WHO-EM/STD/170/E

Module 2

Natural history and clinical aspects

# HIV basic knowledge and stigma reduction in health care settings

World Health Organization
Regional Office for the Eastern Mediterranean

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Natural history and clinical aspects

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(NLM Classification: WC 503)

# Contents

# Introduction

This module will show how HIV impacts the main target cell, the CD4 T lymphocyte. Understanding the role of this cell in the immune system will give important insight into the biological and clinical consequences observed as the disease progresses. The session also aims to explain the nature of this chronic disease, whose progress can nonetheless be checked through antiretroviral treatment.

After looking at the definition of AIDS used in the country, the facilitators will focus specifically on the classifications and definitions used by WHO.

The facilitators will give particular importance to the early manifestations of an HIV infection enabling diagnosis and early care, leading to a better quality of life and reduced HIV transmission.

During the module, the wide range of opportunistic infections and tumours linked to HIV will be reviewed to show the very serious consequences of delayed diagnosis. In each group of pathologies, the facilitators will briefly elaborate on one or two diseases, chosen as examples.

# Specific objectives

After completing the module, the participants should be able to:

- Explain the immunodeficiency mechanism during the HIV infection
- Define AIDS
- Name the main early manifestations of an HIV infection
- Name the main minor and opportunistic infections liable to occur during the HIV infection
- Name the cancers related to the HIV infection
- Describe the typical clinical aspects of a number of opportunistic infections (tuberculosis, pneumocystis pneumonia, toxoplasmosis, candidiasis), Kaposi's sarcoma and HIV encephalopathy.

# Module schedule

| Sessions | Topics | Methods | Length |
|---|---|---|---|
| Session 1<br>Natural history and classifications | Section 1 | | |
| | Natural history of the HIV infection | PowerPoint | 15 minutes |
| | | Discussion | 15 minutes |
| | Section 2 | | |
| | Classifications of the HIV infection | PowerPoint | 15 minutes |
| | | Discussion | 15 minutes |
| Session 2<br>Clinical manifestations of HIV infection | Section 1 | | |
| | Early manifestations of HIV infection | PowerPoint | 15 minutes |
| | | Discussion | 15 minutes |
| | Section 2 | | |
| | Main clinical manifestations of HIV infection | Brainstorming / PowerPoint | 90 minutes |
| | | | 180 minutes |

# Educational tools

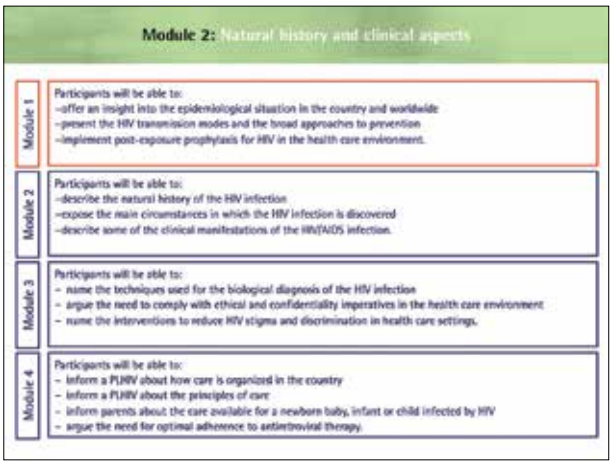
- A series of slides presenting the module's goals and course documentation for session 1.
- A series of slides presenting the module's goals and course documentation for session 2.
- Copies of the WHO classification (or CDC classification if used in the country) to support the brainstorming session.
- Paperboard and different colour markers.

# Content

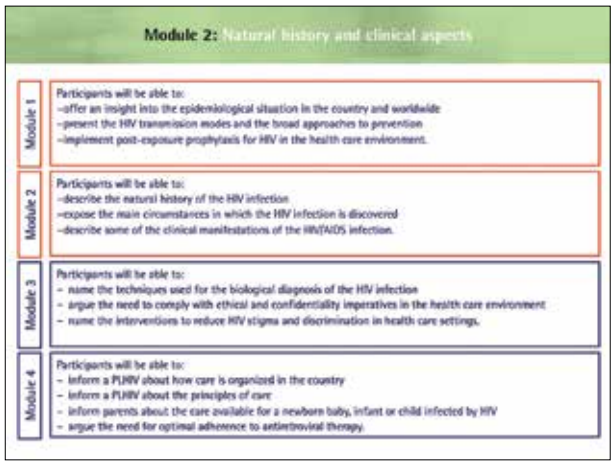
Facilitators should start the module with a reminder of the goals of Module 2.

Slide 1


Slide 2




Slide 3



# Session 1: Natural history and classifications

## Natural history of HIV infection

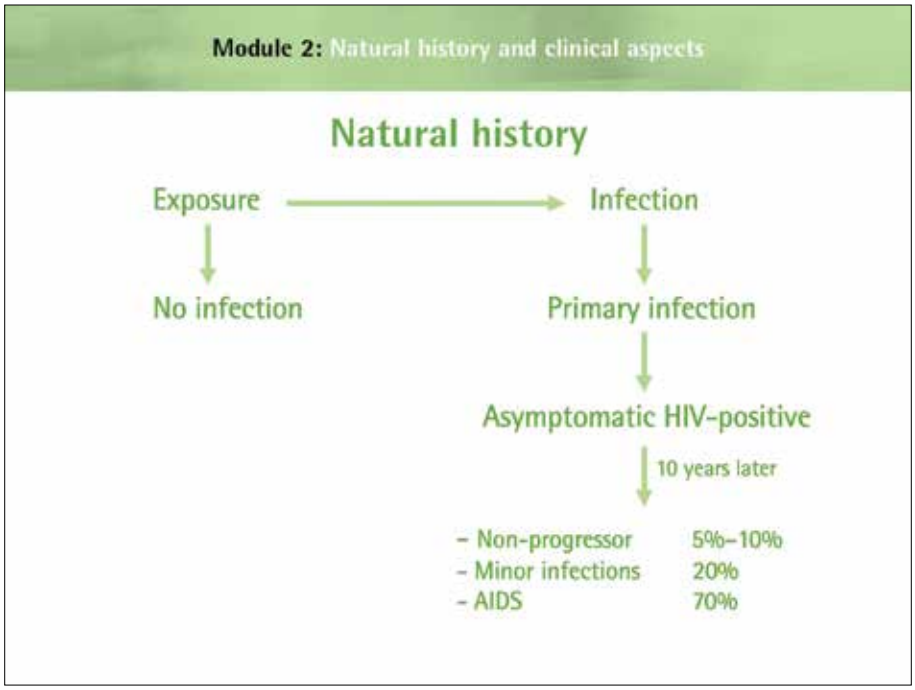
Slide 4


After exposure to HIV a person may develop the disease but may also remain unharmed: the risk of developing the disease varies according to the type of exposure, the severity and other factors that can influence contamination.

When contamination occurs, HIV infection will progress in several phases (Slide 5).

- **Primary infection:** This begins at the time of the contamination and lasts several weeks. In 60% of cases it is manifested by clinical symptoms that are by no means specific to HIV infection. The risk is consequently that conditions such as influenza-like illness, cutaneous eruption or neurological signs may be overlooked as pointers towards an HIV diagnosis.
- **The asymptomatic phase:** This can last for many years and is characterized by clinical latency. After several years, the patient starts to present minor infections that are increasingly frequent and last longer and longer. After a 10-year development, 20% of patients will be at the minor infections stage but 70% will have AIDS. Only a minority (5%–10%) will not have evolved: these are long-term non-progressors.

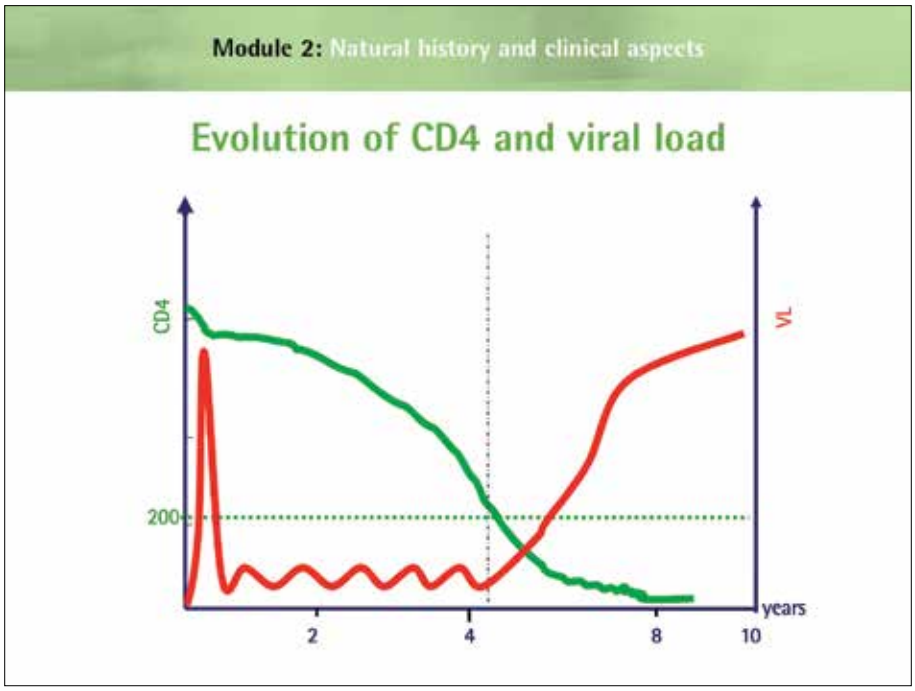
Slide 5: Natural history of HIV infection




- **The AIDS phase:** AIDS corresponds to an advanced state of immunodeficiency characterized by severe clinical manifestations. The definition of this state depends on the classification adopted by the country. If untreated the disease will worsen, culminating in death.

Two laboratory examinations can be used to assess the degree of immunodeficiency and the scale of the multiplication of HIV in a person living with HIV (PLHIV). These are the rate of CD4 decline, measured by the number of CD4 T lymphocytes in 1 mm3 of blood, and the viral load, corresponding to the quantity of viruses in 1 ml of plasma. At the biological level, the different clinical phases can be correlated with the development of CD4 T lymphocytes and the viral load (Slide 6).

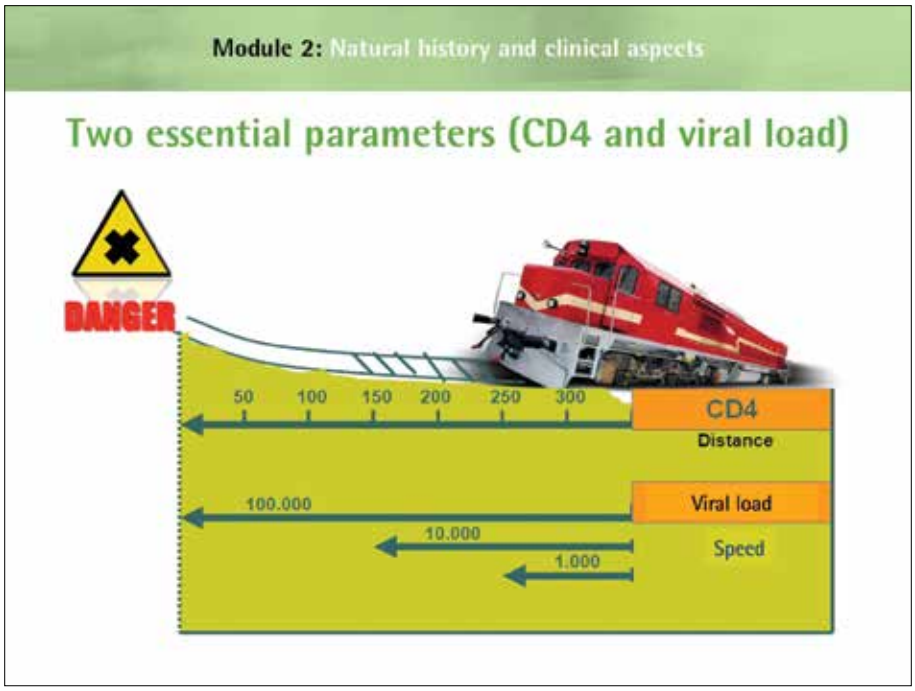
Slide 6: Evolution of the viral load and CD4 (natural history)



- The CD4 diminish continuously during the different phases.
- During primary infection, the viral load increases quickly before being partially checked by the immune system. The viral load, which remained low for several years, will start to increase when the CD4 have fallen to a level at which they can no longer arrest viral multiplication.

