4 Management of Tuberculosis and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology of TB, TB/HIV/AIDS and reciprocal influence of TB and HIV

1. Epidemiology of TB

Tuberculosis (TB) is a serious public health problem in the WHO European Region, where according to the most recent WHO estimates, almost 445 000 new cases and more than 69 000 related deaths occurred in 2004. The overall TB incidence rate for the Region is 50 per 100 000 population, ranging nationally from 2/100 000 in Monaco to 177/100 000 in Tajikistan. By subregion, the rates are 12/100 000 for western Europe, 27/100 000 for central Europe and 96/100 000 for eastern Europe. Among the 22 high-burden TB countries in the world, the Russian Federation ranks 12th *(1, 2)*.

As noted, the highest rates of TB are reported in the countries of eastern Europe, where weakened economies and public health efforts are the main causes of its resurgence, and where internationally recommended control strategies need further expansion and strengthening. In western Europe, there are pockets of increasing incidence, particularly in major cities with socially marginalized immigrants from high-burden TB countries *(3, 4)*.

The European Region has the highest prevalence rates in the world for multidrug-resistant TB (MDR-TB); it includes seven of the nine countries in the world with >6.5% prevalence of MDR-TB in new cases (Estonia, Israel, Kazakhstan, Latvia, Lithuania, the Russian Federation and Uzbekistan), as well as five of the nine countries with >30% prevalence of MDR-TB in previously treated cases (Estonia, Kazakhstan, Lithuania, the Russian Federation and Uzbekistan) *(5)*.

TB is more frequently found among prisoners than in the outside population. The average prison population rate in the European Region is about 100 prisoners per 100 000 inhabitants, with higher rates in the eastern part of the Region. In the Russian Federation, the 2003 rate was approximately 600/100 000 *(6)*. In 2003, more than 7% of the new TB cases reported to WHO Regional Office for Europe were detected in prisons, with large variations among countries (range 0.1–30.4%) *(7–10)*.

2. Epidemiology of TB/HIV coinfection

In eastern Europe there are independent epidemics of TB and HIV/AIDS, and a large majority of TB patients developed their disease without HIV-related immunosuppression. Among people living with HIV (PLHIV), the risk of acquiring TB is higher where the TB prevalence is high. In 2004, western and eastern European countries reported TB as the most frequent AIDS-indicative disease, with respective rates of 24% and 56% of newly reported AIDS cases *(11, 12)*. Unfortunately, knowledge of the real extent of TB/HIV coinfection in Europe is limited due to insufficient surveillance data. As the result of the recent dramatic increase of HIV prevalence in eastern Europe, as well as the high prevalence of TB there, it is expected that the number of TB/HIV patients will dramatically increase in the next few years *(12–14)*.

Prisoners are more vulnerable to becoming infected with TB and HIV due to environmental and nutritional factors that increase their exposure, vulnerability and risk-taking behaviour. Prisons, with their often crowded and enclosed conditions, poor ventilation, inadequate lighting and continuous exposure to TB-infected people, facilitate airborne TB transmission. Malnutrition also contributes to the higher risk for prison transmission. In addition, common prison behaviours – unsafe injecting drug practices, tattooing and unprotected sex – expose prisoners to HIV infection, as well as hepatitis B and C *(15)*.

3. Reciprocal influence of HIV and TB

3.1. Influence of HIV on the development of active TB

HIV promotes the progression of infection with Mycobacterium tuberculosis to active TB, both in people with recently acquired infections and those with latent infections. Undeniably, HIV is the most powerful risk factor known for activation of latent M. tuberculosis infection. For an HIV-infected person-coinfected with M. tuberculosis, the risk of developing active TB reaches 5–10% annually, instead of the 5–10% lifetime risk for an individual not infected with HIV. This discrepancy is clearly linked to the immunodeficiency caused by HIV. Furthermore, HIV infection increases the rate of recurrent TB, which can be due to either endogenous reactivation or exogenous reinfection *(16, 17)*.

3.2. Influence of HIV on the transmission of TB

TB is one of the most common infections in HIV-infected people, especially in high TB prevalence areas. HIV greatly increases the number of TB patients, which in turn increases TB transmission from family members (the highest TB transmission risk is from household contacts, such as children and HIV-positive partners) and community members (through contact in work-places, schools and hospitals) where there is a risk of nosocomial infections from both patients (whether HIV-positive or -negative) and health care workers. Moreover, the risk of MDR-TB transmission may be increased if effective and uninterrupted TB treatment is not ensured *(18–20)*.

3.3. Influence of HIV on the clinical presentation of TB

As HIV infection progresses, CD4 lymphocytes decline by about 50–80 cells/mm^3/year, and the immune system becomes less able to prevent the growth and local spread of *M. tuberculosis*.

Pulmonary TB (PTB) remains, especially in adults, the commonest form of TB, but its presentation depends on the degree of immunosuppression. The clinical pictures, sputum-smear results and chest X-rays are often different in the early stage of HIV infection (CD4 >350 cells/mm^3) and the late stage (CD4 <200 cells/mm^3). The clinical presentation of TB cases in early HIV infection is similar to that of individuals without HIV infection, resembling post-primary PTB, that is, with positive sputum smears (defined as two or more initial smear examinations that are positive for acid-fast bacilli (AFB), or one plus consistent radiographic abnormalities) and often with cavities in the chest X-ray. In contrast, the clinical presentation in late HIV cases resembles primary PTB: the sputum smear is often negative and radiological infiltrates are present instead of cavities *(21–23)*. In case of severe immunodeficiency, the rate of extrapulmonary TB (EPTB) increases in both adults and children. Because of difficulties in diagnosis, disseminated TB may account for a high proportion of misattributed hospital deaths.

