Counselling Skills in Mental Health Problems

Counselling is a helping relationship offered to individuals to help them deal with part or all the problems affecting them. When a person offers counselling he/she is communicating. Several helpful verbal and non-verbal principles regarding communication are necessary to conduct a successful counselling session. However it is important for a counsellor to assess the state of the client and his/her ability to perceive issues under discussion. Counselling should also be extended to family and care takers.
Counselling/helping skills include the following:

- Listening
- Checking understanding
- Asking questions
- Answering questions

Listening:

An effective listener requires the following techniques:
R - be relaxed
O - be open
L - Lean forward towards the client
E - Keep eye contact
S - Sit near the client

In addition the counsellor should take note of non verbal principles which include; facial expressions, gestures, body posture, tone of the voice and use of silence.

Checking understanding:

This is done using the following techniques:

- Repeat what the client is saying
- Summarising what the person has told you
- Identifying the feeling of the client.

Asking questions:

Two types of questioning technique are used: (Closed and open ended questions)

Close ended: Usually requires "yes" or "no" responses. Use of such questions should be avoided as much as possible in a counselling session because they do not encourage a client to open up.

Open ended: Encourage the client to talk more and express themselves more clearly. Words like where, why, when, what are used.

Answering questions and providing information:

When answering questions the counsellor should note that:

- Behind every question there is a story/problem
- Give accurate answers only
- Some questions do not have answers
- Give information not advice
- Use clear simple language
- Before answering questions find out what the client already knows

Sources of Information

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3. *American Psychiatric Association (2000) Practice Guideline for the Treatment of Patients with HIV/AIDS. Am J Psychiatry(suppl) 157(11)*

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5. *Dan H.K., & James W.D (2003) HIV Associated Psychiatric Disorders. HIV in-SITE Web page: http://hivinsite.ucsf.edu*

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Module 11

HAEMATOLOGIC MANIFESTATIONS

Introduction:

Haematologic manifestations are common among people living with HIV/AIDS (PLWHAs). These abnormalities arise from the effects of HIV, opportunistic infections, malignancies and the medications used in the treatment of these conditions. This module introduces the haematologic manifestations of HIV and discusses the approach to the management of these conditions.

Goal:

To equip participants with the knowledge and skills to be able to identify and manage HIV related haematological problems.

Learning objectives:

By the end of this module participants should be able to:

- Name the common haematological abnormalities
- Discuss the aetiology (cause) of these abnormalities
- Discuss the approach to the diagnosis of the common haematological manifestations
- Discuss the management of the individual abnormalities

Content outline:

The following conditions will be discussed in detail

1. Anaemia
2. Thrombocytopenia {HIV-related immune thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP)}
3. Thrombotic disease
4. Pancytopenia

Methodology:

1) Introduction

Steps

1. Lecture: Trainer provides a general overview

2) Haematological disorders in HIV

Steps

1. Brainstorm on causes, diagnosis and treatment
2. Trainer summarises and clarifies as needed

3) Individual disorders:

- Anaemia
- Thrombocytopenia
- Pancytopenia
- Thrombotic disease

Steps

1. Break into groups and if numbers allow one group for each disorder
2. Each group reports back

3. Group discussion
4. Trainer summarises and clarifies as needed

Teaching materials:

- Flip charts
- Transparencies
- Markers (different colours)
- Overhead/slide/LCD projector
- Slides/cases scenarios
- Case discussions
- Notepads
- Pens, pencils

Trainer's notes:

Anaemia

Introduction

Anaemia is defined as a reduction below the normal in the number of circulating red blood cells. It is expressed as the haemoglobin concentration (gm/dl) or the Hematocrit (%) or the number of red blood cells (cells /mm^3).

Anaemia is a common finding among patients with HIV infection, occurring in approximately 30% during the asymptomatic years of infection and 80-90% of patients over the course of disease (1, 2, 3). In a study by Sullivan and others (4), anaemia was prevalent in 8% of asymptomatics 20% of symptomatic HIV and 71% of patients with an AIDS defining illness. The cause of anaemia in an individual maybe multi-factorial but the common causes of anaemia in HIV include:

Causes and Mechanism of Anaemia in HIV Infection

Cause of Anaemia	Mechanism
Decreased RBC production (reticulocyte count low, indirect bilirubin normal or low	**A. Neoplasm infiltrating bone marrow** o Lymphoma o Kaposi's sarcoma o Hodgkin's disease o Others **B. Infection** o Mycobacterium avium complex o Mycobacterium tuberculosis o CMV o B19 parvovirus o Fungal infections **C. Drugs (myelosuppression)** o ARVs; AZT, 3TC, D4T o Antifungals; Amphotericin B, Flucytosine o Anti-PJP;septrin, Trimethoprim, Pyrimethamine, pentamidine o Anticancer drugs; Cyclophosphamide, doxorubicin, methotrexate **D. HIV** o Abnormal growth of BFU-E* o Anaemia of chronic disease o Blunted erythropoietin production E. **Iron deficiency anaemia secondary to chronic blood loss**
Ineffective production (reticulocyte count low, indirect bilirubin high	**A. Folic acid deficiency** o Dietary o Jejunal pathology:malabsoption **B. B12-deficiency** o Malabsorption in ileum o Gastric pathology with decreased production of intrinsic factor o Production of antibody to intrinsic factor as in pernicious anemia
Increased RBC destruction (hemolysis) (reticulocyte count high, indirect bilirubin high)	**A. Coombs positive haemolytic anemia** **B. Hemophagocytic syndrome** **C. Thrombotic thrombocytopenic purpura (TTP)** **D. Disseminated intravascular coagulation (DIC)** **E. Drugs** o Sulfonamides, dapsone o Oxidant drugs in glucose6-dehydrogenase (G6PD) deficiency

* **Blast forming unit-erythroid**

Evaluation of patients with HIV infection and anaemia

1. Conduct a general evaluation for anaemia. The medical history should explore blood loss, dietary/nutritional history and concurrent medications that may be associated with anaemia. Symptoms or history suggestive of other HIV associated illnesses, for example, tuberculosis.
2. Physical evaluation for signs of body system involvement and to assess the severity of the anaemia.

3. The laboratory evaluation should include a CBC, reticulocyte count and a peripheral blood film report. Depending on the results of the CBC, additional investigations will include a stool examination for evidence of occult blood loss and/ or hookworm ova. Other investigations include assessment of iron stores (serum iron, iron binding capacity / transferrin and ferritin). Haemolysis or recent blood loss may be suspected in patients with a rapid fall in the Hb associated with high reticulocyte count. The cause of the haemolysis may be evident on the peripheral blood smear. When haemolysis is suspected, a direct antiglobulin test should be done to exclude autoimmune haemolysis.

4. A bone marrow examination is indicated if the patient has a pancytopenia or if abnormal morphology cells are seen in the periphery. It is also useful in the diagnosis of marrow infiltration or dysplasia, megaloblastic erythropoiesis and as a gold standard for the diagnosis of Iron deficiency anaemia. Disseminated M. tuberculosis, Mycobacterium Avium, Histoplasma capsulatum and non-Hodgkin's lymphoma, are HIV related conditions that may infiltrate the marrow. Patients with these conditions are often quite ill with advanced HIV. Occasionally the cytopenia may result from Parvo-virus infection.

Treatment

The treatment of anaemia in HIV patients depends on the cause. In sub-Saharan Africa, where nutritional anaemia is common among the general population, priority should be given to correcting the iron and folate deficiency particularly among the female and paediatric patients. Appropriate treatment for patients with hookworm infestation should also be given.

Thrombocytopenia

Introduction

Thrombocytopenia is commonly associated with HIV. Most of the HIV-related thrombocytopenia result from shortened platelet survival. The possible causes include: increased destruction of the platelets particularly due to immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura and splenomegaly. Decreased production may arise from toxic effects of medications, marrow infiltration and advanced HIV.

Immune thrombocytopenic purpura (ITP)

HIV related ITP often occurs early in the course of HIV infection, before any AIDS-defining illnesses. Frequently the condition improves as HIV progresses. ITP is a diagnosis of exclusion. The patient has thrombocytopenia without an accompanying fall in the WBCs and the haemoglobin. The peripheral blood smear reveals thrombocytopenia of normal morphology, with no other accompanying abnormalities of the red cells and the WBCs. Anti-platelet autoantibodies are frequently demonstrable but the titre does not correlate with level of thrombocytopenia.

Treatment of HIV-ITP

Therapy is reserved for patients with symptomatic thrombocytopenia, for example, recurrent epistaxis or bruising and patients with severe thrombocytopenia of $<20,000/mm^3$. Patients with a count $>20,000mm^3$ can be observed.

- ITP responds to antiretroviral therapy (ARVs). Most studies have used AZT based antiretroviral combinations but other ART combinations are also effective.
- In the absence of HIV infection, this condition is treated with prednisolone 1mg /Kg/ day for seven days. This often gives a good response in 60-80% of the patients. The response among HIV positive patients is comparable. The short-term use of steroids in this condition is unlikely to impact on the long-term course of HIV infection.
- Intravenous Immunoglobulin (IVIG) at a dose of 1gm/ Kg/ day for two days, is effective. The response to a combination of prednisolone and IVIG is very good but the use of IVIG is often limited by cost.
- Anti-Rh_o (D) immune globulin is also effective, among patients with Rh_o (D)+ blood group and can be used in absence of IVIG. The dose of anti-Rh_o (D) is 50 -70 micrograms (250-350 I.U.) /Kg/day given intravenously for 2 days.
- Refractory cases may be treated with vincristine or splenectomy.

Other treatment options in HIV-ITP

- Interferon-alpha (very expensive and not readily available)
- Danazol 400mg orally once daily until the counts recover. This is restricted to patients who have failed other standard therapies.

Thrombotic thrombocytopenic purpura (TTP)

HIV infection is associated with an increased incidence of thrombotic thrombocytopenic purpura and haemolytic uremic syndrome. Classically, TTP presents with micro-angiopathic haemolytic anaemia and thrombocytopenia. In addition, the patient may have fever, focal neurologic signs and renal dysfunction. Nearly always, the serum LDH is elevated.