To understand the importance of these two parameters, we can compare them with a locomotive heading towards a precipice (Slide 7).

Slide 7: Importance of CD4 and viral load as indicators

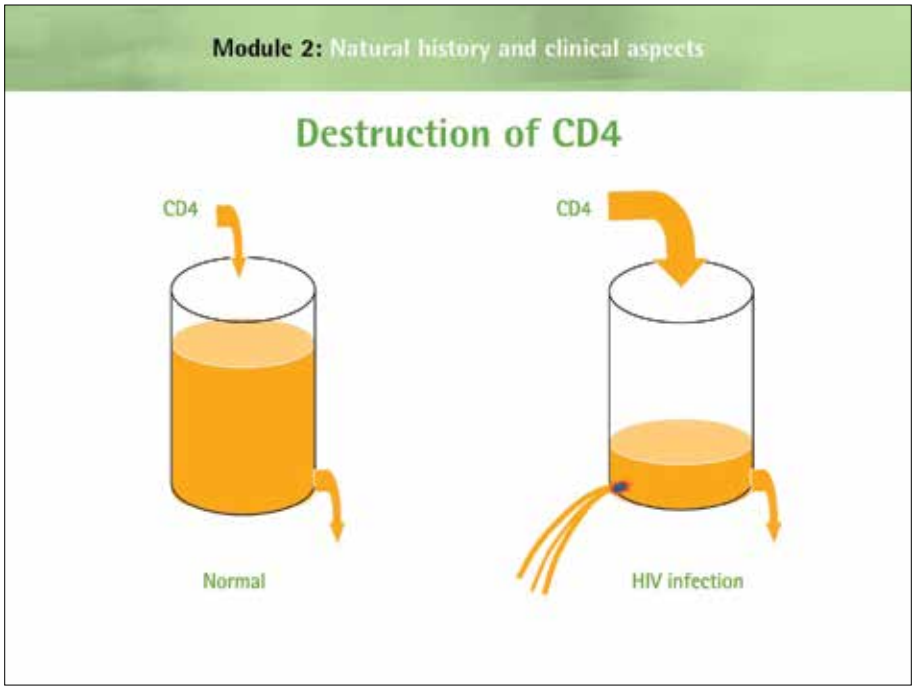



The rate of CD4 decline is represented by the distance between the locomotive and the precipice. The higher the CD4 count, the further the patient is from the terminal phase and death. The viral load is represented by the locomotive's speed. The higher the viral load, the faster the disease evolves towards death. Consequently the prognosis for a PLHIV with a high CD4 count and low viral load will be favourable. When a person is treated with antiretrovirals (anti-HIV medicines), the viral load should fall and the CD4 rise, showing that the treatment is effective.

The viral load correlates with the probability that the disease will develop (the occurrence of classifying events at the AIDS stage and death).

To protect itself, the organism uses several resources that form the immune system. Any shortfall among these defence mechanisms will result in an immunodeficiency. In HIV infection, the virus targets principally the CD4 T lymphocyte. As we have seen, the cell will become nothing less than a factory manufacturing viruses, but will die faster than a healthy cell. This is where the lymphocyte plays a key role in cellular immunity.

Slide 8: Reduction of the number of CD 4 T lymphocytes



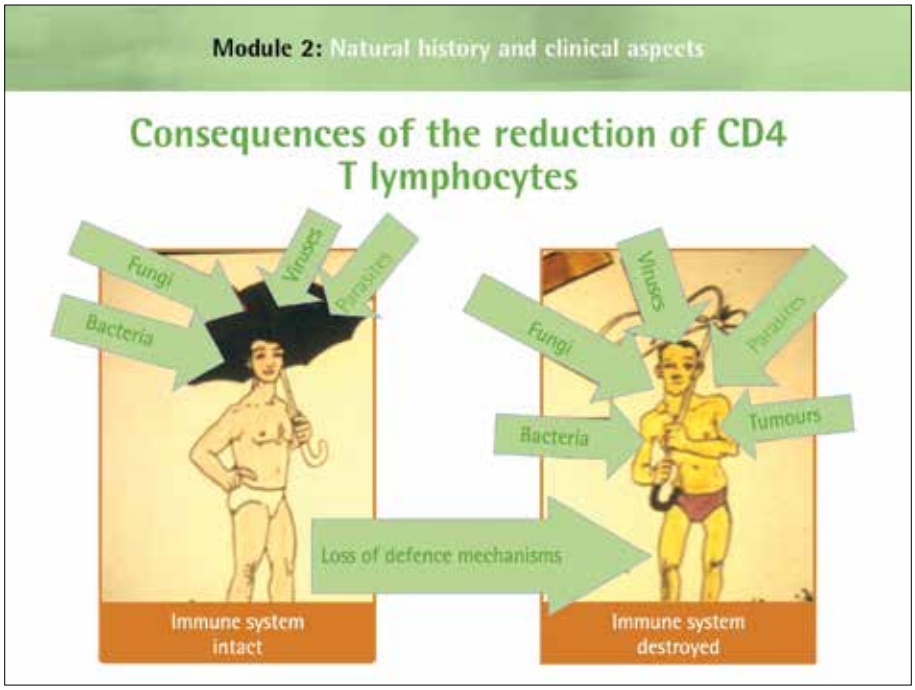

In this diagram (Slide 8), we have represented the quantity of CD4 T lymphocytes by the level of liquid filling up a tank.

In a healthy subject, the physiological destruction of cells is offset by the production of new cells and the tank continues to fill at a constant rate. In this case the immune system remains perfectly efficient.

In the event of an HIV infection, however, cell destruction is not only physiological but also the result of destruction by the HIV. The quantity of CD4 T lymphocytes consequently falls dramatically and the organism is no longer able to compensate for this loss. Immunodeficiency sets in and gradually worsens.

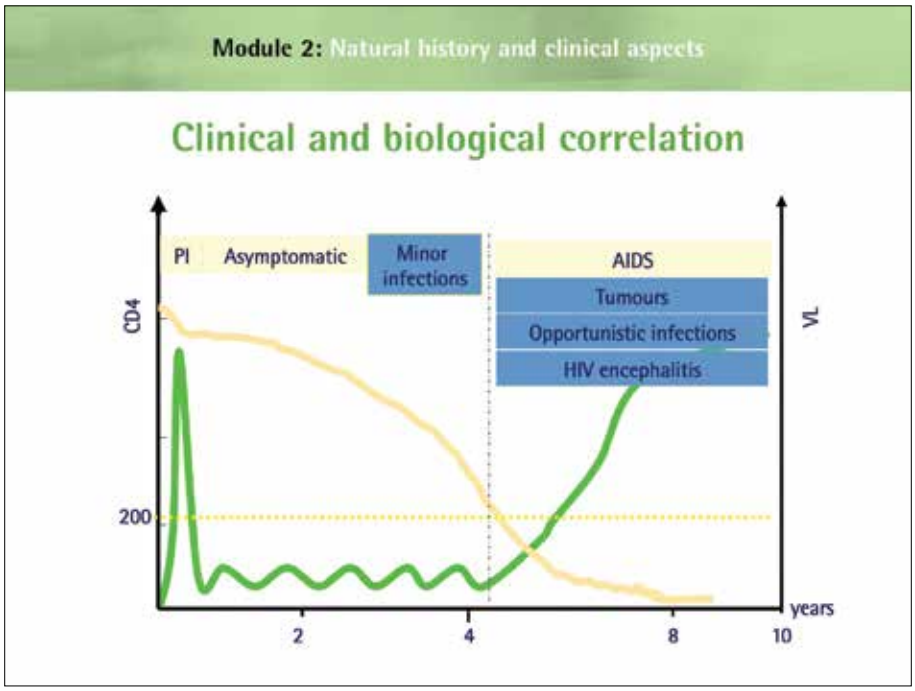
Consequences of immunodeficiency. A healthy person's immune system provides protection against germs, whether bacteria, viruses, parasites or fungi. When the immune defences collapse, the person runs the risk of developing serious infections. These infections can even be caused by germs that are not pathogens for immunocompetent individuals (i.e. those whose immune system is intact); such infections are referred to as opportunistic (Slide 9).

Slide 9: Consequences of the reduction of CD4 T lymphocytes



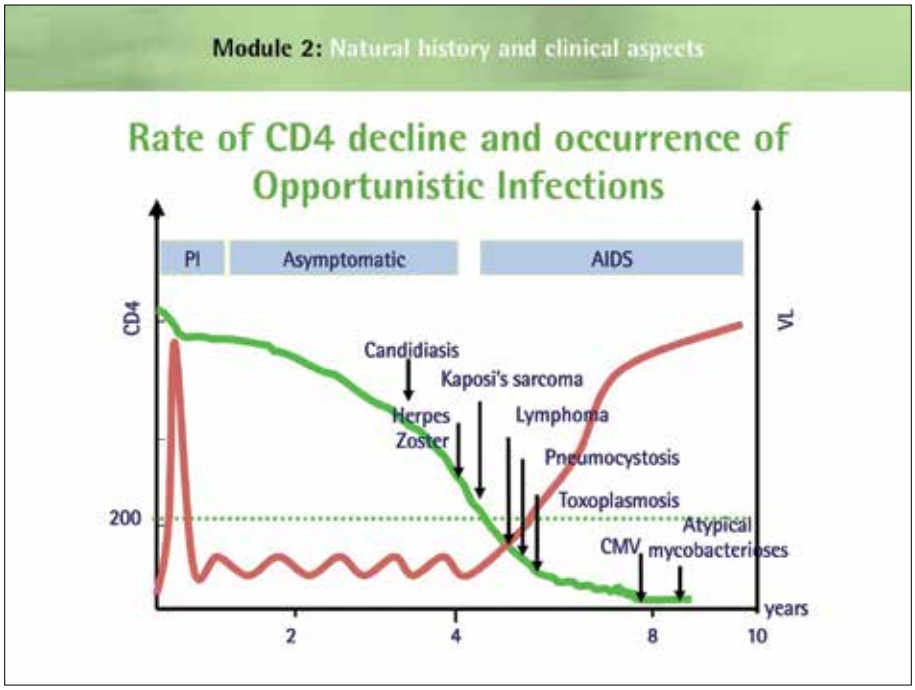

Slide 10 sums up the relationship between CD4, viral load and clinical manifestations.

