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4 Management of tuberculosis and HIV coinfection

Clinical Protocol for the WHO European Region
(2013 revision)

KEYWORDS

ANTIRETROVIRAL THERAPY, HIGHLY ACTIVE
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Contents

Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATV	atazanavir
BCG	bacille Calmette-Guérin
CD4	T cells expressing cluster of differentiation 4
ddI	didanosine
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DRV	darunavir
E	ethambutol
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
FPV	fosamprenavir
FTC	emtricitabine
H	isoniazid
HIV	human immunodeficiency virus
LPV	lopinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse-transcriptase inhibitor
NVP	nevirapine
OST	Opioid Substitution Therapy
PAS	para-aminosalicylic acid
PI	protease inhibitor
PI/r	protease inhibitor with low-dose ritonavir to increase plasma concentration (booster)
PLHIV	PLHIV
PWID	people who inject drugs
R	rifampicin
RAL	raltegravir
Rfb	rifabutin
RNA	ribonucleic acid
RTV	ritonavir
/r	ritonavir given as pharmaceutical booster
S	streptomycin
SQV	saquinavir
TB	tuberculosis
TDF	tenofovir
TST	tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
Z	pyrazinamide
ZDV	zidovudine (also known as azidothymidine)

Acknowledgement

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Definitions for the strength and quality of recommendations

The WHO instructions for guideline development *(1)* were followed, and the strength of the recommendations and the quality of the evidence were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The quality of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The higher the quality of evidence, the more likely a strong recommendation can be made.

Concept relating to the strength of the recommendations for using interventions

Strong	Strong recommendation for the statement
Moderate	Moderate recommendation for a statement
Optional	Optional recommendation for the statement
No recommendation	No evidence to inform the use of the intervention

Concept relating to the quality of the evidence guiding recommendations for using interventions

A	Data from reasonably powered randomized controlled trials using relevant endpoints (high-quality evidence)
B	Data only from well-designed prospective observational studies assessing clinical endpoints only (moderate-quality evidence)
C	Data from case stories and/or expert opinion only (low- or very-low-quality evidence)

Introduction

Tuberculosis (TB) and HIV are important public health conditions in the European Region of WHO. Although the incidence, prevalence and mortality of TB are decreasing in the Region *(2)*, it has the highest documented global rates of multidrug-resistant TB *(3)* and an increasing number of people newly infected with HIV *(4)*. The increasing morbidity and mortality resulting from the intersecting epidemics of TB and HIV, including links between multidrug-resistant TB and HIV, emphasizes the urgent need for the early diagnosis and treatment of TB among all PLHIV and of HIV among all people with TB.

This publication is an updated version of the Management of Tuberculosis and HIV Coinfection clinical protocol released in 2007 by the WHO Regional Office for Europe *(5)*. The protocol reflects the regional context, including the development of TB and HIV epidemics, infrastructure of the health systems and overall capacity in programme management and clinical care of the health personnel. It is intended for all health care workers involved in preventing, diagnosing, treating and caring for people living with TB and HIV in the specific settings of the WHO European Region. The protocol encourages and promotes strong and effective collaboration among the TB and HIV national programmes at the country and subcountry levels to enhance and improve services for the effective clinical management of individuals with TB and HIV coinfection.

The updated version of the protocol is based on the new evidence that became available after the TB and HIV clinical protocol was published in 2007 and that has been documented in peer-reviewed scientific publications and/or considered in WHO-recommended policies such as:

- Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach (6);
- WHO Three I's Meeting: intensified case finding (ICF), isoniazid preventive therapy (isoniazid preventive therapy) and TB infection control (IC) for PLHIV. Report of a Joint World Health Organization HIV/AIDS and TB Department Meeting, 2–4 April 2008, Geneva, Switzerland (7);
- Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update, 2008 (8);
- A guide to monitoring and evaluation for collaborative TB/HIV activities (9);
- Guidelines for surveillance of drug resistance in tuberculosis (10);
- Treatment of tuberculosis guidelines (11);
- WHO policy on TB infection control in health-care facilities, congregate settings and households (12);
- Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for PLHIV in resource-constrained settings (13);
- ART for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision (14);
- Guidance on ethics of tuberculosis prevention, care and control (15);
- Delivering HIV test results and messages for re-testing and counselling in adults (16);
- Joint WHO/ILO policy guidelines on improving health worker access to prevention, treatment and care services for HIV and TB (17);
- Guidelines on couples HIV testing and counselling – including ART for treatment and prevention in serodiscordant couples. Recommendations for a public health approach (18);

- WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders (19); and
- Xpert MTB/RIF increases timely TB detection among PLHIV and saves lives. Information note (20).