TTP is currently considered to result from deficiency of a metallo-protease enzyme that is responsible for the cleavage of the unusually large multimers of Von Willebrand factor (vWF). The latter accumulate and increase platelet activation, and consumption. Tissue biopsy reveals hyaline microvascular thrombi. VWF is predominantly found in the endothelium.

The explanation for the association between HIV and TTP has not been clearly determined but some studies have demonstrated that HIV is capable of infecting endothelial cells. Cytokines, particularly TNF and IL-1 may also play a role in endothelial damage. These two cytokines are increased in HIV infection and may induce endothelial cell expression of adhesion molecules e.g. VCAM-1, ICAM-1 and E-selectin. These adhesion molecules promote localisation of inflammatory cells to the endothelium.

If not treated promptly, TTP is a potentially fatal condition. The treatment of choice for TTP is plasma exchange. The recommended dose is 35-40 ml / Kg /exchange. The number of exchanges is determined by the patient's response. Usually the procedure is repeated until the serum LDH falls to less than 700 IU/dl and the platelet count is at least 50,000/uL. In the absence of plasma pharesis, the patient can be treated with an infusion of plasma. This, however, is not as effective as plasma exchange.

Thrombotic disease

Several cases of venous thrombosis in HIV infected patients have been reported. A recent study by Sullivan and others has revealed an incidence of 2.6 per 1000-person years among 42,935 HIV positive patients. (5)
Predisposing factors in this population included:

- Age >45 years
- CMV retinitis or other infection
- Other AIDS-defining opportunistic infections

- Hospitalisation (i.e. immobility)
- Use of megestrol acetate (not commonly used in Uganda)
- Use of indinavir

Common examples here include deep venous thrombosis (DVT) and arterial thrombosis. Major risk factors for DVT are immobility and protein-S deficiency, which is particularly common among HIV infected patients (6). Deep venous thrombosis is the commonest presentation and can lead to pulmonary embolism if untreated.

Diagnosis
DVT is suspected on the finding of a painful swollen limb. Diagnosis can be confirmed by venous ultrasonography, which demonstrates a non-compressible vein or absence of venous flow with the Doppler method. Some cases may require contrast venography.

Treatment
Treatment should be similar to that in the HIV seronegative patient. This includes:

- Standard Heparin in a dose of 15,000-20,000 iu every 12 hours s/c and concurrent warfarin starting with 5mg once daily and adjusted to achieve an international normalised ratio (INR).
- Monitoring of therapy involves regular INR (warfarin) and activated partial thromboplastin time (APTT) for heparin. Heparin can be stopped once the patient has achieved a therapeutic INR of 2-3 on two consecutive days.
- The duration of treatment is 3 months for a transient risk factor is three months but goes up to 6 months among the others.
- Low molecular weight heparin can be used instead of standard heparin as it can be used without monitoring. Examples include Enoxaparin at a dose of 1-2 mg/Kg s/c once a day or dalteparin at a dose of 100 units/Kg twice daily. These options are more expensive than standard heparin.

Prevention
Avoidance of prolonged hospitalisation and graded exercises can reduce the risk of DVT.

Pancytopenia
Frequently seen in HIV infection and occurs when red blood cells (RBCs), white blood cells (WBCs) and platelets are reduced. When it occurs it signifies bone marrow failure. The causes discussed above for the individual cytopenias can eventually affect all the cells produced by the bone marrow.

Common causes

- Infections e.g. Disseminated TB, MAC, Parvovirus B19.
- Infiltration of the bone marrow due to Lymphoma.
- Nutritional deficiencies e.g. Vitamin B12 and folic acid deficiency
- Drugs e.g. chloramphenical, cotrimoxazole, antiretroviral (AZT)
- Autoimmune disorders e.g. Lupus antibodies

Management
A complete blood count reveals anaemia, leucopenia and thrombocytopenia. Further diagnostic work up should include a bone marrow aspirate or biopsy as discussed above which may give more information on the cause. Treatment depends on the cause. Supportive treatment may include blood or platelet transfusion, and aggressive treatment of infection in severely neutropenic patients.

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Module 12

HIV/AIDS RELATED MALIGNANCIES

Introduction:

HIV infection is associated with a number of malignancies, which include Kaposi's Sarcoma, lymphomas, and carcinoma of the cervix, among others. In general cancers develop in 40% of PLWHA with the risk increasing as the immunity (CD4+cell count) decreases. Often there is rapid progression and poor response to therapy and shortened survival. This module explores the common AIDS associated malignancies and discusses the approach to their diagnosis and management.

Goal

To equip participants with the knowledge and skills to recognise, diagnose and manage HIV related malignancies.

Learning Objectives:

By the end of this module the participants should be able to:

- List common AIDS related malignancies
- Discuss the aetiological (causal) relationship between these malignancies in relation to HIV/AIDS
- Be able to recognise signs and symptoms of some of the common AIDS related malignancies
- Outline the approach to diagnosis of some of the common malignancies
- Discuss the management of these malignancies
- Discuss the assessment and management of pain and other symptoms associated with these malignancies

Content Outline:

1. Common HIV related malignancies
2. Epidemiology, aetiology and pathogenesis of common malignancies
3. Signs and symptoms of HIV related malignancies
4. Diagnosis and management of individual malignancies
5. Prevention of HIV related malignancies

Methodology:

1) Introduction to the module

Steps

1. Brief overview : lecture
2. Questions and Answers (Q+A)

2) HIV related malignancies

Steps

1. Brainstorming
2. Trainer summarises and clarifies

3) Group discussion on individual malignancies

Steps

1. Break into small groups choosing one or more malignancies depending on the number of participants.
2. Report back by each group
3. Trainer summarises and clarifies as needed

4) Listing signs and symptoms of common malignancies

Steps

1. Brainstorming
2. Trainer summarises and clarifies as needed

5) Presentation on individual malignancies

Steps

1. Lecture
2 Q+A

6) Slide show of different malignancies

Teaching materials:

- Flip charts
- Markers (different colours)
- Masking tape
- Projector
- Slides/cases
- Case presentations
- Notepads
- Pens, pencils

Trainer's notes:

Detailed notes on 3 common malignancies:

- Kaposi's sarcoma
- Non-Hodgkin's lymphoma
- Carcinoma of the cervix Pain Management:
- Assessment of pain
- Analgesic ladder
- Adjuvant medications

Outline/Classification of HIV related malignancies

- AIDS Defining:
  - ✓ Kaposi's Sarcoma
  - ✓ HIV related lymphoma
  - ✓ Carcinoma Cervix
- Non AIDS Defining Cancers in HIV Infection (cancers where the incidence in HIV is higher than in the general population)
  - ✓ Hodgkin's Disease
  - ✓ Leiomyomas/Leiomyosarcomas
  - ✓ Anal Rectal Carcinoma
  - ✓ Testicular carcinoma
  - ✓ Renal Cell Carcinoma
  - ✓ Hepatocellular Carcinoma

Kaposi's Sarcoma (Epidemic KS)

Introduction

Moritz Kaposi, a Hungarian dermatologist, first described this tumour in 1872 as an idiopathic multiple pigmented sarcoma in older men of East European or Mediterranean descent. This cancer now occurs very commonly in PLWHAs as an aggressive epidemic form presenting with a variety of coetaneous lesions.

Epidemiology

KS is the most common malignancy in people with HIV disease. 15% to 20% of homosexual men with AIDS have presented with KS as their initial AIDS-defining illness. (1)For the periods 1989-1994 and l996-l997 prevalence declined for the most part in Europe and the United States where rates fell by 66%, which coincided with the widespread use of Highly Active Antiretroviral Therapy (2) In marked contrast for the period 1995-1997 in Uganda the incidence per million population was 51.7. (3)In Mulago Hospital AIDS clinic 7% of patients present with KS. (4) However, at Hospice Uganda among all patients with advanced cancer requiring palliative care, it is most common in males (56%) and the second most common cancer in females (44%) after cancer of the cervix. (5)

Causative agents

The association of Kaposi's Sarcoma with a herpes virus was discovered in the 1980s at the beginning of the epidemic. Serologic and molecular evidence has increasingly supported the role of HHV8 in the aetiology of this malignancy (6). However it is believed that both HIV and human herpes virus 8 (HHV8) are necessary in the development of KS. HHV 8 can be transmitted sexually, parenterally and also through other body fluids, for example, saliva.

Pathogenesis/Pathology

The pathogenesis of this tumour is complex. Initial doubts were held as to whether it was a true malignancy. It is suggested that the HIV–tat gene product, IL-6, TNF alpha, IL-1 Beta and other factors produced as a result of HIV infection or opportunistic infections stimulate tumour growth in cells which are infected by HHV-8. The circulation of KS spindle cells in blood or local deposition of KSHV–infected cells leads to the multifocality of this tumour. As HIV progresses and induces even greater immunosuppression, the tumour enlarges, and may become autonomous in its growth and behave more like a true malignancy.

Pathology (Staging)

Kaposi's Sarcoma in general is divided into four clinical types though their histological appearance is that of a vascular sarcoma with characteristic spindle shaped cells. Detailed discussion will mainly be focused on the epidemic or AIDS related form.

- Classic
- Endemic
- Immunosuppression related
- Epidemic/AIDS related

Epidemic KS can occur in a variety of forms

- Cutaneous
- Visceral
- Lymphadenopathic
- Or a combination of all the above.

Clinical presentation

Epidemic or AIDS related KS may present with a single or multiple skin lesions. Mucosal, visceral and lymphatic involvement may be prominent especially later in the disease.

The typical lesion appears as a painless skin lesion, which may be nodular, or plaque-like. Oral lesions appear as pinkish, red or brown lesions commonly on the palate and gingival. Similar lesions can be seen elsewhere in the mucus membranes, for example, conjunctiva.

