CLINICAL ASPECTS OF HIV/AIDS

Basic training course for nurses

Edited by Raffaella Bucciardini,
Vincenzo Fragola and Paola De Castro

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Abstract. This booklet deals with basic clinical information on HIV/AIDS. It is mainly addressed to nurses working within the CASA project. It provides general knowledge on the natural history of HIV infection, what should patient know about HIV, how to visit patients. HIV testing, ART, WHO guidelines, clinical management of ART side effects and opportunistic infections, viral hepatitis, comorbidities, tuberculosis. The booklet is part of a series of training toolkits developed within the CASA project.

Key words: HIV/AIDS, ART, opportunistic infections in HIV

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For information on this training course, write to: **raffaella.bucciardini@iss.it**
For information on the CASA project, visit the website: **www.casaproject.info**

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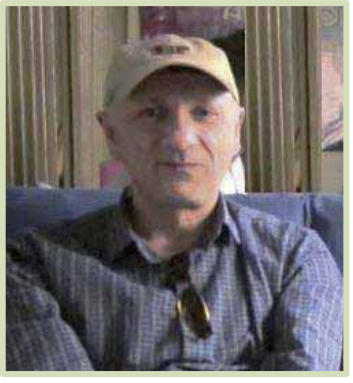
Preface



The role of the nurses in the management of HIV disease has become essential in a context of decentralization of health facilities, where a growing number of patients can access medical care even in remote rural areas.

The need for change has gradually allowed to overcome the boundaries between specific professional skills, leading to a different distribution of responsibilities within the healthcare working groups.

Recent studies have shown that "*task shifting*" from physicians to properly trained nurses, does not compromise quality of care but, on the contrary, may reduce the number of patients lost to follow-up. Nevertheless, the central role of the nurses requires accurate training to shortly provide clinical skills at a higher level.

This course is primarily intended to provide the nursing staff with a basic understanding of clinical and therapeutic aspects of HIV infection. The lessons start with a description of the natural history of infection, specifying the correct clinical approach to the patient and the right information to be given to the patient during the visits. From the first lessons, you will probably feel to be led into an interesting and harmonious learning program, that will require an investment of time and energy compatible with your daily work. Essential aspects of clinical management of HIV infection and its associated diseases will then be treated. In particular, some basic clinical manifestations that nurses

may gradually learn to recognize, even in the absence of scientific and professional knowledge.

On the basis of the current WHO guidelines, information about treatment will finally be provided, such as the right time to start, the drugs to be used, how to monitor the effectiveness of the treatment, and how to recognize and manage the most common side effects.

At the end of each lesson, you will find a learning assessment test. This is a practical way to verify the successful understanding of the topics and, at the same time, a way to repeat and emphasize the essential elements of each lesson. This booklet aims to be a tool to grow together. A valuable contribution to increasing your skills, but also a common basis for group discussions and a starting point for further studies.

I wish you a nice learning experience and all the best in your professional life.

Vincenzo Fragola
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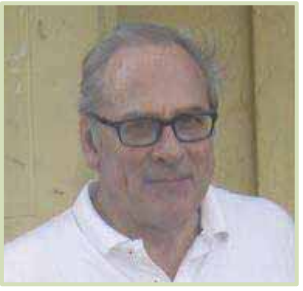
Lesson 1.

The natural history of untreated HIV infection: from acute phase to opportunistic infections



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1.1 Natural history of HIV infection

In this lesson we will review the natural history of HIV infection in an infected patient not treated with antiretroviral therapy (ART) from the transmission event to the acute phase (which lasts just a few days or weeks), to the asymptomatic phase (which may last an average of 10 years), until the final symptomatic phase, which is called AIDS.

This final stage includes the development of opportunistic infections (OIs), which may be responsible, if not treated, of the death of the patient.

We will describe the most important signs and symptoms associated with these three distinct phases of HIV disease. As you well know, it possible today to modify - with ART - the course of the disease and avoid its progression to AIDS. In addition, the majority of OIs can be prevented or treated.

Both ART and treatment of OIs will be the content of subsequent lessons. However, we will illustrate what can happen to an infected individual if he or she is not treated and discuss sign and symptoms of the different stages of the natural history of HIV infection.

1.2 Acute infection phase

Let's start with the first phase, the acute infection phase, which follows - by a week or two - the HIV transmission event.

This first stage is called acute infection or seroconversion phase. It typically happens within two to six weeks after exposure or from becoming infected. This phase is accompanied by a number of constitutional symptoms. The main symptoms of the acute HIV infection include: they include high fever, malaise, headache, peripheral neuropathy, myalgia, liver and spleen enlargement, nausea, vomiting and, sometimes, by a purple non itching rash.

The symptoms of acute infection look similar to those of other viral illnesses and are often compared to those of influenza, so this phase may be difficult to recognize. The symptoms may last a week or two and then they completely go away as the virus goes into a non-symptomatic stage.

To recognize this acute stage of infection is very important, because during this period the virus replicates at high speed and the infected person is highly contagious and can easily transmit the infection to his/her sexual partner.

1.3 Asymptomatic phase

Let's move now to the subsequent phase, the asymptomatic phase. An already weak immune system, for example if the patient is undernourished, may be less

effective in combating HIV and the progression to AIDS may be shorter. So, after the acute/seroconversion period, HIV infection goes into a long stage without symptoms. In the absence of treatment the median time to develop AIDS is 10-11 years. However, during this period without symptoms, HIV is still killing the CD4 T cells and destroying the immune system.

During the period of asymptomatic infection, patients generally have not findings on physical examination except, sometimes, for a generalized lymphadenopathy.

“Persistent generalized lymphadenopathy" (PGL) is defined as enlarged lymph nodes involving at least two non-contiguous sites other than inguinal nodes.

1.4 Symptomatic phase

Let’s move now to the third phase, the moment in which a number of symptoms appear.

This phase is closely linked to the progressive destruction of the immune system, and is accompanied by the appearance of OIs, which we will now describe in some detail.

These are just some of the general health problems which may arise during the symptomatic phase of HIV infection.

They may involve almost all systems and organs of the body, including brain, eyes, mouth, blood, lungs, bones, heart, liver, digestive tract and reproductive system.

In addition, a devastating pathology - called “wasting syndrome” may also appear, and is also known as “slim disease”. In an HIV infected person, the

number of CD4 cells steadily drops, making them vulnerable to other infections and in danger of developing AIDS.

The final stage (AIDS) arrives when the immune system becomes so weak that it is unable to protect the body from “opportunistic infections” and “cancers”.

1.5 Opportunistic infections

These infections are called “opportunistic” because they take advantage of a weakened immune system, and they can cause devastating illnesses. Most life-threatening OIs occur when CD4 count is below 350 cells/mm. OIs are the most common cause of death for people with AIDS. In some cases, medications can be used to prevent some OIs from occurring: this is known as prophylaxis.

A timely diagnosis of OIs is very important because the majority of them are treatable. Starting ART early will increase the number of CD4, reinforce the immune system and therefore prevent the development of OIs.

1.6 Why it is important to treat patients

In conclusion, untreated HIV infection inevitably lead to a profound destruction of the immune system, which, in turn, open the door to numerous and deadly OIs. In the following lessons, we will show how to prevent and treat OIs.

In other lessons, we will see how to prevent the destruction of the immune system by HIV, using ART. Indeed, one of the success of ART is to lower or even putting to zero the risk of getting OIs, by stopping the replication of the HIV and increasing the number of CD4 cells. We will cover in the next lessons different aspects of ART: from when to start, to which drugs to use, how to monitor successful therapy and how to improve adherence to ART.

Questions on Lesson 1

Please select the correct answer, one out of four.

1. The acute infection (seroconversion phase) typically occurs...

a. Within two to six weeks after exposure or from becoming infected
b. Within two to six months after exposure or from becoming infected
c. Sometimes a few years after exposure or from becoming infected
d. Sometimes two years after exposure or from becoming infected

2. The most common symptoms of acute HIV infection...

a. Are usually very strong
b. May look similar to those of influenza
c. Always include peripheral neuropathy and spleen enlargement
d. May look similar to those of measles

3. The acute HIV infection symptoms...

a. May last a week or two, then disappear as the virus goes into a non-symptomatic stage
b. May last a week or two, but never completely disappear and may get worse over time
c. Lasts until the beginning of ART
d. Lasts for the whole life

4. Why is it important to recognize the acute stage of infection?

a. Because in the acute stage the virus replicates rapidly and the infected person is not yet contagious
b. Because in the acute stage the virus replicates slowly and the infected person is not yet contagious
c. Because in the acute stage the virus replicates rapidly and the infected person is highly contagious
d. Because in the acute stage the virus replicates slowly and the infected person is not highly contagious

5. The asymptomatic phase...

a. In the absence of ART the median time to develop AIDS is 10-11 years
b. May last only one month
c. May last only a few weeks
d. None of the above answers

6. During the asymptomatic phase...

a. HIV strengthens the immune system
b. If the patient don't take ART HIV destroys the immune system
c. HIV cannot damage the immune system
d. If the patient takes ART, HIV destroys the immune system

7. During the asymptomatic phase, patients may sometimes show...

a. Night sweats
b. Liver and spleen enlargement
c. Lymph nodes enlargement
d. Cardiovascular diseases

8. During the symptomatic phase and without taking ART…

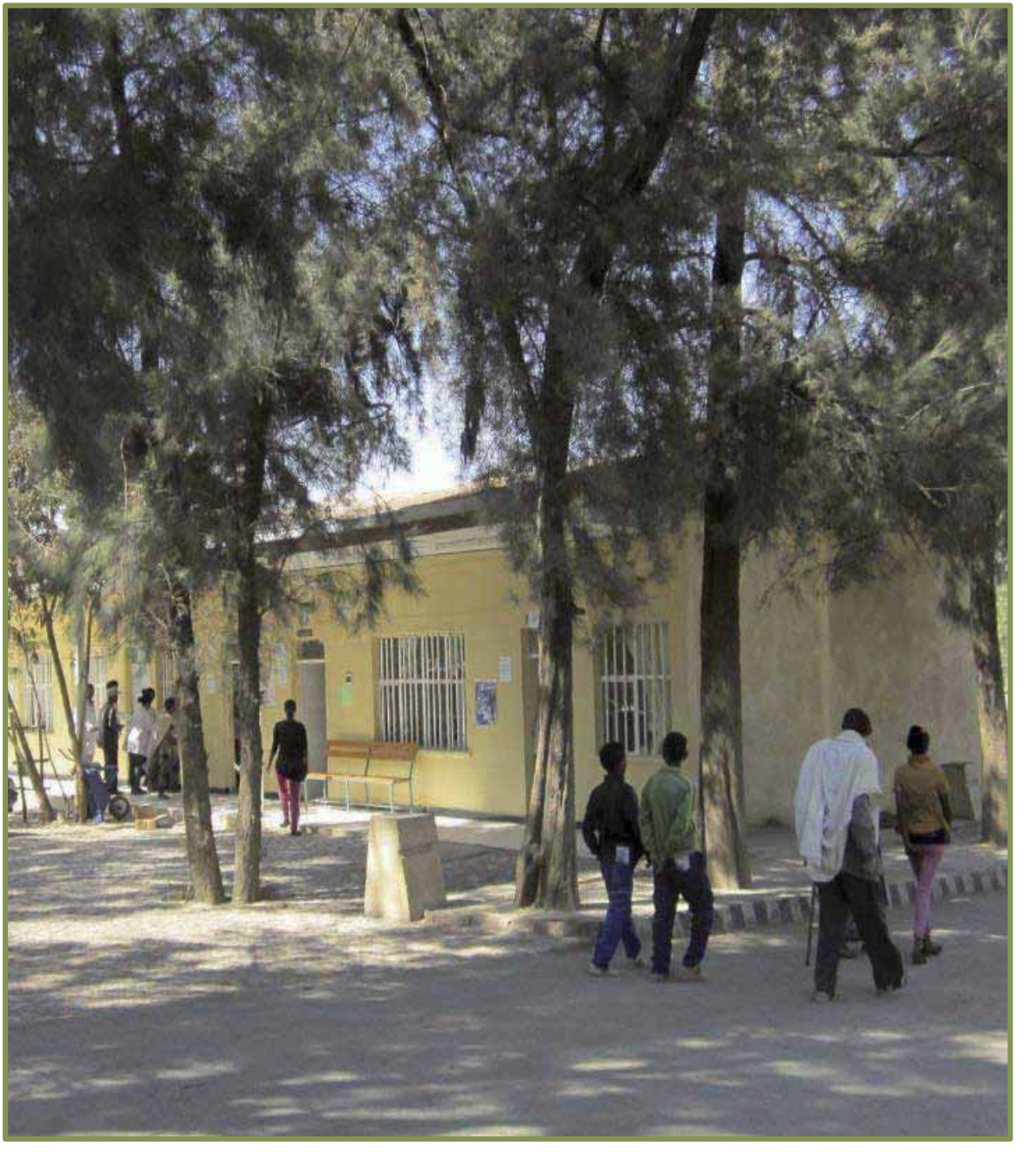
a. HIV strengthens the immune system
b. CD4 number always increase
c. Progressive destruction of the immune system always occurs and opportunistic infection appear
d. HIV strengthens the immune system and CD4 number always increases

9. Opportunistic infections may be prevented...

a. By improving the general conditions of patients
b. By starting ART early
c. Only through adequate prophylaxis
d. By starting ART late

10. The final stage (AIDS) arrives...

a. When the immune system becomes so weak that it is unable to protect the body from “opportunistic infections” and “cancers”
b. When the immune system becomes stronger than in asymptomatic stage
c. When CD4 number increase
d. None of the above answers



Lesson 2.

What should your patients know about HIV and antiretroviral therapy?

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2.1 Why talking about HIV?

It is more than 30 years since the discovery of HIV and it is still difficult to openly speak about it. Many people have great concern talking about HIV because this infection is often surrounded by stigma and prejudice. HIV positive people are often discriminated, insulted and rejected. As a result, HIV positive patients get lonely, fear for the future and find it difficult to have a truly loving relationship.

In addition, many people prefer not to get HIV test because they do not feel they are HIV infected. About this issue, it is essential to inform people why it is so important to get an HIV test and to emphasize that AIDS is a treatable disease.

