

# Features Of The Treatment Of Acute Tuberculosis In HIV-Infected Patients And The Principles Of Chemotherapy

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## **RELEVANCE.**

*Tuberculosis is a serious disease, usually affecting the lungs, and can be life threatening if timely and appropriate treatment is not started. Tuberculosis is one of the most common infectious diseases in the world. Every year, tuberculosis is diagnosed in 2 billion people in the world, and every year 3 million people die from tuberculosis. In industrialized countries, tuberculosis became a rarity many years ago, but its prevalence is still high in certain groups of the population - primarily prisoners and social groups living in poor conditions. People with HIV, especially those with a weakened immune status, are most at risk for tuberculosis. In the world, tuberculosis is the most dangerous opportunistic infection at the AIDS stage.*

## **1. MATERIALS FOR RESEARCH:**

Human immunodeficiency virus type 1 (HIV-1) and *M. tuberculosis* are two intracellular pathogens that interact at the population, clinical, and cellular levels. Initial studies of HIV-1 and TB emphasized the impact of HIV-1 on the natural progression of TB, but mounting immunologic and virologic evidence now indicates that the host immune response to *M. tuberculosis* enhances HIV replication and might accelerate the natural progression of HIV infection. Therefore, the interaction between these two pathogens has important implications for the prevention and treatment of TB among HIV-infected persons. Studies of the immune response in persons with TB disease support the biologic plausibility of co pathogenesis in dually infected persons.

The initial interaction between the host immune system and *M. tuberculosis* occurs in the alveolar macrophages that present mycobacterial antigens to antigen-specific CD4<sup>+</sup> T cells. These T cells release interferon-gamma, a cytokine that acts at the cellular level to activate macrophages and enhance their ability to contain mycobacterial infection. The activated macrophages also release pro-inflammatory cytokines, such as tumor necrosis factor and interleukin (IL)-1, cytokines that enhance viral replication in monocyte cell lines in vitro. The myco-bacteria and their products also enhance viral replication by inducing nuclear factor kappa-B, the cellular factor that binds to promoter regions of HIV.

When TB disease develops in an HIV-infected person, the prognosis is often poor, though it depends on the person's degree of immunosuppressant and response to appropriate antituberculosis therapy. The 1-year mortality rate for treated, HIV-related tuberculosis ranges from 20% to 35% and shows little variation between cohorts from industrialized and

developing countries . The observed mortality rate for HIV-infected persons with TB is approximately four times greater than the rate for TB patients not infected with HIV .

Although the cause of death in the initial period of therapy can be TB , death after the induction phase of antituberculosis therapy usually is attributed to complications of HIV other than TB . Epidemiologic data suggest that active TB accelerates the natural progression of HIV infection. In a retrospective cohort study of HIV-infected women from Zaire, investigators estimated the relative risk of death to be 2.7 among women with active TB compared with those without TB . In a retrospective cohort study of HIV-infected subjects from the United States, active TB was associated with an increased risk for opportunistic infections and death . The risk of death, or hazard rate, for persons with HIV-related TB follows a bimodal distribution, peaking within the first 3 months of antituberculosis therapy and then again after 1 year ; the reasons for this distribution are not clear but might relate to the impact of TB on HIV disease progression. The observation that active TB increases deaths associated with HIV infection has been corroborated in studies of three independent cohorts in Europe

Early in the HIV epidemic, researchers postulated that the immune activation resulting from concurrent infection with parasitic or bacterial pathogens might alter the natural progression of HIV infection . Subsequent observations have demonstrated that immune activation from TB enhances both systemic and local HIV replication. In some patients with active TB, the plasma HIV RNA level rises substantially before TB is diagnosed. Moreover, TB treatment alone leads to reductions in the viral load in these dually infected patients. TB and HIV also interact in the lungs, the site of primary infection with *M. tuberculosis*.