Other presentations:

- **General symptoms-**Oedema of the limbs due to infiltration of lymphatics leading to woody induration and generalised lymph node enlargement, fungating cauliflower like lesions, which may have offensive smell if secondarily infected.
- **Pulmonary KS**-Presents with chest pain, cough, shortness of breath, haemoptysis, and effusions.
- **GIT-**Abdominal pain, GIT bleeding, and abdominal distension. GIT lesions may even lead to intestinal obstruction.
- **Pain-**Advanced disease may present with severe pain, which is usually visceral but can also be neuropathic if nerves are infiltrated. The latter is characteristically described as "burning" or spontaneously "stabbing".

Diagnosis

Diagnosis is usually clinical when characteristic skin or mucus membrane lesions are seen. Confirmation is by histology. Pieces of tissue can be taken off easily and sent for histology. Care should be taken as these lesions can bleed and the wounds can take a long time to heal especially when lymphatics are infiltrated.

Treatment

A number of treatment options exist. Choice will depend on tumour burden, general fitness of the patient, status of the immune system and concurrent AIDS-related complications as well as access to antiretroviral therapy (ART). The majority of patients present late with profound immunosuppression, concurrent illness and/or cannot afford treatment. In this instance palliative care is the only option. Many patients in Uganda may have no access to chemotherapy/radiotherapy or antiretroviral therapy. This means that the mainstay of treatment will be symptom control with what is locally obtainable.

In all cases, it is necessary to counsel patients about the diagnosis, prognosis, treatment options and possible side effects of the different treatment modalities. For purposes of treatment and prognosis, tumours can generally be classified into good and poor prognosis risk groups (ACTG) depending on tumour extent, immune status and presence of systemic illness.

Staging (The AIDS Clinical Trials Group 1997)

	O Good risk (all the following)	1Poor risk (any of the following)
Tumour (1)	Confined to skin, lymph nodes or minimal oral disease.	Associated oedema, ulceration, extensive oral disease; GIT KS; KS in other non-nodal viscera
Immune System	CD4+< 150	CD4+>150
Systematic Illness	No history of opportunistic infection No B symptoms (fever, night sweats, >10% body weight loss, diarrhoea >2weeks) Karnofsky performance status >70	History of opportunistic infection B symptoms present Karnofsky performance status <70 Other HIV disease e.g. neurological

Localized disease

- Radiotherapy:
  - ✓ For localized coetaneous lesions.
  - ✓ Painful lymphadenopathy

- ✓ To relieve bleeding lesions
- Surgery - Excision of localized lesions however, recurrence is common.
- Intra-lesional chemotherapy with vinblastine 0.1 – 0.2 mg

or

- Vincristine 0.1 mg Response rates vary between 70 – 90% ®
  Injection can be very painful.
- Cryotherapy—Liquid nitrogen.

Advanced disease (multiple lesions >25, tumour associated oedema and visceral KS)

1. ART - (Antiretroviral therapy) This is the first line option to be used if available. This causes regression of existing lesions as well as reducing the number of new cases developing KS.
   - ART decreases the viral load directly, possibly improving the immune response to HHV-8 and also acts directly on HHV8.
   - It improves the outcome in patients treated with combination chemotherapy.

Regimens

Any regime that quickly and effectively reduces the viral load and maintains it below detectable levels is advisable.

2. Chemotherapy:
   - Patients with rapidly progressive mucocutaneous disease causing oedema, ulceration, and pain.
   - Visceral disease Combinations:
   - Adriamycin (A)
   - Bleomycin (B)
   - Vincristine (V)

Dosage:

1. Doxorubicin (adriamycin) 10-20 mg/m^2
2. Bleomycin: 10-15 units/m^2
3. Vincristine: 1-2 mg

These are given intravenously every two weeks. Response rates vary between 25-88% worldwide and 20 – 30% in Uganda (UCI) where patients are usually more immunosuppressed and may have concurrent opportunistic infections. There are significant bone-marrow toxicities limiting long-term use of these drugs therefore patients should have regular blood counts measured.

Newer Agents:

Liposomal preparations improve drug kinetics and reduce side effects but are too costly and not available locally.

- Liposomal daunorubicin
- Paclitaxel (Taxol)

Pain and symptomatic management

Pain can be severe in advanced disease**.** Pain can be visceral but also neuropathic and successful control depends on clear diagnosis of the type of pain. Visceral pain usually responds to the drugs in the WHO analgesic ladder while neuropathic pain responds to either anticonvulsants or antidepressants. Burning-type pain usually responds to antidepressants (e.g. amitryptyline 12.5 mg nocte initially and increased if necessary to 25-50 mg) and spontaneous "stabbing" or "shooting" pain responds to anticonvulsants (e.g. Phenytoin and carbamazepine).

Use the WHO Analgesic Ladder for management of pain

Step 1	Paracetamol/aspirin	- mild pain
Step 2	Codeine (weak opioids)	- moderate pain
Step 3	Morphine (strong opioids)	- severe pain

Analgesics for chronic pain associated with AIDS-related conditions should be given regularly (by the clock) by mouth in accordance with the ladder (WHO) and titrated to each patient's individual needs. (Note: Do not forget a laxative in patients on opioids except if the patient has diarrhoea as well). Step 1 analgesics can be used with Step 2 or 3. However Step two and three should not be used together as the work by the same mechanism.

Adjuvant therapy

- Steroids can reduce tumour oedema, thus their role in lymph oedema.
- Antidepressants/Anticonvulsants for neuropathic pain.

Other symptoms

- Fungating tumours - very offensive
  - ✓ Local radiotherapy can help
  - ✓ Metronidazole powder (locally applied to the wound can control the offensive smell)
  - ✓ Nursing care as appropriate
- Lymphedema
  - ✓ Massage
  - ✓ Exercise
  - ✓ Bandaging

Lymphomas

Introduction

These are a group of malignancies of lymphoid origin, which occur more frequently in PLWHAs. Generally lymphomas occur in 5-10% of PLWHA and 1-2% of patients with HIV will develop CNS disease. The risk of developing lymphomas steadily increases with the duration of HIV infection and advancing immunosuppression.

The following malignancies are reviewed:

- B cell immunoblastic lymphomas
- Primary cerebral lymphoma
- Burkitt's lymphoma
- Hodgkin's disease - Mixed cellularity

Epidemiology

It is usually a late manifestation of HIV infection when CD4+ cell count is <200 and there is a prior history of an AIDS defining illness. The incidence of lymphomas per million population according to the Uganda

cancer registry was 65.9 between 1995 and 1997 compared to 41.9 (1991-1994) and 22.6 (1960-71), which corresponds to late in the epidemic, the early epidemic and the pre-HIV/AIDS eras, respectively. (7)

Non-Hodgkin's Lymphomas (NHL)

This tumour is AIDS defining in HIV infected patients.

Causative agents (aetiology)/Pathogenesis

The aetiology and pathology is complex. However, the fundamental cause in all lymphomas is underlying immune deficiency. Epstein Barr virus has been observed in over 50% of tumour tissues from patients with systemic lymphoma especially those with the immunoblastic type and is implicated in the developments of these lymphomas. HIV is also thought to directly or indirectly play a critical role in the development of lymphomas either by damage to the germinal centres of the lymph nodes or also the disruption of normal levels of inflammatory cytokines (chemical messengers) such as IL-6 and IL-10, which in turn stimulate B-cell multiplication.

Pathology

NHL may occur either in peripheral lymph nodes, in the CNS, the GIT, the liver and kidneys. However, it can also affect other tissues.

Clinical presentation

Can present in 3-ways:

- Primary CNS disease,
- Systemic lymphoma, and
- Primary effusion lymphoma.

Primary CNS Lymphoma

NHL confined to CNS (brain and spinal cord) occurs in 25% of patients with HIV who have severe immune suppression with median CD4+<50/μL. (8) There is also a history of multiple opportunistic infections.

Clinical presentation

Common symptoms are confusion, lethargy, memory loss, mass lesion causing headache, partial paralysis, convulsions and loss of speech. Others features include, hemiparesis, aphasia, seizures, cranial nerve palsies and headache. Focal findings do not occur in all cases.

Diagnosis

CT/MRI shows single or multiples discrete lesions that are hypodense but enhance with contrast. Diagnosis is usually difficult because of the difficulty in distinguishing it from toxoplasmosis. CT/MRI only offer clues but are not diagnostic. A solitary lesion on MRI is more likely to be due to NHL but multiple lesions are seen in 50% of cases.

Treatment

Whole brain radiotherapy results in neurological improvement in 62-79%; overall response is 52-70% with clinical remission in 40-50%. Median survival is 2-4.8 months. The majority die from other HIV related complications while 13-55% die as a result of progressive disease (9) Chemotherapy and radiotherapy: Clinical remission was 88% in one series but median survival is 3.5months (10).

Systemic lymphoma

Clinical presentation

Presents in patients with CD4+ counts between 100-180 cells/μL (11) but 75% may occur in those with CD4+>50, and approximately 30% in those with CD4+ >200.

Extra-nodal disease is the most common (87-95%) including CNS 42%, BM involvement 33% and GIT is the only site of disease in 31% (12).

GIT NHL is seen in 27% and involves the stomach (in the majority), oral cavity, esophagus, small and large intestines, appendix and anorectal region. GIT lymphoma should be suspected in patients with bleeding, dysphagia, abdominal pain, rectal pain etc.

Anorectal disease may mimic perirectal or perianal abscess. Liver and hepatobiliary tree involvement is frequent and extra and intrahepatic biliary obstruction can occur leading to jaundice.

Bone marrow and meninges also are involved

Other sites include soft tissue of the epidural space, gingiva, paranasal sinus, and cardiac and pericardial sites.

- Systemic Lymphoma: May be non-specific.
  - ✓ Fever
  - ✓ Weight loss
  - ✓ Night sweats

Burkitt's lymphoma is the most common form occurring in children usually presenting as large jaw tumours.

Diagnosis

Systemic Lymphoma:
Examination of the affected body tissue, usually the bone marrow or a lymph node confirms the diagnosis. Serum Lactate Dehydrogenase (LDH) is normally elevated.