[1] In the picture

Moreover, people are not informed well enough on how to protect themselves from the risk of HIV infection. We have mentioned these points for giving you an idea on how important it is to talk about HIV.

2.2 Understanding how HIV is transmitted

Understanding how HIV is transmitted will help you take steps to protect yourself and the others.

An HIV infected person can transmit the virus in the following ways:

- Sexual contact without a condom (included oral sex and any type of sexual intercourse)
- Drug injection
- Vertical transmission from HIV infected mother to child during pregnancy, birth, or breastfeeding, if no specific treatment was established
- Occupational exposure (be careful about working procedures in your health centre!)
- Blood transfusion

HIV is not spread with either via saliva, or through unbroken skin contact.

2.3 The risk of getting HIV varies widely depending on the type of exposure

Exposure to HIV during blood transfusion carries a much higher risk of transmission than other exposures. Moreover, a third of children born from an HIV-infected woman will have HIV infection if the mother does not take antiretroviral therapy (ART) during pregnancy [1].

2.4 How can people reduce the risk of HIV infection through sexual contact?

First of all, the condom is the best way to prevent sexually transmitted diseases. There are two types of condoms: for men and women. Both are effective in preventing HIV infection and also other sexually transmitted diseases, like syphilis.

Moreover, they should properly take ART, because it has been shown that taking ART reduces the chance of transmitting HIV to sex partners.

ART consists of the combination of antiretroviral drugs to suppress HIV virus and stop progression of HIV disease. These drugs must be taken exactly as health care provider prescribes.

Finally, HIV-infected patients should be encouraged to talk about their HIV status with their sexual partners [2-4]. In this manner, partners of HIV-positive patients who are not infected with HIV can get tested at least once a year.

2.5 When should a person be tested for HIV infection?

In the case of any of the previously exposed conditions (sex with partners of unknown HIV status, blood transfusion, sharing syringes etc.).

It is important to know that many people do not have any symptoms at all for 10 years or more! Patients should know that the only way to know if they are infected with HIV is to get tested. Moreover, it is very important to get an HIV test if a patient is pregnant. The test allows the mother to be sure to be HIV–negative, or otherwise she can promptly start ART.

HIV-exposed infants and children younger than 18 months should be promptly tested for HIV in order to rapid initiate ART in the case of a positive result [5-7].

In fact, mortality is very high among untreated HIV- infected infants in the first year of life [6].

WHO recommends provider-initiated testing and counselling for all children who are malnourished, have TB, are admitted to hospital or have other signs or symptoms of HIV infection *(source: WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection guideline. June 2013).*

2.6 Is it possible to treat HIV infection?

Actually, there is no definitive cure for HIV infection.

However, antiretroviral drugs have dramatically reduced mortality and improved survival.

Since the introduction of ART, mortality rates for HIV-infected persons have become much closer to mortality rates of the general population [8].

To improve HIV-infected patients survival, it is crucial that people get tested for HIV early, so that medical care and treatment can be established as soon as possible.

2.7 How to improve patient adherence to ART?

Health care providers should carefully discuss with new diagnosed HIV positive patients about pros and cons of ART. So, patient who has been recommended treatment will be ready and willing to initiate it [1-2].

Clinicians should explain patients how the ART works, how to take the medicine and their possible side effects. It is also necessary to explain how important it is to be adherent to therapy and not to miss the scheduled monitoring visits.

If a patient decides to postpone the therapy, the physician should periodically remind patient how important it is to take early the therapy. Patients should know that if they do not take the therapy their immune system deteriorates and exposing themselves to the danger of getting sick. Patients should be counselled that disclosure of their HIV seropositivity to somebody (partners or trusted persons) can be helpful in acceptance of their status. Talking about HIV with both HIV-infected and not infected people could reduce stigma and improve patient adherence to care.

Furthermore, patients' associations or community based organizations can be a very useful tool for improving the adherence to therapy and reducing loss to follow-up.

2.8 When should the patient contact clinicians beyond routinely visits?

It is important to build a trusting relationship with the HIV positive patient.

He should be reassured and encouraged to refer to the health center in the following cases:

- new symptoms

- pregnancy or planning a pregnancy

- side effects of therapy: for example cutaneous rash, gastrointestinal or other symptoms.

2.9 What about confidentiality?

Confidentiality is as important aspect for HIV patients as it is for all other patients.

Being an infected HIV person is a strictly personal matter and a patient can be worried about confidentiality.

Health care providers must maintain confidentiality and keep an appropriate attitude towards affected patients. Patient should feel confident that data about their health status are only accessible to medical personnel or can be used for research purposes only after a written approval by the patient.

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You can find more information about patient counseling in the World Health Organisation and Centers for Disease Control and Prevention websites and reading the following articles.

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Questions on Lesson 2

Please select the correct answer, one out of four.

1. **Speaking about HIV with both HIV-infected and HIV-uninfected people could:**
   a. Reduce stigma and improve patient adherence to care
   b. Cause fear and lack of confidence in the health workforce
   c. Create social discrimination
   d. Lead people to escape

2. **Someone who has HIV can transmit the virus in the following ways:**
   a. Having sex with a condom
   b. Sharing needles, syringes or other equipment (works) used to prepare injection drugs
   c. Through saliva
   d. b+c

3. **Which of the following sentences is true?**
   a. Viral concentration is the same among various organism fluids
   b. An exposure to HIV during a blood transfusion carries a lower risk of transmission than other exposure
   c. It is important to discourage the partners of HIV-positive patients who are HIV-negative to get tested for HIV at least once a year
   d. HIV-infected patients have a 0.2% chance of transmitting HIV during a heterosexual intercourse

4. **Someone who has HIV:**
    a. May have no symptoms for 10 years or more
    b. Can rely on symptoms to know whether he has HIV
    c. Should consult his doctor as soon as possible to begin treatment
    d. a+c

5. **Infants and children younger than 18 months:**
    a. Should be tested within four to six weeks of birth
    b. In this population HIV infection can be definitively confirmed using standard HIV serological tests
    c. Untreated infants with HIV in the first year of life have the same mortality of infants who started early ART
    d. There is no possibility to prevent vertical transmission of HIV

6. **ART:**
    a. Reduces the amount of virus (viral load) in the blood and body fluids
    b. Greatly reduce the chance of transmitting HIV to sex partners if taken consistently and correctly
    c. Can dramatically prolong the lives of many people living with HIV
    d. a+b+c

7. **Which of the following sentences is true?**
    a. It is important that people get tested for HIV and know that they are infected early
    b. ART has no side effects
    c. ART always consists in a single pill daily
    d. It is possible to skip some doses of ART

8. Health staff:

a. Should set an example by maintaining confidentiality and an appropriate attitude towards affected patient
b. Can freely inform the sexual partner of the patient
c. Should not discuss with the patient questions regarding privacy
d. Laboratory staff is not obligated to confidentiality

9. When should patients refer to clinicians beyond routinely visits?

a. In case of new symptoms
b. If they discover pregnant or plan to become pregnant
c. In case of acute toxicity related to ART
d. a+b+c

10. A pregnant woman:

a. Should receive proposal of HIV testing
b. Can recognize a misdiagnosed HIV infection and protect her child
c. Should not take ART
d. a+b

Lesson 3.

How to visit patients: collecting clinical history and performing physical examination

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An ordinary visit is composed of two parts: patient's history and physical examination.

3.1 The setting

To collect patient's history the setting is important because it creates the environment in which you and the patient interact and influence how comfortable the patient feels.

A trusting relationship between the nurse and the patient is essential to decrease the stress the patient may have from being physically exposed and vulnerable. The patient will be much more relaxed and cooperative if you explain what will be done and the reason for doing it.

3.2 What to check?

What are the most important things you should check during the first interview with the patient?

Start from general questions to know your patient and his/her habits.

Does the patient smoke or drink alcohol? These habits are important to know how they can cause comorbidities. Moreover, alcohol can have possible interaction with some medications.

Does the patient have any other comorbidities? (for example: cardiovascular diseases, renal impairments, psychiatric disorders or others).

Does the patient take any drugs? If yes collect names, dosage and reason for treatment

Does the patient have any pain or difficulty in eating? Does the patient have any vision and/or hearing problems? Does the patient have any allergy to medications? If yes collect names and which side effect he/she has.

3.3 If the patient is a woman

If your patient is a woman, don't forget to evaluate, during the first interview, her gynecological and obstetrical history.

How many previous pregnancies did she have? Does she have seropositive children? Did she have any abortion? If yes check the reason.

3.4 Subsequent visits

What should you check during subsequent visits?

Does anyone else know about the patient's HIV status?. If nobody knows it, check the reasons why (for example stigma and discrimination).

Does the patient have sexual contacts? If yes, are they casual sexual contacts? Does the patient use a condom, usually?

Does the patient have problems taking regularly the antiretroviral therapy (ART) If yes, check the reasons (for example: difficulty in reaching health facilities, doubts on antiretroviral therapy efficacy and/or safety, fear of stigma or of medications).

Does the patient observe new signs or symptoms? If yes, it is very important to evaluate when his/her symptoms started and if they are related to the ART assumption.

3.5 What is a physical examination?

Physical examination is the process of evaluating objective anatomic findings through the use of observation, palpation, percussion and auscultation [1]. The information obtained should be integrated by checking vital signs. Observation together with listening are the most important parts of your exam. They start from the beginning, since the patient enters the visit room:

How does he/she enter the room? Does he/she walk without needing help? Does he/she limp? Does his/her face look normal or are his/her eyes and/or

mouth asymmetrical? Does he speak clearly? The data collected may provide you a lot of information regarding the neurological status of your patient.

You should continue the visit by evaluating vital signs. These are very important as they immediately suggest if there is any clinical urgency. Vital signs are pulse, blood pressure, respiratory rate and temperature. Furthermore, body weight is another important physical parameter to be monitored. Indeed, its changes can be considered as an expression of health problems.

3.6 Pulse

As the heart forces blood through the arteries, you feel the beats by firmly pressing on the arteries, which are located close to the surface of the skin at certain points of the body [2].

The pulse can be measured at any part of body where there is a large artery; for most people, it is easiest to take the pulse at the wrist.

How can you measure the pulse? Using the first and second fingertips, press firmly but gently on the arteries until you feel a pulse. Begin counting the pulse when the clock's second hand is on the 12. Count your pulse for 60 seconds (or for 15 seconds and then multiply by four to calculate beats per minute). When counting, do not watch the clock continuously, but concentrate on the beats of the pulse. If unsure about your results, ask another person to count for you [2].

3.7 Blood pressure

Blood pressure is the force of the blood pushing against the artery walls. It is measured using a blood pressure cuff and stethoscope.

Two numbers are recorded when measuring blood pressure: systolic pressure, that is the highest number, and diastolic pressure, that is the lowest one. Both are recorded as millimeters of mercury. Please note that it is very important to check the high blood pressure, also known as hypertension, which increases the risk of coronary heart disease (heart attack) and stroke (brain attack).

How do you take blood pressure? Hold the pressure gauge in your left hand and the bulb in your right. Close the airflow valve on the bulb by turning the screw clockwise. Inflate the cuff by squeezing the bulb with your right hand. You may hear your pulse in the stethoscope.

Watch the gauge. Keep inflating the cuff until the gauge reads about 30 points (mm Hg) above your expected systolic pressure. At this point, you should not hear your pulse in the stethoscope.

Keeping your eyes on the gauge, slowly release the pressure in the cuff by opening the airflow valve. The gauge should fall only 2 to 3 points with each heartbeat. (You may need to practice turning the valve slowly) [3].

Listen carefully for the first pulse beat. As soon as you hear it, note the reading on the gauge. This reading is your systolic pressure (the force of the blood against the artery walls as your heart beats).

Continue to slowly deflate the cuff. Listen carefully until the sound disappears. As soon as you can no longer hear your pulse, note the reading on the gauge. This reading is your diastolic pressure (the blood pressure between heartbeats).

Allow the cuff to completely deflate [3].

According to current guidelines high blood pressure in adults is defined as:one hundred forty millimeters of mercury or greater systolic pressure or ninety millimeter of mercury or greater diastolic pressure [4].

3.8 Respiration rate

The respiration rate is the number of breaths a person takes per minute. The rate is usually measured when a person is at rest and simply involves counting the number of breaths for one minute by counting how many times the chest rises [5].

Respiration rates may increase in presence of fever and other medical conditions. When checking respiration, it is important note whether a person has any difficulty in breathing as well. Normal respiration rates for an adult person at rest range from 12 to 16 breaths per minute.

The main steps in a physical examination are: observation, palpation, percussion and auscultation. The best thing to do would be to ask the patient to undress and then visit him on a bench. If you don't have enough time to visit your patient, you may not be able to complete all these steps.

So, remember that observation still remains the easiest and quicker aspect you can evaluate. You don't need specific instruments or facilities, you only need to look carefully at your patient during the interview.

3.9 Skin

You should be careful if there is any rash, because it may be related to drugs adverse side effect. If this is present, it is necessary to check which drugs the patient is taking and if they have been changed during the last visit.

Check if there is edema at the extremities. And don't forget to analyze mucosae to search for non-visible lesions, oral candidiasis or jaundice in the sclera.

3.10 Thorax

You don’t need to have a stethoscope to make a good evaluation of the thorax.

Start by looking at general comfort and breathing pattern of the patient, the use of accessory muscles of breathing, the color of the patient, in particular around their lips and nail beds [6]. Another aspect to consider is the ability to speak. Sometimes the respiratory rates are so high and the work used for breathing is so great that the patient is unable to complete sentences.

If you have a stethoscope you can listen to the thorax. If you don’t have enough time for all the patients, you should auscultate the thorax at least of those patients who may have pulmonary problems (on the bases of your initial evaluation and observation).

During auscultation be careful to recognize the three types of abnormal breath sounds: wheeze, crackle and gurgle. These can indicate the presence of pulmonary diseases (such as pneumonia, asthma) or cardiac diseases (such as heart failure).

3.11 Abdomen

If your patient has abdominal pain or gastrointestinal discomfort, pay special attention to this part of the physical exam.

Look at the appearance of the abdomen: if it is flat, distended or enlarged and if it is symmetrical or not. It may be useful to palpate the abdomen to verify where the pain is in order to exclude the presence of any mass.