3.4. Influence of TB on HIV morbidity and mortality

Active TB itself is responsible for a mild immune deficiency. In countries with independent epidemics of TB and HIV/AIDS, TB does not always indicate severe deterioration of the immune system in HIV-infected people because it may occur before HIV infection or in its early stages, before the immune system has deteriorated. When active TB occurs in HIV patients, a worsening of the HIV-related deficiency is commonly observed, facilitating the progression of other opportunistic infections such as *Candida albicans* oesophagitis, *Cryptococcus* meningitis and, particularly, *Pneumocystis jirovecii* (formerly *P. carinii)* pneumonia. Any of these opportunistic infections may be lethal. If so, TB is indirectly responsible for the death *(24)*.

In addition, TB has been found directly responsible for an average mortality rate of 30% among HIV/AIDS cases in many reports *(22, 23, 25)*. These data emphasize the need of early diagnosis and specific treatment of TB in all HIV-infected patients, especially when the clinical pattern of CD4 cells count shows a severe degree of immunodeficiency.

II. Identification of TB/HIV in adults and adolescents

All HIV-positive people should be assessed for risk factors for having or acquiring TB, just as all patients with active TB disease should be offered HIV testing and counselling. The major reasons for this are:

- HIV-positive people are at higher risk for having or developing active TB, one of the major opportunistic infections causing death in PLHIV;
- HIV infection influences the clinical progression of TB and its treatment;
- TB disease influences the clinical progression of HIV/AIDS and its treatment; and
- TB may be an indicative sign of advanced HIV/AIDS disease.

1. TB risk assessment and diagnosis in PLHIV

In assessing PLHIV for TB risk, particular attention should be paid to:

- people with respiratory symptoms;
- household contacts of anyone with an active case of pulmonary TB; and
- coexisting risk factors and vulnerability-increasing factors (e.g. injecting drug use, alcohol abuse and incarceration).

The initial assessment for TB should include:

- a history of TB exposure (individual and household); and
- a history of possibly related symptoms (especially a cough of more than two weeks duration without any clear explanation).

If an HIV-infected person does not have an obvious risk for TB (recent exposure or clinical symptoms), a tuberculin skin test[1] should be performed to identify the status of any latent TB infection that may evolve into TB disease due to HIV-related immunosuppression. (See Fig. 1 below.)

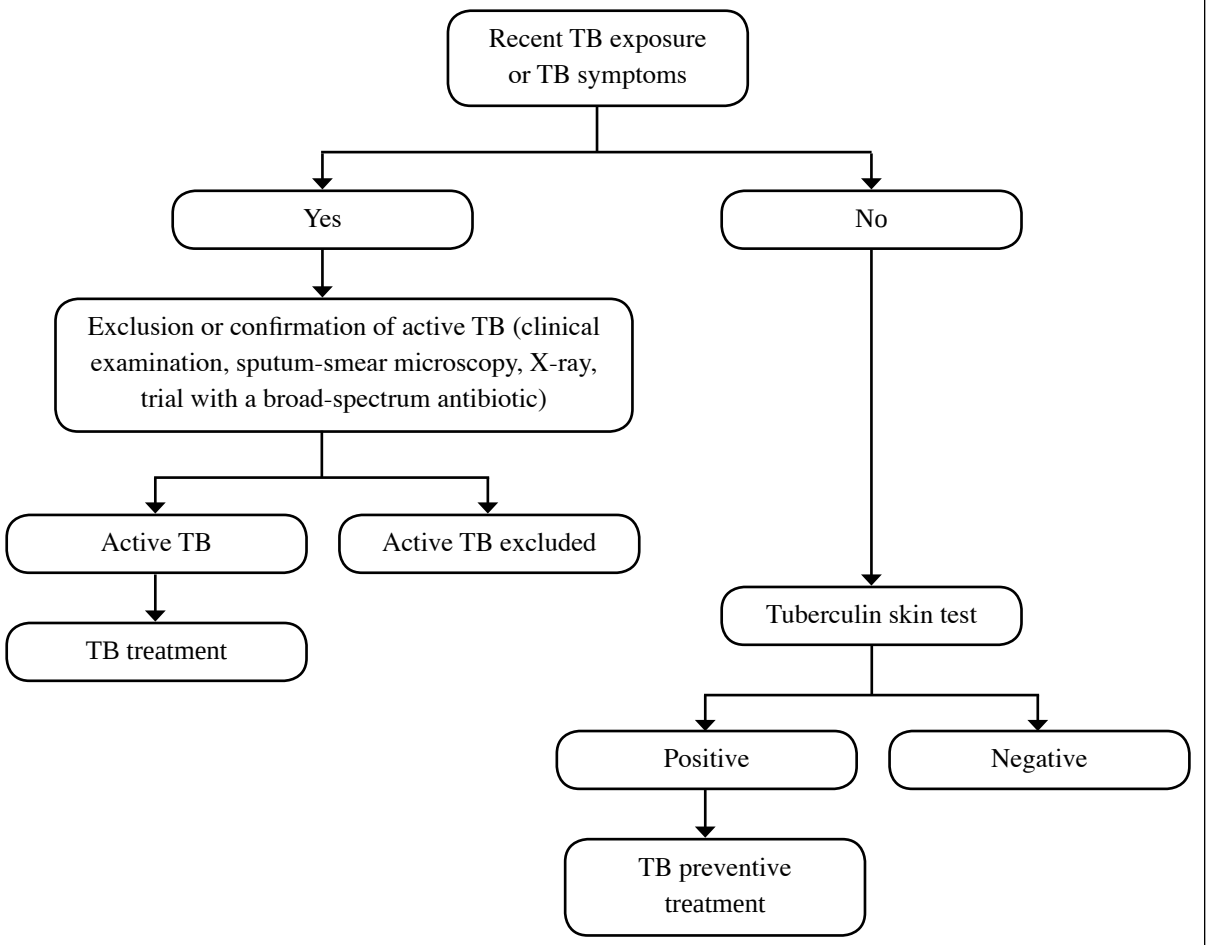
A positive tuberculin skin test is indicative of past or recent TB infection, which is a condition for starting TB preventive treatment (TPT). A negative tuberculin skin test in PLHIV usually means no risk of TB (except in those with severe immunosuppression).