The clinical protocol Management of tuberculosis and HIV coinfection, which was published in 2007 as part of HIV/AIDS treatment and care: clinical protocols for the WHO European Region, was initially revised for the 2013 version by Viorel Soltan (Center for Health Policies and Studies, Chisinau, Republic of Moldova). Masoud Dara, Smiljka de Lussigny and Risards Zaleskis (WHO Regional Office for Europe) then made contributions. Pierpaolo de Colombani and Irina Eramova (WHO Regional Office for Europe) and Alberto Matteelli (WHO Collaborating Centre on the Implementation of TB/HIV Collaborative Activities, University of Brescia, Italy) carried out further revision and editing. The revision process included a regional consultation with clinical experts held in 2010 in Kyiv, Ukraine and review by a panel of experts (see the list in the acknowledgements).

Background information

Globally, TB is one of the most common opportunistic infections among PLHIV, especially in areas with a high TB prevalence *(21)*. PLHIV who are also infected with TB are about 20 times more likely to develop TB disease compared with those who are HIV-negative *(21,22)*. TB has been found to be directly responsible for an average mortality rate of 30% among PLHIV in many reports *(23)*. Existing data for the European Region demonstrate independent epidemics of TB and HIV, and a large majority of people with TB developed their disease without HIV-related immunosuppression *(24)*. The situation may be different among special populations, including prisoners and people who inject drugs, vulnerable to both infections *(25–28)*. Unfortunately, knowledge of the real extent of TB and HIV coinfection in Europe and among these groups is limited because of incomplete surveillance data.

The available literature shows that drug-resistant TB outbreaks among PLHIV are associated with a significantly higher mortality rate and short survival *(29,30)*.

HIV promotes the progression from infection with *Mycobacterium tuberculosis* to active TB disease, among both people with recently acquired infection and those with latent infection *(31,32)*. As HIV infection progresses, CD4/mm^3 lymphocytes decline by about 50–80 cells/mm^3 per year, and the immune system becomes less able to prevent the dissemination of *M. tuberculosis* in the body *(33)*. For a person living with HIV and 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. Further, HIV infection increases the rate of TB recurrence, which can be caused by either endogenous reactivation or exogenous reinfection *(34)*. The clinical presentation, sputum-smear results and chest X-rays often differ from those of people who are uninfected with HIV, depending on the degree of immunodeficiency *(35–37)*. The clinical presentation of TB among people with early HIV infection is similar to that of individuals without HIV infection, resembling post-primary pulmonary TB, which often presents with cavities in the chest radiography and positive sputum-smear bacteriology. In contrast, the clinical presentation among people with late HIV infection resembles primary pulmonary TB, with radiographic infiltrates instead of cavities and the sputum-smear bacteriology, which is often negative. In case of severe immunodeficiency, the rate of extrapulmonary and disseminated TB increases and, because it is difficult to diagnose, it may account for misattributed hospital deaths.

In countries with independent epidemics of TB and HIV, TB may occur before HIV infection or in its early stages, before the immune system has deteriorated. The risk of acquiring TB remains higher among PLHIV than among uninfected people even after starting ART (though significantly reduced compared with PLHIV not taking ART). TB disease itself is responsible for mild immunodeficiency. Among PLHIV, TB disease worsens the HIV-related immunodeficiency and facilitates the progression of other opportunistic infections such as *Candida albicans* oesophagitis, *Cryptococcus* meningitis and, particularly, *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia *(38)*. Any of these opportunistic infections may be lethal among coinfected people.

The increased morbidity and mortality resulting from TB and HIV interaction emphasize the need for prevention, early diagnosis and treatment of TB among all PLHIV and HIV among all people with TB *(39–44)*.

1. Diagnosing TB and HIV among adults and adolescents

All PLHIV should be assessed for having TB or being infected by M. tuberculosis and having risk factors for TB exposure. Likewise, all people with TB should be offered HIV testing and counselling. The following are the major reasons for this.

