ADVANCED CLINICAL ASPECTS OF HIV/AIDS

Training course for nurses

Edited by Raffaella Bucciardini,
Vincenzo Fragola and Paola De Castro

ISTITUTO SUPERIORE DI SANITÀ
TIGRAY HEALTH BUREAU
Mekelle University
CASA
TOOLKIT 4

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CASA TOOLKIT 4

Bucciardini R, Fragola V, De Castro P. (Ed.). Advanced clinical aspects of HIV/AIDS. Training course for nurses. Istituto Superiore di Sanità, Roma, 2015, iv, 40 p. (CASA Toolkit 4) (original English version)

Abstract. This booklet represents a continuation of the booklet number 3 (Clinical aspects of HIV/AIDS). It provides useful information on key aspects related to HIV infection. HIV post-exposure prophylaxis, Isoniazid preventive therapy, prevention of mother-to-child HIV transmission and drug-resistant Tuberculosis will be dealt with in detail. This booklet is mainly addressed to those who already have a basic knowledge on the clinical aspects of HIV-infection.

Key words: HIV/AIDS, ART, Tuberculosis

Acknowledgements. Special thanks to Dr. Hagos Godefay, chief of the Tigray Health Bureau and all the members of the CASA project team.
Thanks to Sandra Salinetti for editorial assistance.

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Istituto Superiore di Sanità, 2015
Viale Regina Elena, 299 – 00161 Rome (Italy)

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Preface

Health care quality of HIV-infected people depends on many factors, of which one of the most important is the availability of well trained and motivated health workers. While basic training is fundamental, continuing education is important to maintain a high standard of care. The provision of post-basic training and a continuous update on the main issues related to health care is also a powerful tool to increase motivation to all those who provide care.

Many efforts have been done to increase the quality of care and in this contest task shifting is one of the most important achievements so far. These days expansion of primary care to nurses including ART initiation and prescription is safe and effective.

This course, along with the previous Toolkit 3, can be a useful tool to achieve a better knowledge of some important aspects related to HIV- infection and Tuberculosis co-infection. In particular, this booklet focuses on drug-resistant Tuberculosis, on how to make the correct diagnosis and how to treat patients. It also focuses on isoniazide preventive therapy (IPT), emphasizing when and how to give the IPT. Another relevant topic included in this booklet is the HIV post-exposure prophylaxis. It is an important emergency procedure which can reduce the risk of being infected after an exposure to the virus, and requires a well trained personnel. Finally , a chapter is dedicated to prevention of mother to child transmission of HIV, which still represents a way of HIV transmission.

An important aspect of all booklets of the CASA training course is the learning assessment test at the end of each lesson. This test can be very useful since it

provides the evidence that the lesson has been learnt, and can also become a tool to discuss, evaluate and eventually improve the quality of the future lessons.

Finally, I wish you a useful and productive learning for your professional future.

Andrea Binelli
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Lesson 1.

HIV post-exposure prophylaxis

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1.1 HIV post-exposure prophylaxis (PEP)

PEP is a way for a HIV-negative person who may have been exposed HIV to reduce the possibility of becoming HIV-positive. It consists of taking a short course of antiretroviral (ARV) drugs. It is an emergency procedure. It is not 100% effective and requires a well-trained health staff. PEP does not replace ordinary measures for HIV prevention.
When a person requires for PEP, the health worker has to obtain three basic information: how the person has been exposed, when it happened and - if possible - the source HIV-status. Once the health worker acquires these data, it is possible evaluate whether the patient is eligible for PEP or not.

1.2 Routes of HIV exposure

The commonest routes of HIV exposure are:

- Sexual intercourse, including heterosexual intercourse, men having sex with men and sexual assault. This is also known as “non-occupational exposure”;

- Needle and trauma exposure, including needle contact, mucous membrane exposure to blood (e.g., splash into the eye) and other less common kinds of exposure (e.g., human bite). This is also known as “occupational exposure”.

In all these situations, the risk of HIV transmission depends on several factors. For example, the risk of sexual transmission is higher in case of receptive or anal intercourses (because of the possible destruction of mucous membranes) or if other genital ulcerative diseases coexist. In addition, male to female transmission is more common than female to male transmission. Within occupational exposure, the risk is higher if the source has a high viral load, the volume of blood is large and the exposure is deep.

1.3 HIV-exposed people eligible for PEP

In which cases are HIV-exposed people eligible for PEP?
According to 2014 WHO Guidelines:

- Exposures that may warrant PEP include parenteral or mucous membrane exposure (sexual exposure and splashes into the eye, nose or oral cavity)
- The following body fluids may pose a risk of HIV infection: blood, blood-stained saliva, breast-milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleura fluids [1]. In cases of contact with these fluids, it is necessary to carefully consider whether there is a significant risk of transmission or not.
- Ideally, PEP should be offered as soon as possible and within 72 hours from the exposure. This practice increases PEP effectiveness.

1.4 HIV-exposed people not eligible for PEP

In which cases are HIV-exposed people NOT eligible for PEP?

- After exposure to tears, non-blood-stained saliva, urine and sweat that do not pose a significant risk of HIV transmission [1].
- If the exposed person is already HIV-positive. Therefore, each exposed person should be promptly tested for HIV using a rapid test. If this is not possible, but the potential risk of HIV-transmission is high, PEP should be started anyway.
- If the source is established to be HIV-negative. Therefore, the source should be tested for HIV, and referred to an appropriate health structure if he/she is found positive. Anyway, PEP should not be delayed if the source HIV-status is not determinable.