If an HIV-infected person has been recently exposed to TB or has clinical symptoms indicative of pulmonary or extrapulmonary TB disease, the status of active TB disease should be explored. Active TB can be excluded through careful clinical examination, bacteriological investigation (sputum microscopy and culture) and X-ray. In case of infiltrate in the chest X-ray, a clinical trial with a full course of broad-spectrum antibiotics may be necessary to make a diagnosis differentiating between TB and nonspecific pneumonia. When active TB disease is excluded, the possibility of latent TB infection should be explored through a tuberculin skin test.

If an HIV-infected person has active TB disease, he or she should be treated as described in section III below.

[1] Tuberculin is a purified protein derived from tubercle bacilli. Tuberculin injected into the skin of a TB-infected person produces a delayed local reaction after 24 to 48 hours, which is quantified by measuring the diameter of the related skin induration (thickening). The test is usually considered positive in HIV-infected people when induration exceeds 5 mm. The reaction only shows that the person has at some time been infected with *M. tuberculosis (15, 17).*

Fig. 1. Algorithm for assessing TB risk and disease in an HIV-positive person



2. HIV risk assessment and diagnosis in patients with TB

Offering HIV testing and counselling should be a routine procedure in health care settings dealing with patients who have active TB. Health care providers should explain to the patients the reasons for offering the test and the importance of knowing the results for correct clinical management. However, all patients have the right to refuse an HIV test. The initial assessment of a patient's HIV status should include:

- HIV pretest counselling;
- serological tests (typically, ELISA and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test; and
- post-test counselling, including information on reducing risky behaviour, irrespective of the results of the HIV test.

Further evaluation of patients found to be HIV-infected is required to decide on a clinical management strategy. For more detailed information, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of TB/HIV in adults and adolescents

For clinical management of TB/HIV-coinfected patients, a major consideration is when to start treatment.

After initial assessment of TB and HIV status, a patient with TB/HIV would fit in one of two TB categories, each requiring a different clinical management strategy, and each of which may or may not require ART:
1. TB-infection (positive tuberculin skin test)
2. active TB disease.

1. Management of coinfected patients

HIV-infected patients coinfected with TB have a higher risk of developing active TB; therefore, tuberculosis preventive treatment (TPT) should be initiated with isoniazid 5 mg/kg (300 mg maximum) once daily (OD) for six months.

Alternative schedules have been suggested to improve adherence, but further research is needed to prove their efficacy. Further research is also needed for developing alternative TPT in areas with high prevalence of isoniazid resistance *(26–28)*. The addition of 6 mg pyridoxine daily can prevent peripheral neuropathy, especially in pregnant women, alcoholics and the malnourished.

The decision of when to start ART is based on a number of indicators, of which the most important are the HIV/AIDS clinical stage and immunological criteria (please refer to the section on Initiation of HAART and WHO Clinical staging of HIV/AIDS for adults and adolescents, in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*).

TPT can also be given simultaneously with ART. More evidence is required to identify the threshold of CD4 count above which TPT can be considered less necessary.

2. Management of coinfected patients with active TB

2.1. TB treatment

TB treatment in HIV-infected patients is a priority and should be started as soon as active TB has been diagnosed. Treating TB promptly will reduce TB-related mortality and the risk of transmission *(15, 29, 30)*.

Treatment of TB, regardless of its concomitance with ART, should be based on drugs of known bioavailability. TB treatment regimens consist of two phases: an initial phase and a continuation phase. Each TB drug has an abbreviation (ethambutol: E, isoniazid: H, pyrazinamide: Z, rifampicin: R, streptomycin: S); for further information on drug dosages see Annex 1. The duration of the initial phase is 2–3 months, the continuation phase, 4–5 months. Present evidence clearly shows that TB relapse in HIV-infected patients is minimized by a regimen containing rifampicin throughout the course of treatment.

Table 1. Recommended TB treatment regimens for PLHIV with active TB

Type of TB case	TB treatment regimen[a]	
	Initial phase[b]	Continuation phase
New TB patient	HRZE 2 months[c]	HR 4 months
Previously TB-treated patient, including: • relapse • treatment after default • treatment failure[d]	HRZES 2 months or HRZE 1 month	HRE 5 months
Chronic or MDR-TB cases (still sputum-positive after supervised re-treatment)	A specially designed regimen, whether standard or ad hoc	

E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin; Z: pyrazinamide.
[a] Daily TB treatment is recommended for HIV-positive patients with active TB.
[b] Direct observation of drug intake is recommended during the entire course of therapy, particularly in the initial phase.
[c] Streptomycin may be used instead of ethambutol. In meningeal TB, ethambutol should be replaced by streptomycin, which diffuses more in the meninges.
[d] Whenever possible, drug sensitivity testing should be done to enable an individualized treatment regimen.

2.2. Initiation of antiretroviral treatment

Many patients with active TB have advanced HIV disease and are therefore eligible for ART, which should not be withheld simply because a patient is receiving or is about to receive TB treatment. Nevertheless, it is preferable not to initiate treatment for HIV and TB simultaneously, and when possible to delay ART (see Table 2) *(31–34)*. This strategy:

- simplifies patient management
- avoids antiretroviral (ARV) and TB drug interactions
- avoids overlapping toxicities
- limits risk of immune reconstitution inflammatory syndrome (IRIS)
- minimizes confusion about what drugs to take when, and for which disease
- increases adherence.