In a recently published study of HIV-infected patients with TB, researchers found that the viral load was higher in the broncho-alveolar lavage fluid from the affected versus the unaffected lung and was correlated with levels of tumor necrosis factor in broncho-alveolar fluid

Researchers used V3 loop viral sequences to construct a phylogenetic tree and observed that the HIV quasispecies from the affected lung differed from those in the plasma within the same patient. These data suggest that pulmonary TB might act as a potent stimulus for the cellular-level replication of HIV. In summary, recent research findings have improved clinicians' understanding of how HIV affects the natural progression of TB and how TB affects the clinical course of HIV disease, and these findings support the recommendation for prevention, early recognition, and effective treatment for both diseases.

Chemotherapy for tuberculous infection (chemoprophylaxis)It is important to differentiate between infection and disease. In tuberculous infection the tuberculin skin test is positive, the chest radiograph is normal, and the patient asymptomatic. In tuberculous disease the skin test is usually positive and there are clinical signs and symptoms or radiographic changes present. Asymptomatic, tuberculin positive patients with normal chest radiographs (infection) are usually treated (chemoprophylaxis) with either one drug for six months or, alternatively, with two drugs for three months. Infection, in contrast to disease, implies the presence of small numbers of tubercle bacilli in the body.

The administration of one or two antituberculosis drugs for a shorter period of time than for disease (chemoprophylaxis) is likely to kill these organisms, preventing possible progression to disease at a later date.

Many studies have shown that chemoprophylaxis with isoniazid for 12 months is highly effective and that six months is probably as effective [A]. Regimens of rifampicin and isoniazid lasting only three months have been used in clinical practice in some areas of the

United Kingdom with good effect and no increased adverse reactions, and have been shown to be as good as six months of treatment with isoniazid in a randomised controlled trial in Hong Kong [B]. In contacts of an isoniazid resistant patient, rifampicin for six months has been shown to be effective.

**2. MAIN PART OF WORK:**

Chemotherapy for tuberculosis in patients with human immunodeficiency virus infection should be started as early as possible after the diagnosis is made. The empirical prescription of anti-tuberculosis drugs for suspected tuberculosis in patients with human immunodeficiency virus infection is justified in the case of a serious patient's condition.

The choice of the mode is based on the data of the anamnesis and the spectrum of drug resistance of the isolated pathogen. From the anamnesis it matters: whether the patient was previously treated for tuberculosis (registration group), the results of pulmonary tuberculosis in a man in previous cases of treatment, the outcomes of previous treatment, contact with a patient with tuberculosis.

Before receiving the results of lung tuberculosis in a man, it is important to correctly determine whether the patient belongs to high-risk groups. multiple drug resistance in a patient.

High-risk groups multiple drug resistance of tuberculosis in a patient:

- sick from reliable contact with a patient; multidrug-resistant tuberculosis in a patient;
- patients with tuberculosis who have previously received 2 or more ineffective courses of chemotherapy for tuberculosis;
- patients with recurrent tuberculosis and other cases of re-treatment, if they have previously been diagnosed with an addiction to one of the main drugs - isoniazid or rifampicin;
- patients with negative clinical and radiological dynamics of the process, as well as with persistence or appearance of bacterial excretion against the background of controlled treatment according to standard chemotherapy regimens;
- children with acutely progressive forms of tuberculosis from contact with patients who previously received two or more ineffective courses of chemotherapy for tuberculosis or who died from tuberculosis in the absence of results of determining the drug sensitivity of the pathogen.

Table 1  
 Chemotherapy regimens and combinations of anti-tuberculosis drugs

Point	Phases of the chemotherapy course	
	Intensive	Continuation phase
I	2-3 H Rb/R Z E	6 H Rb/R E [Z] 9* H Rb/R E [Z]
II	3 Km/Am[Cm]Rb/RZ Lfx [Sfx Mfx] [E] [Pto/Eto]	9 Rb/R Z Lfx [Sfx Mfx] [E] [Pto/Eto]
III	2-3 H Rb/R Z E	6 H Rb/R E [Z] 9* H Rb/R E [Z]

IV	8 Cm Lfx Z Cs/Trd Pto/Eto PAS [Km/Am] [E] [Mfx Sfx] [Bq]	12-18 Lfx Z Cs/Trd Pto/Eto PAS [E] [Mfx Sfx]
V	8 Cm Mfx [Lfx] Z Cs/Trd PAS Bq Lzd [E] [Pto/Eto] [Amx Imp Mp]	12-18 Mfx [Lfx] Z Cs/Trd PAS [Lzd][E] [Pto/Eto] [Amx Imp Mp]