- PLHIV are at higher risk for developing active TB.
- TB may be an indicative sign of advanced HIV infection.
- TB is one of the major causes of death among PLHIV.
- TB influences the clinical progression of HIV infection and its treatment.
- The probability of obtaining a positive HIV test is higher among people with TB, especially those from most-at-risk population groups.

It is extremely important that health systems adapt to people's needs and that the diagnosis of TB and HIV be facilitated by outpatient consultations when appropriate, bringing diagnostic services (including rapid testing) closer to the patients and with due attention paid to airborne infection control measures. This could be a challenge for health systems with vertical delivery of services, such as having two separate vertical national TB and HIV programmes. Active TB detection measures and diagnosing latent TB infection in HIV services can contribute to the early identification of infectious cases, thus preventing the unnecessary exposure to TB for PLHIV and increasing access to effective TB treatment. In this scenario, however, establishing effective TB prevention and care in HIV services is of pivotal importance. Involving non-medical and community layers, including outreach workers and nongovernmental actors working with most-at-risk populations, such as people who inject drugs, in different stages of the diagnostic algorithm can increase the coverage of the people who usually have limitations or barriers to access health care services.

1.1 Diagnosing TB disease among PLHIV

Recommendations
1. Adults and adolescents living with HIV should be regularly screened for TB, wherever they receive care, at every visit to a health facility or contact with a health worker (*strong recommendation, A*).
2. TB screening of adults and adolescents living with HIV should start from the investigation of four main symptoms: current cough, fever, weight loss and night sweats. Adults and adolescents with any of these symptoms may have active TB and should be evaluated for TB and other diseases (*strong recommendation, B*).
3. The Xpert MTB/RIF assay should be the first test used to detect TB among adults and adolescents living with HIV (*strong recommendation, B*).

Considering their high risk of TB, all PLHIV, wherever they receive care, should be regularly screened for TB at every visit to a health facility or contact with a health worker *(45,46)*.

The screening for TB should first start from investigating the presence of all the following four symptoms:

- current cough
- fever
- weight loss
- night sweats.

The presence of one or more of these symptoms prompts the application of a diagnostic procedure for TB, since the person is presumed to have TB (Fig. 1).

In settings with a TB prevalence among PLHIV of 5% or more, this symptom-based screening has 79% sensitivity, 50% specificity and more than 97% negative predictive value *(47)*. The lower the prevalence of TB among PLHIV, the higher the negative predictive value of the symptom-based screening strategy. Therefore, under the epidemiological conditions prevailing in the WHO European Region, the number of TB cases missed by the symptom-based screening is so low that it does not represent a public health issue. Moreover, with regular screening at each health visit, such cases would be picked up as soon as any of the symptoms appear. A threshold of TB prevalence (above 5%) at which this strategy is not any more effective in excluding active TB among PLHIV has not been defined so far.

Adding chest radiography to the symptom-based screening (showing the absence of lesions) increases only marginally (1% at a TB prevalence of 5% among PLHIV) the negative predictive value, and it is not routinely recommended. Chest radiography becomes a useful option for initial screening only at very high levels of TB prevalence among PLHIV (20% or more) *(47)*.

If any of the above symptoms or signs of active TB disease is absent or if the prevalence of latent TB infection among PLHIV is less than 30%, the physician should proceed further to perform a test for diagnosing latent TB infection (see section 1.3).

In contrast, the presence of any of the above symptoms requires the physician to further explore the possibility of active TB disease. The next steps should be taken:
- medical examination;
- the Xpert MTB/RIF assay test (48)[1] of one sputum sample;
- other bacteriological investigation (sputum-smear direct microscopy and culture) of two sputum samples taken even on the same day if Xpert MTB/RIF is not available (see later about drug susceptibility testing);
- chest radiography;
- for people with signs of extrapulmonary TB, microbiological investigations should be performed (using Xpert MTB/RIF or culture) on samples obtained by needle aspiration or tissue biopsy, and mycobacterial blood cultures might be helpful for people with signs of disseminated disease or worsening immunodeficiency; and
- if extrapulmonary TB is presumed, any additional appropriate investigation, including computed tomography and other recommended technologies (if affordable).

WHO promotes the use of diagnostic algorithms that use the Xpert MTB/RIF assay as the entry diagnostic procedure among PLHIV with presumptive TB (both ambulatory and critically ill) (Fig. 2 and 3) *(20)*.