1.5 What does PEP consist of?

It is a 28-day course of ARV regimen. Previously, international guidelines recommended a standard two-drug regimen, with the addition of the third drug only in cases of exposure to a possible resistant virus [2].
Even though a two-drug based regimen is effective, 2014 WHO guidelines recommend a three-drug regimen, for the following reasons:

- To simplify the PEP prescription, removing the need to evaluate the risk of drug resistance.
- Because of the availability of less toxic medications and triple combination therapy.

1.6 Recommended antiretroviral drugs for PEP

For adults and adolescents, tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) is the recommended backbone. Lopinavir/ritonavir (LPC/r) or atazanavir/ritonavir (ATV/r) are preferred as third drug. Raltegraivr (RAL),

darunavir (DRV) and efavirenz (EFV) are viable third drug alternatives. All these drugs are indicated for pregnant and breastfeeding women as well.
The recommend PEP for children ten years old and younger consists of zidovudine (AZT) + 3TC (or FTC) + LPV/r. Alternative backbones are abacavir + 3TC or TDF + 3TC (or FTC). Alternative third drugs are ATC/r, RAL, DRV, EFV or nevirapine (NVP).

1.7 PEP and further issues

About using PEP, there are further issues to consider:

- Adherence: In order to be effective, PEP requires optimal adherence during the whole 28-day period of ARV drugs prescription. Counselling is essential to support patient's adherence to therapy.
- Other infections: HIV-virus shares routes of transmission with hepatitis B virus (HBV), hepatitis C virus (HCV) and syphilis. Furthermore, other sexually transmitted infections (e.g., gonorrhoea) can co-exist with HIV-exposure. A careful screen should be done for these infections.
- Pregnancy: A pregnancy test should be proposed to girls and women; emergency contraception is also indicated within 5 days after sexual intercourse.
- Tetanus: People displaying bites or cuts should be investigated about their tetanus status and be offered immunization, if indicated.

1.8 Follow-up in course of PEP

Scheduled appointments in course of PEP are not mandatory, but patients should be advised to refer to a health structure if they experience drug-related side effects. Moreover, counselling about safe practices to reduce the risk of transmission (e.g. using condoms) is essential. Blood donation should be

deferred until HIV-infection is excluded. If in course of PEP the source results HIV-negative, the exposed person can stop taking the ARV drugs. Patients should repeat the HIV-testing three months after the exposure. If they result positive, a linkage to care should be guaranteed.

1.9 Some special considerations for health workers

They are constantly at risk of exposure to HIV, HBV and HCV because of contacts with potentially infected bodily fluids. Therefore, primary prevention is necessary: they need to learn the universal precautions to avoid unwanted exposure, as well as how to practice safe injections.
After a needle stick injury, the risk of transmission is higher for HBV (30%) than for HCV (3%) and HIV (0.3%). For this reason, health personnel should be vaccinated against HBV.
Additionally, after any exposure to blood, the exposed site should be immediately washed. In case of skin exposure, it should be washed with soap and water. Alcohol-based antiseptic may also be used, since alcohol is virucidal to HIV, HBV and HCV [3]. In case of mucus membranes exposure, these should be washed with water. Eyes should be irrigated with saline solution or water. PEP procedure for occupational exposure is the same as non-occupational exposure.

1.10 Key steps of PEP

To sum up, PEP includes the following main key steps:

1) Assessment of the eligibility of the exposed person; HIV testing of exposed and source person; emergency care of the exposed site; screening for other infections.

2) Counselling on the risk of becoming infected, the effectiveness of PEP, drug-related side effects and adherence to therapy.
3) Prescription of a 28-day course of PEP, consisting of three ARV drugs.
4) Follow up: HIV-testing three months after exposure and linkage to care in case of HIV transmission.

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Questions on Lesson 1

Please select the correct answer, one out of four.

1. Choose the correct definition of post-exposure prophylaxis (PEP)

a. PEP is a perioperative prophylaxis
b. PEP is a new way for a HIV-positive people to cure HIV
c. PEP is a way for a HIV-negative person to reduce the risk of becoming HIV-positive before a sexual intercourse
d. PEP is a way for a HIV-negative person who may have been exposed to HIV to reduce the possibility of becoming HIV-positive

2. Which of the following is not an occupational exposure?

a. Sexual assault
b. Needle contact
c. Mucous membrane exposure to blood
d. Human bite

3. Which of the following bloody fluids may transmit HIV infection?

a. Breastmilk
b. Genital secretions
c. Urine
d. A+B

4. Which of the following bloody fluids cannot transmit HIV infection?

a. C+D
b. Cerebrospinal fluid
c. Sweat
d. Urine

5. What does PEP consist of?

a. PEP consists of a 3 days course of ARV regimen
b. PEP consists of a 6 months course of ARV regimen
c. PEP consists of a 28-day course of ARV regimen
d. PEP consists of a 28-day course of antibiotic treatment

6. How many drugs are currently recommended for PEP?

a. One for the first month and two for the second and third month
b. One
c. Two
d. Three

7. If in course of PEP the source results HIV-negative, the exposed person should…

a. Continue the ARV regimen
b. Stop the ARV regimen
c. Continue two antiretroviral drugs
d. Continue one antiretroviral drug

8. After a needle stick injury, the risk of transmission is higher for …

a. HCV
b. HBV
c. HIV
d. Tetanus

9. Which of these points should be evaluated during PEP follow-up?

a. Adherence to therapy
b. PEP tolerability
c. A+B
d. There are no points to check

10. Which of the following statements is false?

a. PEP is 100% effective
b. PEP is an emergency procedure
c. PEP does not replace ordinary measures for HIV-prevention
d. PEP is supported by WHO Guidelines

Lesson 2.