Table 2. Strategy for initiation of treatment for both TB and HIV infection

Criteria	TB treatment	ART
Extrapulmonary TB (regardless of CD4 count)	Start immediately	Start ART as soon as TB treatment is tolerated (between two weeks and two months)[a].
Pulmonary TB CD4 <200 cells/mm^3	Start immediately	
Pulmonary TB CD4 = 200–350 cells/mm^3	Start immediately	Start ART after completion of initial TB treatment phase (start earlier if severely compromised).
Pulmonary TB CD4 >350 cells/mm^3	Start immediately	Monitor CD4 count. Consider ART if CD4 cell count drops below 350 cells/mm^3.

[a] The decision to start ART should also be based on clinical evaluation of other signs of immunodeficiency.

2.3. First-line HAART regimens

Highly active antiretroviral treatment (HAART) is the standard recommended ART. It includes three or in some cases more ARV drugs. The main factors to consider in selecting the best ARV regimens for TB patients are:

- potency
- side effects and toxicity
- simplicity, to allow better adherence.

ART during TB treatment requires giving special consideration to:

- interactions between rifampicin and some ARVs
- pill burden
- the importance of high adherence
- drug toxicity
- the risk of immune reconstitution syndrome.

Table 3. Recommended first-line HAART for patients being treated for TB with rifampicin[a]

	ARV drug classes	HAART regimes
Preferred	2 NRTIs + 1 NNRTI	ZDV (or TDF) + 3TC (or FTC) + EFV[b]
Alternative	3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC (or TDF)

[a] See Annex 2 for dosages

[b] Recommended efavirenz (EFV) dose is 600 mg/day especially in patients with <60 kg body weight *(35–37)*. Increasing the dose to 800 mg/day can be considered in patients with >60 kg body weight, though further research is needed. If EFV is not available, Nevirapine (NVP) can be used [200 mg OD for 2 weeks followed by 200 mg twice daily (BID)] with close monitoring of liver function and drug toxicity. [ZDV + 3TC + NVP is available in an fixed-dose combination (FDC).]

2.3.1. Key considerations for first-line regimens

ZDV (or TDF) + 3TC (or FTC) + EFV (see Table 3)

- No rifampicin dose adjustment is required
- EFV decreases methadone levels significantly; this is important to remember for treatment of injecting drug users (IDU) on opioid substitution therapy. For further information please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*

ZDV + 3TC + ABC (or TDF) (see Table 3)

- No rifampicin dose adjustment is required.
- Pregnant women with TB can safely use ZDV + 3TC + ABC.

For additional considerations regarding first-line ART regimens, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

2.3.2. Treatment failure

Response to ART is monitored by clinical symptoms, CD4 count and viral load. For further information on treatment failure criteria please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

TB is not a criterion for treatment failure in itself and if it occurs without other evidence of immunodeficiency in patients on a first-line regimen, they should not be switched to a second-line regimen. If a patient on a second-line ART develops TB during treatment, the protease inhibitor (PI) component needs to be adjusted.

2.4. Second-line HAART regimens

Table 4. Recommended second-line HAART for patients receiving TB treatment with rifampicin

	ARV drug classes	HAART regimens
Preferred	2 NRTIs + 2 PIs (one of them boosted)	ABC + ddI + LPV/r + RTV or TDF + ddI + LPV/r + RTV
Alternative	2 NRTIs + 2 PIs	ABC + ddI + SQV + RTV or TDF + ddI + SQV + RTV

2.4.1. Key considerations for second-line regimens

ABC (or TDF) + ddI + LPV/r + RTV (see Table 4)

- If ddI is administered with TDF, its dosage should be adjusted due to toxic pancreatic and negative immune effects. The recommended dose of ddI when administered with TDF (300 mg OD) is:
  - 250 mg OD for patients with >60 kg body weight
  - 125–200 mg OD for patients with <60 kg body weight *(38, 39)*.
- When LPV/r 400/100 mg BID is administered, RTV 300 mg BID should be added, with close monitoring of liver functions and lipid levels.

ABC (or TDF) + ddI + SQV + RTV (see Table 4)

- When SQV is administered, the recommended daily dosages of SQV and RTV are each 400 mg, and close monitoring of liver functions is required.
- No rifampicin dosage adjustment is required with these regimens.

2.5. ARV and TB drug interactions and management

- Rifampicin stimulates the activity of the hepatic cytochrome P450 (CYP) enzyme system that metabolizes NNRTIs and PIs (see Annex 2 for ARV classes). This mechanism leads to a reduction in the blood levels of NNRTIs and PIs, and consequently the incomplete suppression of HIV replication and the emergence of drug resistance. Rifampicin causes up to a 75% reduction in the serum levels of PIs, thus necessitating dosage adjustment.
- NNRTIs and PIs can also enhance or inhibit CYP and lead to altered blood levels of rifampicin. Therefore, when rifampicin is used concomitantly with NNRTIs and PIs, a daily regimen is preferred *(40–42)*.
- The effects of rifampicin and NNRTIs and PIs on the CYP are both complex and common, but unless a definitive contraindication exists, rifampicin is the preferred TB drug. The reason is that the rate of TB relapse in HIV-positive patients becomes as low as in HIV-negative patients when treated for ≥6 months with rifampicin-containing regimens.
- Rifampicin has no effect on the serum levels of nucleoside reverse transcriptase inhibitors (which are not metabolized by CYP), and no dosage adjustment of these drugs is necessary.
- In patients on second-line ART, rifabutin 150 mg every other day (QOD) or 3 times/week can be used safely as an alternative to rifampicin. Rifabutin may be preferred in settings with a limited capacity to adjust PI dosage; however, it is more expensive than rifampicin.
- Rifabutin should not be prescribed with unboosted SQV, but it can be used with combination of SQV with RTV.