Slide 10: Clinical and biological correlation



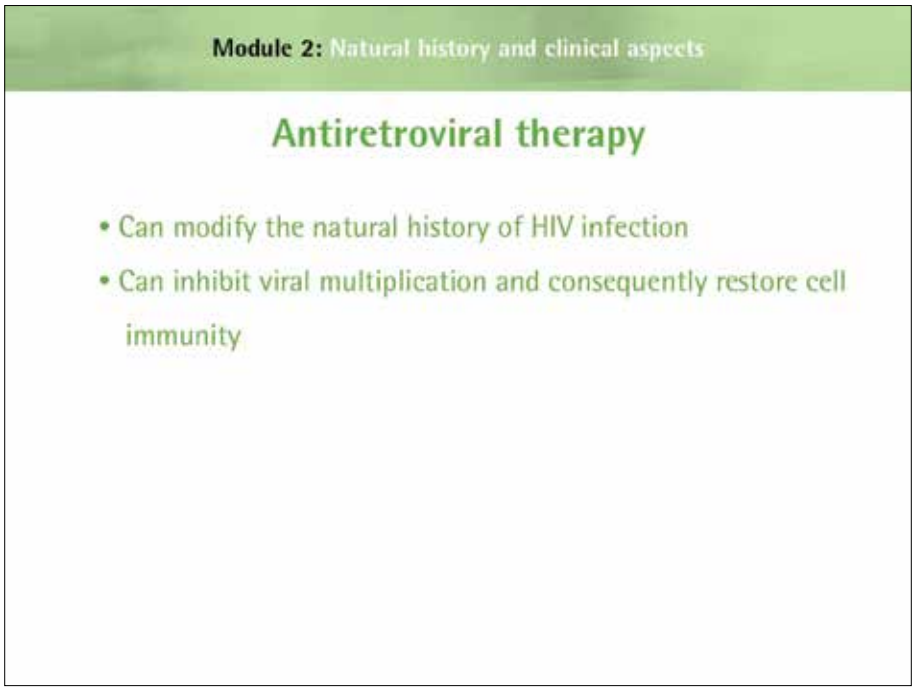

The rate of CD4 decline is a particularly important indicator for the clinician. This is because when a patient infected by HIV presents clinical manifestations, knowing the rate of CD4 decline can provide a guideline for a tentative diagnosis. Oral or genital candidiasis and herpes zoster (shingles) often occur early. Tuberculosis may occur at different levels of immunodeficiency. Pneumocystis pneumonia and toxoplasmosis occur when CD4 falls below 200 cells/mm3. Cytomegalovirus (CMV) infections and atypical mycobacterioses only occur in severe immunodeficiency situations (Slide 11).

Slide 11: Rate of CD4 decline and occurrence of opportunistic infections




The natural progression of HIV infection is significantly modified by antiretroviral therapy, which lowers the viral load and restores CD4 and consequently immunity (Slide 12).

Slide 12: Conclusion



- The main target of HIV is the CD4 T lymphocyte.
- The destruction of CD4 T lymphocytes leads to cellular immunodeficiency.
- HIV infection develops through several phases:
  - Primary infection
  - Asymptomatic phase
  - Phase of minor infections
  - AIDS

# Classifications of HIV infection

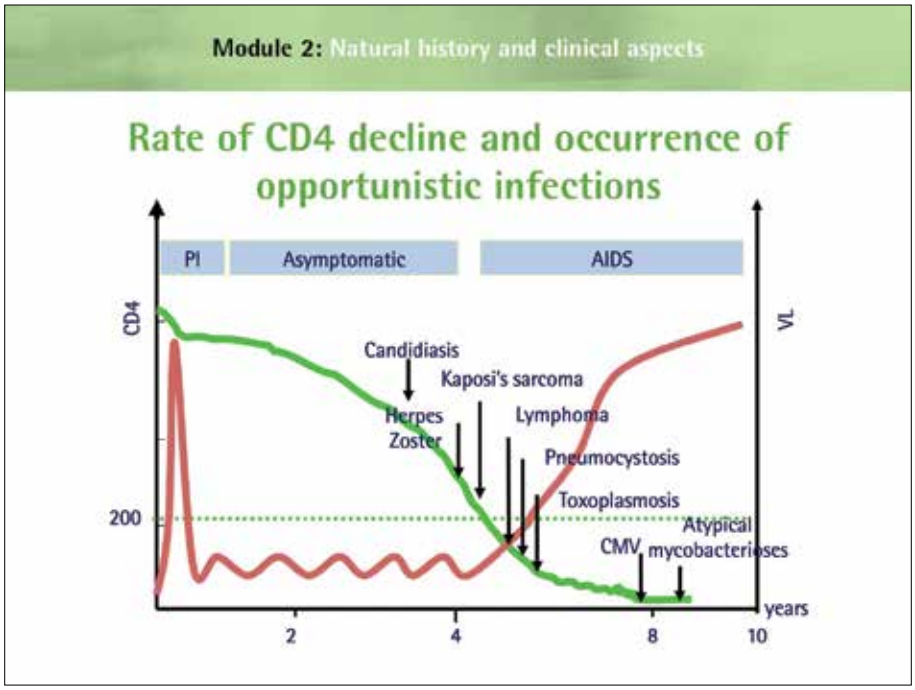
Slide 13


HIV infection is a chronic infection that starts with contamination and goes through different phases through to the stage of severe infections resulting from advanced immunodeficiency.

These different clinical stages may be correlated with the level of CD4, the viral load and the occurrence of certain infections (Slide 14).

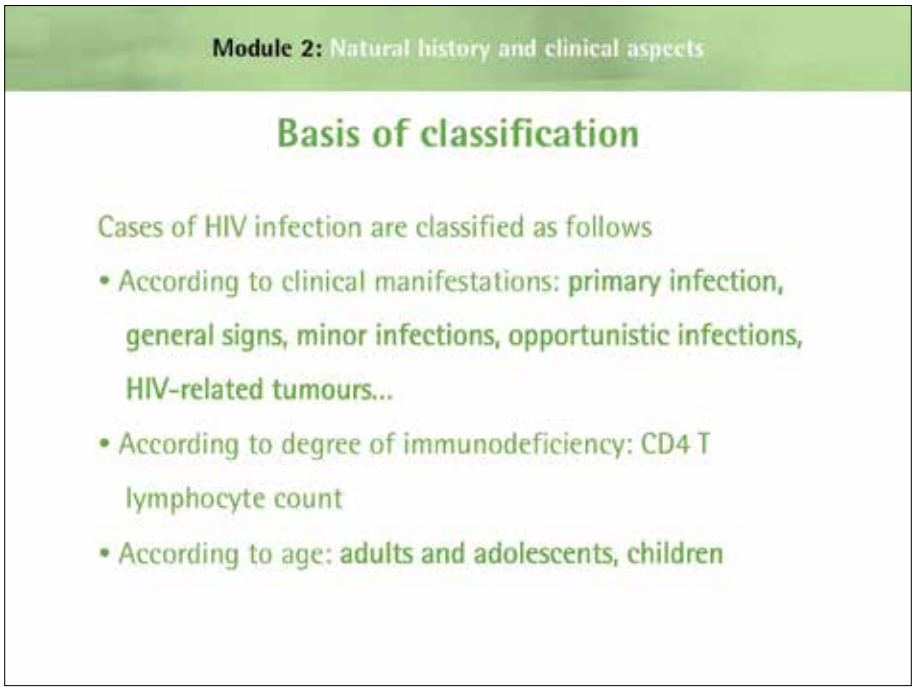
Several classifications have been defined to identify the clinical and even the immunoclinical status of patients infected by HIV. In fact these classifications take into account clinical manifestations (patient with primary infection, or with general signs such as weight loss or fever, minor infections or opportunistic infections and HIV-related tumours) as well as the degree of immunodeficiency indicated by the CD4 count.

Slide 14: Clinical stages and rate of decline of CD4




In addition to these immunoclinical criteria, the classifications differ depending on whether the patient is an adult, an adolescent or a child (Slide 15).

Slide 15: The basis of HIV infection classification

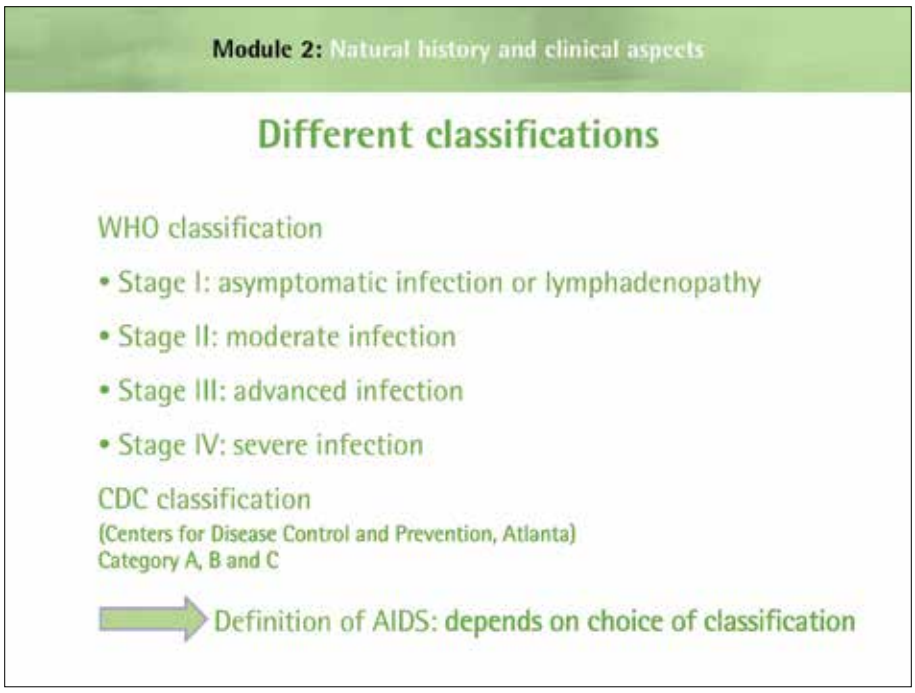


The most widely used classifications in the world are the WHO and CDC classifications (Slide 16).

- The WHO classification has 4 clinical stages:
  - Stage 1: asymptomatic or lymphadenopathy
  - Stage 2: moderate infection
  - Stage 3: advanced infection
  - Stage 4: severe infection.
- The 1993 classification by the Centers for Disease Control and Prevention (CDC) which classifies clinical manifestations into three categories: A, B and C. The CDC classification associates CD4 information with clinical data. The categories in the CDC classification may be correlated with clinical manifestations of the natural history. Category A corresponds to the primary infection and the asymptomatic period. Category B corresponds to minor infections. Category C corresponds to severe immunodeficiency characterized by opportunistic infections, HIV-related tumours, HIV encephalitis or repeated respiratory infections.

The definition of the AIDS stage differs depending on the classification adopted by the country.

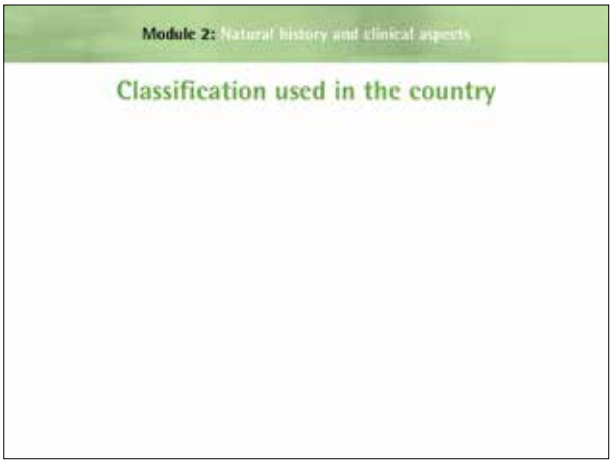
Slide 16: The different classifications



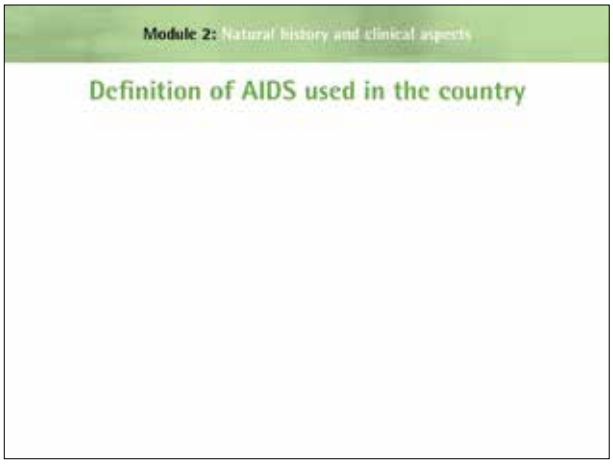

The facilitators should prepare 2 slides to present:

- The classification(s) used by the country (Slide 17)
- The definition of AIDS cases adopted by the country (Slide 18)

Slide 17




Slide 18




The main classifications have been established by:
- The Centers for Disease Control and Prevention (CDC)
- The World Health Organization (WHO).