Isoniazid preventive therapy in people with HIV

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2.1 Natural history of tuberculosis (TB)

Let's briefly review the natural history of TB. After inhalation of Mycobacterium Tuberculosis (MT), the immune system is sometimes able to clear definitely the microorganisms, other times a primary infection is established. In the latter case, the immune system can usually control the MT and finally make it inactive: this is the latent TB infection (LTBI). People with LTBI do not feel sick and are not contagious. However, people with weak immune system may develop TB disease soon after primary infection. In fact, the dormant bacteria may become active, multiply in the body and cause TB disease. In people with LTBI, an isoniazid-based treatment can prevent the development of TB disease.

2.2 TB and HIV infection

HIV infection is one of the major risk factors for TB disease in people with latent or new MT infection. HIV destroys T lymphocytes, which play an important role in TB control, resulting in an increased MT infection susceptibility and progression to active disease [1]. In PLHIV, the risk of developing TB disease is

more than 20 times greater than in HIV-negative people [2]. TB is responsible for more than a quarter of deaths in PLHIV [3]. On the other hand, TB itself increases the risk of HIV progression and death [4].
According to WHO, in 2013 about 13% of the nine million people who developed TB worldwide were HIV-positive; 78% of whom lived in African Region [2]. Ethiopia ranked 17th among the twenty-two higher TB burden countries in the world [5]. In 2013, 71% of Ethiopian HIV-positive people were screened for active TB, 11% of whom had TB/HIV coinfection [2]. The management of this two epidemics represents a challenge for resource-constrained countries, Ethiopia included.

2.3 Isoniazid preventive therapy (IPT)

For the above-mentioned reasons, HIV-positive adults and children should be periodically screened for TB disease. If active TB is not present, IPT should be provided, regardless of CD4 count, antiretroviral therapy, previous anti-TB treatment or pregnancy [6]. The aim of IPT is to prevent TB reactivation and progression to active clinical disease. This practice does not predispose to drug-resistant TB, therefore, there should be no obstacles to IPT prescription. A regular TB screening is an effective way to early identify TB cases, including drug-resistant ones. Early identification, diagnosis and treatment of TB cases is the best practice to prevent TB diffusion.

2.4 WHO strategy

WHO suggests a structured strategy to intensify TB case-finding and IPT for PLHIV in resource-constrained settings [7, 8]. This is based on a clinical algorithm composed of TB-associated symptoms: cough, fever, weight loss and night sweats. People without any one of these are unlikely to have TB disease:

so, they should be offered IPT. On the other hand, people reporting any of these symptoms may have active TB and should be evaluated for TB [8].
In practice, PLHIV should be screened using this algorithm during each clinic visit. If none of the symptoms is present, and there are no contraindications, IPT should be started. If there is any contraindication, IPT should be deferred. Active hepatitis, regular and heavy alcohol consumption, prior allergy or intolerance to isoniazid and symptoms of peripheral neuropathy are the major contraindications for IPT [9].

2.5 Isionazid prevention in children

Some special considerations for children: the diagnosis of TB is difficult and requires a high index of suspicion. A history of a close contact of an infant or child with a TB case should motivate TB screening.
According to WHO, HIV-positive children who have any one of the fallowing symptoms - poor weight gain, fever and current cough - or contact with a TB case, should be evaluated for TB. If TB is excluded, IPT should be offered regardless of age.
Children older than 12 months who are unlikely to have active TB on symptom-based screening and have no contact with TB case should receive IPT. For children younger than 12 months, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive IPT, if TB disease is excluded. Moreover, all HIV-positive children successfully treated for TB disease should receive isoniazid for additional six months [8].

2.6 HOW to do IPT?

WHO recommends preventive therapy with daily isoniazid, at the dose of 300 mg for adults and 10 mg/kg for children, for at least six months [7].

It is also desirable providing B6 vitamin to prevent isoniazid- related peripheral neuropathy [9].
However, since the protective effect of IPT declines over time, a prolonged IPT course should be recommended. In a recent document, WHO assesses that PLHIV in countries with high TB and HIV prevalence should receive at least 36 months of IPT [6]. This new recommendation results from recent studies, which have demonstrated that, in these settings, PLHIV benefit more from IPT of 36 months or longer, compared to six-months IPT [6].

2.7 IPT follow-up

People receiving IPT should have clinical follow-up at the ART clinic. They should be investigated about adherence to the treatment, isoniazid safety and tolerability and presence of signs and symptoms of active TB. The main potential isoniazid-related adverse event is hepatotoxicity, clinically showed as nausea, abdominal pain, jaundice and fever. Patients should be informed about these symptoms and trained to stop isoniazid immediately if such symptoms occur and to report to medical staff for confirmation. However, clinically relevant hepatotoxicity in course of IPT occurs in a small number of people.

2.8 Barriers to IPT implementation

The main barriers to IPT implementation are:

- Governance-related, such as poor integration between TB and AIDS programmes
- Service-delivery-related, when TB screening algorithm is not regularly applied
- Supplies and product-related: shortage of INH

- Health workforce-related: fear of developing drug-resistance; problems concerning INH-related toxicity
- Patient-related: poor adherence due to reluctance towards prevention. Indeed, patients are often scared of taking a drug to treat a disease that they do not actually feel [10].

That is the reason why health workers' role is so critical: they should provide a proper counselling on IPT, explain to patients why it is prescribed and inform them about its safety and effectiveness.

To sum up: providing IPT to PLHIV in high TB/HIV prevalence settings is an essential step in the global fight against TB, as well as an effective measure for the improvement of PLHIV's quality of life. Thanks for your attention!

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Questions on Lesson 2

Please select the correct answer, one out of four.