Primary effusion lymphoma

- Accounts for ~5% of all HIV lymphomas
- Body cavity effusions (pleural, pericardial, ascites) and no associated mass lesion and localized to body cavity
- Histology midway between large cell immunoblastic and anaplastic large cell lymphoma.
- Characteristically associated with HHV-8; 50-100% with EBV
- B & T-cell associated antigens usually absent
- Median CD4+ count 78-84/μL
- Treatment similar to those for systemic lymphomas
- Median survival 2-5 months with no long-term disease-free survivors

Management

Staging

- The Ann Arbor staging system is commonly used for patients with NHL.
- Stages SI-SIV in adults are subdivided into A and B categories: B for those with generalized symptoms and A for those without.

- Patients in the B category have the following symptoms.
  - ✓ Unexplained loss of >10% of body weight in the 6 months preceding diagnosis
  - ✓ Unexplained fevers with temperature >38^{o}C
  - ✓ Drenching night sweats
- SI: involvement of a single lymph node region (I) or localized involvement of a single extra lymphatic organ or site (IE)
- SII: involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extra lymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE). Note: The lymph node number involved may be indicated by a subscript (e.g.II3)
- SIII: involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extra lymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E)
- SIV: disseminated (multifocal) involvement of one or more extra lymphatic sites with or without associated lymph node involvement or isolated extra lymphatic organ involvement with distant (non-regional) nodal involvement.

CNS Lymphoma
Treatment

- Radiotherapy improves CNS symptoms, though the outlook is poor.
- Steroids can reduce /shrink the tumour and associated oedema and therefore improve associated symptoms.

Systemic Lymphoma
Treatment

- Combination chemotherapy: CHOP (Cyclophosphamide, doxorubicin, vincristine and predinisolone) is effective in more than 75% of recipients. Low dose M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone or infusion of CDE (cyclophosphamide, doxoribicin, and etoposide). All have comparable response rates.

- HAART: People treated with chemotherapy for lymphoma who are also being treated successfully with anti-HIV drugs may have better survival. Paradoxically, however improved long-term survival due to anti-HIV therapy may increase the risk of lymphoma developing through extending the risk period. Care needs to be taken with some anti-HIV drugs, for example AZT when combined with chemotherapy especially in order to avoid bone-marrow suppression. For patients on HAART the incidence of AIDS-related lymphoma is low if the CD4+ cell count is above 200 cells/μL.

When combined with HAART multi-agent chemotherapy appears to be better tolerated in terms of haematological toxicity and also results in higher response rates to chemotherapy and longer survival. Infusional EPOCH regimen (the same drugs as CHOP plus etoposide), without antiretroviral therapy, has been associated with good response rates and excellent outcome free of relapse. Optimal treatment for patients with relapsed or refractory AIDS lymphoma remains undefined at this time.

Prognostic Factors in patients with systemic AIDS-related lymphoma:

The factors associated with short survival of patients with AIDS-related lymphoma include:

- CD4+ cell count < 100 cells/mm^3
- Stage III or IV disease
- Age >35 years

- Karnofsky score < 70%
- Prior AIDS diagnosis
- Bulky tumour as measured by elevated lactic dehydrogenase
- M>F

Prognostic factors & survival

- 0 or 1 factor: median survival 46 weeks, 3 year survival 30%
- 2 factors: median survival 2-44 weeks, 3 year survival 17%
- 3 or 4 factors: median survival 18 weeks, 3 year survival 0%

Cancer of the Cervix

Introduction

HIV disease is associated with an increased risk of cervical dysplasia and invasive cancer in women (13). Invasive cervical cancer is one of the AIDS defining illnesses although its incidence and natural history has not significantly increased in HIV positive women.

Causative agent

Human papilloma virus (HPV) has a role in the pathogenesis of both cervical dysplasia and invasive cervical cancer. There is strong evidence both biologically and epidemiologically for a causal relationship between HPV and cervical cancer (14). Both HIV and HPV, the virus associated with cervical cancer, are sexually transmitted with similar risk factors for acquisition. HIV is associated not only with a higher prevalence of HPV in the cervix, a higher frequency of multiple HPV phenotypes and persistence of HPV in the cervix but also with a higher prevalence of cervical intra-epithelial neoplasia/squamous intra-epithelial sessions, a higher progression from low-grade to high-grade squamous intra-epithelial lesions and a greater likelihood of relapse of cervical intra epithelial neoplasia after therapy. The risk of squamous intra-epithelial lesions is greatest among women with CD4+counts < 200 cells/ml.

Links between HIV and Cancer of the Cervix (15)

- Those with HIV are more likely to have HPV too. Those with CD4+ <200 were 9.7 times more likely to have HPV
- HIV positive women are more likely to have more subtypes of HPV
- Half of all women with CD4+ <200 will have high-grade Squamous Intraepithelial Lesions (SIL) within 4 years
- HIV infection speeds progression from cervical disease to cancer; 20% have low-grade and 9% with high-grade SIL
- Regular cytology on HIV positive women prevents progression of cervical disease.

Pathogenesis

Decreased cellular immunity and a direct interaction between HIV and HPV at a cellular level as well as increased secretion of cytokines by HIV-infected lymphocytes are thought to facilitate neoplasia.

The course of cervical disease goes through several stages

Precursor lesions: Cervical Squamous Intraepithelial lesions (CSIL)

Low grade CSIL

- Mild dysplasia
- Cervical Intraepithelial Neoplasia (CIN I)

High grade CSIL (CDC category B conditions)

- Moderate dysplasia
- Severe dysplasia
- Cervical Intraepithelial Neoplasia II (CIN II)
- Cervical Intraepithelial Neoplasia III (CIN III)
- Carcinoma-in-situ

Invasive disease (CDC category C AIDS indicator condition)
Almost all invasive cancers arise from high grade SIL and not low grade SIL.

- Micro invasive
- Occult invasive
- Invasive carcinoma

Risk factors

The risk of developing cervical disease is greater in women with advanced HIV disease.

- HPV infection
- Advanced HIV disease (CD4+< 200)
- Young age groups (adolescents) - all age groups are affected.
- Multiple sexual partners.

Diagnosis

- Young HIV positive patients are particularly at risk

Clinical presentation

Early: No symptoms until late

Late: PV bleeding
Abnormal vaginal discharge
Post coital bleeding

Lower abdominal pain

Advanced: Metastatic disease will present with other symptoms depending on organs involved
Backache
Pelvic bone pain
Fistulae

Prevention of invasive disease should be the major approach to management of HIV in infected women.

Screening

The following can be done to identify patients who are at a higher risk.

- PAP smear at initial evaluation of HIV patient
- Repeat PAP smear after 6 months and if normal at yearly intervals
- More regularly (4-6 months) in those with prior HPV infection or a previous cervical lesion

Treatment of pre-malignant disease in HIV positive women

Abnormal cytology should be followed by biopsy of suspicious areas to grade the lesion. LSIL lesions are followed up every 3-6 months and may regress spontaneously. HSIL are managed by excision or ablation of the lesions. Recurrence can be a big problem

- Cryotherapy, no bleeding
- Laser therapy
- LEEP (Loop electrosurgical excision procedure)
- Cone biopsy All do not work well in HIV positive women; failure 40% at 1 year and 55-60% at year 2. These treatments delay or prevent progression to cervical cancer.

Treatment of invasive disease

HIV sero-positive patients should be managed the same way as HIV sero-negative women. After appropriate staging of their cancer, therapy that is appropriate for their stage of disease is indicated including cone biopsy, radical hysterectomy, radiation therapy and combined modality with radiation and chemotherapy. Pain and symptom control is basic at all stages of the disease.

Decision on which modality to use should be made depending on:

- Stage of the disease
- Degree of immune suppression
- Concurrent illnesses

Use of ARVs

- Reduce prevalence of cervical intra epithelial neoplasia
- Regression in the pre invasive stages.
- Can improve general patient condition.

Prevention

- Two pap smears in first year after HIV diagnosis if negative.
- Pap smears every six months optional for high-risk women.
- Treat and repeat for inflammation.
- Annual follow up for atypical cells of undetermined significance.
- Mild dysplasia to be followed either by repeat pap or colposcopy.

Hodgkin's Disease

This is one of the cancers, which is increasingly being seen in HIV patients. Recent epidemiological studies have demonstrated an increase in risk for Hodgkin's disease among HIV sero-positive individuals. Epstein Barr virus is implicated in the aetiology and pathogenesis of this tumour.

Clinical Presentation

The clinical course among patients with HIV is different from that in patients without HIV. B symptoms and extranodal involvement are common and in general the disease is more lethal in this population.

Symptoms:

- B Symptoms – fever, weight loss, anorexia, excessive sweating.

Signs:

- Lymphadenopathy – pain firm and especially mobile
- Hepatosplenomegally
- Bone marrow involvement may lead to anaemia.

Diagnosis

- Clinical but histology can be done to confirm.

Treatment

Prognosis is worse than in the general population.

Chemotherapy

- ABVD (doxorubicin, bleomycin, vinblastin, dacarbazine) remission rates vary between 45-60% and survival being 8-18 months.
- Patients usually die from other opportunistic infections.

Squamous Cell Carcinoma of the Conjunctiva

(see Module 9 The Eye for more detail)

This is an extreme form of eye surface squamous neoplasia. It ranges from mild dysplasia to carcinoma in situ and invasive carcinoma.

It is rare in other places but common in sub-Saharan Africa and other tropical areas.

- Associated with exposure to solar UV radiation. Incidence of SCC of the eye increases as exposure to ambient solar UV radiation increases. Levels are higher at the equator.
- 10-fold increased risk of the tumour in HIV infected; patients are young adults
- HPV especially type 16 has been reported in some ocular surface squamous neoplasias

Treatment

Surgery and radiotherapy

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Module 13

DIAGNOSTICS (Laboratory component)

Introduction:

Opportunistic Infections (OIs) are infections caused by agents that take advantage of a suppressed immune system. A number are normal flora, whereas others are pathogenic and have previously been eliminated or controlled by a normal functioning immune system. Due to immunosuppression there will be reinfection or the controlled pathogens get reactivated. Examples include agents that cause TB, Herpers zoster (shingles), Toxoplasmosis or Histoplasmosis.