When TB diagnosis is still uncertain, a full course of broad-spectrum antibiotics *(49)* could be useful in ruling out non-specific bacterial infections. Repeat diagnostic tests and further clinical

[1] The Xpert MTB/RIF assay is the nucleic acid amplification test currently available and endorsed by WHO for the rapid diagnosis of TB and multidrug-resistant TB. It is preferred to the line probe assay, because it is more sensitive and consequently recommended as the first test, also in sputum-smear negative samples. Other tests might become available in the future.

evaluation may be required. First-line anti-TB drugs and fluoroquinolones (second-line anti-TB drugs) should not be used for antibacterial empirical treatment under these circumstances.

1.2 Diagnosing drug-resistant TB disease among PLHIV

Drug susceptibility testing from a bacteriological culture should be performed among all people with TB because it is a valuable diagnostic support for selecting the most appropriate TB treatment regimen based on the drug-resistance pattern. This is particularly important in the WHO European Region, which faces the highest level of multidrug-resistant TB. In specific circumstances when drug susceptibility testing of all newly diagnosed people with TB is unfeasible, at least all previously treated people with TB[2] and everyone presumed to have drug-resistant TB should undergo drug susceptibility testing *(11)*.

Rapid molecular-based identification of drug-resistant strains (such as the Xpert MTB/RIF assay) should be performed among everyone with presumptive TB. However, when this is not feasible, people with epidemiological risk factors for multidrug-resistant TB (such as previously treated people with TB and prisoners) should have priority for rapid molecular-based testing. If rifampicin resistance is detected using Xpert MTB/RIF, drug susceptibility testing for the first- and second-line TB drugs should be performed for optimally managing second-line drugs.

1.3 Diagnosing latent TB infection among PLHIV

Recommendations

1. The tuberculin skin test (TST) should be used to diagnose latent TB infection before TB preventive treatment (see section 2.6) in areas in which the prevalence of latent TB infection among PLHIV is expected to be less than 30% (*strong recommendation, A*).
2. TST is not required for starting TB preventive treatment in areas in which the prevalence of latent TB infection among PLHIV is expected to be equal to or higher than 30% (*strong recommendation, B*).
3. Interferon gamma release assay might be used instead of TST in settings in which BCG (bacille Calmette-Guérin) vaccination coverage is high, organization of testing is feasible and overall costs are affordable (*optional recommendation, B*).
4. A positive TST or interferon-gamma release assay result and/or actual TB exposure (close contact) among PLHIV without clinical signs of active TB should be considered to indicate latent TB infection and be a reason for implementing TB preventive treatment (*strong recommendation, A*).

For all PLHIV who do not have any of the four symptoms used for screening active TB disease (current cough, fever, weight loss and night sweats), the physician should proceed further by investigating a status of latent TB infection, if the prevalence of latent TB infection among PLHIV dictates.

[2] Previously treated people with TB are defined as those who have received at least one month of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomic site. They may be the result of a relapse from previous TB episode successfully treated (cure or treatment as documented outcomes), a treatment failure or the return after defaulting on treatment (defaulting on treatment for more than two months).

Fig. 1 summarizes the recommended diagnostic algorithm for assessing TB among adults and adolescents living with HIV.

In settings with a low prevalence of latent TB infection (below the threshold of 30%) *(13)* and with enough resources and capacity, a diagnostic test should be used to detect latent TB infection.

The standard test for detecting latent TB infection is the tuberculin skin test (TST)[3], which is based on the exposure to purified protein derivatives of *M. tuberculosis* (Mendel–Mantoux technique). A positive TST, defined among PLHIV as ≥5 mm of skin induration, indicates a past or recent TB infection *(50)*.

TST has a few well-recognized limitations: (1) low specificity (false-positive results may occur among people previously vaccinated with BCG vaccine or following exposure to non-tuberculous environmental mycobacteria; (2) the need for reading the skin reaction 48–72 hours after administering the test; and (3) reduced sensitivity, which is directly proportional to the progression of immune suppression. In recent years, a new technique based on testing a blood sample using an interferon-gamma release assay has become available to investigate latent TB infection. The interferon-gamma release assay is more costly than TST but does not confound with previous BCG vaccination or environmental mycobacteria, requires only one testing visit and has been successfully used in many countries. The sensitivity of the interferon-gamma release assay, similarly to what observed for TST, is reduced among people with a low CD4/mm^3 cell count.