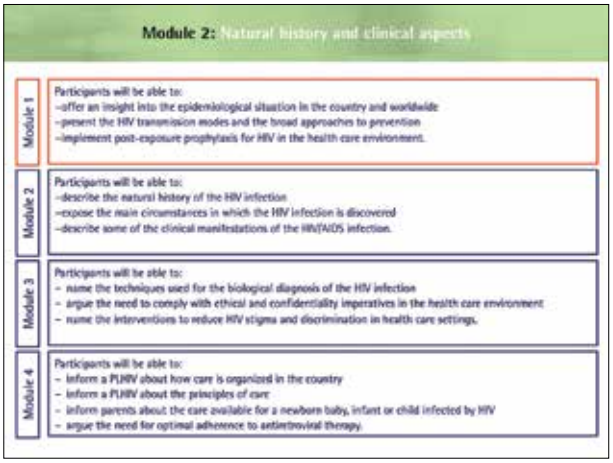
The definition of AIDS cases depends on the classification adopted.
The stages in the classification can be correlated with clinical and biological manifestations.

# Session 2: Clinical manifestations of HIV infection

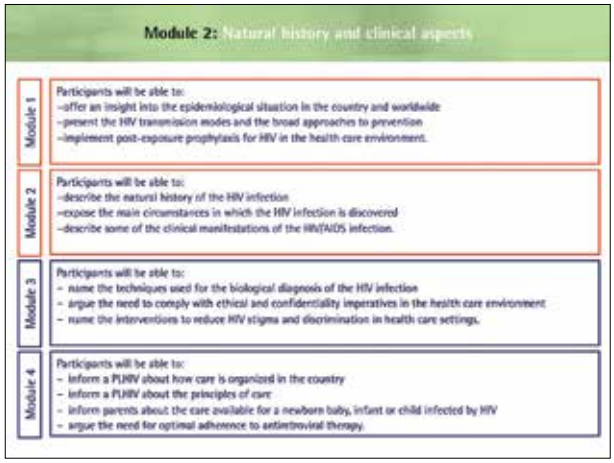
Facilitators should start session 2 with a reminder of the goals of Module 2.

Slide 1


Slide 2




Slide 3



# Early manifestations of the infection

Slide 4

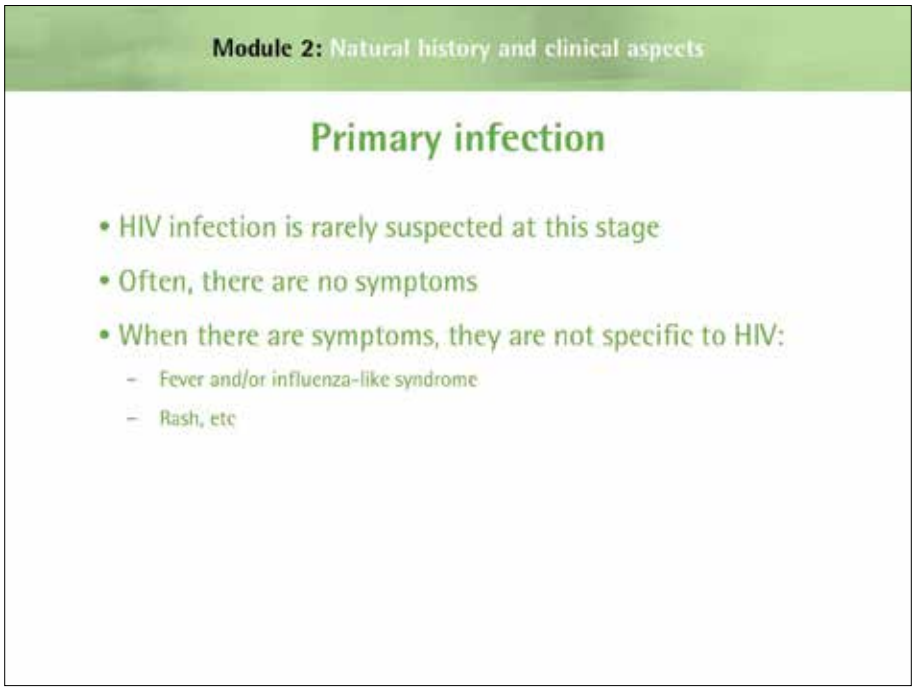

Clinical manifestations of HIV infection are highly polymorphous and of variable severity depending on the evolution of the patient's condition. It is important to diagnose early to offer the patient appropriate care even before immunodeficiency has reached an advanced stage.

## Primary HIV infection

This is the earliest stage in the disease, and it is rare that the diagnosis of a HIV infection is suspected at this stage. This is because primary infection can be asymptomatic and, when there are symptoms, they are not specific to the infection.

From 30% to 50% of patients will exhibit clinical signs of primary infection in the 2 to 4 weeks that follow the contaminating contact. The symptoms may last 1 to 4 weeks. In over 50% of cases, a flu-like state is observed, with fever, headaches, myalgia, arthralgia, asthenia and local or general adenopathy. There may also be occurrences of non-pruriginous maculopapular rashes and also rare cases of meningoencephalitis (Slide 5).

Slide 5: Clinical manifestations during primary infection

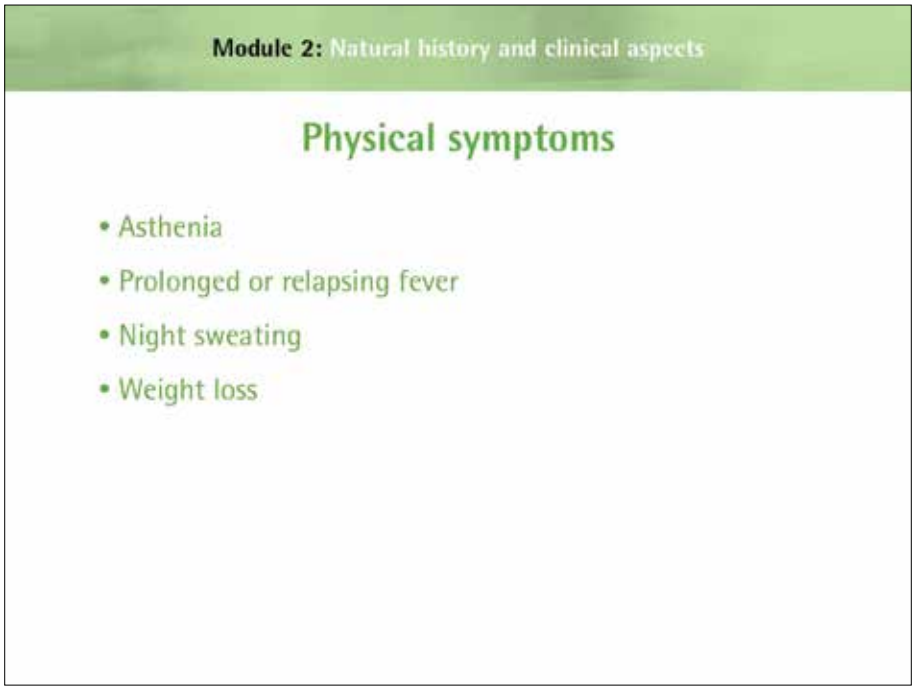



## The physical symptoms

After the asymptomatic phase, certain physical symptoms can be circumstances in which the HIV infection may be identified.

These may include unexplained persistent asthenia, prolonged or relapsing fever, nocturnal sweating or weight loss (Slide 6).

Slide 6: Constitutional symptoms

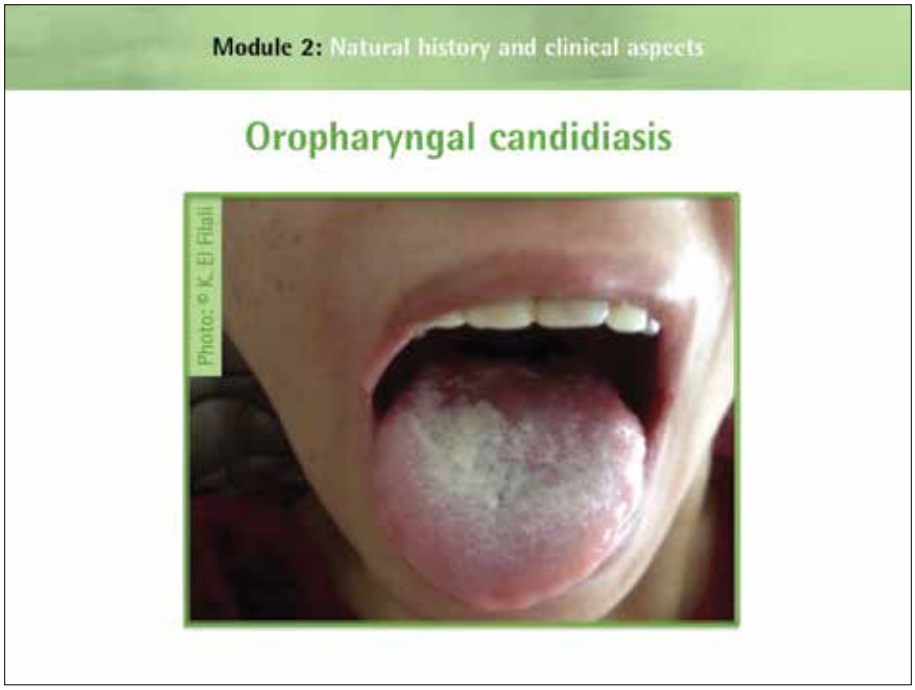


## Mucocutaneous manifestations

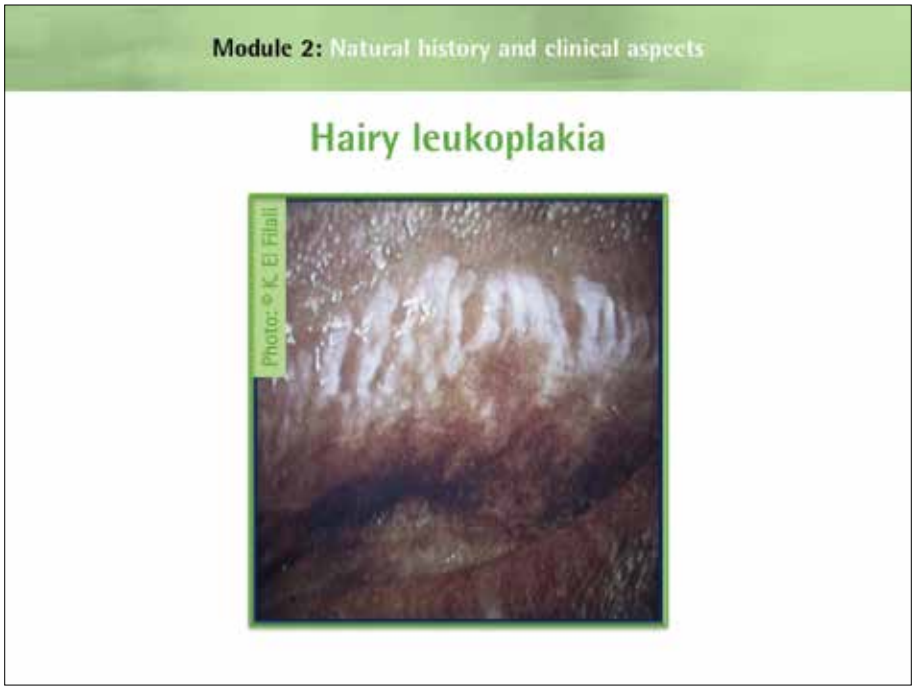
Slide 7


Mucocutaneous impairment (Slide 7) during HIV infection is dominated by minor manifestations and Kaposi's sarcoma. Minor manifestations such as oropharyngal (Slide 8) or vulvo-vaginal candidiasis and hairy leukoplakia caused by an Epstein-Barr virus (EBV) infection, appear at an early stage. Apart from hairy leukoplakia (Slide 9), considered as pathognomonic for HIV infection, the other symptoms are not specific to the infection, but their frequency in HIV infection make these very valuable signs for diagnosis.