Goal:

This module is intended to equip Laboratory personnel in Uganda with appropriate knowledge and skills in Laboratory diagnosis of OIs among PLWHAs.

Learning Objectives:

By the end of this module the participant should be able to:

- Appreciate the importance of quality laboratory procedures (investigations)
- Collect appropriate specimens
- Transport /store the specimens
- Process specimen
- Document, interpret and forward the results to requesting clinicians.

Content outline

1. Good laboratory practice
2. Specimen collection
   - sterile parts
   - areas with normal flora (that join with skin /mucus membranes)
3. Biology of the infectious agents
4. Specimen containers /storage conditions
5. Processing
   - Microscopy - Light
   - Phase /Darkground
   - Immuno-Fluorescence (IF)
   - Electron microscopy (EM)
   - Cultivation - Media/cell lines /animals
   - Special systems e.g. Bactec
   - Serology Antigen (Ag) or Antibody (Ab) detection
   - Molecular Techniques
   - PCR
   - Insitu hybridisation
   - RFP/PFGE
6. Recording, interpreting and forwarding of results.
7. Quality assurance

Methodology:

1) Good Laboratory Practice (GLP) which involves the following:
   - Quality assurance (QA)

- Trained staff
- Equipment properly functioning
- Samples safely collected and stored
- Standard Operating Procedures (SOP)
- Quality Control (QC)
- Laboratory Safety Methods
- Ethics

The Methodology will include the following in all practices:

- Lecture/demonstration/hands on
- Brainstorming
- Group discussion

Steps for each practice will include:

1. Trainer will provide a description and demonstration
2. Brainstorming
3. Trainer gives standard descriptions
4. Trainer will lead a discussion covering the advantages and disadvantages of each practice.

Teaching materials:

- Notepads
- Pens, pencils
- Slides
- Projector
- Specimens
- Reagents
- Equipment, for example, microscope
- Laboratory space

Trainer's notes:

Specific learning objectives

By the end of the module the lab person should be able to:

1. Name and group the common HIV associated infections
2. Know and perform tests for the diagnosis of the most common opportunistic infections
3. Appropriately document the results
4. Appropriately forward results to requesting physician (s)
5. Know how to protect him/herself and others against laboratory

- Note: The infectious agents affect many body systems. However this module, unlike the preceding modules, will not focus on body systems but rather handle organism by organism. The biology of organisms should be discussed.

(The same methodology and steps outlined above for Practices should be followed for all infectious agents described below)

Bacterial Infections

Bacterial infections are a recognized cause of morbidity and mortality in PLWHAs. A number of bacterial infections continue to be a source of concern for many PLWHAs, including those who are responding well to antiretroviral therapy.

1) Mycobacterium group

Mycobacteria covers the microorganisms causing Tuberculosis- Mycobacterium tuberculosis. Atypical mycobateria such as M.avium can also manifest in immune compromised individuals as respiratory tract infections, CNS, and other disseminated diseases.

Specimens: Sputum, Broncho-alvealor lavage (BAL), CSF, aspirates, and tissue biopsy.
Tests: Macroscopic (naked eye specimen assessment)
Microscopy: Ziehl-Neelsen, Auramine Phenol (Immuno-Fluorescent)
Culture: Lowenstein-Jensen Bactec (Radiometric)

Serology for research

Serology, molecular tests such as (PCR, Direct detection and identification by Nucleic Acid Amplification and Hybridisation, RFLP) are mainly for research

2) Other bacterial diseases

a) Salmonella - non typhoidal
- typhoidal

Source of sample: Stool, Blood, CSF, other lesions e.g. aspirate, pus.

Sample collection: sample should be in the appropriate sterile container, for example, for blood it should be in blood culture bottles

Tests:

Gram staining and Culture Identification by serology

Strep.pneumonie and H. influenza

Source of sample: sputum, Nasal swab, blood, CSF
Sample collection: the sample is collected in the appropriate sterile container

Tests:

Gram staining
Culture Identification

Ps.aerugenosa
Staphylococci, other streptococci
Enterobacteriaceae and Norcardia

Source of sample: Any of these areas can be used as appropriate, for example abscess, blood, urine, CSF, sputum, aspirate

Sample collection: sample should be in an appropriate sterile container, for example, in blood culture bottles

Tests:

Gram staining Culture and Identification

- These normally cause infections in immune competent individuals but show as disseminated disease in immune compromised individuals*

Antigen-Antibody tests and PCR in this group are mainly limited to research work

Syphilis (1, 2)

Syphilis is a systemic chronic infectious disease caused by Spirochete Trepanoma pallidum. In immune compromised individuals syphilis progression from primary to tertiary stage is rapid. Serological techniques are the routine method of diagnosis. However, organism identification can also be done where facilities allow.

Specimens:

Blood, CSF, or Aspirate/ exudates, Tissue biopsy

Samples should be collected in the appropriate sterile containers.

Tests

- Microscopy:
  - ✓ Dark field microscopy
  - ✓ Direct fluorescent antibody technique (DFA)
- Serology
  - ✓ RPR/VDRL, TPHA
  - ✓ PCR
- Molecular techniques
  - ✓ PCR

Fungal infections

Fungal infections are a significant group of infections among PLWHAs. Common infections in this group include:

- Candidiasis
- Cryptococcus
- Aspergillosis
- Histoplasmosis
- Coccidioidosis
- Penicillium marneffei infection
- Pneumocystis jiroveci (PJP)

(a) Candidiasis:

Candidiasis is the most common fungal condition associated with HIV infection. Almost every person living with HIV will have an episode of candidiasis (thrush) at some stage of their illness. Candida rarely disseminates systematically but tends to affect mucous membranes.

Specimens: sputum, blood, CSF, throat swab/vaginal swab

Tests:

- ✓ Microscopy:
- Wet prep-10% KOH
- Gram stain
- ✓ Culture:

- Sarboroid's Dextrose Agar,
- Corn meal agar
- Germ tube
  - ✓ Identification
- Germ tube
  - ✓ Serology can be done but it is still limited to research.

(b) Cryptococcus

Infections /disease due to this organism manifest as CNS, respiratory, skin or disseminated conditions
Specimens: CSF, Sputum, Blood, Tissue

Tests

- Microscopy:
- Indian Ink, Gram stain, H&E
- Serology: Antigen-antibody detection e.g. CRAG
- Culture and identification (Phenol-oxidase(bird seed agar, urease)

(c) Aspergillus

Infection /disease manifests as allergy, aspergilloma and disseminated/ invasive disease

Specimens:

Specimen: sputum, blood, Biopsy

Test:

- Microscopy-wet prep (KOH),Gram, H&E, IF (Calcoflor white)
- Gomori Methanamine Silver (GMS)
- Culture: sabouraud's dextrose agar
- Identification; Lactophenol-cotton blue stain
- Serology : Antigen/Antibody

(d) Histoplasma (3, 4)

This manifests as Sepsis, Respiratory disease, CNS and disseminated disease
Specimens: blood, biopsy, sputum/Broncho-alveolar lavage (BAL), urine, bone marrow

Tests:

- Microscopy: H&E, Wright-Giemsa
- Culture:
- Sabouraud's medium
- Serology-Antigen/ antibody;Complement Fixation Test, Radio immuno Assay for H.capsulatum polysaccharide antigen

Note: The need for safety cabinet containment at Level III or IV

(e) Penicillin Marneffei

This manifests as systemic disease, skin, and respiratory tract infections
Specimens: Broncho alveolar lavage, Tissue biopsy, blood

Tests:

- Microscopy; wet pep, Gram stain, Wright giemsa, H&E, GMS
- Culture & identification (Sabouraud's Dextrose agar, Czepak yeast extract, malt extract agar, glycerol nitrite agar)
- Serology

(f) Pneumocystis jiroveci

Infection /disease manifests as respiratory or disseminated disease.
Specimens: induced sputum, Broncho alveolar lavage, lung biopsy, other tissue biopsies

Tests

- Microscopy
- Giemsa, PAS, Methenamine-Gomori silver stain, Toluidine O blue, Fluorescent stains
- Serology and PCR remain mainly for research

(g) Mallesizia
(h) Onychomycosis
(i) Coccidioides immitis

Protozoa

a) Toxoplasma gondii (5, 6)

Infection/disease manifests as CNS, RT I, disseminated disease
Specimens: CSF, Blood, Biopsy, Broncho alveolar lavage

Tests

- Microscopy
- Giemsa stain, H&E,
- Peroxidase anti peroxidase technique (immuno histo chemistry)
- Culture: Animal inoculation
- Serology: Antigen/Antibody; Sabin –Feldman dye test, Direct agglutination test,
- ELISA
- PCR

b) Crytosporidium

Manifests as secretory diarrhoea, Cholangitis, RTI

Specimens: Stool, Intestinal Biopsy, Billiary aspirate, Sputum/Broncho alveolar lavage

Tests

- Microscopy
- Modified Ziehl-Neelsen, Phenol auramine,H&E, Immunofluorescence
- PCR

The above procedures can be applied to Isospora belli and Cyclospora cayetanensis in addition to a wet preparation to stool as a specimen.

c) Microsporidium (7, 8)

Infections /disease manifests as secretory diarrhoea, RT, (ENT), Disseminated disease

Specimens: Stool, Biopsy, Blood, Broncho alveolar lavage

Tests

- Microscopy:
- Trichrome stain, Immuno Fluorescence stain, Electron Microscopy,
- Culture: Tissue culture
- PCR and serology for research

d) Giardia intestinalis

Manifests as secretory diarrhoea

Specimens: stool, Duodenal aspirates

Tests:

- Microscopy
- Wet prep
- Iodine Stain

e) Leishmania spp (9, 10)

Infections/disease manifests as mucocutaneous, cutaneous and disseminated disease

Specimens: Tissue biopsy and blood

Tests

- Microscopy
- Giemsa stain, H&E
- Serology Direct Haemagglutination test - (Montenegro test– skin sensitivity test)

f) Amoeba

Free living (Acanthoamoeba, Naegleria and Balamuthia spp) can cause encephalitis and other chronic granulomatus encephalitis

Specimens: Tissue biopsy, CSF

Tests

- Microscopy
- Wet prep, Giemsa, H&E
- Serology (Antigen/Antibody)-ELISA
- PCR

g) Sarcocystis species

h) Strongyloides stercoralis

Specimens: stool, duodenal aspirate, tissue biopsy

Tests

- Microscopy
- Wet prep, H&E

i) Trichnella spirallis

Specimens: Blood, Muscle biopsy (tendinous insertion)

Tests

- Microscopy; wet prep,
- Giemsa stain
  (post digestion with Pepsin and hydrochloric acid then concentrate ammonium hydroxide)
- Serology: Antigen/antibody
  (Bentonite flocculation test, ELISA, Latex agglutination, CFT)

Viruses

When viruses infect an individual they multiply in the cells. In the immune competent individual the infection is controlled/eliminated by the immune system, while in an immune compromised individual the infection persists, manifesting in a severe form or as a chronic condition. Some of the viruses undergo a latent stage in immune competent individuals and become reactivated when the immune system is compromised.