2.6. Cotrimoxazole primary prophylaxis

TB/HIV-coinfected patients may die soon after the commencement of treatment if it is started at too advanced an HIV/AIDS stage. Death may be related to the progression of TB itself, but in many cases the death is related to the progression of other opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PCP) or *Toxoplasma gondii* encephalitis (TE) *(32)*. Therefore, primary prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole) is needed as prophylaxis against PCP and TE.

- Patients with a CD4 count <200 cells/mm^3 or who are at Clinical Stage 3 (with oropharyngeal candidiasis, for example) or Clinical Stage 4 should receive cotrimoxazole simultaneously with TB treatment (if indicated) until the CD4 cell count has stabilized for 4–6 months, or at least 3 months at >200 cells/mm^3.
- The recommended prophylaxis with cotrimoxazole in adults is one double-strength tablet: 160/800 mg OD.
- Adherence to cotrimoxazole is critical, and direct observation of its administration, together with the administration of TB drugs, may be useful, particularly in very ill patients.

For more information, please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS*, section on OI prophylaxis in HIV infected patients.

3. Clinical management of TB/HIV in special conditions

3.1. Renal failure

- Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosage to patients with renal failure.
- Patients with severe renal failure should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.
- Streptomycin and ethambutol, however, are excreted by the kidney. They should be given in reduced doses, and renal function should be monitored closely (creatinine level monthly).
- TDF should be avoided in ARV regimens due to its known nephrotoxicity.

Table 5. Recommended TB regimens for patients with renal failure[a]

	Initial phase	Continuation phase
Preferential	HRZ 2 months	HR 4 months
Alternative (if monitoring of renal function is possible)	HRZE 2 months	HR 4 months

[a] Renal failure is defined as occurring when the creatinine level increases to 130–160 micromoles/litre.

3.2. Liver disease

- Isoniazid, rifampicin and pyrazinamide are all associated with drug-induced hepatitis.
- Pyrazinamide is the most hepatotoxic, followed by rifampicin. Rifampicin is less likely to cause hepatocellular damage, although it is associated with cholestatic jaundice.
- Patients with liver disease should not receive pyrazinamide. Alternative TB treatment regimens are listed in Table 6.
- Clinical monitoring of the liver and laboratory monitoring of liver enzymes should be performed to detect any exacerbation of the condition. They should be done on a regular basis, at a frequency that depends on the patient's condition.

Table 6. Recommended TB regimens for patients with liver disease[a]

	Initial phase	Continuation phase
Preferential	SHRE 2 months	HR 6 months
1st Alternative	SHE 2 months	HE 10 months
2nd Alternative	RE 9 months	–

[a] Liver disease is defined as an alanine aminotransferase (ALT) exceeding three times the normal level, or the presence of chronic hepatitis or cirrhosis.

3.3. Women of childbearing age

- Rifampicin and some ARV drugs (mainly PIs) can reduce estrogen levels, so oral contraceptives containing estrogen may not be effective. For more information on contraception choices, please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV.*
- If effective contraception is ensured, TB/HIV-coinfected women may receive a regular TB treatment regimen and the same ARV regimen as men, including EFV; otherwise, EFV must be avoided. ABC is a recommended alternative to EFV.

3.4. Pregnant women

- The strategy for initiating TB treatment and ART in pregnant women is the same as in men and non-pregnant women (please see Table 2 in section III.2.2 above).
- Condoms should be recommended to TB/HIV-coinfected pregnant women as well as to all HIV monoinfected women to reduce risk of HIV superinfection (additional infection with the same or another HIV subtype) and other STIs.
- Most first-line TB drugs are safe for use in pregnancy. The exception is streptomycin, which is ototoxic to the fetus and should not be used during pregnancy (except for meningeal infections) or lactation due to the potential for serious adverse reactions in nursing infants *(43).*
- If a TB/HIV-coinfected woman decides to carry a pregnancy to term, she should receive ARV prophylaxis for prevention of mother-to-child transmission. For further information please refer to Protocol 10, *Prevention of HIV infection transmission from HIV-infected mothers to their infants*.
- If proper case management of TB and ART is carried out, the monitoring of treatment should be the same as for other adults.

3.5. Injecting drug users

The clinical management of TB/HIV in IDUs is challenging and requires more effort due to the following factors:

- interaction of TB and ARV drugs with illicit drugs and resultant increased hepatotoxicity in those IDUs receiving opioid substitution therapy;
- a decrease in methadone levels (33–68%) or withdrawal caused by rifampicin (the methadone dose may need to be increased);
- larger likelihood of coinfection with hepatitis C and/or B, and therefore of potential drug interactions with hepatitis drugs;
- decreased adherence levels; and
- decreased access to the health care system.

Collaboration with harm-reduction programmes *(44, 45)* may be essential in organizing effective outreach services such as education, screening, TB preventive treatment, directly observed treatment (DOT) for TB and the tracing of treatment defaulters.

It is important to keep in mind the following.

- Rifampicin should not be administered with LPV/r, NFV or SQV in patients receiving methadone substitution therapy. Rifabutin is an option, administered as 150 mg 3 times/week with

LPV/r or 300 mg 3 times/week with NFV.
- Rifabutin should not be used together with SQV.

For more information, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*.

4. Monitoring TB/HIV-coinfected patients

4.1. Monitoring TB treatment

For most patients, unless there is drug resistance, TB treatment is effective, and their clinical status improves starting in the second or third week. In TB patients with advanced HIV infection or with late diagnoses for both diseases, a clinical or radiological worsening may be observed. Moreover, treatment with normally effective TB drugs may be unable to reverse clinical course in the late stages of HIV.