1. Choose the correct statement about latent TB infection (LTBI)

a. LTBI is contagious
b. LTBI is characterized by fever, cough and weight loss
c. LTBI means that Mycobacterium Tuberculosis is replicating
d. LTBI means that Mycobacterium Tuberculosis is dormant but may become active

2. Which of the following statements is false?

a. There is no relationship between TB and HIV infection
b. HIV-related immune-deficiency predispose to active TB disease
c. TB is an AIDS-defining event
d. TB increases the risk of HIV progression

3. What is the aim of isoniazid preventive therapy?

a. To prevent TB reactivation in people with TB disease
b. To prevent TB reactivation in people with latent infection
c. To prevent TB primary infection
d. To treat TB disease

4. Should HIV-positive adults and children be screened for TB disease?

a. Yes, periodically
b. Yes, once in their life
c. No, because they are not at risk for TB
d. No, because TB screening is not effective

5. WHO algorithm to intensify TB cases…

a. Is contra-indicated in resource-constrained settings
b. Is based on the research of typical TB symptoms: itching and diarrhoea
c. Is based on the research of typical TB symptoms: cough, fever, weight loss and night sweats
d. Is not indicated for HIV-positive people

6. What does isoniazid preventive therapy consist in?

a. Isoniazid once a week for six months
b. Daily isoniazid for three months
c. Isoniazid twice a week for six months
d. Daily isoniazid for at least six months

7. Which of the following are contraindications for isoniazid preventive therapy?

a. Active hepatitis
b. A+C
c. Allergy or intolerance to isoniazid
d. There are no contraindications

8. HIV-positive people taking isoniazid preventive therapy…

a. Do not need additional support
b. Should receive regular follow-up at the Antiretroviral Clinic
c. Do not need regular follow-up
d. Can stop antiretroviral therapy

9. Which points should be evaluated during isoniazid preventive therapy follow-up?

a. Adherence to therapy
b. Isoniazid tolerability
c. A+B
d. There are no points to check

10. Which of the following statements is false?

a. Health personnel has no responsibility in increasing patients' adherence to isoniazid therapy
b. There are several barriers to isoniazid preventive therapy implementation
c. Patients may be afraid to take a drug for a disease that they do not actually realize they have
d. Shortage of isoniazid is a relevant structural barrier to preventive therapy implementation

Lesson 3.

Prevention of mother-to-child HIV transmission

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3.1 Mother-to-child HIV transmission

Mother-to-child transmission is one of the main ways of HIV transmission, together with sexual transmission and blood transmission. HIV infection can be passed from a HIV-infected mother to her fetus during pregnancy (in utero), labor/delivery (intrapartum) or breastfeeding (postnatal). In the absence of any prevention strategy, the risk of perinatal HIV transmission varies between 15 and 45 percent, depending on various risk factors. Approximately 10-25% of transmissions happen in utero, 35-40% intrapartum and 35-40% during breastfeeding [1].

Several factors can increase the risk of mother-to-child HIV transmission. Let's see some of the major ones.

Maternal factors are:

- High viral load
- Low CD4 count
- Advanced disease
- Viral or parasitic placental infections
- Nipple fissures, mastitis

Infant factors include:

- Breastfeeding
- Oral disease

Obstetric and delivery-related factors are:

- Rupture of membrane for more than four hours
- Ante-partum procedures
- Invasive childbirth procedures
- Vaginal delivery
- Delayed infant cleaning and eye care
- Routine infant airway suctioning [2]

3.2 Prevention of mother-to-child HIV transmission (PMTCT)

That said, the milestones of PMTC are maternal antiretroviral therapy (ART), obstetric assistance, infant prophylaxis, maternal and infant follow-up care.
However, the first step of the PMTC program is to invite all pregnant women to attend antenatal care services to be tested for HIV. Indeed, HIV testing in this setting is highly accepted, thereby providing a unique chance to prevent perinatal transmission. If a pregnant woman is found HIV-positive, antenatal care should include:

- CD4 count measurement
- Cotrimoxazole prophylaxis (if indicated)
- Treatment for opportunistic infections
- Screening for tuberculosis
- Additional counselling on malaria: HIV-positive pregnant women in malaria endemic areas should receive malaria prophylaxis and treatment [2]

3.3 ART in pregnancy (When and What to start)

Now, let's see when to start ART in pregnancy, what to prescribe and for how long, according to WHO Guidelines on ART [3, 4]. Pregnancy and breastfeeding require per se the starting of ART. Specifically, all pregnant and breastfeeding women with HIV should start, as soon as possible, triple ART - regardless of their CD4 cell count or disease stage [3]. Indeed, making maternal viral load undetectable through an effective antiretroviral regimen is a necessary condition in order to prevent HIV transmission.

WHO recommends a once-daily, fixed-dose combination therapy containing tenofovir (TDF) plus lamivudine (3TC) [or emtricitabine (FTC)] plus efavirenz (EFV). This regimen has many advantages: it is effective, safe and simple, and can be maintained during pregnancy, through delivery and during breastfeeding period. In the past, there were some concerns about the safety of EFV in pregnancy, particularly during the first 28 days. However, there is currently no evidence of increased risk of congenital anomalies associated with EFV [5]. Anyhow, continued monitoring for toxicities and birth defects in this setting is necessary to ensure both short-term and long-term antiretroviral safety.

According to 2013 WHO Guidelines, after the period of mother-to-child transmission risk, women who meet the WHO ART-eligibility criteria should continue ART forever. Women who are not eligible for therapy for their own health, have the two options. In accordance with the Option B, they should stop the ART. On the contrary, in accordance with the Option B+ they should continue ART for life. This latter approach is advisable, since 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 [3]. Since after the release of 2013 Guidelines many countries moved to adopt Option B+ within PMTCT programmes [4], Option B is no longer relevant.