While you are observing the abdomen you have to check for indirect signs of advanced liver disease: jaundice, ascites, breast development (gynecomastia), spider angiomata, varices (it is very important to verify the presence of Caput Medusae).

If you see one or more of these signs you must check the hepatitis serology. Don't forget that HCV-HIV co-infection is quite common in these patients.

3.12 Neurological exam

If patients have headache and/or some troubles in vision, listening, walking don't forget to include in your evaluation the meningeal signs.

The three most important signs that you can easily recognize and evaluate are: Brudzinski sign's where chin to chest evokes hip flexion, Kernig sign's where a resistance to knee extension evokes pain in hamstrings and nuchal rigidity [7].

3.13 If the patient is a child

It is needed to highlight some important things you should evaluate when you visit a child.

Firstly, it is better to note weight and height of the children during every visit. This easy but important thing will help you to understand if the child is growing regularly or not. Moreover, noting the weight of the children is very important for the correct dosage of the ART and for any other medication. In addition, you should rapidly check the neurological condition observing the motor activity, the language (in particular when the child started talking), the memory and the ability to concentrate. This part of the exam provides you important information about the child's psycho-physical development.

Finally, please pay attention to some important details such as: inconsolable crying, lack of appetite or lethargy. These are important signs that something is not going well in the child's body so it is necessary to carefully see your patient, and, moreover, ask for more exams to investigate the problem.

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Questions on Lesson 3

Please select the correct answer, one out of four.

1. **Which are the main steps in a physical examination?**
   a. Observation and palpation
   b. Percussion and auscultation
   c. Observation, palpation, percussion and auscultation to obtain a more complete view of the problem
   d. None of the previous answers

2. **Why the setting is important during a physical examination?**
   a. Because it helps the patient to reduce the effects of stress
   b. Because it creates the environment in which you and your patient must interact and influence how comfortable the patient feels
   c. Because it helps to create a trust relationship between you and your patient
   d. All the previous answer

3. **What are the main symptoms of advanced liver disease?**
   a. Jaundice, ascites, breast development (gynecomastia), spider angiomata, varices
   b. There is no particular symptom that can lead you in this diagnosis
   c. Nausea and vomiting, diarrhea, abdominal pain
   d. Only hepatosplenomegaly

4. **What are the main things you should check during the physical examination of the thorax?**
   a. General comfort and breathing pattern of the patient
   b. The use of accessory muscles of breathing
   c. How the patient looks like and his/her ability to speak
   d. All the previous answers

5. **What are the most important things you should check during the first interview?**
   a. Asking general questions in order to know your patient and his/her habits
   b. Focusing on the sexual habits
   c. Checking only comorbidities
   d. Talking about everything without focusing on nothing in particular because the first interview is not as important as the other meetings

6. **Vital signs detection is an important part of physical examination. Is it true?**
   a. No, because it is better to focus only on patient's history
   b. Yes, but it is not necessary to check them at every visit
   c. Yes, it's the most important part of the physical examination, because altered vital signs may immediately reveal clinical emergencies
   d. None of the above answers

7. **According to guidelines, what is the definition of high blood pressure?**
   a. 180 mmHg or greater for systolic pressure and 100 mmHg or greater for diastolic pressure
   b. 140 mmHg or greater for systolic pressure and 90 mmHg or greater for diastolic pressure
   c. There isn't a global definition of high blood pressure because it depends on other comorbidities and presence of other risk factors
   d. All the above answers

8. What are the most relevant things to see during the skin examination?

a. The presence of rash
b. Oral candidiasis
c. The presence of icterus by looking at the sclera
d. All the previous answers

9. Are there any particular things to see during physical examination of children?

a. There are no differences with the adults
b. It's very important to check height and weight to understand whether or not the child is growing regularly
c. The neurological examination is the only important part of the physical examination in children
d. None of the above answers

10. Which are the main signs of neurological impairment due to a meningitis?

a. Nucal rigidity
b. Positivity of Kernig and Brudzinski signs
c. Headache and fever
d. All the above answers

Lesson 4.

HIV testing

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4.1 HIV testing: why is it so important?

Early recognition of HIV infection is important as a preventive intervention. HIV test may be the first step of a process that involves the diagnostic procedure and, most importantly, the therapeutic process. It is the beginning of a process that links the patient with the health care center for the whole life.

In particular, the importance of promoting the test includes:

1. Referral to pre-exposure prophylaxis programs
2. Counseling to promote those changes in behavior that are necessary to reduce HIV transmission
3. Linkage to care

It is important to note that many recent guidelines recommend annual testing for persons considered to be at high risk for HIV infection [1] .

HIV testing should not be considered as a routine test, but rather as a voluntary and informed one, obtained in accordance with local laws. Confidentiality and absence of discrimination towards positive persons are crucial to create a trusting relationship between patients and physicians.

Remember that patients with negative test can be considered as not infected, unless they report a recent probable or proved exposure to HIV, generally within the last 2-3 months.

In fact, the immune system normally takes 2 to 3 months before producing HIV-specific antibodies. If the patient reports a recent possible exposure to HIV the probability of an early infection, undetectable with common serological tests, is consistent and must be evaluated.

4.2 Types of HIV testing

There are different types of HIV diagnostic tests: traditional tests and rapid ones.

Traditional HIV tests. These tests include enzyme immunoassay on blood, oral fluid, or urine to detect HIV antibodies. Results for these tests can take up to two weeks. The most commonly used HIV traditional test is an ELISA test (enzyme-linked immunoassays), normally used for detection of anti HIV antibodies. A combination test that detects both p24 antigen and HIV antibody can be also used [2] .

Rapid HIV tests. The development and use of rapid HIV tests began in the late 1990s in order to facilitate the expansion of HIV testing services. There are different rapid tests that can be performed on finger stick, serum or plasma, oral fluid or urine. Results for these tests can take from 2 to 20 minutes.

Rapid tests offer you considerable advantages: they are very suitable in all those situations when your patients can't reach a health center and when you want to test a great amount of persons in a short time. Nonetheless, these tests have disadvantages as well. In particular, they are not as sensitive as an antigen/antibody immunoassay on serum or plasma and only few are validated for combined HIV-1/HIV-2 infection (dual infection).

In general, if someone gets a positive result from these tests, it is necessary to take another test, called a Western blot test, to confirm that result [3].

4.3 HIV test and privacy

HIV test results fall under the same privacy rules as all other medical information. Information about the HIV test cannot be released without the permission of the patient [4] .

The testing can be confidential and/or anonymous. Confidential testing means that the name and other identifying information will be attached to the test results. The results will go in the medical record of the patient and may be shared with the healthcare providers.

Anonymous testing means that nothing ties the test results to the patient. When someone takes an anonymous HIV test, it gets a unique identifier that allows him/her to get the test results. Not all HIV test sites offer anonymous testing [5] .

4.4 Practical advice

As we mentioned before, HIV testing is not perfect. As any other approach, it has its advantages and disadvantages. Normally, the best rule is to be as

effective as possible, respecting the so-called “5 C’s”: counseling, consent, confidential testing, correct test results and connection (or “linkage”) to care. These five advice must guide the work of the medical and non-medical staff involved in the process [6].

4.5 Counseling

It is a provision of advice or guidance in decision-making, in particularly in emotionally significant situations.

The counselor should help the patient trying to understanding his/her state of mind, as the patient is often demoralized, distressed or in a negative state of mind.

Counseling before and after a HIV test is important because it provides critical information about HIV itself and about the testing process. It is possible to give pre-test and post-test information.

A pre-test counseling session should provide the following information:

- Information about the HIV test—what it measures and how long it takes to get results
- Information about how HIV is transmitted and how the person can protect him/herself from infection
- Information about the confidentiality of the test results
- A clear, easy-to-understand explanation of what the test results mean.

A post-test counseling generally includes:

- Clear communication about what your test result means
- HIV prevention counseling, if the results are negative
- A confirmatory test, called a **Western blot test**, if the result are positive.

The results of Western blot test should be available within 2 weeks. If the result of the test is positive the figure of the counselor becomes even more important.

The counselor should be the person to refer to for any questions or doubts and in particular: the counselor will discuss what it means to live a healthy life with HIV and how the patient can keep from infecting others. The counselor will also talk about treatments for HIV and can link the person to a physician for immediate care.

Getting into treatment quickly is important, it can help to keep the immune system healthy and keep from progressing to AIDS .

4.6 Pregnancy

Diagnose HIV during pregnancy is a public health priority.

Unfortunately, diagnosis in pregnancy is difficult for the increased false-positive rates of ELISA screening assays.

Furthermore, women may present at delivery without a proper previous evaluation [7].

This last condition may be avoided by providing information regarding HIV testing and with early test, especially in high risk population, during the third trimester.

For women that present at delivery without a previous test, it is mandatory to assess HIV status with a rapid test. If the result is positive, an antiretroviral therapy must be started at once [7].

4.7 Conclusions

HIV testing and counseling services have helped millions of people learn their HIV status and for those testing positive, learn about options for long term care and treatment [6].

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Questions on Lesson 4

Please select the correct answer, one out of three.

1. **What is the purpose of HIV test?**
   a. To obtain a diagnose
   b. Referral to pre-exposure prophylaxis programs
   c. Counseling to promote the behavior change necessary to reduce HIV transmission
   d. All of the above

2. **A negative HIV test generally means:**
   a. The person is HIV negative
   b. The person must be submitted to another HIV test after three months
   c. The person should repeat HIV test after at least two years if it is considered at high risk
   d. The person is negative unless he or she has had a recent known or possible exposure to HIV

3. **What is the best option for an HIV test, in term of specificity and sensibility?**
   a. Rapid test
   b. Traditional test
   c. Western Blot
   d. p24 antigen

4. What is the most used traditional test?

a. ELISA test
b. Blood test
c. NAT test
d. None of above

5. What is the main difference between a confidential test and an anonymous test?

a. Anonymous test can be requested in all health centers, confidential test can be requested only in some centers
b. Confidential test requires the presence of the name of the patient on the specimen, while the anonymous test requires other clinical data
c. Confidential test requires the presence of the name of the patient on the specimen, while the anonymous test requires only a number of identification
d. There is no significant difference

6 What of the following sentences is true?

a. A post test counselling must follow each HIV test result
b. A pre test counselling can be useful in some cases
c. A pre test counselling must be done in front of the patient's sexual partner
d. A post test counselling must include the patient's partner

7. How long does a rapid HIV test usually take?

a. One day
b. One hour
c. 20 hours
d. 20 minutes

8. What are the advantages of a rapid test?

a. Better specificity
b. Better linkage to care
c. Better clinical outcome
d. Rapid test can be done without pre-risk assessment

9. Is an HIV test important for a pregnant woman?

a. Yes but only during third trimester
b. It is sufficient to run a rapid test before delivery
c. No, it is not important
d. There are several options, the best one is to run the HIV test during all trimesters

10. What of the following information about an HIV counsellor is false?

a. HIV counselor must discuss every aspect of what it means to live an healthy life with HIV
b. HIV counselor must always refer the patient to a physician
c. HIV counselor must always remember to understand the importance of emotion during counselling
d. HIV counselor must discuss the best option to keep the patient from infecting other people

Lesson 5.

Antiretroviral therapy of HIV infection and the WHO guidelines (2013)

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This section will review the new World Health Organization (WHO) guidelines about antiretroviral therapy (ART). We will discuss the key features and main recommendations about when to start, what to use, how to monitor and improve adherence. WHO draws up guidelines about ART since 2002. The 2013 edition is innovative because it is based on a public health approach and because it aims to expand the use of ART for HIV treatment and prevention, with a particular focus on resource limited-settings.

5.1 The new recommendations

The most important new clinical recommendations regard when to start ART.

ART should be initiated, as a priority in all individuals with severe or advanced HIV clinical disease, and in all individuals with CD4 count under 350 cells/mm3.

Moreover, the therapy should be started in people with a CD4 count between 350 and 500 cells, regardless of WHO clinical stage.

Note: the 2010 WHO guidelines recommended starting ART for all individuals with a CD4 count ≤350 cells/mm3 regardless of WHO clinical stage.

The new recommendation is based on a systematic review of 21 observational studies and three randomized controlled trials: it shows that starting ART at a CD4 count >350 cells/mm3 compared with treatment at a CD4 count ≤350 cells/mm3 reduces the risk of progression to AIDS and/or death, TB, development of a non-AIDS-defining illness and increases the likelihood of immune recovery.

5.2 When to start

We have selected situations in which ART should always be started: pregnancy and breastfeeding; active tuberculosis (TB); hepatitis B virus (HBV) co-infection with severe chronic liver disease and serodiscordant couples.

This last point is a very important recommendation: to recommend ART to serodiscordant couples, regardless of CD4 count, make ART a concrete way to reduce HIV transmission.

5.3 Pregnancy

To prevent mother-to-child transmission, all pregnant and breastfeeding women with HIV should start triple ART and maintain it at least during the delivery and breastfeeding period.

After this, the 2 following options are feasible.

According to the so-called the **"Option B+",** all women, eligible or not for treatment, should continue ART for life. This approach is advisable, because it provides the best protection for the mother's health, prevents sexual transmission and new infections in the general population and enables early protection against mother-to-child transmission in future pregnancies.

Otherwise, following the **"Option B",** women not eligible for therapy for their own health status should stop it after the period of mother-to-child transmission risk.

As you know, there is a high risk of HIV transmission during labour and delivery.

This risk can be minimized by: reinforcing antenatal clinic visits; promoting facility-based delivery by trained birth attendants; avoiding unnecessary instrumentation and premature rupture of membranes; lastly, washing away blood in the new-borns. Moreover, although elective caesarean section protects against HIV transmission, this is not recommended specifically for HIV infection in resource limited settings.

Anyway, postnatal infant care remains critical: infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily nevirapine (NVP).

5.4 Breastfeeding

HIV-infected mothers should exclusively breastfeed their infants for the first 6 months of life, introducing complementary foods thereafter, and to continue breastfeeding for the first 12 months of life.

Then, breastfeeding should stop only once a nutritionally adequate diet can be provided.