Abbreviations: H - isoniazid, R - rifampicin, Rb - rifabutin, Z - pyrazinamide, E - ethambutol, Km - kanamycin, Am - amikacin, Pto - prothionamide, Eto - ethionamide, Cm - capreomycin, Fq - fluoroquinolone Lfx - levofloxacin Mfx - moxifloxacin, Sfx-sparfloxacin, Cs - cycloserine, Trd - terizidone, PAS - aminosalicyclic acid, Lzd - linezolid, Amx - amoxicillin-clavulanic acid, Imp - imipenemscilastatin, Mpq – meropenem

The first chemotherapy regimen is prescribed for tuberculosis patients with drug sensitivity of mycobacterium tuberculosis ... In the absence of bacterial excretion and information about mycobacterium tuberculosis, regimen III is assigned. The regimens include 4 drugs of the first (main) line: isoniazid, rifampicin or rifabutin, pyrazinamide, ethambutol. Rifabutin is prescribed instead of rifampicin if it is preferable in terms of interactions with antiretroviral therapy.

In the continuation phase of therapy, three main drugs are prescribed with the mandatory inclusion of isoniazid, rifabutin / rifampicin. The main course of treatment should be at least 8-9 months. In patients with tuberculous meningitis, meningoencephalitis, osteoarticular and generalized tuberculosis, the duration of the main course of treatment, even with preserved drug sensitivity, should be at least 12 months

People living with HIV with a drug-susceptible pathogen should receive an 8-9-month chemotherapy regimen:

intensive phase - at least 2-3 months isoniazid, rifampicin or rifabutin, pyrazinamide, ethambutol;

continuation phase of treatment - 6 months at least three drugs: isoniazid, rifabutin / rifampicin, pyrazinamide / ethambutol.

The second chemotherapy regimen is prescribed to patients with drug-resistant M. tuberculosis at least to isoniazid, but not to the combination of isoniazid and rifampicin, according to the drug susceptibility test at the beginning of the current course of chemotherapy.

The regimen includes five drugs: rifampicin or rifabutin, pyrazinamide, ethambutol, the latest generation fluoroquinolone, an aminoglycoside (kanamycin or amikacin), or capreomycin. Drugs to which there is resistance of mycobacteria are not prescribed to the patient, and the regimen is formed in the intensive phase of treatment from at least four, and in the continuation phase - from at least three drugs to which the sensitivity of the pathogen is preserved. The main course of treatment should be at least 12 months.

IV chemotherapy regimen can be prescribed without laboratory confirmation (standard):

- if it is reliably known that there was contact with a patient with multidrug-resistant tuberculosis (multidrug resistance at a probable source of infection should be documented);
- patients with tuberculosis who previously received 2 or more ineffective courses of chemotherapy for tuberculosis;
- patients with recurrent tuberculosis and in other cases of repeated treatment, if the patient has previously been diagnosed with LU to one of the main drugs - isoniazid or rifampicin;
- patients with tuberculosis in the absence of clinical improvement during controlled chemotherapy according to the I / III regimen for 2 weeks (provided that the inflammatory syndrome of the restoration of the immune system (IRIS) is excluded).

Correction of the initial empirical regimen (III or IV modes) of treatment is carried out after receiving a drug sensitivity test. If negative clinical and radiological dynamics is observed against the background of anti-tuberculosis treatment for 1 month according to the empirical regimen, it is necessary to repeat the sensitivity test by the accelerated molecular genetic method.

Children with TB / HIV co-infection should receive therapy with a combination of four drugs (isoniazid, rifampicin / rifabutin, pyrazinamide, ethambutol) for at least 3 months, followed by triple therapy (isoniazid / rifampicin / rifabutin / ethambutol / pyrazinamide) in for at least 6 months. It is strongly recommended to use a drug of the rifampicin group (rifampicin / rifabutin) in the anti-tuberculosis therapy regimen during the entire course of treatment. Therefore, the ARVT regimen in children for the period of tuberculosis treatment should be adjusted taking into account drug interactions of antiretroviral drugs with rifampicin or rifabutin.