Therefore, in 2015 WHO has gone beyond the previous distinction between the two options and now recommends that ART should be continued lifelong in all

pregnant and breastfeeding women, regardless of CD4 cell count and WHO clinical stage [4].

3.4 Infant post-exposure prophylaxis

In addition to maternal ART, postnatal care is another important issue: the WHO recommends that all infants receive post-exposure prophylaxis in order to prevent transmission from exposure to HIV during delivery and breastfeeding period. Breastfeeding infants should receive six weeks of infant prophylaxis with daily nevirapine (NVP). If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP or twice-daily zidovudine (AZT) [3]. If NVP has to be discontinued due to infant toxicity or drug shortage, it can be replaced by 3TC. Dosing of NVP/AZT prophylaxis depends on the age and birth weight of the infant, as you can see in the following Tables.

Table 1. Infant prophylaxis dosing recommendations: NVP

Infant age	Daily dosing
Birth to 6 weeks • Birthweight <2000 g • Birthweight 2000-2499 g • Birthweight 2500 g	 2 mg/kg once daily 10 mg once daily 15 mg once daily
> 6 weeks to 6 months	20 mg once daily
> 6 months to 9 months	30 mg once daily
> 9 months until breastfeeding ends	40 mg once daily

Table 2. Infant prophylaxis dosing recommendations: AZT

Infant age	Daily dosing
Birth to 6 weeks • Birthweight <2000 g • Birthweight 2000-2499 g • Birthweight 2500 g	 2 mg/kg twice daily 10 mg twice daily 15 mg twice daily

A longer duration of infant prophylaxis (12 weeks) is reasonable in breastfeeding infants if there is the likelihood of absent or delayed maternal viral suppression (e.g. women who did not receive antepartum ART). Moreover, if a breastfeeding mother interrupts ART, infant NVP should be provided during this period of maternal interruption until six weeks after maternal ART restarting or until 1 week after breastfeeding has ended [3].

3.5 How to manage prophylaxis: different scenarios

Table 3 summarizes how to manage prophylaxis in different scenarios, according to WHO guidelines [3].

3.6 Labour and delivery

With regard to the delivery: although elective caesarean section protects against HIV transmission, it is not specifically recommended for HIV infection in resource-limited settings, but rather for obstetric and other medical indications. To reduce the risk of HIV transmission during labour and delivery, the following interventions are recommended: 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 newborns [3].

Table 3. Prophylaxis in different scenarios

Scenario	Maternal Antiretroviral Prophylaxis	Infant Antiretroviral Prophylaxis	Duration of Infant Antiretroviral Prophylaxis
Mother diagnosed with HIV during pregnancy	Start maternal ART	NVP	6 weeks
Mother diagnosed with HIV during labour or immediately post-partum and plans to breastfeed	Start maternal ART	NVP	6 weeks; consider extending this to 12 weeks
Mother diagnosed with HIV during labour or immediately post-partum and plans replacement feeding	Refer mother for HIV care	NVP	6 weeks
Infant identified as HIV-exposed after birth (through infant or maternal HIV antibodies testing) and is breastfeeding	Start maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV-exposed after birth (through infant or maternal HIV antibodies testing) and is not breastfeeding	Refer mother for HIV care	No drug	Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding	Choose an alternative antiretroviral regimen	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

3.7 Breastfeeding

Breastfeeding is essential for the infant nutrition and his overall health. HIV-infected mothers should exclusively breastfeed their infants for the first 6 months of life, introducing complementary food thereafter, and continuing breastfeeding for the first 12 months of life. Then, breastfeeding should stop only once a nutritionally adequate diet can be provided [3].

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. Therefore, by suggesting this strategy, WHO aims to improve the HIV-free survival of HIV-exposed infants.

3.8 Maternal adherence to ART

A big challenge for PMTCT programs is to obtain and maintain a good maternal adherence to ART for the whole risk-transmission period. Indeed, studies show that adherence is usually better prior to delivery but it tends to decline in the post-partum period [6, 7]. Inadequate maternal adherence threatens both maternal and infant health and increases the potential development of drug-resistance. A good strategy for improving adherence is to integrate PMTCT service into the Maternal and Child Health services.
The early identification of HIV-positive mothers is essential. If a woman presents at labour with unknown HIV status, a rapid HIV test should be performed. If she is found out positive, ART should be provided to both the mother and child and a prolonged infant prophylaxis should be considered. Women who deliver outside health facilities should receive a medical assessment at a Maternal and Child Health facility as soon as possible after delivery.

3.9 Postpartum care

Postpartum care is another essential step. Follow-up care of mother and exposed-infant should include: postpartum check, family planning counselling, ART refills, toxicity monitoring, adherence support, counselling on feeding, early infant diagnosis testing and scheduled vaccines. Most of all, HIV-exposed infant are recommended to start cotrimoxazole therapy for prevention of Pneumocystis pneumonia, toxoplasmosis and bacterial infections. That should be started four-six weeks after birth, and continued until the risk of HIV transmission ends or HIV infection is excluded [3].

3.10 Early infant diagnosis

Finally, let's explore early infant diagnosis. If not treated, HIV-positive infants have a high morbidity and mortality: that is why a correct and prompt diagnosis of HIV infection is essential. Maternal HIV antibodies cross the placenta are detectable in the infant for many months. In the light of that, HIV serological assay cannot be used as a diagnostic assay in HIV-exposed infant younger than 18 months. In that context, a virological assay (such as HIV-DNA or HIV RNA testing) is recommended.