This recommendation is based on evidence that the maximum benefit of breastfeeding in preventing mortality from diarrhoea, pneumonia and malnutrition takes place in the first 12 months of life and that the risk of transmitting HIV through breastfeeding is low in presence of ART.

Suggesting this strategy, WHO guidelines aim to improve the HIV-free survival of HIV-exposed infants.

5.5 WHO guidelines on childhood

WHO guidelines also focus on childhood.

Infants and young children have a high risk of poor outcome from HIV infection.

Up to 52% of children die before the age of 2 years in the absence of any intervention.

ART should start in the following settings:

- all children below 5 years of age, regardless of WHO clinical stage or CD4 cell count
- all children with CD4 cell count under 500 cells/mm3
- all children with severe or advanced symptomatic disease.

5.6 Recommended ARV regimens

WHO expects to treat all children younger than 5 years old to facilitate a significant expansion of ART coverage for young children.

Moreover, WHO also expects to have the threshold CD4 increased to 500 cells for five years old children.

Now let's see the recommended antiretroviral regimens.

5.7 First-line ART

First-line therapy should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).

Tenofovir (TDF), lamivudine (3TC) (or emtricitabine, FTC) and efavirenz (EFV) as a fixed-dose combination is recommended as the preferred option.

Indeed, this regimen is less frequently associated with severe adverse events and has a better virological and treatment response compared with other once or twice-daily regimens

If this therapy is contraindicated or not available, one of the following treatment is recommended:

- AZT + 3TC + EFV or NVP
- TDF + 3TC (or FTC) + NVP

Countries should discontinue stavudine in first-line regimens because of its well-recognized metabolic toxicity.

A once-daily fixed-dose combination of TDF, 3TC (or FTC) and EFV is also recommended in pregnant and breastfeeding women, including in the first trimester of pregnancy and in women of childbearing age. Indeed, there is no evidence of increased risk of birth defects with EFV, compared with other antiretroviral drugs used during the first trimester of pregnancy.

What about ART for children? There are different indications based on age and weight. Compared to previous guidelines, the new recommendations harmonize treatment with adult regimens to improve children's access to ART. For infants and children younger than 3 years old, ABC or AZT + 3TC is the preferred ART backbone. Lopinavir/ritonavir (LPV/r) is the recommended third drug. If this is not feasible, NVP should be started. In fact, LPV/r was demonstrated to be superior to NVP and is known to have a better resistance profile. However, LPV/r oral liquid should be avoided in premature babies or in full-term babies younger than 14 days old.

For children 3 to less than 10 years old (or adolescents less than 35 kg), ABC + 3TC, available as a fixed-dose combination, is the best choice. AZT or TDF + 3TC (or FTC) is the second choice.

Indeed, AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but it's dosed twice daily and can cause severe anemia. TDF has recently been approved for use in children, and is once-daily dosing. However, paediatric TDF formulation is not widely available, experience in children is limited and there are concerns about the long-term effects of bone toxicity.

Concerning the third drug, for children three years old and older (including adolescents), EFV is the preferred one and NVP is the alternative one: EFV has a better short-term toxicity profile and is associated with better virological response than NVP.

For adolescents (10 to 19 years old) weighing 35 kg or more, the NRTIs backbone should align with that of adults and be, in preferential order:

- TDF + 3TC (or FTC)
- AZT + 3TC
- ABC + 3TC

Please note that TDF-containing fixed dose combinations are currently only available for adults. At or above 35 kg, the dose of TDF and of EFV in adult combination are acceptable for use in adolescents.

Reading WHO guidelines you will find simplified tables with prescribing information and weight-based dosing of available antiretroviral formulations for infants and children. Please remember that children have to be weighed at each clinic visit, and that dose changes are required as children grow and/or gain weight.

Tuberculosis is one of the most common opportunistic infection affecting children with HIV. Therefore, selecting regimens compatible with TB therapy is essential. Interactions between rifampicin and LPV/r or NVP are well known. Thus, for infants and children younger than 3 years old who develop TB treatment with ABC + 3TC + AZT is recommended. Once anti-TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

5.8 Second line ART

Using two NRTI plus a boosted protease-inhibitor (PI) is recommended for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART.

In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended based on age.

Once ART started, monitoring individuals is important to ensure successful treatment, to identify adherence problems and to determine whether and which drug should be switched in case of treatment failure. How are we supposed to do that?

- Asking people how many doses of medication they have missed since their last visit, is the most commonly method used to estimate non-adherence.
- Pharmacy refill records and pill count are complementary methods.
- Viral load is recommended as the preferred monitoring approach to diagnose ART failure, which is defined by a persistently detectable viral load exceeding 1000 copies/ml after at least 6 months of treatment. Viral load should be tested at 6 months after starting ART and then at least every 12 months.
- If it is not routinely available, CD4 count and clinical monitoring should be used, with targeted viral load testing to confirm virological failure.

5.9 Adherence and retention in care

Last but not least, let's see how to improve adherence and retention in care.

For ART, a high level of adherence is necessary to:

- suppress viral replication and improve immunological and clinical outcomes
- decrease the risk of developing drug resistance
- reduce the risk of transmitting HIV.

No single adherence intervention is effective for all populations and all settings.

A) Programme-level interventions include:

- avoiding imposing out-of-pocket payments at the point of care,
- using fixed-dose combination regimens
- and reinforcing drug supply management systems to procure and deliver ART and prevent stock-outs.

B) Individual-level interventions include:

- patient education and counselling when ART is started and throughout the course of treatment
- mobile phone text message, as a reminder tool for promoting adherence to ART
- depression treatment and management of substance disorders
- nutritional care and support
- financial support

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Questions on Lesson 5

Please select the correct answer, one out of four.

1. A person who receives diagnosis of HIV infection and TB

a. Can wait for several years before starting ART
b. Should start ART if the CD4 cell count is <350 cell/mmc
c. Should start ART if the CD4 cell count is <500 cell/mmc
d. Should start ART immediately

2. A 3 years-old HIV-infected child

a. Should start ART regardless of the CD4 cell count
b. Should start ART if the CD4 cell count is <500 cell/mmc
c. Should start ART only in case of advanced disease
d. Is too young for starting ART

3. According to "B+ option" HIV-infected pregnant women

a. Should start ART and interrupt it after delivery
b. Should start ART and interrupt it after the end of breastfeeding
c. Should start ART and continue it for life
d. Should start ART if the CD4 cell count is <500 cell/mmc

4. Elective caesarean delivery for HIV-infected pregnant women

a. Is not specifically recommended for HIV infection
b. Is always recommended
c. Is recommended if there is an obstetric indication
d. A+C

5. Should women on ART breastfeed their infants?

a. No, because the risk of transmitting HIV is higher than the possibility of preventing infant mortality
b. Yes, for the first 12 months of life
c. Yes, even for more than the first 12 months of life
d. Usually HIV-infected women are not able to breastfeed

6. What is the first-line ART recommended for adults?

a. TDF + FTC + EFV
b. AZT + FTC + EFV
c. TDF + FTC + NVP
d. ABC + 3TC + EFV

7. Is EFV recommended in pregnancy?

a. No, it is not recommended
b. Yes, it is recommended
c. Yes, but only if the patient is intolerant to NVP
d. Yes, but only if the patient was already taking it when she found out to be pregnant

8. What is the recommended third drug in children younger than 3 years old?

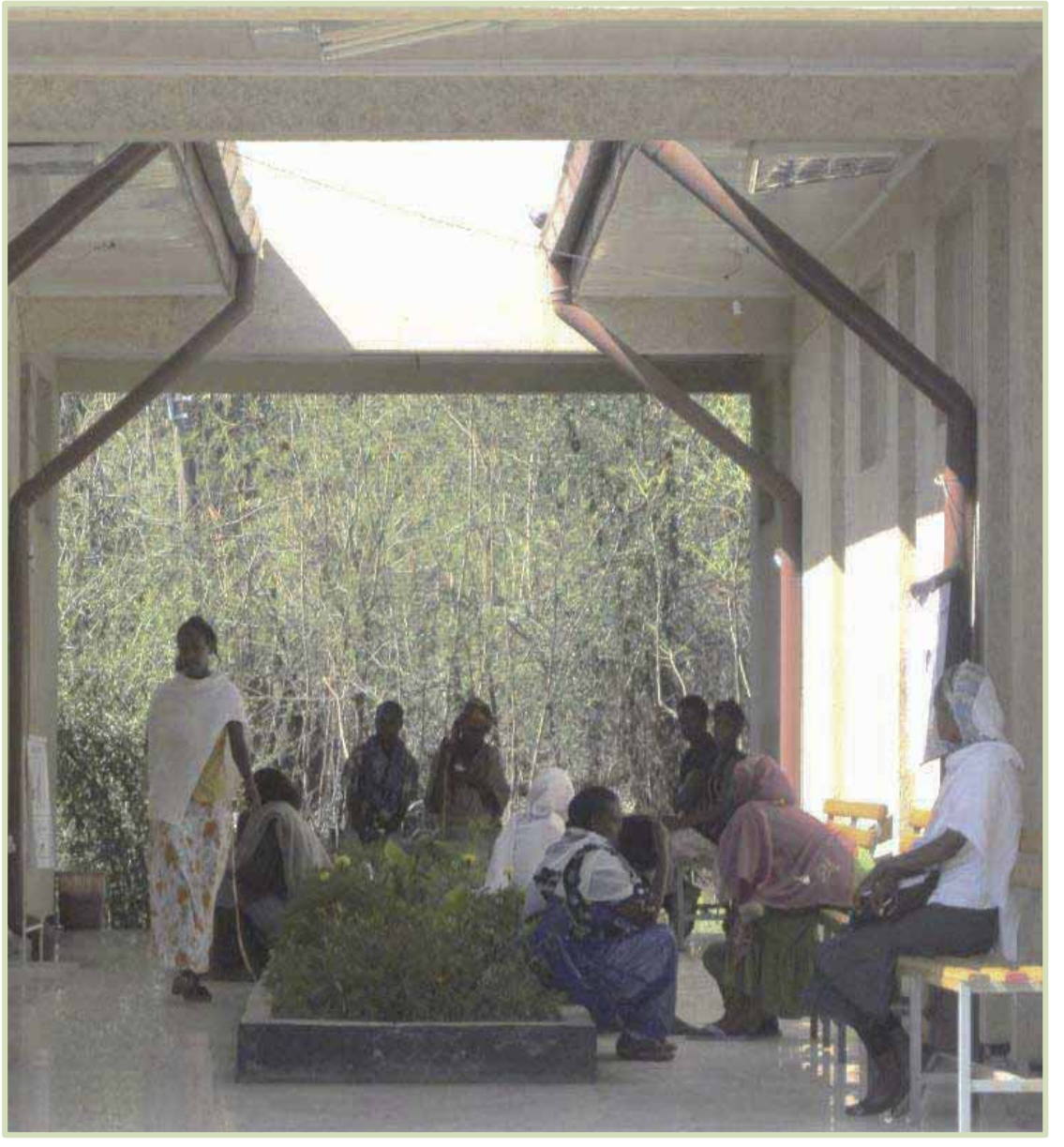
a. NVP
b. EFV
c. C – Children younger than 3 years should take only 2 drugs
d. LPV/r

9. Rifampicin has drug interactions with...

a. LPV/r
b. NVP
c. A+B
d. EFV

10. Which of the following options is the preferred monitoring approach to diagnose ART failure?

a. Testing viral load 6 months after starting ART and then at least every 12 months
b. Testing CD4 cell count every 6 months
c. Symptom-directed laboratory monitoring
d. There is nothing we can do to diagnose ART failure



Lesson 6.

Clinical management of antiretroviral drugs side effects

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We discussed before the WHO guidelines about antiretroviral therapy (ART). In this section, we will review the clinical management of antiretroviral (ARV) drugs side effects.

The goals of ART include achieving and maintaining viral suppression and improving immune function, with a regimen that is not only effective but also as tolerable and safe as possible. This requires consideration of the potential toxicity of an ARV regimen, as well as of the individual underlying conditions, concomitant medications and prior history of drug intolerance. ARV drugs toxicity is one of the main concerns in HIV infection care, because it represents a common source of lower treatment adherence and treatment suspension. Moreover, it can harm patients' health status.

Thus, to know ARV drugs related side effects is essential in order to prevent them, to early recognize them, to treat them and to change drug, if indicated.

Before starting, let's focus on some basic definitions:

- a **severe effect** is an event that can put a **person's** life at risk and that represents a medical emergency.
- a **frequent effect** is an event expected in at least 10% of treated HIV-positive persons [1].

Now let's see the most common and well-known types of ARV drugs toxicities.

6.1 Cardiovascular disease

Cardiovascular disease can be the consequence of drug-induced dyslipidemia and low glucose tolerance. Most protease inhibitors (PIs), efavirenz (EFV), stavudine (d4T) and zidovudine (AZT) increase total cholesterol and triglyceride levels. Myocardial infarction (MI) is primarily driven by PI therapy. Abacavir (ABC) has also been associated with increased risk of MI in some cohort studies.

6.2 Liver disease (hepatotoxicity)

Hepatotoxicity is a common side effect, associated with most ARV drugs. It is more frequent among patients with chronic concomitant viral hepatitis, using hepatotoxic drugs or alcohol abusing. Mechanisms of hepatotoxicity include direct ARV toxicity, steatohepatitis secondary to mitochondrial toxicity, hypersensitivity and immune reconstitution in patients with chronic viral hepatitis [2].

Please pay attention: a worsening of liver function (so-called: hepatic flare) can be caused by chronic HBV infection reactivation after tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC) suspension.

6.3 Skin and mucosal diseases

The Stevens-Johnson syndrome and toxic epidermal necrolysis are acute inflammatory diseases that affect the skin and mucosal membranes. They are mainly associated with no nucleoside reverse transcriptase inhibitors (NNRTIs), as well as ABC and Darunavir (DRV). In the acute stage, these diseases predispose patients to life-threatening complications such as sepsis, respiratory dysfunction and multiorgan failure. Mucosal sites, including the ocular surface and oral membrane, commonly are involved at the onset of fever and skin eruption. Although skin usually heals without dysfunction, severe corneal opacity and dry eye often persist during the chronic stage, leading to severe visual impairment or blindness [3-4].