A. Herpes Virus

Type 1 (Oral)
Type 2 (genital)
Type 3 (herpes Zoster)
Type 4 (Epstein Barr virus- EBV
Type 5 (Cytomegalovirus- CMV
Type 8 Kaposi's Sarcoma associated virus

Pox

e.g. Molluscum - contagiosum

B. Human Papilloma Virus-HPV
C. Hepatitis viruses (B, C)

Specimens: Blood, Scrapings, Tissue biopsy, Secretions (swab/aspirate)

Tests

- Microscopy
- IFT/Electron Microscopy
- Culture; Tissue culture
- Serology: Antigen/Antibody
- PCR

References:

1. *Murray R.Patrick, Baron JO Ellen, Pfaller A Michael, Tenover C Fred, Yolken H*

2. *Robert. Manual of Clinical Microbiology. 6th Ed. Washington DC ASM,1995*

3. *Koneman WE, Allen DS, Janda WM, Schreckenberger PC, Winn CW. Colour Atlas and Text Book of Diagnostic Microbiology, 5th Ed Philadelphia, NewYork Lippincott, 1997*

4. *Murray et al as above*

http://hivinsite.ucsf.edu/Histoplasma and HIV

6. *Murray et al as above*

http://hivinsite.ucsf.edu/Toxoplasma and HIV

8. *Murray et al as above*

9. *http://hivinsite.ucsf.edu/Microsporidium and HIV*

10. *Murray et al as above*

11. *http://www.kit.nl/biomedical_research/html/leishmaniasis.asp*

Module 14

POST EXPOSURE PROPHYLAXIS

Introduction

The health care worker just as all other professionals has occupational hazards while executing his/her duty. The commonest one is acquiring disease from the patient. The spectrum of disease and their mode of transmission from the patient to the health worker is wide. Among the diseases transmitted are Hepatitis B, Hepatitis C and HIV. And this is commonly through needle stick injuries though other modes can transmit infection.

Aims

The module is aimed at equipping the health worker with

- Knowledge of the occupational risks.
- Skills of limiting the danger of the risks
- Available options when accidentally exposed.

Definition:

Remedies available to minimize the risk of transmission of infection after accidental exposure to a potential source

Content

- Dos and Don'ts of limiting disease transmission in health care setting.
- Interventions after accidental needle stick injury.
- Rationale for "timely" intervention
- Therapeutic interventions

Sources of infection/hazardous material

- blood,
- semen,
- amniotic fluid etc

People at risk in the health care setting.

- health workers-laboratory personnel, clinicians, nursing staff, phlebotomists etc
- auxiliary health care setting staff-cleaners, mortuary attendants etc
- patients' attendants.

Transmissible infections

- HIV
- HBV
- HCV

1. DOs and DONTS

Prevention is possible by following universal precautions.

- DOs
  - ✓ Proper refuse disposal
  - ✓ Use of surgical gloves
  - ✓ Operating gurgles

- DONTS
  - ✓ Don't recap needle after use

2. Intervention after accidental needle stick injury.

After percutanous accidental blood exposure the risk of disease transmission varies with the disease.

- 30% HBV (30/100)
- 3% HBC (3/100)
- 0.3 HIV (3/1000)

The risk of HIV transmission also depends on

- volume of inoculate
- nature of the biological fluid. Blood+++
- type of syringe
- stage of disease in the source patient
- patient not on HAART
- Percutanous injury (needles, instruments, bone fragments, bite breaking the skin)
- exposure of broken skin (abrasions, cuts, eczema etc)
- mucous membranes eg the eye

After the exposure, do the following first AID measures

- LIBERALLY wash with soap and water. (*avoid scrubbing, antiseptics)*
- Encourage free bleeding of the wound. *(avoid sucking)*
- Contact the designated doctor to do risk assessment IMMEDIATLY.

If SIGNIFICANT exposure is suspected

- health care worker takes start doses PEP pending HIV status of the patient.
- Seek for informed consent from the patient and the health worker for HIV serology.
- If the source unknown, epidemiological likelihood of HIV can be used.
- recommended when risk is high

-

Risk assessment. The exposure is considered significant if :

- Source HIV + and severe injury*(broken skin)*
- Source patient's HIV Status unknown and high prevalence rates in the locality.

Rationale for early intervention.

- Post exposure prophylaxis should be started within 2-3 hours, avoid delays
- Thus 24 hr access of the facilities, starter packs with 2 day supplies in all departments at risk.
- After exposure there is 4-8 hr lag before the cell get in contact with CD4 receptor cells. The virus is more vulnerable to the drugs at that stage.
- CDC 1997-AZT case control studies showed PEP decreased risk of sero-conversion by 79%
- document all findings
- keep all records.
- keep it confidential thus use codes for the laboratory results

Therapeutic interventions

- 2NRTI+1PI eg AZT+3TC(combivir) + nelfinavir (viracept) or indinavir(crixivan)

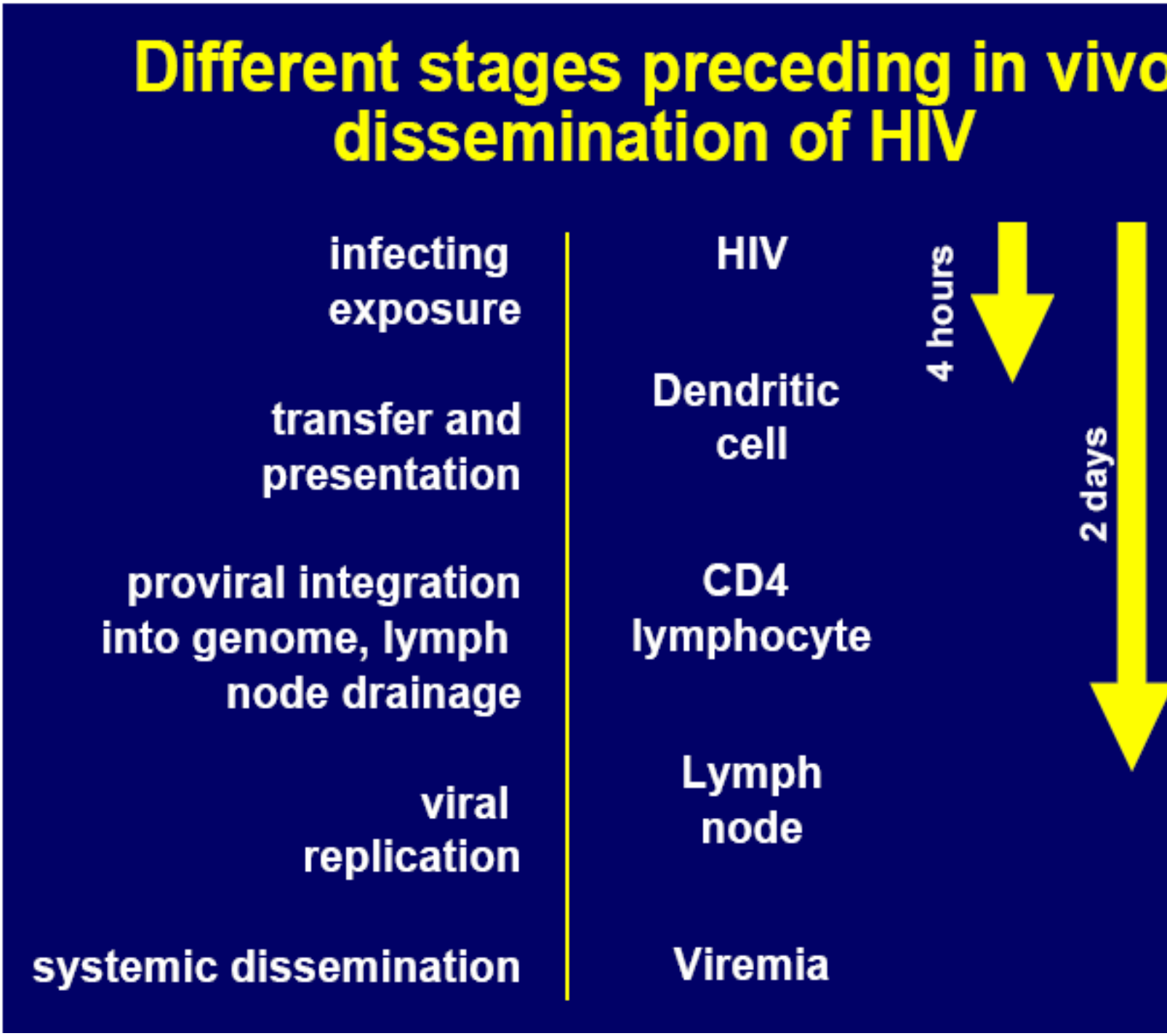
- 2NRTI+1NNRTI eg AZT+3TC+EFFERVIRENZ(avoid in preg)

Guidelines for the health worker.