Given comparable performance but increased cost, replacing the TST by the interferon-gamma release assay is not recommended as a public health intervention in resource-constrained settings *(51)*.

In the European Region, the selection of the most suitable test for detecting latent TB infection should consider:
- the context for testing: the likeliness that the person will return for reading the skin reaction after 48–72 hours, has been vaccinated with BCG or has been exposed to nontuberculosis environmental mycobacteria;
- the capacity and training of the health care personnel to use the test; and
- the test availability and the overall cost of testing.

In some settings, TST or the interferon-gamma release assay might be an operational challenge (remote geographical areas, lack of resources or skills among health care workers for performing TST), limiting the access to TB preventive treatment (see Chapter 2.6), and it should not be required as a precondition for initiating TB preventive treatment among PLHIV.

PLHIV with CD4$^+$/mm^3 counts <200 cells/μl who have fibrotic lesions consistent with TB on a chest radiograph and no prior history of treatment should be considered as having *M. tuberculosis* infection irrespective of the results of latent TB infection diagnostic tests.

PLHIV who are close contacts of a person with pulmonary TB should receive treatment for latent TB infection irrespective of the results of TST or interferon-gamma release assay.

[3] 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 reaction only shows that the person has at some time been infected with M. tuberculosis.

People with negative diagnostic tests for latent TB infection, advanced HIV infection ($CD4^+$/mm^3 count <200 cells/μl) and without indications for initiating empirical latent TB infection treatment should be retested for latent TB infection once they start ART and attain a $CD4^+/mm^3$ count ≥200 cells/μl.

Annual retesting for latent TB infection is recommended for PLHIV who have a negative test and who are in a high-risk category: people who actively use drugs, prisoners, etc.

1.4 Delivering TB diagnostic services to PLHIV

Recommendations
1. The national HIV programme should ensure the detection of active TB among PLHIV in close collaboration with the national TB programme (*strong recommendation, C*).

It is extremely important that health systems adapt to people's needs and that the diagnosis of TB be facilitated by external consultation from TB to the HIV services if needed and bringing diagnostic services (including rapid testing) closer to the people with TB and/or HIV, with due attention paid to infection control measures. Access to diagnosing TB and latent TB infection in HIV services would contribute to early diagnosis of TB among PLHIV, increased access to TB treatment, prevention of TB transmission during transport between health care facilities and unnecessary exposure to TB among PLHIV.