6.4 Lipodistrophy

Lipodistrophy is characterized by peripheral subcutaneous lipoatrophy in the face, arms, legs and buttocks, and by central fat accumulation in the neck, breast and abdomen (lipohypertrophy)[2]. The two most implicated drugs are d4T and AZT.

6.5 Mitochondrial toxicity

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) can decrease mitochondrial function, resulting in hyperlactataemia, neuropathy, myopathy, steatohepatitis, pancreatitis and lipoatrophy. Lactic acidosis is a rare severe condition, which manifests as nausea, fatigue, weight loss, abdominal pain, dyspnea and circulatory collapse [2]. This syndrome mainly occurs in the first year of therapy with didanosine (ddI), AZT and d4T.

6.6 Neurologic and psychiatric alterations

Central nervous system and psychiatric effects are typical in course of EFV. Please ask patients about these effects! Peripheral nervous system effects include sensory neuropathy of the lower extremities, often associated with d4T and ddI.

6.7 Nephrotoxicity

Renal disease has been mainly associated with TDF. More rarely, atazanavir (ATV) is associated with nephrolithiasis.

6.8 Bone alterations

And finally, we have bone disease: reduced bone mineral density with increased fracture risk is possible in course of TDF.

We can now review the most used ARV drugs to focus on their major toxicities and see how to manage them, according to WHO guidelines.

6.9 Tenofovir (TDF)

TDF has two main potential side effects: kidney and bone toxicity. However, the clinical significance and magnitude of these side effects, especially in prolonged therapy, need to be investigated further. Nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute or chronic kidney disease. The “Fanconi syndrome” is a severe event which consists in loss of solutes by the proximal tubule with electrolytes imbalance. TDF can cause

decrease in bone mineral density, increasing fractures risk. This risk is higher in people with other conditions predisposing to osteoporosis, such as inadequate intake of calcium and D vitamin and malnutrition. Currently, it is unclear how using TDF in children might influence future growth [5].

WHO guidelines provide us some clinical considerations as to the use of TDF:

- laboratory monitoring is not mandatory to initiate treatment with TDF;
- urine dipsticks may be used to detect glycosuria in individuals without diabetes using TDF;
- if the creatinine test is routinely available, use the estimated glomerular filtration rate at baseline before starting TDF;
- do not start TDF when the estimated glomerular filtration rate is <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure;
- monitor growth in children using TDF [6].

6.10 Efavirenz (EFV)

The main type of EFV toxicity involves the central nervous system: dizziness, sleep disturbances (which are frequent events) and depression. These effects can be reduced taking EFV after feeding, and typically resolve after a few weeks. Convulsions are a severe EFV-related side effect. EFV can also cause hepatitis: this should be considered in presence of underlying hepatic disease or while using hepatotoxic drugs. Despite concerns about the potential risk of teratogenicity associated with using EFV during pregnancy, a recent meta-analysis has shown no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV drugs [6]. So, as previously said, EFV is recommended as first-line therapy in pregnancy.

6.11 Abacavir (ABC)

ABC can cause a potentially fatal hypersensitivity reaction (HSR) in presence of HLA-B*5701 gene. Clinic presentation includes severe constitutional symptoms, rash, gastrointestinal and respiratory signs [2]. Permanent discontinuation of ABC is mandatory after HSR. Please note that HLA-B* 5701 has a low prevalence in sub-Saharan Africa, so this kind of test is not cost-effective in these regions [6].

6.12 Zidovudine (AZT, ZDV)

AZT is associated with a risk of hematological toxicity. Thus measuring hemoglobin is recommended before starting AZT, mainly among adults and children with low body weight, low CD4 counts and advanced HIV disease. People with HIV with severe anaemia at baseline (hemoglobin <7.0 g/dl) should avoid AZT as first-line therapy [7].

6.13 Nevirapine (NVP)

NVP has two main side effects: hepatotoxicity and severe skin reactions. Risk factors for hepatotoxicity are CD4 >250 cells/mm^3 for women and CD4 >400 cells/mm^3 for men, underlying hepatic disease; concomitant use of hepatotoxic drugs or alcohol abuse.

NVP produces a symptomatic hepatitis in 2.5-11% of patients, mainly in the first 12 weeks. Approximately 50% of these reactions are associated with fever, rash or arthralgias. Severe and fatal cases can occur.

NVP-associated skin rash usually occurs within the first 6 weeks of therapy.

Some studies have shown an increased relative risk for severe hepatic and skin reactions in pregnant women using NVP at higher CD4 cell counts, but the evidence supporting this theory is weak. The need for lead-in dosing for initial use of NVP and the absence of a fixed-dose combination are important considerations to be made. NVP should therefore be used with caution in pregnant women and women who might be pregnant [6].

Please consider the following indications while using NVP:

- monitor hepatic enzymes if feasible, especially for women who have CD4 cell counts >250 cells/mm^3 and people co-infected with hepatitis B or C virus;
- use lead-in dose during the first two weeks of therapy;
- if rash occurs during the lead-in period, do not increase dose until rash resolves;
- discontinue NVP permanently and do not restart it in children or adults who develop severe rash, rash with constitutional symptoms or rash with elevated hepatic transaminases;
- discontinue NVP permanently and do not restart it when patients develop symptomatic hepatitis or severe transaminase elevations [7];
- the use of systemic corticosteroids for the care of patients with severe skin reactions is controversial; intensive topical corticosteroid drops may be safely used to decrease the ocular surface damage during the acute phase [3].

6.14 Protease Inhibitors (PIs)

Concerning PIs, they share gastrointestinal toxicity and dyslipidemia. DRV can also cause hepatic and skin side effects, while atazanavir can cause jaundice – because of indirect hyperbilirubinaemia – and nephrolithiasis.

6.15 Stavudine (d4T)

d4T is not currently recommended in first-line regimens because of its well-recognized toxicity. Indeed, it frequently causes hepatomegaly with steatosis, lipoatrophy and peripheral neuropathy. D4T can also cause severe effects such as lactic acidosis and pancreatitis. So we have acute and chronic drug-related adverse events.

The first can occur within few days after starting therapy, and include: Central nervous System (CNS) effects, epatotoxicity, gastrointestinal effects and hypersensitivity reactions. The last can occur after months or years and include anaemia, bone disease, dyslipidemia, lypodistrophy, myocardial infarction, mytocondrial toxicity, peripheral nervous system effects and renal disease.

Please remember that ART side effects – as well as effectiveness – can be influenced by interactions with other drugs. Providers should be aware of all drugs that people with HIV are taking when ART is started and new drugs that are added in course of treatment.

6.16 How to monitor drug toxicity

In principle, the availability of laboratory monitoring is not required for starting ART. Symptom-directed laboratory monitoring for safety and toxicity can be used for people receiving ART.

At the same time, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs (such as renal function monitoring among TDF users)[6].

6.17 How to manage ARV drugs side effects

First, drug interruption is essential for any severe event. Clinicians should consider that:

- delaying interruption in course of severe events may cause patient harm;
- delaying substitutions in presence of toxicity may affect adherence, leading to drug resistance and treatment failure;
- ARV drugs have different half-lives, so when NVP needs to be discontinued, a staggered approach should be used by prolonging the use of the NRTI backbone for two to three weeks;
- in case of interruption of TDF, 3TC or FTC in patients with chronic active B hepatitis, an alternative drug for B hepatitis treatment should be started [6].

Secondly, drug regimen or single agent substitution may be required because of drug toxicity or to avoid drug interactions.

An ARV drug can be replaced with another of the same class – example given: TDF with ABC or EFV with NVP - or of a different class – such as EFV with lopinavir/ritonavir (LPV/r).

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Questions on Lesson 6

Please select the correct answer, one out of four.

1. What should I know about my patient before starting ART?

a. Underlying conditions
b. Concomitant medications
c. Prior history of drug intolerance
d. A+B+C

2. What is Stevens-Johnson syndrome?

a. A lipodystrophy syndrome
b. A kind of inflammatory disease involving skin end mucosal membranes
c. A kind of drug-induced hepatotoxicity
d. An infectious disease

3. Which of the following options are manifestations of NRTI-related mitochondrial toxicity?

a. Neuropathy
b. Steatohepatitis
c. Renal failure
d. A+B

4. Which of the following drugs have typical effects on the central nervous system?

a. EFV
b. AZT
c. LPV
d. TDF

5. Only one of these sentences is true. Which one?

a. EFV is contraindicated in pregnancy because of its teratogenic effect
b. EFV is contraindicated in pregnancy because it doesn't cross the placental barrier
c. EFV is recommended as part of first line therapy in pregnancy
d. EFV is the second choice for pregnant women after NVP

6. The most frequent hematological toxicity of AZT is

a. Neutropenia
b. Thrombocytopenia
c. AZT doesn't have hematological toxicity
d. Anemia

7. Which of the following options are risk factors for NVP-related hepatotoxicity?

a. Underlying hepatic disease
b. CD4 cell count>250 cells/mm^3 for women and CD4 >400 cells/mm^3 for men
c. Concomitant hepatotoxic drugs
d. A+B+C

8. What is the most frequent protease-inhibitor associated side effect?

a. Bone toxicity
b. Gastrointestinal symptoms
c. Renal disease
d. Anaemia

9. In case of NVP-related severe skin reaction you should...

a. Immediately stop the whole ARV regimen
b. Continue NVP and add steroid therapy
c. Continue NVP and stop other ARV drugs
d. Stop NVP immediately and stop NNRTIs after 2-3 weeks

10. Which of the following options is a chronic ARV side effect?

a. Lipodystrophy
b. Skin reactions
c. Dizziness and abnormal dreams
d. Diarrhea

Lesson 7.

Clinical management of opportunistic infections

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7.1 Why opportunistic?

Infections are called “opportunistic” (OIs) because they take advantage of the of the opportunity offered by a weakened immune system and they can cause devastating diseases [1]. Immunocompromised patients are susceptible to bacterial, fungal and viral infections that usually a healthy immune system can prevent.

Prevention and therapy of these infections in patients with HIV disease are very important.

Normally, mortality and morbidity in HIV-related infections increase when CD4+ T-lymphocytes counts falls towards 350 cells/microliter and below. CD4+ count

must be performed during the previous 4 months to determine the immediate risk of infection in a specific patient.

CD4+ count is a reliable indicator of the current risk of acquiring OIs. CDC classification has grouped HIV patients in three different categories depending on CD4 counts.

Rates of OIs depend on CD4+ count. In addition the same diseases can occur in different shapes depending on CD4 count, for example oral candidiasis is much more common when CD4 count is between 350 and 250, esophageal localization of candida are more common when CD4 count is under 250 cells/mmc.

7.2 How to recognize opportunistic infections

As we mentioned before, CD4 count is an important tool to understand the general immunological condition of a patient. However to better understand the clinical situation a careful and complete physical examination is mandatory. We will consider in the following paragraphs the most common HIV-related OIs.

7.3 Oral candidiasis

Oral candidiasis also known as "oral candidosis" or "oral thrush", and vulvovaginal candidiasis are two common conditions, usually easy to diagnose during physical examination. Oral candidiasis can be treated with topical antifungal agents (such as nystatin and clotrimazole) or systemic oral azoles (such as fluconazole). Usual treatment is based on fluconazole at the dosage of 400 mg per day. Vulvovaginal candidiasis can be treated with oral fluconazole.

Remember that HIV diseases can worsen the response to therapy, so if CD4+ count is below 50 cells/ml, a higher dose of fluconazole (up to 800 mg/die) can be necessary to achieve recovery.

7.4 Tuberculosis

Another, and more dangerous, condition that can occur in immunocompromised patients is pulmonary tuberculosis (TB).

You have to consider that TB may result in typical symptoms, however some of them are also insidious. The latter situation is common among HIV infected people. In many cases, the physical examination can be silent. Please consider that TB, despite its definition as an OI, can be observed in patients with CD4 count superior than 350 cells per milliliter. For all these reasons, a clinical suspicion, the appropriate use of laboratory tests and imaging techniques are necessary tools to diagnose TB.

TB is a condition normally linked to higher CD4 counts. In these cases the immune response is still capable of withholding the infection in the site of the inoculum (namely in the respiratory tract). When CD4 count becomes lower, the immune system cannot sustain this condition, causing the so-called extrapulmonary (or miliary) tuberculosis.

Laboratory diagnostic procedures can be very helpful. Sputum smear of the patient must be sent to your laboratory for “acid fast bacilli smear and culture”. Remember to obtain this specimen according to your local safety rules. Chest radiograph should be performed to detect possible associated pulmonary findings. A computed tomography scan (CT scan) of the chest may help to better define abnormalities in patients with vague findings on chest x-ray.

A positive acid fast bacilli smear plus a radiographic finding indicative of TB show a clear indication to begin TB treatment. Further details about TB diagnosis, treatment and prevention are discussed in the lecture “A close look at TB”.

7.5 Kaposi sarcoma

Kaposi sarcoma appears as a tumor on the skin or on mucosal surface. It is caused by HHV-8, a virus that can induce the proliferation of spindle cells. Its presentation can be different, depending on the localization of the lesion (skin, mucosal surface of the gastrointestinal or pulmonary tract).

Usually Kaposi sarcoma heals spontaneously after starting antiretroviral therapy (ART).

7.6 Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia (PJP) is a fungal infection. It is one of the most common OI in HIV infected people. PJP can be fatal if it is not treated. Fortunately, it is preventable and curable with antibiotic therapy and close monitoring. Its signs and symptoms are very similar to a form of severe pneumonia.

A patient with PJP is usually highly dyspneic and has fever, dry cough and chest pain. It is important to control vital parameters and to carefully assess the clinical status of the patient with a complete physical examination. In case of PJP the chest radiograph may be normal (usually in case of early mild disease) or may show diffuse bilateral infiltrates in the perihilar region. Less commonly you can find patchy asymmetric infiltrates.

Currently the treatment of choice is Trimethoprim-sulfamethoxazole, with second-line agents including pentamidine, dapsone (with pyrimethamine) or atovaquone. Recommended duration of treatment is 21 days.

Corticosteroids are used as adjunctive initial therapy in HIV-infected patients who have severe PJP [2].

PJP preventive therapy is an integral part of HIV-infected people care. Chemoprophylaxis for PJP is recommended in patients with a CD4 count less than 100 and a suppressed viral load [3].