- If health worker baseline HIV sero-status is negative then duration of treatment is 4 weeks. If baseline status is found positive manage like any other HIV patient.
- In instances where source patient is on ARVs, choice of drugs for health worker should be in line with resistance profile.
- psycho-social support
- Contraception is recommended for the female health workers for the 3/12 post exposure.
- screen for other pathogens eg HBV,HCV
- continuous adherence counseling
- monitor side effects like any other patient on ARVs
- adopt safe sexual practices during the period of follow-up/avoid blood donations
- HIV antibody testing for the health worker- baseline, 6/52, 3/12 and 6/12

Guidelines for the source patient.

Patient should be enrolled into chronic HIV care which includes psycho-social support, post test conselling. Screening for other opportunistic infections etc.


Different stages preceding in vivo dissemination of HIV
infecting exposure
HIV
4 hours
transfer and presentation
Dendritic cell
2 days
proviral integration into genome, lymph node drainage
CD4 lymphocyte
viral replication
Lymph node
systemic dissemination
Viremia

Module 15

Patient evaluation

Goal:

To enable a health worker in Uganda to conduct a thorough evaluation of a patient presenting with HIV/AIDS.

Learning objectives:

By the end of this module the participants should be able to:

- Properly evaluate a patient with the aim of planning a treatment plan.
- Recognise signs and symptoms of the HIV/AIDS
- Know how to make a definitive diagnosis of the different pathogenic organisms
- Manage the infections and associated complications including referral where necessary

Methodology:

1) Introduction

Steps

1.Trainer gives a brief overview of patient evaluation.

2) Listing of steps of patient evaluation.

Steps

1. Brainstorming
2. Trainer clarifies and makes additions as needed
3. Trainer gives simple and easily remembered format.

Teaching materials:

- News print
- Markers (different colours)
- Flip chart
- Chalk board
- Over head projector
- Slide projector
- Transparencies
- Computer (Power point presentation)
- Pencils, pens
- Notebooks

Trainer's notes:

Aim of patient evaluation

1. Make a diagnosis/Stage disease
2. Identify OIs
3. Clinically stage the patient
4. Know when to start OI prophylaxis
5. Know when to start ARVs

Approach to patient with HIV /AIDS

- History

- Clinical Examination
- Laboratory Investigations
- Plan of Management

History

- Current complaints
  1. Any symptoms the patient may have on the current visit.
- Past illnesses (OIs)
  1. Major AIDS related illness treated in the past
- Drugs
  1. Current and previous medication
- Allergies
  1. Drug and food allergies, esp. in relation to sulphonamides since they form the backbone of OI treatment and prophylaxis
- Hospitalisations

Personal Information
Name,
Date of birth
Address,
Family, education and socio-economical status, profession etc.

Past medical history

Hypertension

Diabetes
First HIV test positive
History of opportunistic infections (past and on-going)

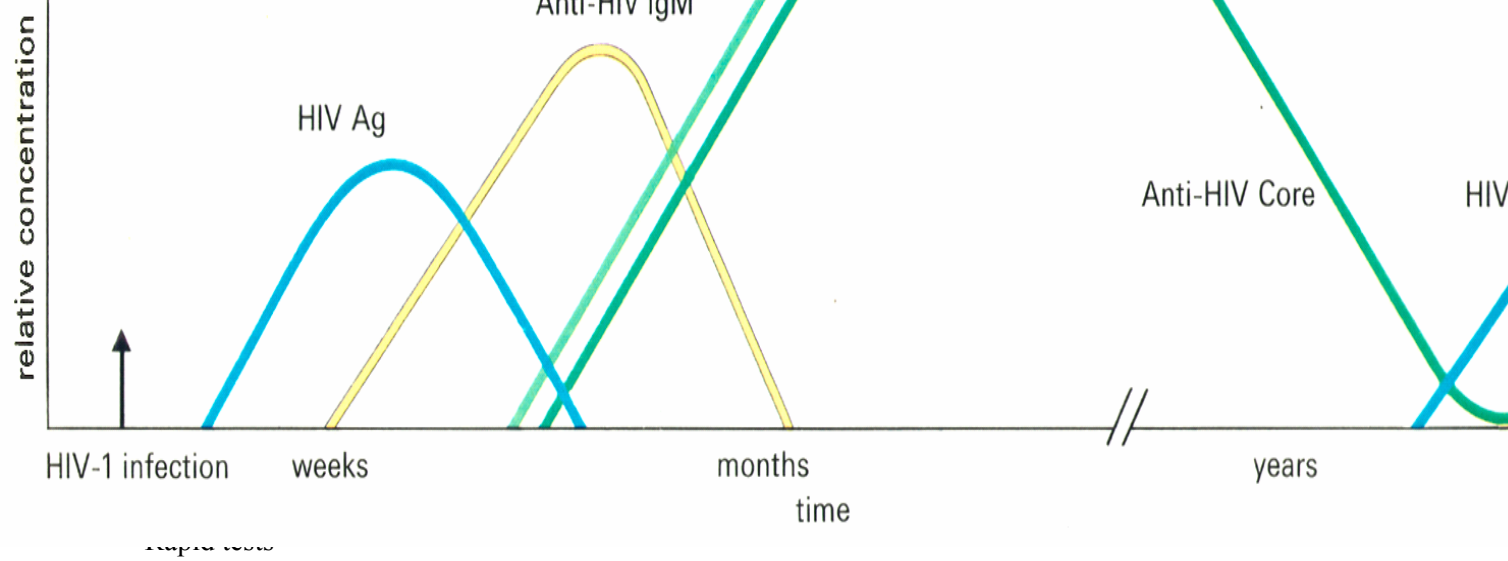
General examination

- Anaemia
- Weight loss <10% or >10%
- Skin-rash, ulcers, sinuses, blisters etc

Systemic examination

Head to toe

- Central nervous system
- Respiratory
- Cardiovascular
- Abdominal exam.
- Musculo-skeletal
- Genital urinary

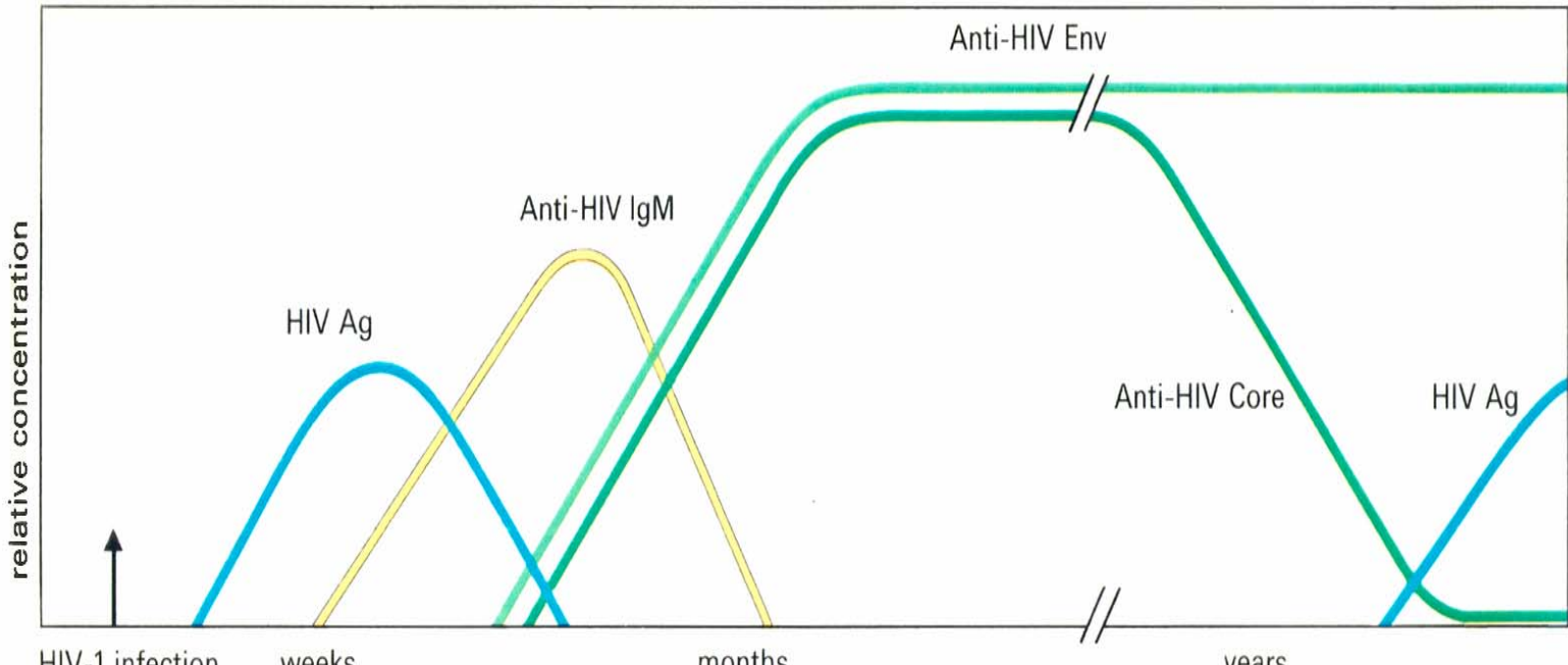


Elisa (detects Ag and Ab)
Confirmatory (WB)
Antigen tests

HIV RNA/DNA
Viral load

Assay	**Sensitivity**	**Comments**
Routine serology	99.7%	Readily available and inexpensive Sensitivity > 99.7% and specificity >99.9%
Rapid test (SUDS [Murex Diagnostics, Norcross, Ga.])	99.9%	Results are available in <10 min. but test must be performed by lab technician.
Saliva test (Orasure Test System)	99.9%	Salivary; Sensitivity and specificity are comparable to standard serology.
Urine test (Calypte)	>99%	Use for EIA test only. Must be administered by physicians
PBMC Culture	95-100%	Very expensive
DNA PCR assay	>99%	Used to detect cell associated provirus DNA sensitivity >99% specificity 98%
HIV RNA PCR	95 -98%	False positive test in 2-9%. Sensitivity depends on viral load.

ratory tests done at evaluation



Module 16

Chemoprophylaxis of opportunistic infections

Introduction:

Since AIDS was first recognized more than 20 years ago, remarkable Progress has been made in improving the quality and duration of life of HIV-infected persons in the industrialized world. During the first decade of the epidemic, this improvement occurred because of

- better recognition of opportunistic disease processes,
- better therapy for acute and chronic complications,
- Introduction of chemoprophylaxis against important opportunistic pathogens.