During the initial 2–4 weeks of TB treatment, during which patients are preferably hospitalized, a complete clinical evaluation should be done at least weekly. ALT must be assessed at least once at the end of the first month. Hepatotoxicity may be observed in up to 5–10% of coinfected patients.

A patient's ability to swallow a pills should be verified, and adherence should be checked regularly. Exceptionally, severe chronic diarrhoea can be responsible for drug malabsorption and treatment failure; such a condition requires the use of injectable TB drugs. Even without diarrhoea, HIV-infected patients may not absorb rifampicin adequately. In case of severe gastrointestinal intolerance, which occurs in up to 10% of HIV patients, priority should be given to TB treatment and ART stopped until recovery from gastrointestinal symptoms.

TB treatment stops at the end of the continuation phase. There is still not enough evidence supporting the utility of secondary TB treatment in preventing further relapses.

For patients who adhere to TB regimens, the prognosis for TB itself is good. Exceptions are:
- patients with MDR-TB, who should be referred to specialized treatment centres because of their complex management; and
- patients who are just beginning TB treatment at an advanced HIV/AIDS stage.

4.2. Monitoring antiretroviral treatment

Monitoring patients receiving ART should include clinical signs and symptoms, immunological and virological criteria, and ARV toxicity and side-effects. After initiation of ART, immune reconstitution inflammatory syndrome (IRIS) can occur, especially in severely immunosupressed patients. Such worsening of clinical HIV/AIDS disease after initial improvement may occur in up to a third of patients with TB who have started ART. The average time of onset is two months after ART initiation, but it can occur as early as five days after. IRIS is thought to be the result of immune restitution due to administration of antiretroviral and/or TB drugs. IRIS is more common if ART is started early in the course of TB treatment, and if the patient has a very low CD4 count *(46, 47)*.

The exacerbated signs and symptoms are due to a more effective local tissue reaction to infection, due to *M. tuberculosis* or some other opportunistic infection(s). These signs and symptoms include a combination of:
- high fever
- occurrence or enlargement of peripheral or mediastinal lymphadenopathy
- expanding lesions in the central nervous system
- worsening of chest radiographic findings.

The diagnosis of IRIS should be made only after a thorough evaluation has already excluded other etiologies, particularly a failure of the TB treatment. Most cases resolve without any intervention, and ART can be safely continued. Serious reactions, such as tracheal compression due to massive adenopathy or respiratory therapy, may require a short course of steroids. Prednisone may be given at the dose of 20–60 mg/day for at least two or three weeks, gradually decreasing in dose over at least one month *(48, 49)*.

For information about ARV drug toxicity and its management please refer to the section Management of ARV toxicity and side-effects in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

Patients treated for TB and HIV should be followed regularly for clinical evaluation of tolerance to treatment. The tests to be performed are summarized in Table 7.

Table 7. Monitoring of patients on ARV and TB treatment

Assessment	Week				Month									
	0	2	4	8	3	4	5	6	7	8	9	10	11	12
TB and HIV disease history	X													X
Physical examination	X	X	X	X	X			X						X
Comorbidities	X				X			X						X
Gynaecological examination	X							X						X
Routine laboratory tests: • haemoglobin • full blood count with differential and platelets • liver function tests (ALT, possibly AST and bilirubin) • creatinine • urine	X	X	X	X	X			X						
CD4 count	X			X				X						X
Viral load (if available)	X			X				X						X
Chest X-ray	X													X
Pregnancy test	X													X
Sputum-smear examination[a]	X			X	X		X	X		X				
Adherence (both TB and ART treatment)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Required at the end of the third and eighth month only when on 8-month TB treatment regimen.

4.3. Adherence to TB treatment and ARV treatment

Adherence is crucial for the success of both TB and ARV treatment. Patients with poor adherence are at very high risk for developing drug-resistant strains of M. tuberculosis and HIV. Drug-resistant TB and HIV are very difficult to treat effectively and can be transmitted to others. DOT is recommended to reinforce adherence to TB treatment, combined with context-specific and patient-sensitive support *(50)*. For ART, more than 95% adherence is required to achieve optimal HIV suppression and treatment outcome *(51)*. The importance of adhering to treatment and consequences of poor adherence should be fully understood by patients and properly covered during patient counselling.

Adherence to treatment of TB and HIV/AIDS should be closely monitored and explored at every visit. The effective management of adverse reactions to drugs is very important and considered an essential condition for ensuring adherence to treatment (For more information on adherence please see the sections Adherence to ART and Monitoring adherence both in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*).

For both TB and ART, adherence may be challenging in special population groups, such as IDUs. (For detailed information about factors influencing adherence in IDUs, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*)

IV. Identification of TB/HIV in infants and children

Children are usually infected with TB through contacts with an adult or another child with sputum smear-positive PTB, often a family member. In the absence of interventions to prevent its transmission, infants typically acquire HIV when exposed to HIV-infected fluids (principally blood) in utero or during labour.

Without preventive TB treatment, 40–50% of HIV-positive infants and 15% of HIV-positive older children will present with symptoms of TB disease within one or two years of becoming infected with TB. In infants, the time between TB infection and TB disease may be as little as 6–8 weeks. Special considerations should be given to infants born to HIV-positive women who start TB treatment less than two months before delivery. These infants should be evaluated for signs and symptoms of congenital TB and be treated if appropriate.

Children older than 7 and adolescents usually develop adult-type pulmonary TB disease with classic presentation. Many children younger than 4, however, show atypical presentations of extrapulmonary dissemination with hepatomegaly, prolonged fever, lymphadenopathy, anaemia and weight loss, clinical manifestations of more advanced phases of immune suppression.