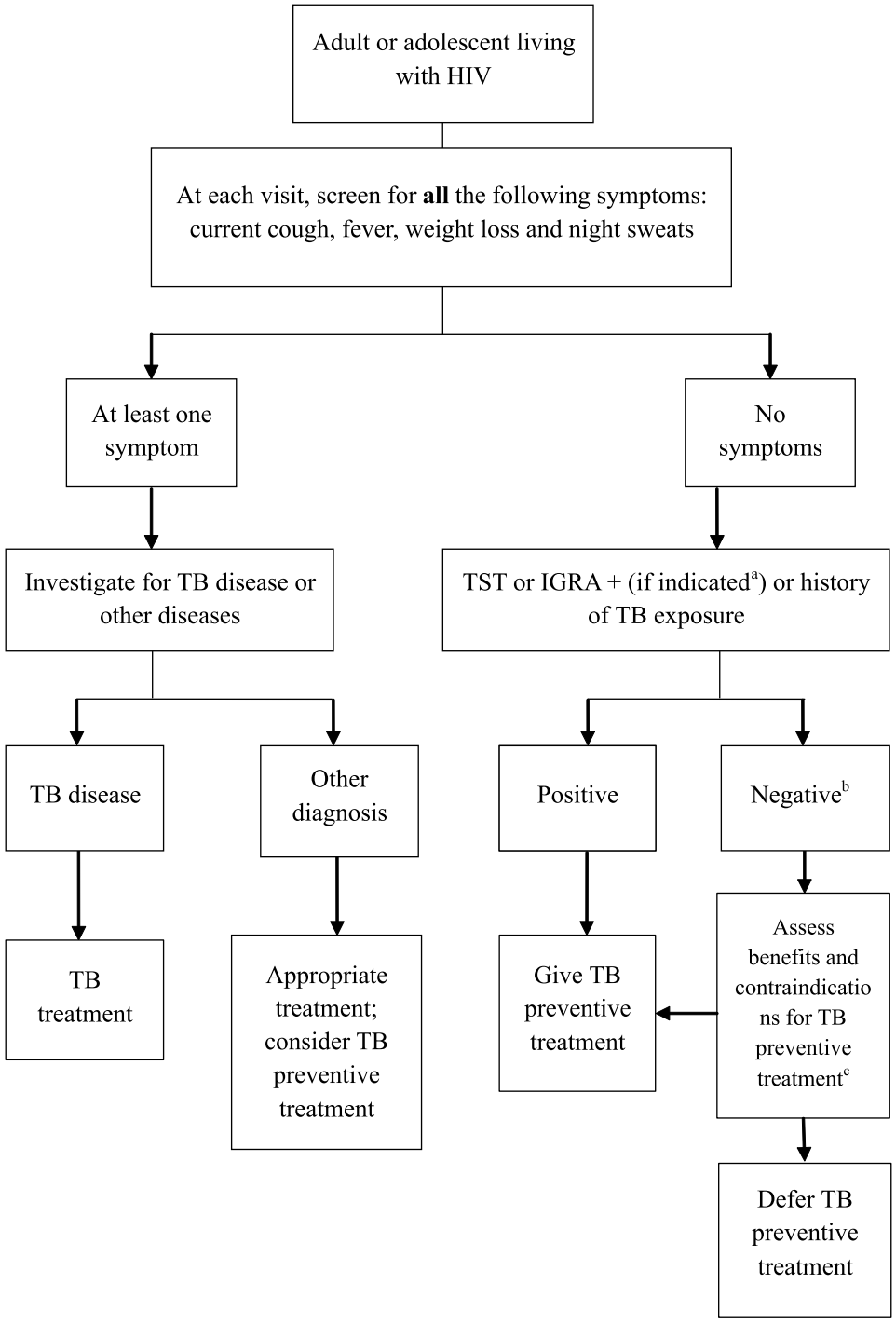
Timely diagnosis of multidrug-resistant TB among PLHIV is crucial to reduce mortality: conventional drug susceptibility testing methods have a turnaround time of a few weeks, which is unsuitable for immediate action. Rapid point-of-care diagnostic tests such as molecular assays would therefore be highly desirable, especially among PLHIV and their communities (52).

Integrating TB and HIV services to allow TB and HIV care to be delivered at the same health facility could provide timely diagnosis of TB and multidrug-resistant TB among PLHIV, especially when the rapid diagnostics, such as Xpert MTB/RIF, are available at the integrated service delivery points of care. The integrated TB and HIV services also enable early ART for people with HIV and TB to be scaled up.

In many countries, teams of experts meet periodically in consilium to evaluate each case and decide which anti-TB and ART to provide. TB and HIV services should take direct responsibility to avoid having this practice delay significantly the start of treatment and putting the people with TB and/or HIV at serious risk.

Involvement of non-medical layers, including outreach workers and nongovernmental actors working with most-at-risk populations, such as people who inject drugs, in different stages of the diagnostic algorithm (Fig. 1–3), would increase the coverage of people who do not usually access health care services.