Slide 8: Oropharyngal candidiasis



Slide 9: Hairy leukoplakia




Impairment of viral origin is frequent, taking the form of oral, genital or peri-anal herpes that may be frequent, relapsing and develop over a prolonged period. Molluscum contagiosum can also produce florid disseminated forms, whence a possible differential diagnosis of cutaneous cryptococcosis. Herpes zoster (Slide 10) occurs in 20% to 30% of infected patients by HIV. The frequency of this infection in early stage HIV infection, and its occurrence in a young subject, is ample justification for an HIV test enabling an early diagnosis. Clinical manifestations related to papillomavirus (HPV) infection often occur in persons infected with HIV: condyloma acuminata, precancerous genital lesions in women and the more frequent evolution towards cervical cancer.

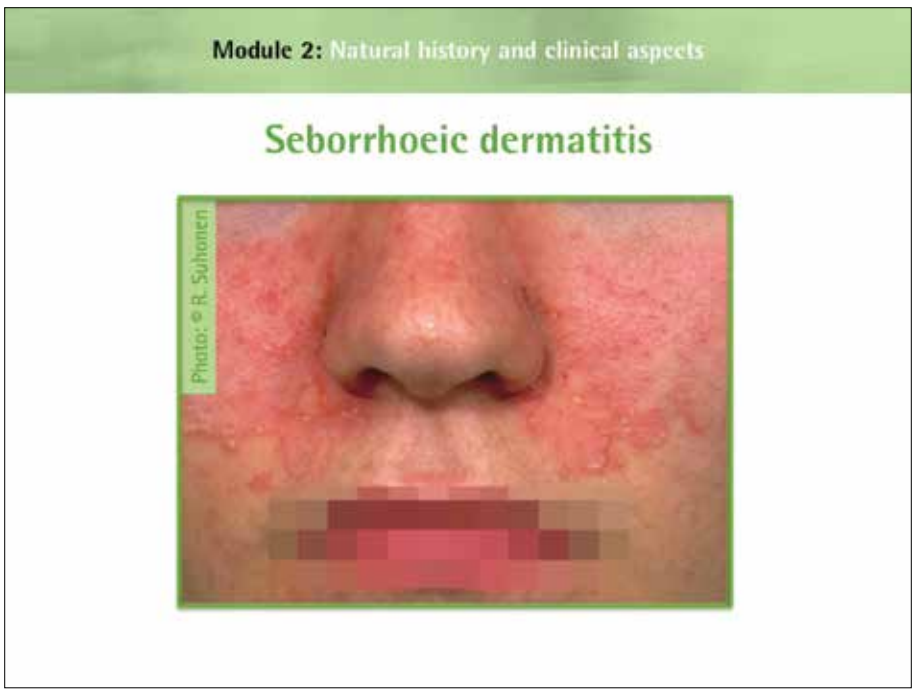
Slide 10: Herpes zoster

Prurigo (Slide 11), red pruriginous lesions, topped with a vesicle, often located on the legs, is frequently a symptom and will prompt a search for folliculitis or intestinal helminthiasis, the treatment of which improves lesions.

Slide 11: Prurigo


Seborrheic dermatitis (Slide 12) appears early 10% of cases at the asymptomatic stage becoming more frequent as the immunodeficiency worsens. Impetigo, folliculitis, oral, genital or peri-anal candidiasis and onychitis are frequent.

Slide 12: Seborrheic dermatitis

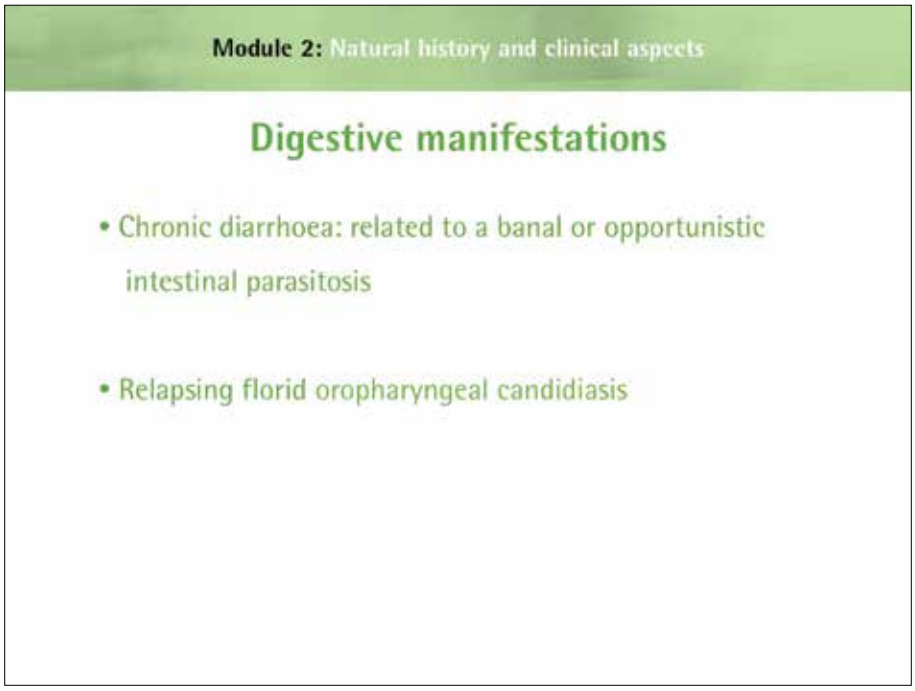


## Digestive manifestations

Digestive disorders (Slide 13) are frequent during a HIV/AIDS infection. The causes are generally infectious and are frequently linked to opportunistic germs, but may also be tumoral or of idiopathic inflammatory origin.

At an early stage, persistent or chronic diarrhoea is frequent and responsible for undernutrition and weight loss, even dehydration. It may be caused by bacteria (salmonella, shigella), or parasites (amoeba, cryptosporidium, microsporidia). Cryptosporidium and CMV can colonize the bile canaliculus and cause acalculous cholecystitis.

Slide 13: Early digestive manifestations




Relapsing florid oropharyngeal candidiasis remains a frequent manifestation and can betray an HIV infection.

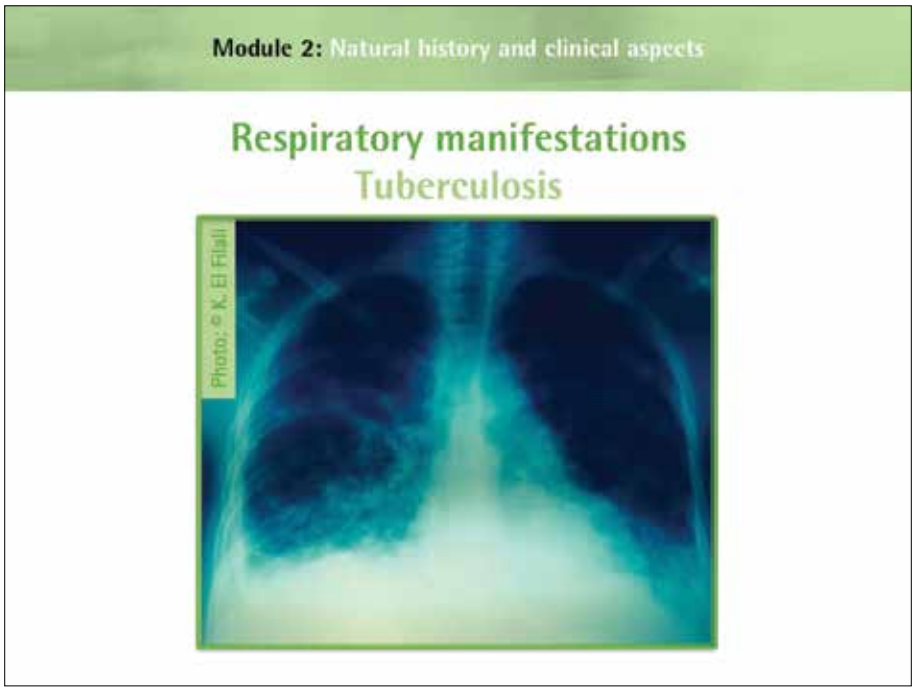
## Respiratory manifestations

Impairment of the upper respiratory tract is frequent. The first localization is sinusitis. Its frequency may be explained by the tendency noted among persons infected with HIV towards significant allergic manifestations. Generally, this is caused by banal germs; in chronic forms, *Pseudomonas aeruginosa* is often identified.

Pulmonary impairment inaugurates AIDS in over 50% of cases. In practice, pulmonary impairment during HIV infection is usually attributed to one of three main causes: pulmonary pneumocystis, pulmonary tuberculosis or pneumonia from banal germs (pneumococcus, haemophilus).

Tuberculosis may occur at all stages of immunodeficiency. When it occurs early, the clinical and radiological manifestations do not differ from those observed in immunocompetent subjects (Slide 14).

Slide 14: Radiological aspects during pleuro-pulmonary tuberculosis

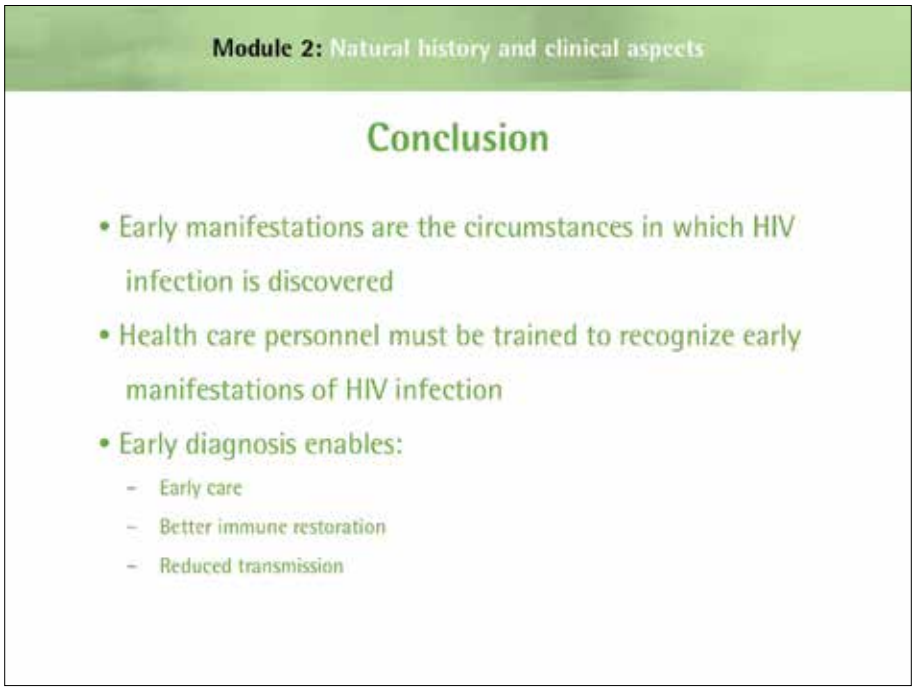



## Neurological manifestations

Neurological manifestations are frequent at an advanced stage of immunodeficiency but remain rarer at early stages. However, mononeuritis (especially peripheral facial paralysis), polyradiculoneuritis or sensitive-motor polyneuropathy can reveal an HIV infection at an early stage. Their occurrence in a young adult should prompt consideration of a possible HIV infection and an HIV test should be proposed.