The most common drug used for prophylaxis is trimethoprim-sulfamethoxazole at the dosage (for adults) of one double-strength tablet three times per week.

Please note that trimethoprim- sulfamethoxazole is indicated in infants, adolescents and pregnant women, and that it is available also in syrup formulations.

7.7 Toxoplasmosis

If CD4 cells count fall under 100 other OIs may appear. One of them is toxoplasmosis, a parasite infection caused by a pathogen named *Toxoplasma gondii*, which typically involves the eyes and the central nervous system. The ocular disease is characterized by loss of vision, eye pain, sensitivity to light and tearing of the eyes. Another common clinical presentation is the appearance of hemiparesis and seizures. These symptoms, often accompanied by intense headache and confusion, are the usual symptoms of a cerebral toxoplasmosis.

This dangerous condition can be treated with pyrimethamine 200 mg orally in the first day, followed by 50 mg daily plus folinic acid at the dosage of 10 mg daily and sulfadiazine 6 g/daily for as long as 6 weeks. Until a CD4 count higher

than 100 cells per milliliter is achieved, a suppressive therapy must be maintained.

Therapy with trimethoprim/sulfametoxazole is a second line option.

To diagnose a toxoplasmosis can be really hard. Normally, in HIV patients the research for anti-Toxoplasma antibodies is positive. If a patient has a clinical condition suggestive of toxoplasmosis but his/her serology is negative, the possibility of a toxoplasmosis is inconsistent.

Please note that trimethoprim-sulfamethoxazole based prophylaxis is also effective against *Toxoplasma gondii*.

7.8 Cytomegalovirus infection

Cytomegalovirus (CMV) usually causes an asymptomatic infection or a flulike syndrome as a first presentation. Afterwards the virus establishes a latent infection. CMV can be reactivated during HIV-related immunodeficiency.

CMV could cause retinitis, with significant visual impairment. This condition is more frequent when CD4+ lymphocytes are less than 50 cells per cubic millimeter. Diagnosis of CMV retinitis is usually made clinically.

Intravenous ganciclovir and foscarnet are equally active against cytomegalovirus. Unfortunately and despite adequate therapy, the outcome can be unsatisfactorily and even blindness can occur in many cases.

Other common complications of CMV infection in the immunocompromised patient are esophagitis (the patient will tell you about a severe dysphagia and painful deglutition), colitis (characterized by bloody or watery diarrhea, fever, malaise, weight loss, dehydration and abdominal pain) and encephalitis.

Prevention of recurrence of CMV-related diseases can be made with oral valganciclovir.

7.9 Mycobacterium avium complex disease

Mycobacterium avium complex disease often manifests as a systemic process characterized by fever, weight loss, elevated serum alkaline phosphatase levels and anemia [4]. Normally the diagnosis is confirmed by the microbiologist by retrieving the pathogen on blood culture, respiratory secretion, stool or urine.

Treatment is based on clinical suspicion and positive results from the microbiology lab. Standard regimen is based on an association of antibiotics for at least 12 months. Moreover, a post-treatment suppression regimen is recommended until the patient has a CD4 count greater than 100 cells for cubic milliliter for at least 6 consecutive months [5].

7.10 Cryptococcal infection

Cryptococcus neoformans can cause OIs, especially when the CD4 count is inferior than 100 cells per milliliter.

Clinical manifestations of cryptococcosis commonly involve the central nervous system, the respiratory system and, occasionally, the skin. Cryptococcal pneumonia typically has a sub-clinic presentation.

Meningitis caused by Cryptococcus is frequent in HIV infected people and has peculiar characteristics. Indeed, patients with cryptococcal meningitis could initially show only fever and headache. In few days the neurological status may get worse, and the patient may develop mental confusion and occasionally blindness. In the course of cryptococcal meningitis, lumbar puncture shows

markedly elevated opening pressure, mononuclear pleocytosis, elevated protein and decreased glucose concentration. Detection of *Cryptococcus* is possible searching for the Cryptococcal antigen in the cerebrospinal fluid.

Treatment should begin with amphotericin B (0,7 mg/kg) with flucitosine (100 mg/kg divided in four doses per day).

After two weeks this therapy can be deescalated with fluconazole 400 mg once or twice daily. Lifelong maintenance with fluconazole 200 mg per day have showed benefit and this regimen of secondary prophylaxis should be maintained until CD4 counts is greater than 100 cells per milliliter and HIV-RNA is persistently negative for at least 3 months [6-7].

7.11 Cryptosporidiosis

Cryptosporidiosis is an infection caused by oocyst of *Cryptosporidium*. It represents one of the most important causes of prolonged diarrhea in HIV patients. The transmission takes place via person to person and waterborne diffusion. If a patient has CD4 count greater than one hundred and fifty the disease has a self-limited course.

If the patient has a count inferior than 150 cells per milliliter or other risk factors the illness becomes chronic, with associated weight loss, foul smelling and bulky stools. Patients may also present with acalcolous cholecystitis, pancreatitis or cholangitis.

Common alterations consistent with Cryptosporidiosis are: elevated levels of transaminase, bilirubin, alkaline phosphatase, and also dilatation of the biliary duct and gallbladder inflammation. The diagnosis can be made via detection of Cryptosporidium in stools using antigen detection, nucleic acid amplification and microscopy.

Therapy and prevention: unfortunately, no curative treatment exists in immunocompromised host. The only effective therapy is reversing the immunodeficiency using antiretroviral treatment.

Nitazoxanide can be used at the dosage of 500 mg orally, twice daily until ART therapy is capable of reestablishing an adequate immune response.

Water treatment with boiling and hand hygiene are key measures to prevent this infection.

If the patient's clinical conditions are unstable or the equipment is not adequate to make a diagnosis, the patient should be sent to a more specialized center.

7.12 Final considerations

Some OIs are mild diseases, which don't necessarily need a specific treatment in addition to ART; others are severe and potentially fatal diseases, which require targeted therapies and hospitalization as well. Remember that correct anamnesis and physical examination are essential in order to diagnose and treat these diseases.

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Questions on Lesson 7

Please select the correct answer, one out of four.

1. **What is the first thing to assess in an HIV positive person who complains for a new symptom?**
   a. CD4 count
   b. Adherence to ART
   c. Clinical status
   d. Laboratory data

2. **What is the most common manifestation of Toxoplasma gondii when CD4 count is inferior than 100 cells/mmc?**
   a. Cerebral toxoplasmosis
   b. Pulmonary toxoplasmosis
   c. Urinary toxoplasmosis
   d. Chorioretinitis

3. **What is the most compelling indication to request the aid of a tertiary health care center?**
   a. CD4 count inferior than 20 cells/mmc
   b. New diagnosis
   c. Respiratory failure
   d. Blindness

4. **Is it possible to diagnose an OI with CD4 count above 500 cells/mmc?**
   a. No
   b. Yes, but only for TB
   c. Yes, if there are other risk factors associated
   d. Only for PJP

5. **What is the most common cause of respiratory failure with CD4 count inferior than 50?**
   a. TB
   b. PJP
   c. Cryptococcosis
   d. CMV

6. **How long is the period of secondary prophylaxis for an infection by Toxoplasma gondii?**
   a. Six months
   b. Twelve months
   c. Until CD4 count is > 200 cells/mmc
   d. Until CD4 count is > 100 cells/mmc

7. **What is the treatment of choice for oral candidiasis in an HIV patient?**
   a. It depends on CD4 count
   b. 400 mg of fluconazole daily
   c. No treatment is required
   d. 200 mg of fluconazole daily

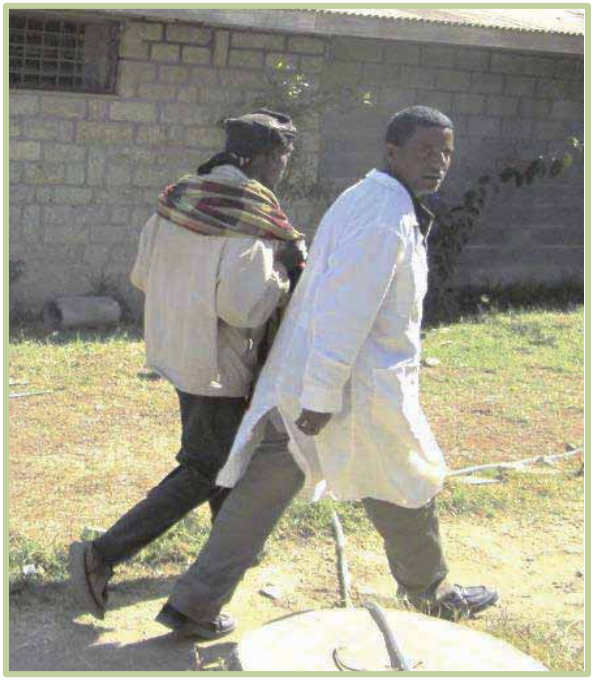
8. **What is a possible cause of raising of Alkaline phosphatase in an HIV patient who is suffering of severe weight loss?**
   a. Toxoplasmosis
   b. Cryptococcosis
   c. Cryptosporidiosi
   d. Kaposi sarcoma

9. Kaposi sarcoma is caused by:

a. Proliferation of splindle cells
b. Proliferation of granular cells
c. HIV proliferation
d. Stem cells proliferation

10. What is the most common radiologic finding during a severe form of PJP?

a. Normal chest
b. Diffuse bilateral infiltrates on perihilar region
c. Asymmetric infiltrates
d. Symmetric patchy infiltrates on the lower region.



Lesson 8.

Viral hepatitis

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8.1 What is hepatitis?

As you may know, hepatitis is an inflammation of the liver, that can be related to viral infection, alcohol abuse, drug toxicity and other diseases affecting specifically the liver or the entire organism (i.e. autoimmune diseases).

Among viral causes of hepatitis, five hepatitis viruses are the most frequently involved:

- hepatitis A virus (HAV)
- hepatitis B virus (HBV)
- hepatitis C virus (HCV)
- hepatitis D virus (HDV)
- hepatitis E virus (HEV)

[2] In the picture

8.2 Acute hepatitis

Viral hepatitis can show as acute infection or chronic infection. Acute hepatitis can be caused by all the aforementioned hepatitis viruses. There are no clinical features that allow to identify the virus responsible for the acute clinical presentation.

Moreover, acute hepatitis may occur with limited or no symptoms, or may show debilitating symptoms like malaise and weakness, anorexia, nausea, vomiting for some days; then patients could present with jaundice (which means yellow discolouration of the skin and sclera of the eyes, dark urine and pale stools). Other symptoms like fever or right upper quadrant abdominal pain are less frequent.

Adults usually present signs and symptoms of illness more often than children; the severity of disease and mortality increase in older age groups. Acute hepatitis is more likely to be asymptomatic if it is caused by HCV infection [1].

As clinical symptoms are not specific, diagnosis is based on patient interview and blood testing. In rare cases, acute hepatitis can result in fulminant hepatitis (which means acute liver failure) which is associated with high mortality.

8.3 Diagnosis and treatment of acute viral hepatitis

As mentioned before, clinical findings are not specific for acute viral hepatitis. Therefore diagnosis is based on patient interview and blood testing. The concomitant presence of risk factors and clinical symptoms lead to suspicion of acute viral hepatitis. It is important to exclude alcohol abuse and to investigate drug intake.

A liver enzyme elevation (i.e. alanine aminotransferase – ALT, and aspartate aminotransferase -AST) is usually present, but, similarly to clinical symptoms, this does not allow to distinguish among different acute viral hepatitis.

Specific diagnosis is made by the detection of specific antibodies for every hepatitis virus in the blood. Moreover, no specific therapy for acute viral hepatitis is available and treatment is only aimed to replacement of fluids lost with vomiting and diarrhoea and to avoid intake of greasy food until recovery.Following infection may be slow and may take several weeks or months, especially in the case of HAV.

8.4 Chronic hepatitis

HBV, HCV, and HDV infection can also cause chronic infection of the liver. Hepatitis B antigen S (HBsAg) and HCV viral load detectability in the blood for more than 6 months are diagnostic for chronic HBV and HCV, respectively. HDV is a defective virus that can give infection only in presence of HBV.

The persistence of viral infection causes progressive injury of the liver and remains usually asymptomatic until the development of cirrhosis, which is an increased stiffness of the liver that usually develops after several years from the infection.

8.5 Complications of chronic hepatitis

The principal consequence of cirrhosis is portal hypertension, an elevation of hepatic venous pressure. Clinical symptoms can appear in this phase, consistently with the development of complications of portal hypertension, consisting in ascites (free fluid in the abdomen) and hepatic encephalopathy [1].

Typically patients with ascites have an increase in body weight, abdominal distension and a decreased urine output. Initially diuretic therapy may be helpful, but ascites usually reappears after a short time.Hepatic encephalopathy is characterized by confusion and flapping tremors (a tremor of the hand when the wrist is extended).

Another possible complication of chronic hepatitis and cirrhosis is liver cancer (hepatocarcinoma), which could show with liver failure and anorexia.

8.6 Who is at risk for HAV and HEV infections?

HAV and HEV are typically transmitted through ingestion of contaminated food and water or through oral contact with fecal matter (oral–fecal route). Most HAV and HEV infections occur during early childhood.

Anyone who has not previously been vaccinated or infected can contract HAV. Risk factors include [2]:

- *lack of hand washing before preparing food*
- *lack of safe water*
- *injecting drugs*
- *living in a household with an infected person*
- *being a sexual partner of someone with acute HAV infection*
- *travelling to areas of high endemicity without being immunized.*

HEV is characterized by a food borne transmission from ingestion of products derived from infected animals; HEV can also be transmitted from a pregnant woman to her fetus and by transfusion of infected blood products. *Pregnant women are at risk of obstetrical complications from HEV, which can induce a mortality rate of 20% in the third trimester [3].*

8.7 Who is at risk for HBV, HCV and HDV infections?

The routes of transmission are the same as those of HIV infection and include: receipt of contaminated blood products; sharing syringes; transmission from mother to child; sexual contacts.HBV transmission from family member to child for sharing of toothbrush, combs, is common.