In settings where these tests are not available and breastfeeding is usual, the infant should be clinically monitored: if at nine months of age the child is in good health, a serologic test should be done. If that is negative, HIV infection is unlikely but it cannot be excluded; for this reason, the test must be repeated at 18 months and/or six weeks after stopping breastfeeding [3].

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Questions on Lesson 3

Please select the correct answer, one out of four.

1. HIV infection can be transmitted from mother to child

a. In utero
b. Intra-partum
c. During breastfeeding
d. A+B+C

2. The risk of mother-to-child HIV transmission

a. Is influenced by infant, maternal and obstetric factors
b. Is higher in utero than during labor/delivery
c. Is not influenced by any external factor
d. Is not influenced by maternal viral load

3. Which of the following statements is false?

a. Pregnancy requires per se the starting of ART
b. Pregnant and breastfeeding women should start ART if they have less than 200 CD4
c. Breastfeeding requires per se the starting of ART
d. Pregnant and breastfeeding women should start ART regardless of their CD4 cell count

4. Which of the following is the recommended antiretroviral regimen in pregnancy?

a. A fixed-dose combination therapy containing TDF plus FTC [or 3TC] plus EFV
b. There is no recommended regimen
c. TDF plus FTC [or 3TC] plus NPV
d. TDF plus D4T plus EFV

5. One of these sentences is false. Which one?

a. Infants post-exposure prophylaxis is a milestone of PMTCT
b. Infants post-exposure prophylaxis consists of 6 weeks of daily nevirapine
c. Infants post-exposure prophylaxis is not recommended in infants receiving replacement feeding
d. Nevirapine dose is based on age and birth weight

6. If a mother is diagnosed with HIV during pregnancy (choose the correct answer)

a. She should start ART as soon as possible
b. The infant should receive NVP prophylaxis
c. Infant prophylaxis is not indicated
d. A+B

7. Which of the following sentences about cesarean section for HIV-positive women is false?

a. It protects against HIV transmission
b. It is not specifically recommended by WHO in resource-limited settings
c. It is specifically recommended by WHO in resource-limited settings
d. It is indicated in resource-limited settings in presence of obstetric or medical indications

8. One of these sentences about breastfeeding is false. Which one?

a. HIV-infected mothers should exclusively breastfeed their infants for the first 6 months, then introduce complementary food and breastfeed for the first 12 months of life
b. HIV-infected mothers should not breastfeed their infants
c. The maximum benefit of breastfeeding in preventing infants' mortality takes place in the first 12 months of life
d. HIV transmission through breastfeeding is low in presence of ART

9. Which of the following statements about cotrimoxazole therapy is false?

a. It should be part of postpartum care
b. It protects infants against Pneumocystis pneumonia, toxoplasmosis and bacterial infection
c. It can be avoided in asymptomatic children
d. It should be started four-six weeks after birth

10. Which of the following statements about early infant diagnosis is false?

a. HIV serology can be used as a diagnostic assay in HIV-exposed infants younger than 18 months
b. HIV serology cannot be used as a diagnostic assay in HIV-exposed infants younger than 18 months
c. If a virological assay is not available, a serologic test should be repeated at 18 months and/or six weeks after stopping breastfeeding
d. Maternal HIV antibodies cross the placenta and are detectable in the infant for many months

Lesson 4.

Drug-resistant Tuberculosis

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4.1. Definitions

Let's start from the basics: drug-susceptible TB responds to an usual 6-month (or more) therapy with first-line drugs (which traditionally are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin). Drug-resistant TB is not susceptible to one or more anti-TB drugs: therefore, it requires a more complex and longer treatment. Drug-resistant TB can be classified as follows:

- Multidrug-resistant TB (MDR TB), if the Mycobacterium Tuberculosis (MT) is resistant to at least isoniazid and rifampicin, which are the core of the anti-TB treatment.
- Extensively drug-resistant TB (XDR TB), if the MT is resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) [1].

4.2 Development of Drug Resistance

Drug resistance can develop by two pathways:

- Acquired (secondary) drug resistance occurs when a drug-susceptible TB is treated with inadequate or incomplete treatment, for example if a patient

takes the drugs in wrong dose or with poor adherence or for a shorter period than the prescribed one. In all these cases, an initial susceptible infection may become resistant.
- Initial (primary) drug resistance occurs when a person, who has never been treated for TB, is infected with a drug-resistant TB strain.

It is easy to understand how the two main ways to control drug-resistant TB are:
- Early detection and high quality treatment of drug-susceptible TB [1], that prevents the development of acquired drug resistance, and
- Early detection and high quality treatment of drug-resistant TB [1], which prevents new primary drug-resistant cases.

4.3 Global burden

The World Health Organization (WHO) estimates that globally 5% of TB cases have MDR-TB. Among new TB cases, an estimated 3.5% have MDR-TB; among people previously treated for TB, the percentage is higher (20.5%). In 2013, an estimated 480,000 cases of MDR-TB have been recorded worldwide. MDR-TB is a global problem, but it has higher levels in Eastern Europe and central Asian countries, with more than half of the cases recorded in India, China and the Russian Federation. Drug-resistant TB is to be especially suspected when TB is diagnosed in people previously treated for TB and in people coming from the above-mentioned countries [2].

Despite progress made in recent years in the fight against TB, this is still one of the leading causes of mortality for infectious diseases in Ethiopia [3]. MDR-TB too is a relevant challenge: Ethiopia is one of the 27 high MDR-TB burden countries [4]. According to the 2014 national TB report, 2.3% of new TB cases and 17.8% of previously treated TB cases were estimated to be MDR [3]. Furthermore, Ethiopia is one of the 100 countries that have reported at least one case of XDR-TB [4]. Therefore, it is critical for health workers to be aware of this problem.