In conclusion, health care personnel should be trained to recognize early manifestations of HIV infection. In fact an early diagnosis enables early care and better immunorestoration, while reducing the potential for transmission of the infection (Slide 15).

Slide 15: Conclusion




- Primary HIV infection, even when it is symptomatic, is hard to recognize because the clinical signs are not specific.
- Health care personnel should be able to recognize the early manifestations: mucocutaneous, respiratory, digestive and neurological.
- An early diagnosis enables better response to treatment and early reduction of the risk of transmission.

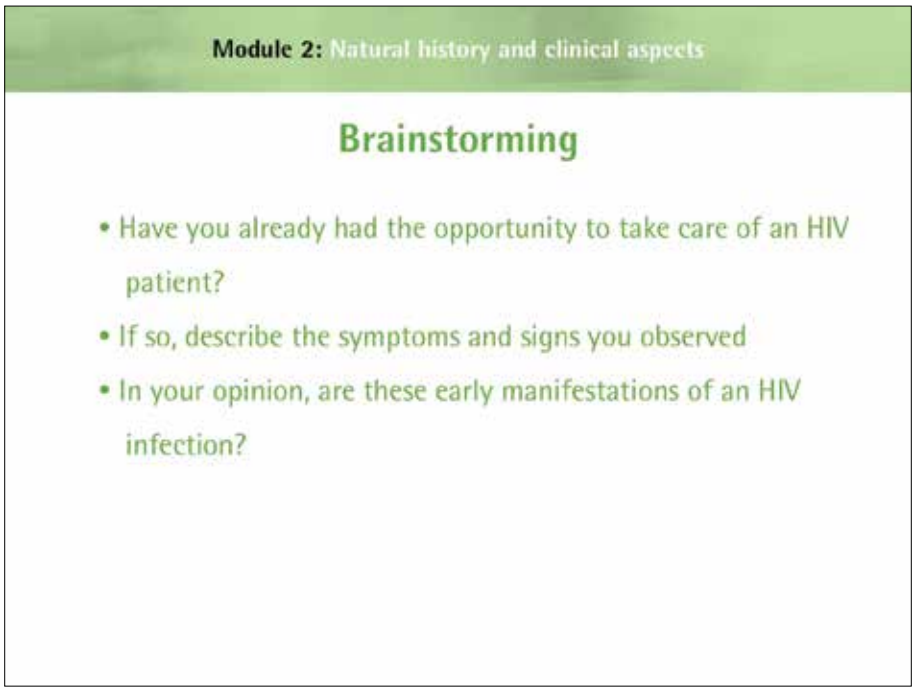
# Main clinical manifestations of the HIV infection

## Brainstorming and presentation

Slide 16


In this section (Slide 16), the facilitator provides guidance by asking the questions suggested on the PowerPoint presentation, and will discuss in more detail several HIV-related opportunistic infections or cancers as examples, illustrating the different types of clinical manifestations. The choice of which slides to show or ignore from the available set should be made in advance (Slides 17, 18, 19).

Slide 17



**Have you already had the opportunity to take care of a patient infected by HIV?**

This question is designed to prompt an account of a real experience by one or more participants.

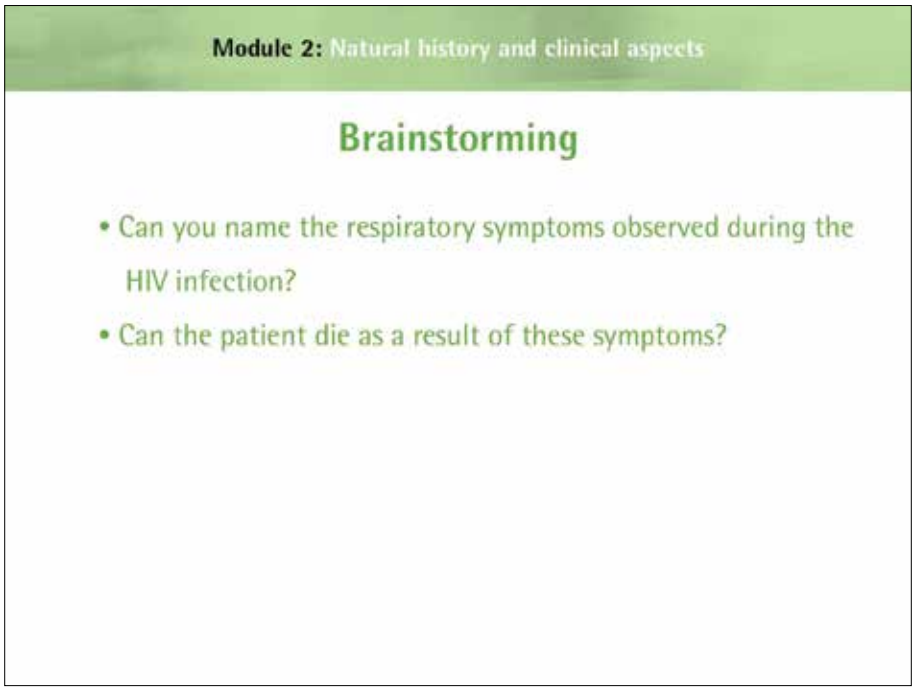
**If so, describe the symptoms and signs that you have noted.**

The facilitator will ask those who have prior experience of caring for a person infected with HIV to briefly describe the experience. If the participants have never taken care of a patient infected with HIV, the facilitator will present a personal experience.

**In your opinion are these early manifestations of the HIV infection?**

The aim of this question is to show that, very often, the diagnosis is belated!

Slide 18



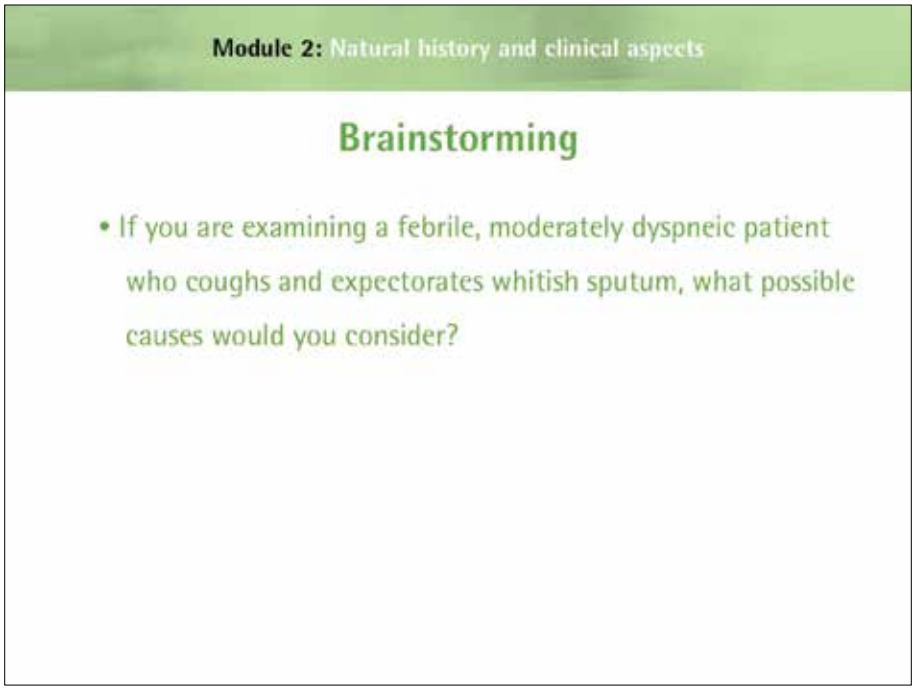

**Can you name the respiratory symptoms observed during the HIV infection?**

This question enables the facilitator to explore the participants' knowledge of respiratory manifestations of an HIV infection. This knowledge can come from reading, previous training, the media or clinical experience.

**Can the patient die as a result of these symptoms?**

The aim is to make participants aware that the symptoms of advanced stage immunodeficiency are by definition severe or will worsen and risk causing the death of the patient.

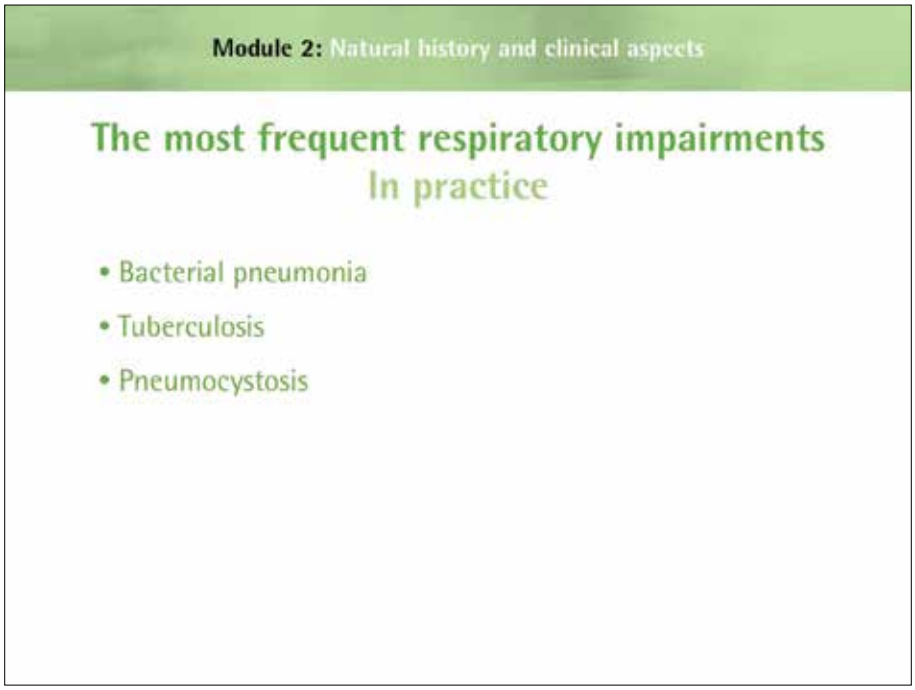
Slide 19




**If you are examining a febrile, moderately dyspneic patient who coughs and expectorates whitish sputum, what possible causes would you consider?**

Participants are expected to suggest: tuberculosis, bronchopneumopathy from banal germs and pneumocystosis (Slide 20).

Slide 20: Most frequent causes of respiratory manifestations

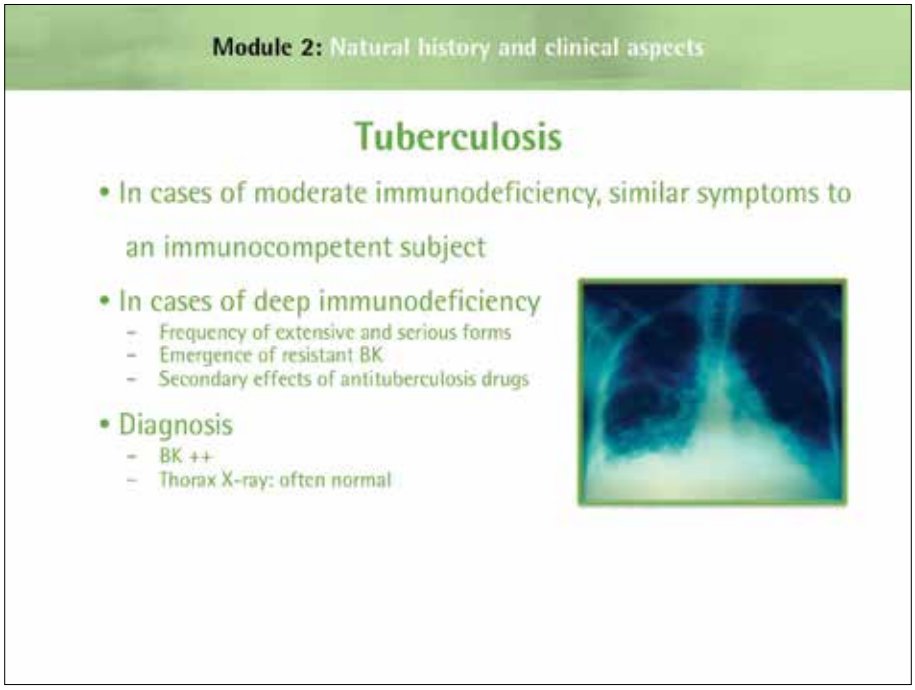


The facilitator may develop one of several pathologies.