If resistant tuberculosis is detected or if there is a high risk of MDR-TB for HIV-infected children and adolescents, reserve anti-tuberculosis drugs can be prescribed for health reasons, regardless of the patient's age (restrictions are indicated in the instructions for use of the drug), subject to the consent of the child's parents or his legal representative.

The progression of the tuberculous process in the first 3 months of (more often in the first month) may be associated with the inflammatory syndrome of immune reconstitution. Differential diagnosis and drug-resistant tuberculosis requires the use of accelerated molecular genetic methods for detecting mycobacteria and drug resistance.

#### *Diagnosis of tuberculosis in patients with HIV infection*

Approach to the diagnosis of tuberculosis in HIV-infected persons (adults and children) does not differ significantly from that of the uninfected.

This approach may have limitations for PLHIV for the following reasons:

- Clinical manifestations similar to those of tuberculosis may be associated with other secondary diseases, and therefore less specific for tuberculosis than in people with HIV-negative status.

- Immunological tests (TST, ATP test) in HIV-positive individuals (adults and children) with immunosuppressant have less sensitivity than HIV-negative.
- HIV-infected people are much more likely than HIV-negative people to have diseases due to several causes, which can mask the response to anti-tuberculosis therapy.
- In HIV-infected persons, radiographic changes in the lungs with tuberculosis can be similar to other secondary and opportunistic diseases, which complicates the interpretation of the ski logic picture by specialists in radiation diagnostics.
- Tuberculosis developing in patients with significant immunosuppressant (CD4 + lymphocyte count less than 200 cells /  $\mu$ l), often generalized with simultaneous damage to several systems and organs.
- Most HIV-infected children contract the virus perinatally. Therefore, the highest prevalence of HIV infection among children is in infants. And children under 5 years old, who make up the age group where it is most difficult to find out the cause acute or chronic lung disease, including tuberculosis.
- HIV-infected children are more likely to have chronic or acute pulmonary diseases than HIV-negative. All newly diagnosed HIV patients (adults and children) should be examined to exclude latent tuberculosis infection and active tuberculosis. On the other hand, all patients with tuberculosis should be offered HIV testing with conducting pre- and post-test counseling.

### *Tuberculosis symptoms*

The main symptom of pulmonary active tuberculosis is chronic cough. Also, the symptoms of tuberculosis include:

- Labored breathing.
- Sudden weight loss.
- Fever and fever.
- Increased night sweats.
- Severe chronic fatigue.
- Swollen lymph nodes.

All of these symptoms are "classic" symptoms of pulmonary tuberculosis. However, in people with HIV, they can have various causes that are not related to TB. However, when these symptoms appear, it is imperative to consult a doctor to rule out tuberculosis. People with very low immune status can suffer from "atypical" or "extra pulmonary" tuberculosis, which develops when the bacteria spreads from the lungs to other organs.

Tuberculosis can affect the lymph nodes; bone tissue, including the spine; tissue surrounding the heart (pericardium); membranes surrounding the lungs; organs of the digestive system; kidneys and urethra. Sometimes tuberculosis causes inflammation of the brain or spinal cord - meningitis. Symptoms of meningitis include irritability, insomnia, severe or worsening headaches, confusion, loss of consciousness, and seizures. In atypical tuberculosis, symptoms depend on which organs or tissues are infecting the bacteria, but symptoms such as fever, severe chronic fatigue, and sudden weight loss are "universal" for all forms of tuberculosis. HIV infection is spreading extremely quickly in our country.

A profound defect in cellular immunity in patients with HIV infection in the late stages of the disease when infected with tuberculosis can cause a severe course of the disease. Therefore, in the presence of patients with steadily progressive and widespread forms of tuberculosis

that do not respond to treatment, one should be wary of HIV infection. One of the factors explaining the pattern of the predominant combination of tuberculosis and HIV infection is the peculiarities of the mechanisms of the pathogenesis of both diseases. It has been proven that HIV infects and leads to death mainly T-lymphocytes, especially the population of T-helpers (CD4 + cells), which play a key role in anti-tuberculosis immunity.