8.8 HBV: prevalence and clinical implications

Now let's look at the HBV distribution. Ethiopia is a country at high endemicity for HBV, which affect more than 8% of Ethiopian people [4]. *In this setting, HBV is most commonly spread from mother to child at birth, or from person to person in early childhood* [5].

More than 90% of healthy adults who are infected with the HBV will recover within 6 months. Less than 5% of patients infected in the adulthood will develop chronic infection [5]. By contrast, 80–90% of infants infected during the first year of life will develop chronic HBV infection [5]. HIV-infected patients are at increased risk of chronic disease and progression to cirrhosis and hepatocarcinoma. For this reason people with both HIV and chronic HBV infection can benefit of early HIV treatment [6].

8.9 Diagnosis of HBV infection is based on HBV serology

HBV serologic testing involves measurement of several hepatitis B virus specific antigens and antibodies. The most important marker is HBsAg which is present both in acute and chronic HBV infection. Chronic infection is characterized by the persistence (>6 months) of HBsAg.

Resolved HBV infection is evidenced by the disappearance of HBsAg [5]. By using different serological markers or combinations of markers, it is also possible to determine if a patient has acute or chronic HBV infection, and if the patient is immune to HBV as a result of prior infection or vaccination, or is susceptible to HBV infection [7].

8.10 Treatment of chronic HBV infection

Some anti-HBV drugs can slow the progression of liver disease to cirrhosis, reducing incidence of Hepatocellular carcinoma (HCC) and improving long term survival [7]. Treatment, however, is not readily accessible in many resource-limited settings.

These drugs include tenofovir, emtricitabine and lamivudine, that are also active against HIV. So, tenofovir plus emtricitabine or tenofovir plus lamivudine should be used as part of the first line regimen in this kind of patients [6]. Withdrawal of these drugs in patients with HIV/HBV co-infection would result in hepatitis flares (increase of liver enzymes) and liver disease progression.

8.11 HCV: who is at risk for chronic disease?

On the one hand, about 55–85% of persons with acute HCV infection will develop chronic HCV related hepatitis; on the other hand, 15–45% of infected persons will spontaneously clear the virus within 6 months of infection without any treatment [8].

In patients with chronic HCV infection, *the risk of cirrhosis of the liver is 15–30% within 20 years [8]*. HIV-infected patients are at increased risk of developing chronic HCV infection and of progression to cirrhosis.

8.12 HCV: diagnosis and treatment

HCV antibodies (HCV-Ab) are positive in all people that have been infected with the virus and persist even after the infection resolution. Persistence of HCV viral replication for more than 6 months is the only diagnostic criteria for chronic infection, but it is difficult to do in low-resource settings.

The current standard treatment for HCV is a combination of interferon and ribavirin for 24-72 weeks. Unfortunately this is not widely available. New antiviral drugs for HCV, which are much more effective, safer and better tolerated than interferon, are in development.

8.13 HDV: who is at risk and how to manage it?

HDV can only infect the organism in the presence of HBV active infection. Consequently, only patients with positive serum HBsAg are at risk for HDV. Thus, preventing measures against HBV infection like HBV vaccination are also effective in HDV prevention. The only drug active against HDV is interferon.

8.14 Prevention of viral hepatitis

Improved sanitation, food safety and regular hand-washing can reduce the risk of both HAV and HEV transmission [2]. Several HAV vaccines, which are similar in terms of efficacy and safety, are available internationally [2] .

WHO recommends all blood donations to be tested for HBsAg, which indicates active HBV infection, in order to avoid HBV transmission to recipients [5].

The HBV vaccine is available and represents the basis for HBV prevention. *The complete hepatitis B vaccine series induces protective antibody levels in more than 95% of infants, children and young adults [5]* .

Household contacts and sexual partners of people with HBV are at high risk of infection and should benefit of HBV vaccination[5]. This is also effective in preventing HDV infection. Finally, no vaccine is available for HCV and HEV.

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Questions on Lesson 8

1. **Which of the following virus can cause chronic hepatitis?**
   a. Hepatitis A virus
   b. Hepatitis B virus
   c. Hepatitis B, C and D viruses
   d. Hepatitis A and B viruses

2. **How can you diagnose a chronic hepatitis B?**
   a. Persistence of HBsAg for more than 6 months
   b. Persistence of HBcAb for more than 6 months
   c. Persistence of liver enzymes elevation
   d. Persistence of HCV-Antibody positivity

3. **What are risk factors for hepatitis A infection?**
   a. Having an hepatitis B virus infection
   b. Poor sanitation and lack of safe water
   c. Transfusion of infected blood products
   d. Ingestion of safe food and water

4. **Which of the following sentences is true?**
   a. Hepatitis A and E are usually mild to severe illnesses
   b. Cases of chronic hepatitis A infection have been reported in immunocompromised people
   c. No hepatitis A vaccines are currently available
   d. Fulminant hepatitis E occurs less frequently during pregnancy

5. Who is at risk for hepatitis B infection?

a. Patients who received transfusion of infected blood products
b. Patients who undergo invasive medical procedures using contaminated equipment
c. Children born from an hepatitis B infected woman
d. a + b + c

6. What is the incubation period of the hepatitis B virus?

a. 30 days
b. 2 weeks
c. 3 days
d. 30 to 180 days

7. Which of the following sentences is true?

a. More than 90% of healthy adults who are infected with the hepatitis B virus will develop chronic infection
b. Less than 5% of patients infected in the adulthood will develop chronic infection
c. 80–90% of infants infected during the first year of life develop chronic HBV
d. b + c

8. Which of the following drugs are active both against HBV and HIV infections?

a. Tenofovir, lamivudine and emtricitabine
b. Lopinavir
c. Abacavir
d. Stavudine

9. Which of the following sentences is false?

a. About 85% of persons with acute HCV will clear the infection within 6 months of infection without any treatment
b. Of people with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years
c. HIV-infected patients are at increased risk of developing chronic HCV infection and of progression to cirrhosis
d. After spontaneous clearance of acute hepatitis C infection, results of anti-HCV antibodies test will be negative

10. Hepatitis C: prevention. Which of the following sentence is true?

a. There is no vaccine for hepatitis C
b. Prevention of HCV infection depends upon reducing the risk of exposure
c. Avoid ingestion of usafe food and water is necessary to prevent hepatitis C infection
d. a + b

Lesson 9.

Comorbidities in HIV patients

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Comorbidities represent a very important topic to be addressed because a patient with HIV infection could show other concomitant problems that could affect the action of some antiretroviral treatment. Moreover comorbidities should be considered differently from HIV related diseases.

9.1 Cardiovascular diseases

Cardiovascular diseases refer to a group of diseases that affect the heart or blood vessels. Cardiovascular-related events are the main cause of death worldwide and have become one of the primary causes of mortality in HIV infected people as well.

Let's start by evaluating traditional risk factors. These include older age, gender (particularly male), smoking, sedentary work, lack of exercise, high blood pressure and high cholesterol [1]. You can evaluate these factors while you collect the patient's history.

Remember that there may be interactions between antiretrovirals and blood pressure. For this reason it is necessary to ask the patient which drugs he takes.

Moreover, antiretroviral drugs can increase cardiovascular risk. For example, treatment with boosted protease inhibitors can alter metabolism, leading to increased cholesterol and triglycerides and consequently increased cardiovascular risk. Therefore, if your patient has a history of metabolic disorders, these drugs should be avoided. Finally, HIV itself is thought to contribute to a greater risk for cardiovascular diseases because it causes a chronic inflammatory state [1].

9.2 Bone diseases

Osteoporosis is characterized by a low bone mineral density, which can lead to an increased risk of bone fractures.

The traditional risk factors for osteoporosis are: being a postmenopausal women, malnutrition and smoking [1]. However, having a long history of untreated HIV infection and being on antiretroviral treatment, for example with tenofovir and/or protease inhibitors, are additional risk factors for osteoporosis. That's why you should be careful if you have to use these drugs in patients at risk.

9.3 Psychiatric disorders

A high proportion of HIV infected patients have psychiatric disorders. The most frequent are anxiety and depression. Anxiety and depression are often associated to neurocognitive disorders, such as a low capacity of concentration, reduced memory and irascibility.

A good relationship with your patient can help him/her to trust in the medical staff, this can reduce stigma, improve awareness and acceptance of the HIV infection and help control anxiety and depression.

Remember that both HIV infection and opportunistic infections can lead to neurological disorders. Moreover, antiretroviral therapy (ART) can be also one of the causative agents of these disorders. For example, efavirenz can lead to hallucination if assumed in the morning, or nightmares if taken in the evening. That's why efavirenz should be avoided in these cases or when psychiatric disorders are already present.

9.4 Anemia

The criteria for determining the presence of anemia, as recommended by the World Health Organization (WHO), are based on hemoglobin cut-off values adjusted for age and sex with an additional epidemiological criterion for assessing the severity and magnitude of the problem in the target populations [2]. From surveys we know that about the 20% of people living in Ethiopia suffer of anemia [3]. The main causes of anemia are:

- Diet. The lack of dietary diversity results in a deficiency of minerals and vitamins. Furthermore, it reduces the iron intake.
- Parasites, in particular hookworm.
- Other illness, like HIV infection itself [4].

Some antiretrovirals can cause anemia as well. For example zidovudine is associated with haematological toxicity. This haematological toxicity is observed in most of the patients within 3-6 months and is reversible if patient stops zidovudine intake [5]. We should continue to use zidovudine in the first-line combination therapy in HIV/AIDS patients with haemoglobin levels >8g/dl but we should also perform a continuous surveillance for development of haematological disorders [5]. In particular, it is necessary to ask your patients who take zidovudine if they have experienced any signs of fatigue, difficult concentration and asthenia [6].

9.5 Kidney

The main job of the kidneys is to remove wastes and water from the body. Acute and chronic kidney diseases are the rapid or the slow loss of kidneys function over time. The most common kidney diseases in HIV patients are: HIV associated nephropathy and nephrotoxicity due to antiretroviral drugs. The HIV associated nephropathy is a damage to your kidneys caused by the HIV itself. It is extremely uncommon in individuals with HIV who have a suppressed viral load [7]. Therefore, if a patient has HIV-associated nephropathy, it is very important to start ART at the earliest signs of kidney problems. The most common symptoms are: changes in urination (for example you may ask the patient if he/her urines more often or less often and if urine contains blood), swelling especially at the extremities, and fatigue. In advanced diseases you can also find ammonia breath, nausea and vomiting as they are associated to high level of uremia. Some antiretrovirals like protease inhibitors and nucleoside reverse transcriptase inhibitors are themselves possible risk factors for renal damage. Tenofovir for example is known to cause kidneys problems. If a patient is taking Tenofovir, health care provider should regularly monitor creatinine levels [7].

Finally, you should be aware that the majority of antiretrovirals are excreted by kidneys, so it is important to regularly check creatinine levels in all patients. In fact, an impaired renal function results in an increased permanence of drugs in the body with an increased risk of toxicity.

9.6 Diabetes

Diabetes is a disease in which levels of blood glucose (also called blood sugar) are too high [8]. Diabetes is rapidly becoming an important public health problem all over the world. From studies, in Ethiopia, the number of deaths attributed to diabetes reached over 21,000 in 2007 [9].

Symptoms of diabetes include unusual thirst, frequent urination, extreme hunger, unusual weight loss or weight gain, extreme fatigue and irritability, frequent infections, blurred vision, tingling or numbness in the hands and feet, slow healing of cuts or bruises [8]. There are two types of diabetes. Type one it is also called “insulin-dependent diabetes”.

The onset of type 1 is usually acute and usually occurs before a person reaches the age of 30. Type two, also called "adult onset diabetes", is related to high weight, sedentary life and, more importantly, to certain medications [10]. Some HIV drugs, like nucleoside reverse transcriptase inhibitor (for example zidovudine) and protease inhibitors can increase the risk of diabetes.

These HIV medicines seem to make it harder for the body to respond to insulin, causing the so called insulin resistance. Insulin resistance leads to high blood glucose levels, which can result in type 2 diabetes. So remember to check blood sugar in those patients who are at risk for diabetes and that take these medications as part of their ART.

9.7 High blood pressure

Hypertension is an independent and reversible risk factor for cardiovascular, cerebrovascular and renal diseases that is underdiagnosed and undertreated. According to guidelines high blood pressure for adults is defined as: one hundred forty millimeters of mercury, or greater, for systolic pressure and ninety millimeters of mercury, or greater, for diastolic pressure [11-12]. Some HIV drugs, particularly protease inhibitors, can increase blood fats, so they may cause problems that are similar to those caused by a high fat diet. Because of this, people taking HIV treatment may be at increased risk of high blood pressure, particularly if they have other risk factors such as a family history of the condition, a fatty diet, heavy drinking, smoking or lack of exercise.

Moreover, HIV drugs can interact with other medications used to treat blood pressure, and this fact can be harmful. It has to be clear that there is an interaction among these drugs in order to modify properly your patient's therapy.

9.8 Recurrent urinary tract infection

The urinary tract infection is an infection of the urethra and urinary bladder. It is very common in HIV persons because of a weakened immune system caused by the HIV itself, in particular it is related to unprotected sex and promiscuous relationships. It is important, to ask your patient if he/her has experienced any symptoms of urinary infection such as: dysuria, frequent but scanty urination, urgency in urination, pain in the lower abdomen or low back pain, fever, presence of macroscopic blood in urine. It is also important to remember how these kind of infections most often require hospitalization in HIV patients or at least an antibiotic treatment and strict follow up.

9.9 Final considerations

When you take care of HIV patients it is very important to consider comorbidities along with the HIV virus itself, because these can significantly affect the health and life of the patient. In conclusion, the above considerations are important because comorbidities:

- may affect the response to antiretroviral treatment
- should be considered differently from HIV related diseases
- can determine ART choice
- need to be treated.

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Questions on Lesson 9

Please select the correct answer, one out of four.