4.4 Highlights

Drug-resistant and drug-susceptible TB share how they transmit and also how they show clinically. However, the first one requires specific considerations regarding laboratory diagnosis and treatment. Early diagnosis of TB and drug resistance allows for the use of an appropriate treatment, which in turn has a strong influence on both the patient's outcome and TB control. Indeed, a rapid diagnosis can improve the prognosis, increase the survival, prevent the acquisition of further drug resistance and reduce the spread of drug-resistant strains [1].

4.5 Risk factors for drug-resistant TB

In order to diagnose drug-resistant TB, the first step is to suspect it. This is possible by keeping in mind some known risk factors for drug-resistant TB:

- Residence in areas with high drug-resistant TB prevalence
- Exposure to a known drug-resistant TB case
- Failure of a first-line anti-TB treatment (patients who are sputum-smear positive after five month of therapy)
- Sputum smear-positivity at month two or three of a first-line TB treatment
- Patients relapsed or returned after loss of follow-up
- Comorbidities associated with malabsorption, which can result in low serum drug levels
- HIV co-infection

4.6 Diagnosis of drug-resistant TB

The second step is to obtain a microbiological result that could confirm the diagnosis of MDR-TB and suggest which drugs to take. This is usually possible only in high-level health facilities (general or specialized hospitals) were drug

susceptibility testing (DST) are performed. Therefore, health workers facing patients suspected to have drug-resistant TB should send them to the closest referral TB center where DST are available.
There are two major DST types:

- Conventional DST, in which the MT is isolated in culture and then evaluated its ability to grow in the presence of drugs. This process takes a long time and requires a specialized technician.
- Molecular DST, which detects TB DNA and the presence of mutations in the TB genome associated with drug-resistance. This technique is faster and automatized.

4.7 WHO recommendations

Since 2010, WHO endorsed Xpert MTB/RIF assay: a genotypic DST that simultaneously identifies MT DNA and the mutations associated with rifampicin resistance directly from sputum specimens. This is a fully automated test, providing accurate results in less than two hours [5]. It is important to know that resistance to rifampicin is rarely isolated: 95% of rifampicin-resistant strains are also isoniazid-resistant. Thus, rifampicin-resistance could be considered a marker of MDR TB. Therefore, if Xpert MTB/RIF assay reveals a rifampicin-resistant MT strain, we could assume that this is resistant to isoniazid as well: thus, this represents a case of MDR TB. Information about susceptibility to other anti-TB drugs is obtained only through conventional DST.
The WHO strongly recommends using Xpert MTB/RIF assay as the initial diagnostic test:

- In adults and children presumed to have a MDR-TB or HIV-associated TB (the latter since HIV-positive people with unrecognized drug-resistant TB have very high mortality)
- In testing cerebrospinal fluid specimens from patients presumed to have TB meningitis [5]

Anyhow, Xpert MTB/RIF assay cannot be used in the monitoring of treatment response, therefore conventional DST remains crucial during the follow-up.

4.8 Implications of drug-resistant TB

The diagnosis of drug-resistant TB has peculiar consequences and deserves further remarks.
First: it means that patients can spread drug-resistant TB. Therefore, proper precautions for infection control must be taken.
Second: the treatment is more complex, toxic, expensive and longer than the treatment of conventional TB. Indeed, it includes drugs not specific for TB and not routinely used - so called "second line drugs" – instead of the "first line" ones. Thus, patients with drug-resistant TB need to be referred to a specialized health facility, where second line drugs are available and health workers are experienced in their management.
Third: the treatment's success rates are slight, about 50% for MDR-TB cases and less than 20% in XDR-TB cases [6, 7].

4.9 Anti-TB drugs

The requirement to understand the treatment of drug-resistant TB is to know which drugs are available and how to choose and administer them. The WHO classifies the anti-TB drugs into five groups, as you can see below:

1. First-line oral agents
2. Injectable drugs
3. Fluoroquinolones
4. Oral bacteriostatic drugs
5. Drug with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB [1].

While susceptible-TB regimen is based on the first line oral agents of the first group, treating drug-resistant TB requires the use of the other groups of drugs.

4.10 WHO General principles for MDR-TB treatment

WHO established basic general principles for the treatment of MDR-TB. Here you can find some of the main ones:

- MDR-TB treatment should last at least 20 months. The regimen consists of two phases: in the first phase (intensive phase) an injectable agent is included together with the oral ones for eight months; in the second phase (continuation phase) only oral drugs are maintained for 12 months.
- The intensive phase should include at least four second line drugs that are likely to be effective, as well as pyrazinamide. These four drugs should be one fluoroquinolone, one injectable drug and two oral bacteriostatic drugs. The drug dosage is determined by age and weight.
- Oral drugs are to be given seven days a week, possibly under direct observation. Injectable drugs can be administered five to seven days a week, depending on the presence of health workers able to perform intramuscular injections.
- Any drug-related adverse effects should be promptly managed.
- Patients should be treated in an ambulatory setting, rather than in a hospital one.

4.11 XDR-TB

XDR-TB cure relies mostly on the same general principles mentioned above, with some clarifications: since XDR-TB is resistant to isoniazid, rifampicin, any

fluoroquinolone and at least one of three injectable second-line drugs, its treatment necessarily requires drugs from the Group 4 and 5. To be effective, the treatment should provide at least six drugs in the intensive phase and four in the continuation phase. Moreover, the injectable agent (if included in the treatment) should be used for an extended period (12 months or longer).