A decrease in their amount in the human body seriously disrupts cellular immunity. The production of CD4 + lymphocytes of polonizing antibodies, interleukin-2, interferon- $\gamma$  decreases, which adversely affects the reactions of other effective cells. HIV also affects alveolar macrophages, monocots, and polynuclear cells, reducing their ability to migrate to the lungs. HIV infection significantly affects the state of immune-reactivity in tuberculosis, causing an absolute and relative decrease in the number of CD4 + cells, changing the relationship in the cellular immunity system, disrupting the differentiation of macrophages and the formation of specific granulation tissue.

While the morphology of tuberculosis inflammation does not change significantly in the early stages of HIV infection, specific granulomas do not form in the late stages of AIDS.

At the same time, the high incidence of tuberculosis among the population suggests that the majority of cases of this disease developing in HIV-infected people are associated with the reactivation of latent tuberculosis infection. This assumption is supported by the frequent detection of old fibrous or calcified tuberculosis changes in the lungs and in the in-trathoracic lymph nodes during autopsy of HIV-infected patients, containing viable mycobacterium tuberculosis and which were the source of tuberculosis reactivation. To diagnose latent tuberculosis, that is, to determine the presence of Mycobacterium tuberculosis, a tuberculin test (usually the Mantoux test) is most often used.

During this test, a tuberculosis protein is injected under the skin. After three days, redness should appear on the skin, as the immune system's reaction to protein. The immune response to the test indicates the presence of a past or present infection or vaccination. A large skin reaction is highly likely to indicate a bacterial infection. Unfortunately, the lack of response does not prove the absence of the pathogen. In HIV, the immune system may be suppressed and a skin test may be negative even if the bacteria is present in the body.

Also, vaccination against tuberculosis makes diagnosis by skin test difficult. More accurate tests for active or latent infection, ELISPOT, have recently been developed, which detects lymphocytes that respond to fragments of two unique proteins in the bacteria. This test is more reliable and provides results the next day. There are also other methods for determining the activity of a bacterium.

The gold standard for diagnosing active tuberculosis is the ability to culture the bacteria M. tuberculosis in a patient's sputum sample. However, this process can take weeks or even months. Treatment of active tuberculosis cannot be postponed for that period. Diagnosis and treatment are usually based on a combination of various factors, including symptoms, chest x-rays, and microscopic examination of sputum. It should be borne in mind that in people with HIV, the X-ray image for TB may look normal or similar to the image for other pulmonary diseases. In classic pulmonary tuberculosis, the sputum often contains bacteria that can be seen under a microscope. The diagnosis of pulmonary tuberculosis can be made with a repeated positive sputum test. However, this method is not as reliable for people with HIV.

Another problem is that a sputum sample is more difficult to obtain from people with HIV, as they may not have a chronic cough with sputum. Sometimes this requires taking a tissue sample from the lungs or lymph nodes for examination. Sometimes, when it is difficult to diagnose, the doctor will prescribe antibiotics for tuberculosis to see if the symptoms go away. Extra pulmonary tuberculosis is the most difficult to diagnose.

This often requires complex procedures to obtain tissue samples from an organ suspected of being affected by tuberculosis. The main clinical manifestations of tuberculosis against the background of HIV infection are asthenia, persistent or intermittent fever, prolonged cough, significant weight loss, diarrhea, enlarged lymph nodes, mainly cervical and auxiliary, less often inguinal, dense consistency, lumpy, poorly displaced on palpation.

The severity of the clinical manifestation of tuberculosis in HIV-infected and HIV-infected patients largely depends on the suppression of cellular immunity. At the initial stage, when the number of CD4 + lymphocytes is still high enough, the manifestations of tuberculosis may be the most typical and do not differ from the clinical and radiological picture in HIV-negative patients.