1- Tuberculosis (Slide 21): the manifestations depend a great deal on the extent of the immunodeficiency. If it is moderate, the symptoms are similar to those observed in immunocompetent subjects. In cases of deep immunodeficiency, the extensive and severe forms are frequent, such as the emergence of resistant BK viruses. The secondary effects during antituberculosis treatment are more frequent in an HIV/BK co-infected patient compared with a patient monoinfected with BK.

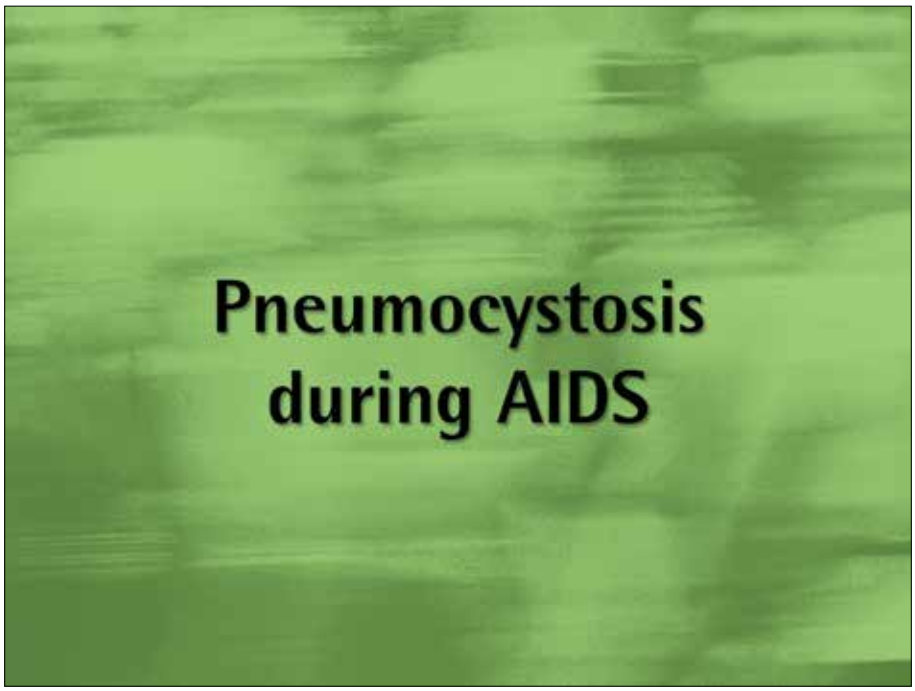
The thoracic radiograph often shows no abnormal signs.

Slide 21: Tuberculosis and HIV infection



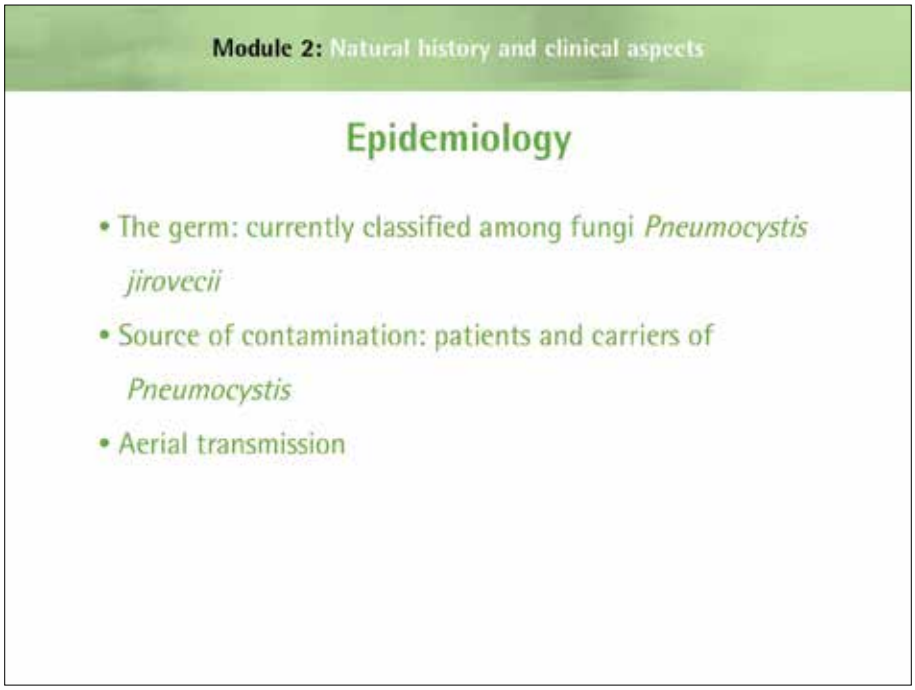
2- Pneumocystosis:

Slide 22



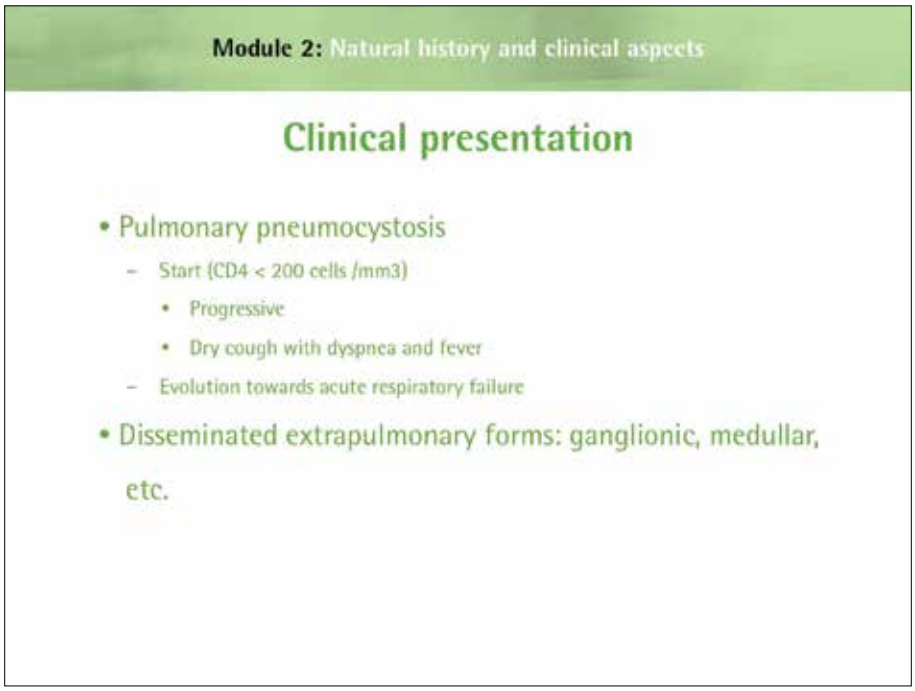

This is an infection caused by a fungus, *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). This pneumocystis has species specificity, and the source of contamination is made up of patients and healthy carriers. The germ reservoir is unknown, but is probably in the nearby environment. Transmission is by the aerial route (Slide 23).

Slide 23: Epidemiology of pneumocystosis



*P. jirovecci* is responsible for one of the most frequent opportunistic infections during HIV infection. The probability of an occurrence is high when the CD4 T lymphocytes are fewer than 200 cells per cubic millimetre. The respiratory impairment is manifested by a dry cough with gradually worsening dyspnea in a fever context. Untreated, the condition will develop towards an acute respiratory failure with a poor prognosis. Other locations are possible in disseminated forms: ganglionic, medullary, etc. (Slide 24)

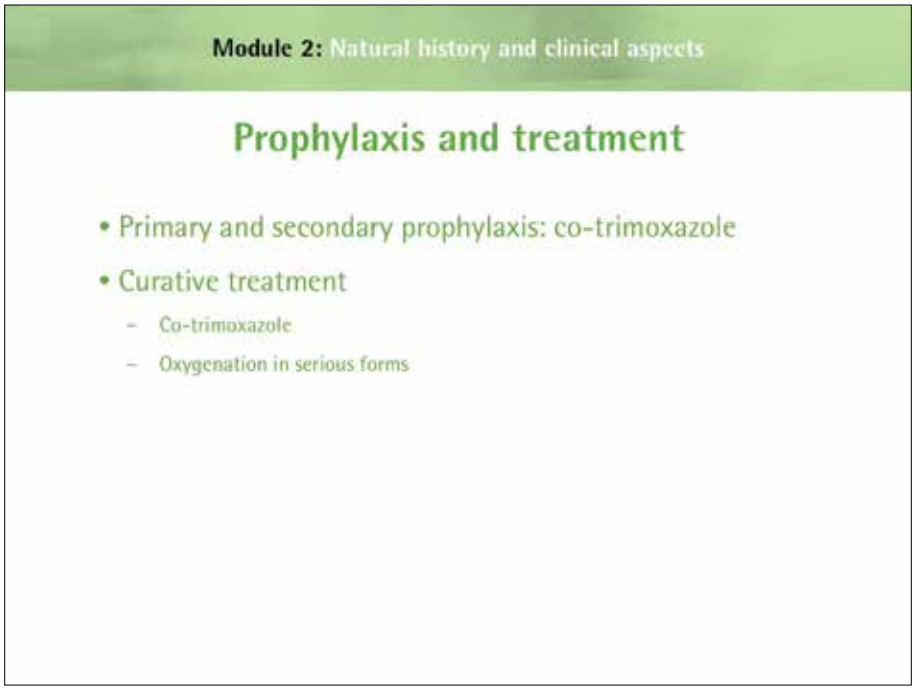
Slide 24: Clinical presentations of pneumocystosis




This infection can be prevented by co-trimoxazole. For a patient with less than 200 CD4 cells/mm3, primary prophylaxis is indicated. Secondary prophylaxis can be assimilated with maintenance therapy for pneumocystosis. Prophylaxis can only be stopped after immunity has been restored as a result of successful antiretroviral therapy.

The curative treatment uses co-trimoxazole with, in the event of severe dyspnea, short-term corticotherapy and oxygenation (Slide 25).

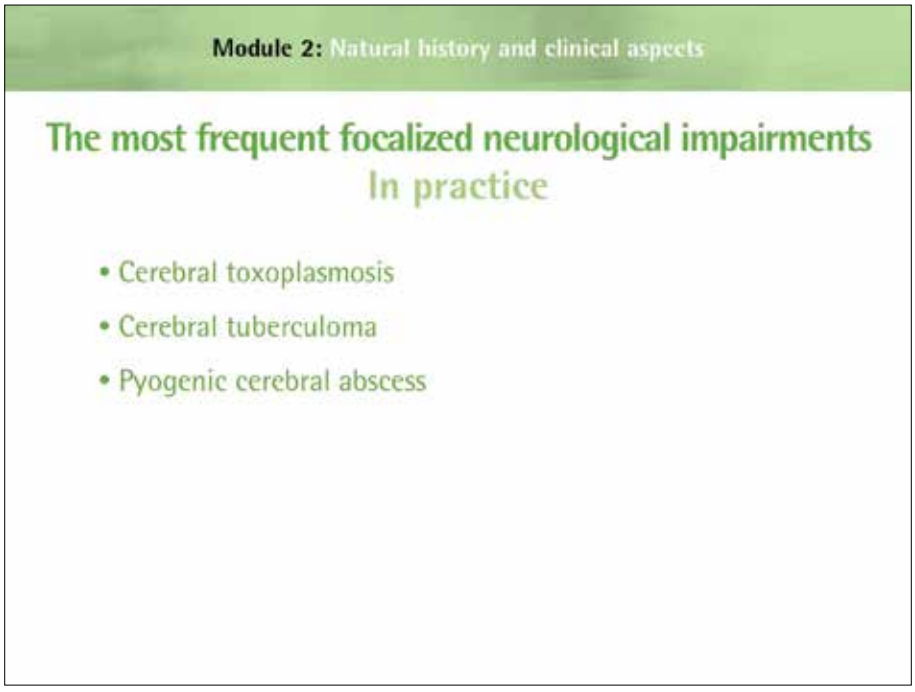
Slide 25: Prophylaxis and treatment of pneumocystosis




**If you are examining a patient infected with HIV who presents a motor deficiency of monoplegia or hemiplegia type accompanied by fever, what possible causes would you consider?**

Participants are expected to suggest: cerebral toxoplasmosis, cerebral tuberculoma, pyogenic cerebral abscess (Slide 26).