1. Identification of TB in HIV-infected infants and children

Diagnosis of TB in infants and children is difficult, whether or not they are infected with HIV, because they rarely have cavitary pulmonary disease and do not produce sputum for bacteriological examination. Other methods of obtaining material, such as gastric lavage, can be problematic. Consequently, bacteriological confirmation is usually not possible, and the diagnosis of pulmonary TB in children is often presumptive. The diagnosis of TB in HIV-infected children is even more difficult, as several HIV-related diseases may present in a manner similar to TB, and the interpretation of the tuberculin skin test is also less reliable. TB diagnosis is thus often based on a combination of a history of contact with an adult TB infectious case, TB clinical signs and symptoms and the results of the investigations. See Table 8 *(15)*.

Table 8. Conditions linked to active TB disease in children

Suspected tuberculosis • A history of contact with a confirmed case of pulmonary TB • Failure to regain normal health after measles • Weight loss, cough and wheeze that do not respond to antibiotic treatment for respiratory disease • Painless swelling in a group of superficial lymph nodes
Probable tuberculosis Suspected TB with any of the following: • positive (≥5 mm) induration on tuberculin skin test • suggestive appearance on chest radiograph • suggestive histological appearance on biopsy material • favourable response to TB-specific therapy.
Confirmed tuberculosis • Detection by microscopy or culture of tubercle bacilli from secretions or tissues • Identification of tubercle bacilli as Mycobacterium tuberculosis by culture characteristics

2. Identification of HIV in children with active TB

HIV infection may be suspected in children with TB. Diagnosis of HIV infection in infants <18 months old should be done using the HIV DNA polymerase chain reaction (PCR) test. In children 18 months and older, the ELISA serological test followed by a confirmatory western blot test is recommended. For further information please refer to Protocol 11, *Paediatric HIV/AIDS treatment and care*.

V. Clinical management of TB/HIV in children

1. Treatment of TB

TB treatment of HIV-infected children is a priority and should start as soon as active TB disease is diagnosed.

The recommended TB treatment regimens for children are the same as those recommended for adolescents and adults (see Table 1 in section III.2.2.1. above). The drug dosages per kilogram of body weight are also the same (see Annex 1).

2. Treatment of HIV/AIDS

2.1. Initiation of ART

In HIV-infected children with confirmed TB disease, initiating TB treatment should be a priority. ART should be initiated as soon as possible *(52)*, taking into consideration the clinical and immunological criteria summarized in Table 9.

Table 9. Strategy for initiation of ART in HIV-infected children with active TB

Criteria		TB treatment	ART
Paediatric Clinical Stage 4[a, b]		Start immediately	Start ART soon after TB treatment (2–8 weeks after starting TB treatment).
Paediatric Clinical Stage 3[a]	Advanced immunodeficiency[c]		
	Mild or no immunodeficiency[d]	Start immediately	ART may be delayed and the need for it reassessed after completion of TB therapy. Closely monitor response to TB therapy; if there is no improvement, consider starting ART.

[a] For paediatric clinical staging, see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 1.
[b] All children with Clinical Stage 4 should be initiated on ART, regardless of CD4 criteria.
[c] Advanced immunodeficiency is assumed to be a CD4 percentage of 5% above the age-specific CD4 threshold for severe immunodeficiency, or a CD4 count of 200–350 cells/mm^3 for children ≥5 years of age (see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 2).
[d] Mild or no immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency (again, see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 2).

2.2. Recommended HAART regiments

The ART regimens recommended for TB/HIV-coinfected children differ slightly from recommendations for HIV-monoinfected children. The choice of ART regimen is complicated by the limited options for paediatric drug formulations and/or dosing information (particularly for children younger than 3).

2.3. Key considerations for ARV drugs

- In case of ZDV toxicity or intolerance, stavudine (d4T) can be substituted.
- If NVP is administered concomitantly with rifampicin, potential liver toxicity needs to be monitored clinically and with a liver function test.
- EFV is not currently recommended for children <3 years of age, nor should it be given to sexually active girls who do not use adequate contraception or are in the first trimester of pregnancy.
- Following completion of TB treatment, it is preferable to maintain the ART regimen outlined in Table 10.

Table 10. HAART regimens for TB/HIV-coinfected children being treated with rifampicin

Age of child	ARV drug classes	ARV drug combination
<3 years	*Preferred* 3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC
	Alternative 2 NRTIs + NVP	ZDV + 3TC + NVP
≥3 years	*Preferred* 2 NRTIs + 1 NNRTI	ZDV + 3TC + EFV
	Alternative 3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC

2.4. Cotrimoxazole primary prophylaxis

TB/HIV-coinfected children should receive cotrimoxazole prophylaxis during the whole TB treatment phase, independent of their level of immune suppression. For cotrimoxazole formulations and dosages, please see Protocol 11, *Paediatric HIV/AIDS treatment and care,* section on prevention and management of OIs.

3. Monitoring of TB/HIV-coinfected children

Routine monitoring of TB/HIV-coinfected children and their response to treatment should include monitoring of clinical signs and symptoms, laboratory indicators, adherence and growth (nutrition). Sputum-smear assessments should be performed the same as for adults: week 8, month 5, month 6, month 8 and month 12 after initiation of TB treatment.