As the number of CD4 + lymphocytes in the blood decreases (up to 200 per 1 mm<sup>3</sup>), along with pulmonary lesions (or instead of them), extra pulmonary localizations of tuberculosis are more often found. The peculiarities of the clinical symptoms of tuberculosis in these cases are the increased frequency of extra pulmonary and disseminated lesions; negative skin reactions to tuberculin as a manifestation of energy, atypical changes on radiographs of the lungs and the relative rarity of cavity formation. In the later stages, the most severe, acutely progressive and widespread processes develop, such as military tuberculosis and meningitis, which are characterized by a sharp decrease in the number of CD4 + lymphocytes to 100 per 1 mm<sup>3</sup>.

Tuberculosis changes in the lungs in patients with HIV infection are characterized by the more frequent development of hilar adenopathy, military rashes, the presence of predominantly interstitial changes and the formation of pleural effusion. In about half of all cases, tuberculosis is ahead of other manifestations of AIDS by an average of 2 years.

When treating patients with tuberculosis in combination with HIV infection, it is usually necessary to simultaneously prescribe antiretroviral drugs. The higher efficiency of complex antiretroviral and anti-tuberculosis therapy is explained by the restoration and normalization of the body's immune responses. This is accompanied by an increase in the number of CD4 + lymphocytes in the blood and reversal of coetaneous tuberculin reactions.

Often, the restoration of immunity is clinically manifested by paradoxical reactions in the form of exacerbations of the tuberculosis process against the background of complex treatment. They reflect the elimination of energy and the normalization of the inflammatory response to tuberculosis infection. Currently, the prescription of antiretroviral drugs is becoming a necessary element of the treatment of tuberculosis with advanced forms of infection.

The number of such antiretroviral drugs is increasing every year, and their effectiveness is encouraging. However, side reactions, mainly hepato - and hematotoxic, with a combination of pathology are much more common. Broad promotion of preventive measures in the fight against tuberculosis, as well as health education about HIV infection will reduce the incidence of these infections.

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Clofazimine (Cfz)  
Amoxicillin/clavulanate (Amx-clv)  
Linezolid  
Thioacetazone  
Imipenem/cilastatin  
Clarithromycin  
High-dose isoniazid (16–20 mg/kg per day)

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Figure 1: Other drugs of uncertain efficacy used in treatment of DR-TB

The anti-tuberculosis therapy is a unique, two-phased chemotherapy consisting of initial intensive phase with multiple drugs (three or more) and continuation phase with two or three drugs. The multidrug initial intensive phase is given to take care of the drug-resistant organisms and to achieve ‘a quick kill’ to reduce the bacillary load, which in turn reduces the number of “persisters” in the lesions. “Persisters” are drug-sensitive organisms, which become dormant and are later responsible for relapses. The continuation phase of chemotherapy, consisting of two drugs is therefore given to kill the “persisters,” which show intermittent activity.

The role of individual drugs in first-line chemotherapy of TB is unique. Isoniazid is responsible for the initial kill of about 95% organisms during the first two days of treatment. Its bactericidal role is then replaced by rifampicin and pyrazinamide during the intensive phase. In the continuation phase, rifampin is the most effective drug against dormant bacilli (persisters), as shown by the similarity of response by patients with initially isoniazid-resistant or sensitive strains.

When either rifampin or isoniazid is not used, the duration of chemotherapy is 12 to 18 months. When both isoniazid and rifampin are used in treatment, the optimum duration of chemotherapy is 9 months. Addition of pyrazinamide, but not neither streptomycin nor ethambutol reduces the duration to six months. Prolongation of chemotherapy beyond these periods increases the risk of toxicity while providing no additional benefit. Second-line therapy duration ranges from 18 to 24 months.

Public health programs in many countries follow guidelines for treatment of TB developed by the World Health Organization (WHO). These guidelines were practiced till 2009 in which the treatment regimes were categorized into four categories. Categories 1–3 used a combination of first-line drugs for the shortest acceptable period. Category 1 is for treatment of new cases (an initial intensive phase (IIP) of four drugs ethambutol, isoniazid, rifampicin, pyrazinamide for 2 months and 4 months of continuation phase (CP) of two drugs isoniazid and rifampicin -2EHRZ/4HR).