Slide 26: The most frequent causes of focal neurological deficit

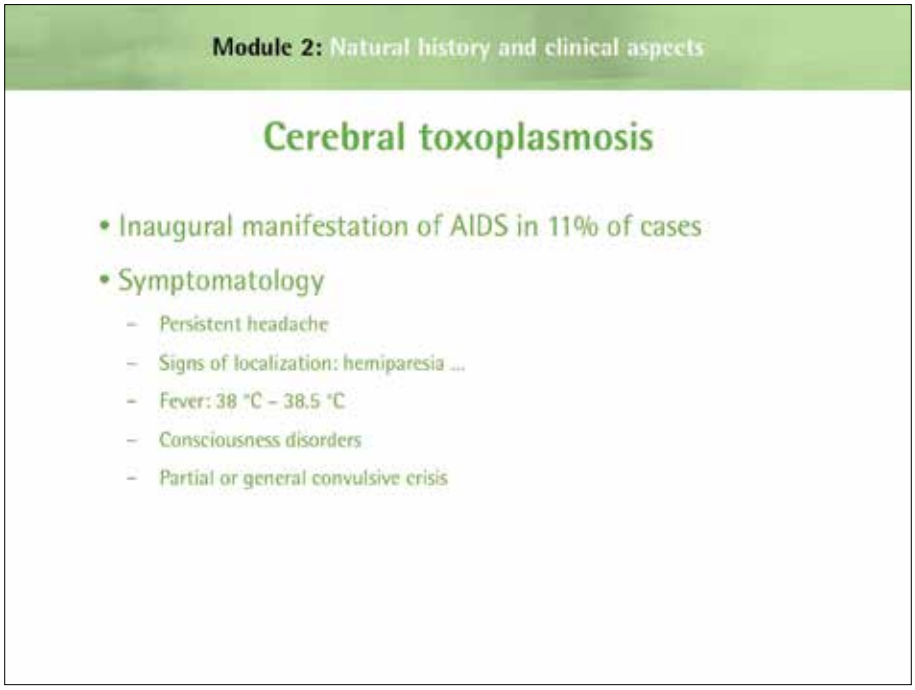


Neurological manifestations are frequent during the HIV infection, especially at the AIDS stage. The aetiology is multiple: the opportunistic infections come first, followed by lymphoma and HIV encephalopathy. Moreover, the secondary effects of drugs may also explain certain neuropsychiatric disorders. The neurological manifestations may be of central or peripheral origin and have variable consequences on quality of life and autonomy.

Confronted with central neurological manifestations, the clinician will be guided by the existence or absence of signs of focusing. The focusing symptoms require the start of a trial treatment of toxoplasmosis type. If after 14 days of treatment the patient improves, the toxoplasmosis diagnosis is accepted. Otherwise the diagnosis is reconsidered. When there is no sign of focusing, a lumbar puncture should be carried out and the cerebrospinal fluid, with an India ink stain, can be examined to identify the cause.

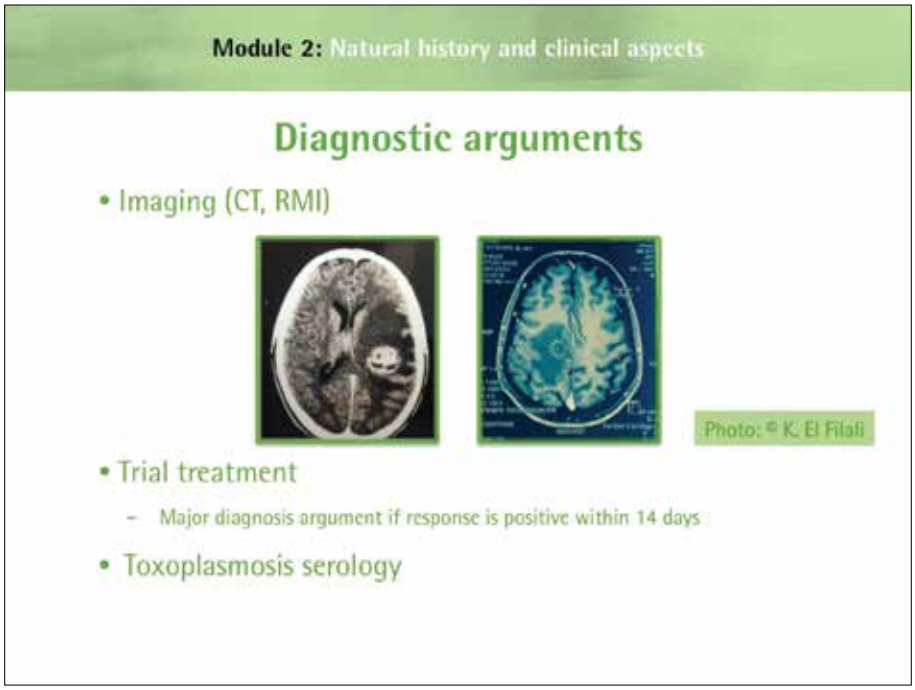
Cerebral toxoplasmosis can be an inaugural manifestation of AIDS in nearly 11% of cases. Clinical presentations include headaches, fever and focalized motor deficit and can extend to hemiplegia. Complications can include consciousness disorders and convulsions (Slide 27).

Slide 27: Symptomatology of cerebral toxoplasmosis



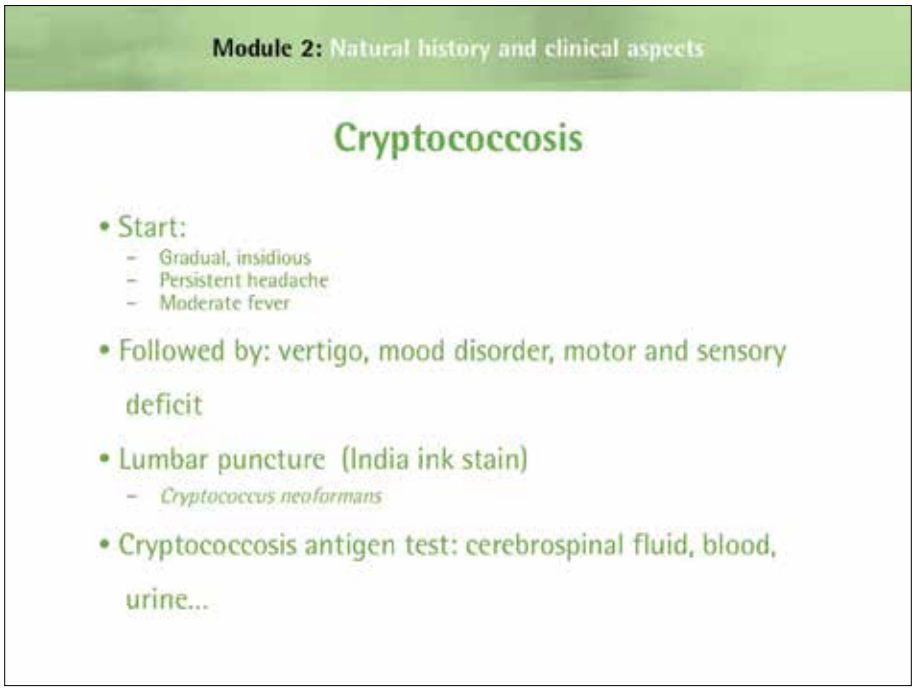

The cerebral toxoplasmosis diagnosis is based on a set of arguments: vivid imaging (CT or MRI), effective trial treatment and a positive toxoplasmosis serology (Slide 28).

Slide 28: Arguments for a toxoplasmosis diagnosis

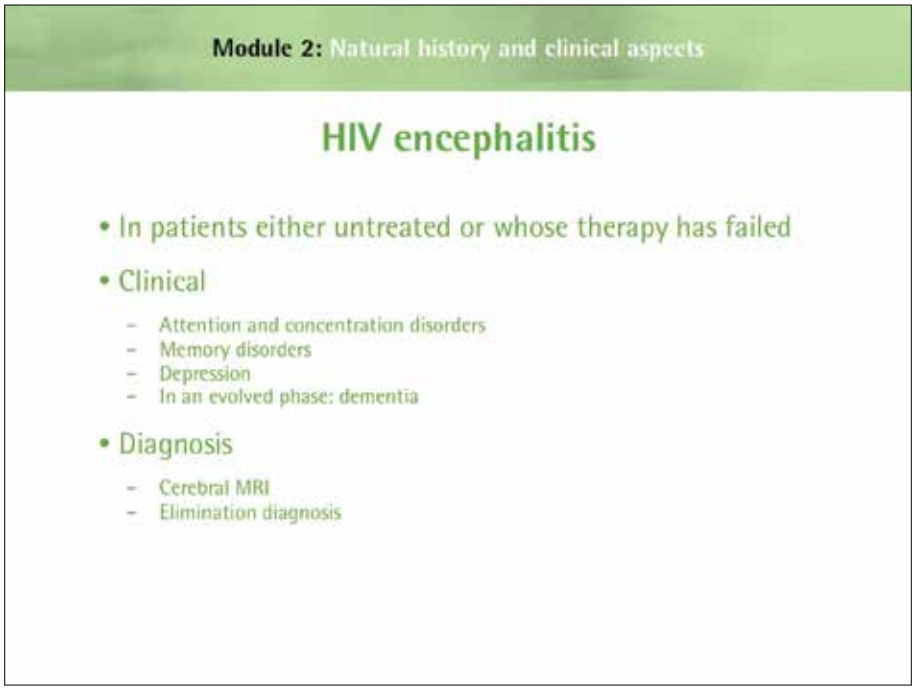



The facilitator may also provide some information on cryptococcosis (Slide 29) and HIV encephalitis (Slide 30).

Slide 29: Cryptococcosis



Slide 30: HIV encephalitis




- The clinical manifestations of HIV infection are highly polymorphous.
- The respiratory manifestations are dominated by tuberculosis, pneumocystosis and lower respiratory infections induced by pyogenic germs.
- The central neurological manifestations are dominated by toxoplasmosis.

# End-of-module quick evaluation

Module title: .....

Please give us your opinion about the session by giving a score using the following rating scale:

1: Strongly disagree

2: Disagree

3: Neither agree nor disagree

4: Agree

5: Strongly agree

| Item | Score |
|---|---|
| 1. The objectives of the session were clearly stated | |
| 2. The trainer communicated effectively | |
| 3. The information presented was new to me | |
| 4. The trainer was enthusiastic about the subject | |
| 5. The session content was practical and not too theoretical | |
| 6. The session was well-organized | |
| 7. The trainer asked questions and involved me in the session | |
| 8. The content was relevant to my work | |

Which aspects of the module were *not* clear?

Comments:

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**HIV-related stigma and discrimination are major barriers to the delivery of quality services by health care providers. This comprehensive training package consists of essential information and tools for training health care workers in countries of the WHO Eastern Mediterranean Region. It comprises four modules covering the key activities and information necessary to reduce HIV-related stigma and discrimination in the health care setting.**