For more information on the clinical management of HIV/AIDS in children, please refer to Protocol 11, *Paediatric HIV/AIDS treatment and care.*

VI. Suggested minimum data to be collected at the clinical level

It is recommended *(52)* that the following data be collected on a regular basis (e.g. monthly, quarterly or semi-annually) at the clinical level to improve clinical management of TB/HIV-coinfected patients and to monitor the implementation of collaborative TB/HIV activities:

- number of registered TB patients;
- number of registered TB patients who are tested for HIV;
- number of registered TB patients testing positive for HIV;
- number of HIV patients seen for treatment and care who are screened for TB symptoms;
- number of HIV patients who have TB infection:
  - number of HIV patients with TB infection who have received tuberculosis preventative treatment (TPT) with izoniazid;
- number of HIV patients who are newly diagnosed with TB disease:
  - number of HIV patients newly diagnosed and registered with TB disease who have CD4 ≥350 cells/mm^3;
  - number of HIV patients newly diagnosed and registered with TB disease who have CD4 <350 cells/mm^3;
  - number of HIV patients newly diagnosed with TB disease who have received cotrimoxazole preventive therapy[2] (CPT);
- number of HIV/TB patients who are receiving TB treatment;
- number of HIV/TB patients receiving both TB treatment and ART;[3]
- number of HIV/TB patients in each category of TB treatment outcome;[4]
- number of HIV/TB patients who have died, including cause of death (e.g. TB-related deaths, other HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

[2] Defined as at least one dose during their TB treatment.
[3] Including the number of patients who have started on ART or are continuing previously initiated ART during or at the end of TB treatment
[4] This indicator should be calculated for each of the following possible outcomes: cure, treatment completion, treatment failure, death, default and transfer out. For definitions of these outcomes please refer to *Treatment of tuberculosis: guidelines for national programmes (53).*

Annex 1. TB drugs (adults, adolescents and children)

Table 11. Recommended dosage of first-line TB drugs

Drug	Recommended dose	
	Daily dose[a] (usual dose or range)	**Thrice-weekly dose (usual dose or range)**
Isoniazid (H)	5 mg/kg	10 mg/kg
Rifampicin (R)	10 mg/kg (450 mg if <50 kg; 600 mg if ≥50 kg)	10 mg/kg (450 mg if <50 kg; 600 mg if ≥50 kg)
Pyrazinamide (Z)	25 mg/kg (20–30 mg/kg)	35 mg/kg (30–40 mg/kg)
Ethambutol (E)	15 mg/kg (15–20 mg/kg)	30 mg/kg (20–35 mg/kg)
Streptomycin (S)	15 mg/kg (12–18 mg/kg)	15 mg/kg (12–18 mg/kg)

[a] When rifampicin is used concomitantly with antiretroviral drugs in TB/HIV patients, a daily TB treatment regimen is preferred *(20)*.

Table 12. Recommended formulations of first-line TB drugs

Drug(s)	Dose form	Strength (mg)
Single drugs		
Isoniazid (H)	Tablet	100, 300
Rifampicin (R)	Tablet or capsule	150, 300
Pyrazinamide (Z)	Tablet	400
Ethambutol (E)	Tablet	100, 400
Streptomycin (S)	Powder for injection in vial	750, 1000
Fixed-dose combinations		
Isoniazid + rifampicin	Tablet Tablet Tablet Tablet or pack of granules Tablet or pack of granules	75 + 150 150 + 300 30 + 60 150 + 150 (thrice weekly) 60 + 60 (thrice weekly)
Isoniazid + ethambutol	Tablet	150 + 400
Isoniazid + rifampicin + pyrazinamide	Tablet or pack of granules	75 + 150 + 400 30 + 60 + 150 150 + 150 + 500 (thrice weekly)
Isoniazid + rifampicin + pyrazinamide + ethambutol	Tablet	75 + 150 + 400 + 275

Annex 2. ARV drugs (adults and adolescents)

Table 13. Recommended formulations of first-line ARV drugs

Drug(s)	Recommended dose (mg)
NRTIs	
Abacavir (ABC)	300 BID
Didanosine (ddI)[a]	400 OD (250 if <60 kg) or 200 BID
Lamivudine (3TC)	150 BID or 300 OD
Zidovudine (ZDV)	300 BID
Tenofovir (TDF)	300 OD
NNRTIs	
Efavirenz (EFV)	600 OD
PIs	
Lopinavir/ritonavir + ritonavir (LPV/r + RTV)	(400/100 + 300) BID
Saquinavir + ritonavir (SQV + RTV)	(400 + 400) BID

[a] When ddI is administered concomitantly with TDF, the recommended dose is ddI 250 mg OD for patients with a body weight of >60 kg and 125–200 mg OD for patients with a body weight of <60 kg.

Table 14. Recommended ARV formulations for TB/HIV-coinfected adults and adolescents

Drug(s)	Dose form	Strength
Single drugs		
Abacavir (ABC)	Tablet Oral solution	300 mg 20 mg/ml
Didanosine (ddI)	Tablet Single-dose packets of buffered powder for oral solution Paediatric powder for oral solution Delayed-release capsules	25, 50, 100, 150, 200 mg 100, 167, 250 mg 4- and 8-ounce glass bottles containing respectively 2 and 4 g didanosine 125, 200, 250, 400 mg
Lamivudine (3TC)	Tablet Oral solution	150, 300 mg film coated 10 mg/ml
Zidovudine (ZDV)	Tablet Capsule Oral solution/syrup Retrovir IV infusion/sterile solution for IV infusion	250, 300 mg 100 mg 50 mg/5 ml 10 mg/ml
Tenofovir (TDF)	Tablet	300 mg
Efavirenz (EFV)	Capsule Tablet film coated	50, 100, 200 mg 600 mg
Lopinavir/ritonavir (LPV/r)	Tablet Capsule Oral solution (contains 42.2% alcohol)	200/50 mg 133.3/33.3 80/20 mg/ml
Saquinavir (SQV)	Capsule Tablet	200 mg 500 mg
Ritonavir (RTV)	Capsule Oral solution	100 mg 80 mg/ml
Fixed-dose combinations		
Zidovudine + lamivudine (ZDV + 3TC)	Tablet film coated	300 + 150 mg
Zidovudine + lamivudine + abacavir (ZDV + 3TC + ABC)	Tablet	300 + 150 + 300 mg
Tenofovir + emtricitabine (TDF + FTC)	Tablet	300 + 200 mg
Abacavir + lamivudine (ABC + 3TC)	Tablet	600 + 300 mg

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