Category 2 is “retreatment” regimen (8 months of isoniazid, rifampin, ethambutol, with pyrazinamide, and streptomycin added for the first 2 months—2SHRZE/1HRZE/5HRE) was recommended for relapse and retreatment cases. Category 3 recommended omission of ethambutol for children, patients, with smear-negative pulmonary or extra-pulmonary TB that is fully drug-susceptible and patients negative for Human immunodeficiency virus (HIV).

Category 4 was for treatment of drug-resistant TB using a standard treatment regimen (STR) using combination of second-line drugs; the initial phase five drugs, pyrazinamide (Z), kanamycin (Km), ofloxacin (Ofx), ethionamide (Eto) and cycloserine (CS) for 6-8 months and the continuation phase of three drugs, ofloxacin (Ofx), ethionamide (Eto) and cycloserine (CS) for 12 months. For treatment of XDR-TB, salvage chemotherapy may be considered using capreomycin (Cm), moxifloxacin (Mfx), para amino salicylic acid (PAS) +/- cycloserine (Cs) and two or three of additional agents from

Category	Treatment regimen
New sputum smear positive, Severely ill sputum smear negative Seriously ill extra pulmonary	2EHRZ+4HR
Relapse Retreatment Defaulter	2SHERZ+HERZ+5HRE
New sputum smear negative Not seriously ill extra pulmonary	2(E)HRZ/+4HR
Treatment failure	8Km-Ofx-Eto-Cs-E-Z+12Ofx-Eto-Cs-E

Figure 2: Previous World Health Organization (WHO) treatment categories

The category 1 treatment regimen was recommended based on the results of randomized trials. This regimen was found to have good bactericidal property (infectious patients quickly become non-infectious and sputum conversion occurs at two months in more than 90% cases) and good sterilizing property (low relapse rates of 0–2%), is equally efficacious in primary isoniazid resistant cases and has high cure rates even after premature discontinuation.

Further it was found suitable for adults and children, for pregnant and lactating women, for cases associated with diabetes mellitus (DM) and HIV infection, for cases with pre-existing liver diseases (but normal liver functions) and mild renal failure.

Unlike the category 1, the category 2 retreatment regimen was a product of expert opinion. It was originally designed for resource-poor settings with low prevalence of initial drug resistance, and for patients previously treated with a regimen that used rifampin only for the first two months of therapy.

However, this regimen was increasingly criticized because of poor results, particularly in settings where rifampin was used throughout initial therapy or prevalence of initial drug resistance was high. When used after failure of category 1 treatment, this regimen effectively allowed addition of SM, addition of one drug to a failing regimen, which was against the basic principle of TB chemotherapy. Similarly, in category 3 ethambutol omission was recommended based on the assumption that lesions in some cases like those negative for HIV, smear-negative pulmonary or extra-pulmonary TB harbour fewer bacilli and hence have little risk of selecting resistant bacilli. However, as initial resistance to isoniazid is common in many areas; a revised guideline in 2004 recommended that ethambutol be included as a

fourth drug during the initial phase of treatment even for smear-negative pulmonary or extra-pulmonary TB patients and effectively eliminated category 3.

These treatment categories were not only controversial but also created confusion for the treating physician. Therefore the WHO guidelines were revised and updated in 2009. It remains to be seen if the revised guidelines address deficiencies of the previous guidelines. However, the recommendation to start empiric second-line therapy in previously treated cases with high likelihood of MDR may result in hasty and casual initiation of second-line therapy and create further drug resistance resulting in XDR/XXDR/TDR. It would be reasonable to allocate treatment groups into more definitive categories.

While standard 2EHRZ/4HR should be used for all new cases, in cases where retreatment is required for relapse after first-line therapy, it is prudent to start first-line therapy and order drug susceptibility testing (DST). If DST is not available and the patient shows good response in 2–3 months or DST shows drug-sensitive disease, CP may be commenced and given for 7 months. Cases that show failure of fully supervised first-line therapy or show MDR-TB on DST should be treated with second-line drugs. Cases failed on MDR treatment or showing XDR on DST may be treated with salvage regimens.