1. **Which are the risk factors for cardiovascular diseases in HIV patients?**
   a. A combination of traditional risk factors (such as age, smoking, high blood pressure) and some antiretroviral drugs
   b. Only ART can be considered a risk factor
   c. HIV patients don't have risk factors for cardiovascular diseases
   d. Only high blood pressure

2. **Why can protease inhibitors cause cardiovascular problems?**
   a. They don't cause any cardiovascular problems
   b. They alter metabolism, leading to increased cholesterol and triglycerides so they can increase cardiovascular risk
   c. They interact with other medications and predispose to cardiovascular diseases only in patients with other comorbidities
   d. None of the previous answers

3. **Which are the risk factors for osteoporosis in HIV patient?**
   a. Mainly, some antiretrovirals (i.e. tenofovir), postmenopausal women and smoking
   b. Only ART
   c. Only traditional risk factors because antiretroviral therapy doesn't influence the pathogenesis of osteoporosis
   d. HIV patients don't suffer from osteoporosis

4. **Which is the antiretroviral treatment related to hematological toxicity?**
   a. Zidovudine
   b. Tenofovir
   c. Stavudine
   d. Efavirenz

5. Is the prevalence of psychiatric disorders important in HIV people?

a. No, it is not
b. Yes, there is a high incidence in this population
c. No, there are only neurocognitive impairment due to HIV itself
d. There are no specific information about this topic

6. Which are the main symptoms of kidneys' diseases?

a. There are no specific symptoms to be noted
b. Nausea, nucal rigidity and confusion
c. Changes in urination, swelling especially at the extremities, fatigue, ammonia breath, nausea or vomiting
d. Only fever and low abdominal pain

7. Why can some antiretroviral drugs cause diabetes?

a. Because they make it harder for the body to respond to insulin, causing insulin resistance
b. There aren't any antiretroviral drugs that cause diabetes
c. There isn't a specific mechanism because they cause diabetes only in predisposed patients.
d. None of the previous answers

8. According to guidelines, what is the definition of high blood pressure?

a. 180 mmHg or greater for systolic pressure and 100 mmHg or greater for diastolic pressure
b. 140 mmHg or greater for systolic pressure and 90 mmHg or greater for diastolic pressure
c. There isn't a global definition of high blood pressure because it depends on other comorbidities and presence of other risk factors
d. All the previous answers

9. What are the symptoms you should consider to diagnose a urinary tract infection?

a. Unprotected sex
b. Promiscuous relationships
c. Weakened immune system caused by the HIV itself
d. All the previous answers

10. Why should you consider comorbidities in HIV patients?

a. They affect HIV patient's outcome
b. They determine ART choice
c. They affect HIV patient's outcome ,they determine ART choice, they should be put in differential diagnosis with HIV related diseases
d. They determine virological failure

Lesson 10.

A closer look at tuberculosis

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10.1 What is tuberculosis?

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium Tuberculosis* (MT). It can cause two types of illness: an **inactive** form (latent TB infection, LTBI) and an **active** form (TB disease).

TB usually affects the lungs (pulmonary TB), but it can also affect other body parts (extrapulmonary TB), such as the brain, the spine or the kidneys.

Among systemic TB symptoms we find fever, night sweats, weight loss and feeling of weakness. Typical pulmonary TB symptoms are coughing for more than 3 weeks, coughing up of blood and chest pain.

Extrapulmonary TB symptoms depend on the involved area. TB can be fatal if it is not treated. Fortunately, it is preventable and curable.

10.2 Tuberculosis epidemiology

TB is one of the world's deadliest communicable diseases. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360000 of whom were HIV-positive.

TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 thanks to effective diagnosis and treatment. However, given that most deaths from TB are preventable, the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated [1].

10.3 How is tuberculosis spread?

TB is spread through the air [2]. When a person with pulmonary or throat TB disease coughs, sneezes, speaks, or sings, people close by may breathe in these bacteria and become infected. It is estimated that a person with TB disease can infect up to 10-15 persons per year. Family members, friends, co-workers or schoolmates have a higher risk of becoming infected. Usually, young children are less infectious than adults, because of their inability to produce sputum when they cough. When adequate treatment is started, infectiousness declines rapidly.

10.4 Tuberculosis natural history

To better understand the natural history of TB infection, we have to distinguish between the first contact with MT (primary infection) and its reactivation.

Usually, people who get primary TB infection are able to fight the bacteria and make them inactive: this is the LTBI.

Most of these people will never develop TB disease. However, some of them may get sick years later, when these dormant bacteria become active because of immune system weakening. Otherwise, some people – especially children and HIV infected people – may develop TB disease soon after primary infection.

Anyhow, if the immune system is not able to control TB bacteria, these multiply in the body, destroy tissues and cause TB disease.

10.5 Differences between LTBI and TB disease

People with LTBI don't feel sick and cannot spread TB bacteria to others. Usually they have a positive skin test reaction; they should consider LTBI treatment [3].

The risk of developing TB disease is greater in the following situations:

- People infected in the last two years
- Babies and young children
- People with HIV infection
- Substance/alcohol dependence
- Diabetes mellitus
- Severe kidney disease
- Solid/haematological malignancy
- Low body weight
- Silicosis
- Corticosteroid treatment
- Transplants.

10.6 In case of tuberculosis suspect

People suspected of having TB disease should be referred for a medical evaluation, which will include:

- Medical history
- Physical examination
- Test for TB infection (TB skin test or TB blood test)
- Chest radiograph
- Laboratory tests [3].

Physical examination is essential in order to detect any anomaly in the lungs, in the central nervous system or in other organs that may be affected by TB. Early detection of TB is essential to:

- improve health outcome for people with TB
- reduce TB transmission more effectively.

To detect TB infection physicians can use the Mantoux tuberculin skin test (TST). This test is performed by injecting a fluid containing *Mycobacterium spp* proteins into the forearm skin. If the patient has TB infection, his immune system will react against these proteins, producing a hard area or a swelling on the forearm. Therefore, 48-72 hours after the injection, physicians have to look for this reaction and, if present, measure it: the result of the skin test depends on the size of the reaction. Keep in mind: redness is not part of the reaction.

Please note that TST can give

- a false positive result in people vaccinated with Calmette-Guerin Bacille
- a false negative result in people with immune system depression

Therefore, a patient with positive TST has TB infection. A chest x-ray and a sample of sputum are needed to see whether he has TB disease or not.

TB radiographic features depend on the type of illness (LTBI/TB disease), the affected organ and the patient's characteristics. In case of LTBI, the chest radiograph may look normal or show pleural thickening. In course of typical pulmonary TB disease, radiological findings include unilateral infiltrates in the upper lobe or in the superior segment of the lower lobe and parenchymal cavitation. The haematogeneous dissemination of MT, frequent in HIV-positive patients, is known as miliary TB. Its typical radiological findings are multiple 1-3 mm diameter nodules. In the lungs, they usually are bilaterally distributed.

According to WHO guidelines, *all patients suspected of having pulmonary TB disease should submit at least two sputum specimens for microscopic examination*, which consists in acid-fast bacillus research. Based on bacteriological results, we can have smear-positive and smear-negative cases. *The first are the most infectious ones, so they are the focus for infection control measures and contact investigations. However, bacteriological monitoring of treatment progress is most feasible in these patients*. Smear-negative cases are frequent among HIV-positive people [4]. Therefore, if a patient has clinical history, physical examination and radiological findings that are highly suggestive of TB disease but a negative sputum examination, it is advisable to ask for a medical evaluation and eventually start an anti-TB therapy.

Currently, a new microbiological diagnostic test is available: Xpert MTB/RIF. It is an automated molecular test that simultaneously detects TB and rifampicin resistance in less than two hours. Moreover, it has minimal bio-safety requirements and training needs. According to WHO recommendations*, it should be used as the initial diagnostic test in adults and children with pulmonary disease, presumed to have multidrug resistant-TB or HIV-associated TB. It should also be used in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis* [5].

10.7 Tuberculosis disease treatment

TB is a serious but curable infection. Treatment requires taking several drugs for 6 to 12 months, with strong adherence to physicians' instructions. If patients do not complete the treatment, they can become sick again; if they do not take the drugs correctly, the bacteria may become resistant to those drugs.

New patients with pulmonary TB should receive the following 6 months regimen: isoniazide (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for 2 months (induction phase), followed by H and R for another 4 months (maintenance phase): [2HRZE/4HR]. This regimen is valid also for extrapulmonary TB. Some experts suggest a 9-12 months regimen (prolonging the maintenance phase) in case of the central nervous system, bone or joint disease. Indeed, anti-TB drugs penetrate more hardly these sites, because of anatomical reasons. Moreover, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis.

In the table, you will find the first-line anti-TB drugs and their recommended doses for adults. Please note that fixed-dose combinations of anti-TB drugs are recommended in order to reduce prescription errors and improve patient adherence [4].

	Recommended daily dose	
Drug	Dose and range (mg/kg body weight)	Maximum (mg)
Isoniazid	5 (4-6)	300
Riampicin	10 (8-12)	600
Pvrazinamide	25 (20-30)	-
Ethambutol	15 (15-20)	-

10.8 Treatment side-effects monitoring

Anti-TB drugs can cause cutaneous, gastrointestinal, hematological, hepatic and neurological adverse events.

Physicians should teach patients how to recognize these side effects and, during routine controls, ask them about the occurrence of any drug-related symptoms. Routine laboratory monitoring is not necessary.

Isoniazid-induced peripheral neuropathy is more frequent in pregnant women, people with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease and renal failure. Such individuals should take pyridoxine to prevent it.

10.9 Monitoring response to therapy

Patients' response to therapy can be assessed through microbiological and clinical monitoring.

For smear-positive pulmonary TB patients, sputum smear microscopy may be obtained after 2 months of treatment. If by this time the test is positive, it should be performed again at the end of the third month. If the latter specimen is smear-positive, sputum culture with drug susceptibility testing should be performed.

Patients with smear-negative TB before treatment have to be monitored clinically. Body weight gain is a useful indicator of positive response to the treatment. The same goes for patients with extrapulmonary TB.

10.10 Tuberculosis transmission prevention

Since TB is an airborne contagious infection, prevention is an integral part of its management, especially in the case of health care workers, who have close contacts with sick patients.

In order to prevent TB transmission in health care settings, we need to observe some precautions, such as wearing a mask while visiting infectious patients (those who are coughing or have positive sputum smear examination) and ventilating the waiting rooms. These measures have to be undertaken for community's sake and are not meant to create any form of discrimination.

10.11 Relationship between HIV and TB

The risk of progression to TB disease is 10 times greater for HIV infected people; a person who has both HIV infection and TB disease has an AIDS-defining condition; HIV infected people are more likely to present with extra-pulmonary or sputum smear-negative disease. So, there are specific WHO recommendations for the management of this co-infection:

- *HIV testing for patients who present with signs or symptoms that suggest TB*

- *Implementation of HIV prevention strategies for patients with TB[1].*

The first priority for HIV-positive TB patients is to initiate TB treatment. This is the same and with the same duration as for HIV negative people. Co-trimoxazole preventive therapy should also be initiated as soon as possible and given throughout TB treatment. Antiretroviral therapy (ART) should start as soon as possible and within the first 8 weeks of starting TB treatment. Patients with CD4 counts less than 50 cells/mmc should receive ART within the first 2

weeks of starting TB treatment. The recommended regimen is tenofovir (TDF)+emtricitabine/lamivudine (FTC/3TC)+ efavirenz (EFV), the latter having minimal interactions with anti-TB drugs.

When TB is diagnosed in patients already receiving ART, TB treatment should start immediately [6]. *Overlapping toxicities between ART, TB therapy and co-trimoxazole may happen: they include rash and, more rarely, hepatic dysfunction. Therefore, vigilant monitoring of side effects is essential* [4].

10.12 Latent tuberculosis infection management

Let's now briefly focus on LTBI management. *Systematic testing and treating LTBI should be performed in people with HIV and in adult and child contacts with pulmonary TB cases. It should also be considered for health-care workers. Individuals should be asked about TB symptoms before being tested for LTBI. Chest radiography can be done if efforts are intended also for active TB case finding [7].*

Once latent TB is diagnosed, treatment should start to prevent the development of active TB. Recommended treatment options include 6-month isoniazid, 9-month isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone. Rifampicin and rifampertine containing regimens should be prescribed with caution to HIV infected people who are on ART due to potential drug-to-drug interactions. To monitor drug adverse events and improve patients' adherence to the treatment, a monthly clinical visit is recommended [7].

So, this concludes our look at tuberculosis. We have discussed the main features, diagnosis and treatment of TB.

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Questions on Lesson 10

Please select the correct answer, one out of four.

1. How is pulmonary tuberculosis transmitted?

a. By surface contact
b. Tuberculosis is not an infectious disease
c. Through the air from a negative-smear person to another
d. Through the air from a positive-smear person to another

2. Which of the following sentences about people with latent tuberculosis infection is false?

a. They are contagious
b. They can develop active TB
c. They are asymptomatic
d. They can be treated

3. Which of the following situations constitutes a risk factor for TB development?

a. HIV infection
b. Female gender
c. A+D
d. Low body weight

4. One of these sentences about smear-positive TB cases is wrong. Which one?

a. They are contagious
b. At completion of 2 months of treatment they should undergo sputum smear microscopy
c. For the first 2 months they need a 4 drugs treatment
d. They are more likely to result HIV-positive

5. The standard treatment for TB is...

a. 2 HR/4HRZE
b. 2HRZE/4HR
c. 2HRZ/4HRE
d. 4HR/2HRZE

6. Therapy should last more than 6 months in case of...

a. Bone TB
b. TB in HIV-positive people
c. Central Nervous System TB
d. A+C

7. How would you monitor treatment response in negative-smear TB cases?

a. You can't monitor these case
b. Clinically (e.g. monitoring body weight)
c. Performing TST at the end of the therapy
d. Performing blood tests at the end of the therapy

8. Which of the following sentences about HIV positive TB patients is true?

a. They should start anti-TB therapy 8 weeks after starting ART
b. They should start ART within the first 8 weeks of starting TB treatment
c. B+D
d. They should start cotrimoxazole preventive therapy

9. One of these sentences about the treatment of latent TB infection is wrong. Which one?

a. It is contraindicated in HIV-infected people
b. It is based on isoniazid administration for 6 months
c. It requires clinical monitoring
d. It prevents future TB development

10. All of these are characteristics of Xpert MTB/RIF, but one:

a. It is a fully-automated molecular test
b. It simultaneously detects TB and rifampicin drug resistance
c. It requires less than two hours
d. It has complex bio-safety requirements and training needs

Notes

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