4.12 Adjunctive therapies

Drug-resistant TB treatment can benefit from some adjunctive therapies:

- Corticosteroids in course of central nervous system TB or pericardial TB, to improve patients' outcome.
- Nutritional support, since TB itself cause anorexia with weight loss and malnutrition that, in turn, makes the patients fragile and predispose them to other infections. Moreover, some of the second-line anti-TB drugs can further produce gastro-intestinal disturbs and decrease appetite. Finally, providing food can improve patients' adherence to treatment.

4.13 People living with HIV – special recommendations

Let's focus on people living with HIV (PLHIV). It is now recognized that they are vulnerable to drug-resistant TB, and that they have higher mortality rates than HIV-negative people. For these reasons, this topic includes special recommendations to :

- perform HIV-testing and counseling in people with drug-resistant TB
- use Xpert MTB/RIF assay in PLHIV suspected for TB
- start an empiric MDR regimen in patients at high risk for MDR-TB, even before laboratory confirmation of MDR-TB [1]
- start antiretroviral therapy (ART) within the first eight weeks after starting the anti-TB treatment, since early initiation of ART is associated with

decreased mortality [8]. Consider possible interactions and the sum of the potential toxicity of ART and anti-TB drugs
- prescribe co-trimoxazole preventive therapy, according to current guidelines [9]
- integrate TB and HIV services to reduce the risk of mistakes or poor adherence related to the high pill burden and the potential high number of side-effects
- implement nutritional and socio-economic support.

4.14 Follow-up

After starting treatment for drug-resistant TB, patients should be properly monitored. The main markers of treatment response are:
- Improvement of TB symptoms
- Improvement of radiographic controls
- Conversion of a sputum culture from positive to negative. This is the main evidence of improvement, thus, culture-conversion should be monitored on a monthly basis.

Moreover, a regular follow-up is mandatory to check treatment tolerance and adherence. Therefore, any health worker facing a TB patient has public health responsibilities, since patient's adherence to treatment has public health consequences.

4.15 To Prevent the Spread of MDR-TB

Finally, let's talk about the management of contacts of MDR-TB patients. A big issue concerning drug-resistant TB control usually is the MDR-TB delayed diagnosis. Patients wait a long period before starting an effective treatment and, in the meantime, they might infect their close contacts. The WHO defines

"close contacts" as people living in the same household as the index patients, or spending many hours a day together with the patient in the same indoor space [1]. To prevent the spread of MDR-TB, the first step is to trace close contacts. After that, they should be investigated in order to detect active TB and, in that case, promptly treated for drug-resistant TB. Indeed, it has been shown that close contacts of MDR-TB patients who develop active TB almost always have MDR-TB themselves [10, 11]. On the other hand, if a close contact of a drug-resistant TB patient is diagnosed with latent TB infection, clinical evaluation and follow-up are only recommended [12].

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Questions on Lesson 4

Please select the correct answer, one out of four.

1. Multi-drug resistant TB means that

a. Mycobacterium Tuberculosis is resistant to isoniazid
b. Mycobacterium Tuberculosis is resistant to rifampicin
c. Mycobacterium Tuberculosis is susceptible to all first-line drugs
d. Mycobacterium Tuberculosis is resistant to at least isoniazid and rifampicin

2. Which of the following is the correct definition of extended drug-resistant TB?

a. Resistance to isoniazid, rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs
b. Resistance to isoniazid, rifampicin, plus any fluoroquinolone
c. Resistance to isoniazid, rifampicin, plus at least one of three injectable second-line drugs
d. Resistance to isoniazid, rifampicin and pyrazinamide

3. Which of the following statements is false?

a. Drug-resistance TB is a challenge for Ethiopia
b. XDR-TB cases have never been reported in Ethiopia
c. XDR-TB cases have been reported in Ethiopia
d. Drug-resistance is a global health challenge

4. Which of the following is not a risk factor for drug resistant TB?

a. Pregnancy
b. HIV co-infection
c. Residence in areas with high drug-resistant TB prevalence
d. Exposure to a known drug-resistant TB case

5. One of these sentences is false. Which one?

a. Xpert MTB/RIF assay detects TB DNA and resistance to rifampicin
b. Xpert MTB/RIF assay is a fully automated test
c. Xpert MTB/RIF assay takes a long time
d. Xpert MTB/RIF assay is a molecular drug susceptibility test

6. In which cases does WHO recommend Xpert MTB/RIF?

a. Patients with extra-pulmonary TB
b. TB suspicion in HIV-positive patients
c. TB meningitis
d. B+C

7. Which of the following sentences about MDR-TB treatment is false?

a. It should last at least 20 months
b. It should include an injectable agent during the induction phase
c. It has no side effects
d. It should include nutritional support

8. One of these sentences about MDR-TB in HIV-positive people is false. Which one?

a. It has higher mortality than in HIV-negative people
b. Its treatment should last less than 15 months
c. Its treatment is the same that for HIV-negative people
d. Its treatment should be followed by antiretroviral-therapy

9. Which of the following is a marker of response to drug-resistant TB treatment?

a. Improvement of TB symptoms
b. Improvement of radiographic controls
c. A+B
d. Weight loss

10. Which of the following statements about close contacts of MDR-TB patients is false?

a. They should not be investigated at all
b. They should be investigated for active TB
c. If they have active TB, they should be treated for MDR-TB
d. If they have latent TB, should receive clinical evaluation and follow-up

Printed by
De Vittoria srl
Via degli Aurunci, 19/21
00185 Rome (Italy)
December 2015

This booklet is a part of a training program addressed to health workers and developed within the CASA project, a partnership among the Tigray Health Bureau of Ethiopia, Mekelle University and Istituto Superiore di Sanità (ISS), the National Institute of Health in Italy.

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Edited by the Publishing Unit, ISS