Soon after streptomycin discovery and its clinical application to tuberculosis treatment it became apparent that the bacillus was capable of rapidly developing drug resistance. It was then found that para-aminosalicylic acid (PAS) could be used in combination with streptomycin to prevent, or delay, streptomycin resistance.<sup>1–3</sup> With the discovery of the anti-tuberculosis bactericidal activity of isoniazid, it was found that it was much more powerful in combinations with streptomycin and PAS than when used alone and the first combination chemotherapy regimens were standardized.

#### Tuberculosis chemoprophylaxis regimens

A patient with HIV infection can be assigned one of the regimens for chemoprophylaxis of tuberculosis, comparable in effectiveness and safety:

1. isoniazid (5 mg / kg) and vitamin B6 (15-25 mg / day) - 6 months,

2. isoniazid (5 mg / kg) and vitamin B6 (15-25 mg / day) + rifampicin (10 mg / kg) or rifabutin (5 mg / kg) - 3-4 months;

3. isoniazid 900 mg and vitamin B6 (15-25 mg / day) + rifapentine 900 mg (for a patient weighing more than 50 kg) once a week for three months. Recommended doses of drugs for the third CP regimen: isoniazid: 15 mg / kg; rifapentine (by body weight): 10.0-14.0 kg = 300 mg; 14.1-25.0 kg = 450 mg; 25.1-32.0 kg = 600 mg; 32.1-49.9 kg = 750 mg; ≥ 50.0 kg = 900 mg. The patient makes 12 visits to the doctor (once a week). The CP regimen, including isoniazid and rifapentin, should be carried out under the direct supervision of medical personnel (controlled CP). The drug rifapentine as part of the CP tuberculosis regimen can be used only in patients with HIV infection who are not receiving ART, since the appointment of rifapentine is contraindicated in therapy with HIV protease inhibitors and non-nucleoside HIV reverse transcriptase inhibitors.

For HIV-infected patients who have come into contact with tuberculosis patients with known (documented) MBT resistance to at least isoniazid, rifampicin (MDR), it is possible to prescribe individual prophylactic treatment with reserve anti-tuberculosis drugs for a period of at least 3 months. CP with reserve drugs should be prescribed by a phthisiatrician who

observes the patient by contact, in agreement with the regional coordinator for the combination of HIV and tuberculosis and should be carried out under direct supervision.

*With contraindications to the appointment of rifampicin, rifabutin, rifampentin, alternative treatment regimens are:*

1. isoniazid (5 mg / kg) and vitamin B6 (15-25 mg / day) + pyrazinamide (25 mg / kg) - 3-4 months.

2. isoniazid (5 mg / kg) and vitamin B6 (15-25 mg / day) + ethambutol (15 mg / kg) - 3-4 months

*The priority is the prescription of combined anti-tuberculosis drugs.*

The duration of CP should be increased if a patient with HIV infection continues to be in the focus of tuberculosis infection for the duration of the outbreak or is in prisons, where chemoprophylaxis with isoniazid should preferably be carried out for 36 months (due to the high incidence rate and the possible risk of contact with patients with tuberculosis). When carrying out CP tuberculosis, it is necessary to monitor the functional state of the liver (the level of aminotransferases, total bilirubin) 1 month after the onset of CP and then once every 3 months with isoniazid monotherapy, and once a month with a combined prophylactic treatment regimen. With an initially elevated level of aminotransferases, the first study of a biochemical blood test should be carried out 2 weeks after the start of chemoprophylaxis and monthly thereafter.

Combined treatment regimens are not recommended for pregnant women, only isoniazid monotherapy. The main criterion for the effectiveness of CP is the absence of cases of development of active tuberculosis in persons who received CP during the next 2 years. Tuberculosis chemoprophylaxis and antiretroviral therapy. With indications for the appointment of ARVT and CP in patients with HIV infection with a CD4 + lymphocyte count of less than 100 cells /  $\mu\text{L}$ , in order to prevent the development of the immune system restoration syndrome, chemoprophylaxis of tuberculosis is initially prescribed, and antiretroviral therapy is added after 5-7 days.

When prescribing drugs from the rifampicin group together with ARVT, attention should be paid to their interaction with antiretroviral drugs. The drug interaction scheme is presented. Responsibility for the organization of CP TB for patients with HIV infection is assigned to the regional coordinator for the problems of co-tuberculosis / HIV infection.

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