The second decade of the epidemic has witnessed extraordinary progress in developing highly active antiretroviral therapies (HAART) as well as continuing progress in preventing and treating individual OIs. Through restoring the competence of the immune system, HAART has reduced the incidence of OIs and extended life of people living with HIV/AIDS substantially.

HAART is the most effective approach to preventing OIs and should be considered for all HIV-infected persons who qualify for such therapy. Because of the impact HAART and treatment/prevention OIs have on reducing mortality and morbidity among patients with HIV/AIDS, they were integrated in the comprehensive care package which includes among others

- Clinical management including:
  - ✓ Prophylaxis against opportunistic infections;
  - ✓ Treatment of opportunistic infections;
  - ✓ Antiretroviral therapy;
  - ✓ Palliative care; and

The most effective commonly chemotherapeutic agent used is septrin (cotrimoxazole). It is effective against a number of opportunistic pathogens in HIV/AIDS.

These susceptible pathogens include.

- Toxoplasmosis.
- Pneumocstis jirovenchi pneumonia,
- Malaria,
- Chest infections
- Isospora belli.

Justification for Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is a standard of care for persons with HIV/AIDS in the United States and Europe and is increasingly being used in Africa. Evidence from trials on cotrimoxazole prophylaxis conducted in Africa, including Cote d'Ivoire, South Africa, Malawi, Zambia, and Uganda show reductions in mortality between 25 and 46 percent, and a beneficial effect of cotrimoxazole in reducing morbidity, even in areas with high bacterial resistance.[1-7] Cotrimoxazole prophylaxis has also been found to decrease the frequency of clinic visits and hospitalizations and improve weight.[1, 5, 8] The beneficial effects of cotrimoxazole prophylaxis are similar in early and advanced HIV disease.[5, 7, 9]

In colder climates, the primary benefit of cotrimoxazole prophylaxis has been reduction of incidence of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii* pneumonia), although it has also been shown to decrease rates of bacterial pneumonia, toxoplasmosis, and other infections. Studies in Africa have shown a primary effect of cotrimoxazole prophylaxis on the incidence of mortality due to malaria, non-typhoidal

salmonellas, *Pneumocystis jiroveci* pneumonia, and diarrhea.[1-6] In addition, recent studies in Uganda showed a beneficial effect of cotrimoxazole prophylaxis on CD4 cell count and HIV viral load.[5, 7]

Opportunities for providing cotrimoxazole prophylaxis in Uganda

Current Practice in Africa

The use of cotrimoxazole for the prevention of opportunistic infections in adults and children with HIV/AIDS in Africa has been recommended in guidelines developed from a conference convened by the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization in April 2000.[11] WHO/UNAIDS recommends cotrimoxazole use for prophylaxis in adults and children living with **HIV/AIDS in Africa as part of a minimum** package of care.[11]

WHO/UNAIDS recommendation

Cotrimoxazole prophylaxis should be provided to adults and children living with HIV/AIDS in Africa with symptomatic HIV disease (Stage 2, 3 or 4 of the provisional WHO classification of HIV), or asymptomatic individuals with a CD4 count 500 cells or total lymphocyte count equivalent.[11]

Uganda MoH policy statements

Cotrimoxazole prophylaxis should be given to all HIV-infected adults and children in Uganda, regardless of whether they are on antiretroviral therapy (ART) or not. In addition, cotrimoxazole prophylaxis is indicated for all children born to HIV-infected mothers, unless testing has shown they do not have HIV.

Eligible persons

- All adults testing HIV positive should receive counseling and education about cotrimoxazole prophylaxis and be assessed for allergy to cotrimoxazole.
- All babies born to HIV positive mothers should receive septrin from 4/52 up to when HIV infection has been definitively ruled out AND the mother is no longer breastfeeding.
- Additionally, any child identified as HIV-infected should be given cotrimoxazole prophylaxis regardless of clinical signs or symptoms suggestive of HIV, age or CD4 count.

Recommended regimens

Adults:

Two single strength tablets of cotrimoxazole (2 x 80 mg Trimethoprim/400 mg sulfamethoxazole) or one double strength tablet (1 x 160 mg Trimethoprim/800 mg sulfamethoxazole) daily for life.

Children:

Recommended dosage for children is 4 mg/kg trimethoprim and 20 mg/kg sulfamethoxazole once daily.

- Cotrimoxazole syrup should be administered once a day; syrup use is recommended in very young children up to 10-12 kg; 5ml of cotrimoxazole paediatric suspension contains 40 mg Trimethoprim/200 mg sulfamethoxazole. If syrup is unavailable, crushed tablets may be used and depending on availability, one may switch from syrup to tablet to ensure uninterrupted medication.
- Once tablets can be taken (a single strength tablet provides Sulfamethoxazole 400 mg and trimethoprim 80 mg):
  - ✓ ≤ 10 kg: half of a single strength adult tablet.
  - ✓ 10-25 kg: one whole single strength adult tablet.
  - ✓ > 25 kg: two single strength adult tablets.
- Adjust dosages according to body weight rather than body surface area doses

Antiretroviral therapy and Cotrimoxazole prophylaxis

The Ministry of Health ART policy recommendation for initiation of antiretroviral therapy (ART) is clearly inclusive of eligibility for cotrimoxazole prophylaxis, which complements ART benefits and should be provided to all people on ART. For persons in ART programs, cotrimoxazole prophylaxis should be initiated first while screening and preparing them for ARVs.

Discontinuing Cotrimoxazole prophylaxis

Adults and children: Ideally, cotrimoxazole prophylaxis should be given to adults and children with HIV infection FOR LIFE because of its beneficial effects on the immune function of persons with HIV, regardless of CD4 cell count. However, the benefit of cotrimoxazole prophylaxis for adults and children on ART in Africa whose CD4 cell counts are >200 cells/μL and CD4% >15, respectively, has not yet been evaluated**.** Until more information is available, the decision to discontinue cotrimoxazole prophylaxis in this group should be made on an individual basis by the provider. Cotrimoxazole prophylaxis can be discontinued in an HIV-exposed child ONLY once HIV infection has confidently been excluded in the following ways:

- For a non-breastfeeding child <18 months of age:
  - ✓ Negative DNA or RNA virological HIV testing; or a negative HIV serology test
- For a breastfed, HIV-exposed child:
  - ✓ Negative virological and serological testing are only reliable if conducted 6 weeks after cessation of breastfeeding

Toxicity

Cotrimoxazole prophylaxis should not be given to anybody with a known, severe allergy or hypersensitivity reaction to either of its components (sulpha-containing drugs or trimethoprim). Adverse effects are rare; studies in Africa show they occur in less than 5% of persons per year, although the potential for cotrimoxazole to cause severe reactions does exist.

Commonly seen adverse events:

- Eighty percent of documented adverse effects seen are skin reactions and only 3% are Stevens-Johnson syndrome
- Bone marrow suppression including anaemia, neutropenia.
- Jaundice.

Prior to initiating the prophylaxis, both the provider and client should be aware of the possibility of adverse reactions and what to do in the event of occurrence.

In both adults and children, prophylaxis should be stopped in the event of severe cutaneous reactions, such as a fixed drug reaction or Stevens-Johnson syndrome.

Desensitization

For patients who have an adverse reaction that is non-mucocutaneus and not life threatening, reinstitution of cotrimoxazole should be strongly considered after the adverse reaction has resolved. Patients who have experienced adverse reactions may better tolerate reintroduction of cotrimoxazole with a gradual increase in dose (desensitization) as per published regimens, which gradually increase the dose over a 2 to 4 week period, or reintroduction of cotrimoxazole at a reduced frequency. More than 70% of patients can tolerate such reinstating of therapy. This procedure should only be conducted under the supervision of a qualified medical doctor. Persons who experience Stevens-Johnson reactions should not be desensitized**.**

Alternate drugs to use in case of hypersensitivity to cotrimoxazole

There is no substitute for cotrimoxazole prophylaxis; no single drug is currently known to provide a similar range of protection against morbidity or mortality at such an affordable cost. However, there are some alternative regimens for specific conditions**.**

- Dapsone can be used as an alternative prophylactic agent against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii* pneumonia). When given with pyrimethamine, it also offers protection against toxoplasmosis.
- Sulphadoxine/pyrimethamine offers some preventive activity against *Pneumocystis jiroveci* pneumonia and toxoplasmosis

Pentamidine can be used to prevent *Pneumocystis jiroveci*, however it is expensive, not easy to implement and not as effective as cotrimoxazole.

Cryptosporidiosis

Prevention of Exposure

1. HIV-infected persons should be educated and counseled about the many ways that *Cryptosporidium is* transmitted. esp. drinking contaminated water.
2. They should be advised to wash their hands
3. *Cryptosporidium*-infected patients should not work as food handlers.

Prevention of Recurrence

- No drug regimens are known to be effective in preventing the recurrence of cryptosporidiosis.

Microsporidiosis

Prevention of Exposure

- Other than general attention to hand washing and other personal hygiene measures.

Prevention of Disease

- No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Cryptococcosis

Prevention of Recurrence

- Patients who have completed initial therapy for cryptococcosis should be administered lifelong suppressive treatment, (i.e., secondary prophylaxis or chronic maintenance therapy)