Fig 1. Algorithm for assessing TB among adults and adolescents living with HIV

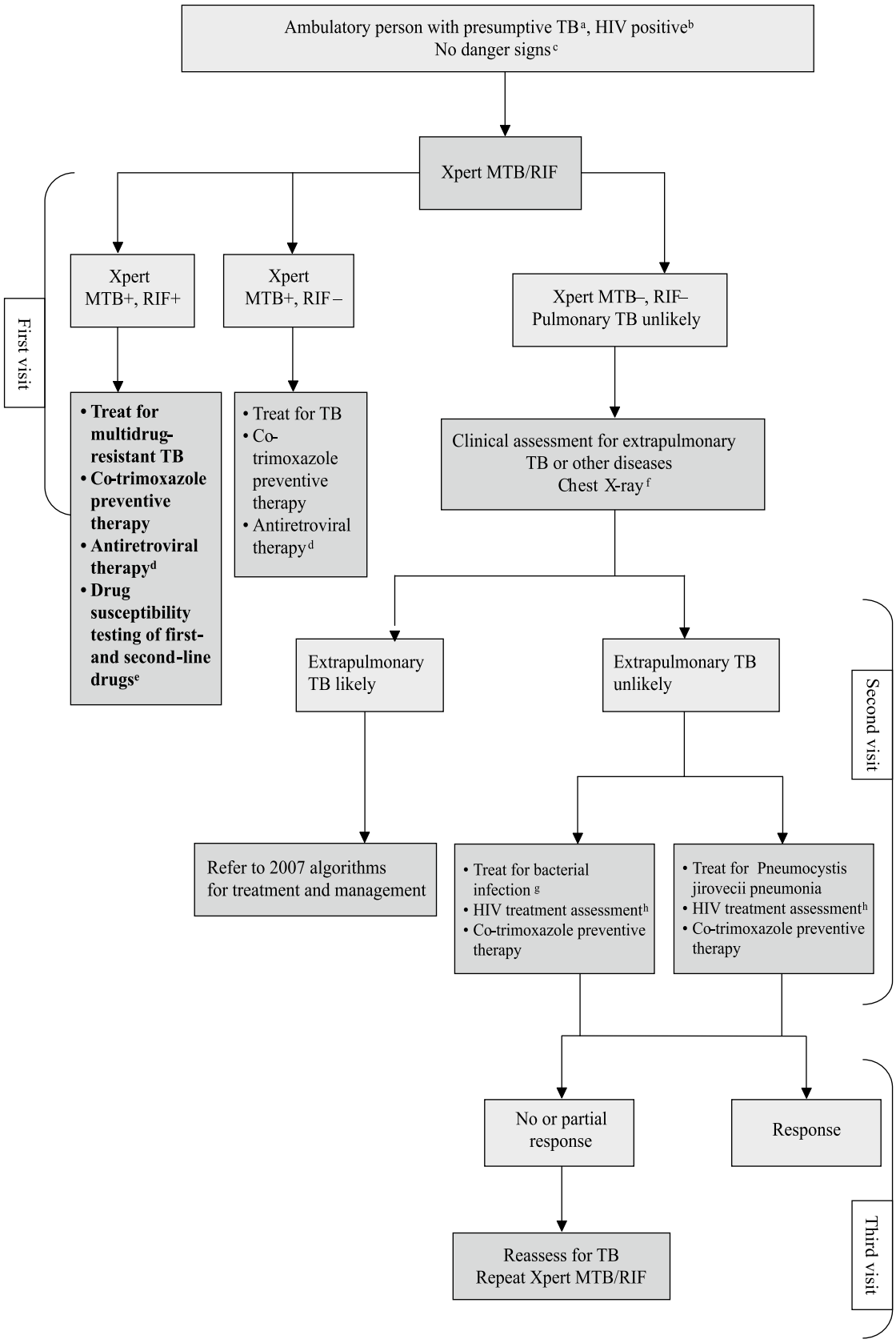


[a] *In areas with a prevalence of latent tuberculosis infection of 30% or more, testing for latent tuberculosis infection is not recommended: all PLHIV are candidates for TB preventive treatment unless there are specific contraindications.*

[b] *In addition to the symptom screening that should be carried out at every visit. Annual testing for latent tuberculosis infection is recommended for PLHIV who are in a high-risk category, such as people who inject drugs and prisoners.*

[c] *n countries in which prevalence of latent tuberculosis infection among PLHIV is less than 30%, PLHIV without documented latent tuberculosis infection or history of TB exposure can benefit from TB preventive treatment when highly exposed to TB, such as in high-risk populations such as prisons.*

Fig 2. Algorithm for management of ambulatory people with HIV and presumptive TB



[a] *Among adults and adolescents living with HIV, a person with presumptive TB is defined as a person who reports any of the following: current cough, fever, weight loss or night sweats. Among children living with HIV, a person suspected of having TB is defined as a child who reports any of the following: poor weight gain, fever, current cough or history of contact with a TB case.*

[b] *Among all people with unknown HIV status, HIV testing should be performed according to the national guidelines. Among people who are HIV negative or whose HIV status remains unknown (such as declining HIV testing), a person suspected of having TB is defined according to national case definitions. A person with unknown HIV status can still be classified as living with HIV if there is strong clinical evidence of HIV infection.*

[c] *The danger signs include any of the following: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.*

[d] *All people with TB and HIV are eligible for ART irrespective of CD4/mm^3 count. Start TB treatment first, followed by ART as soon as possible within the first eight weeks of TB treatment. See the guidelines on ART.*

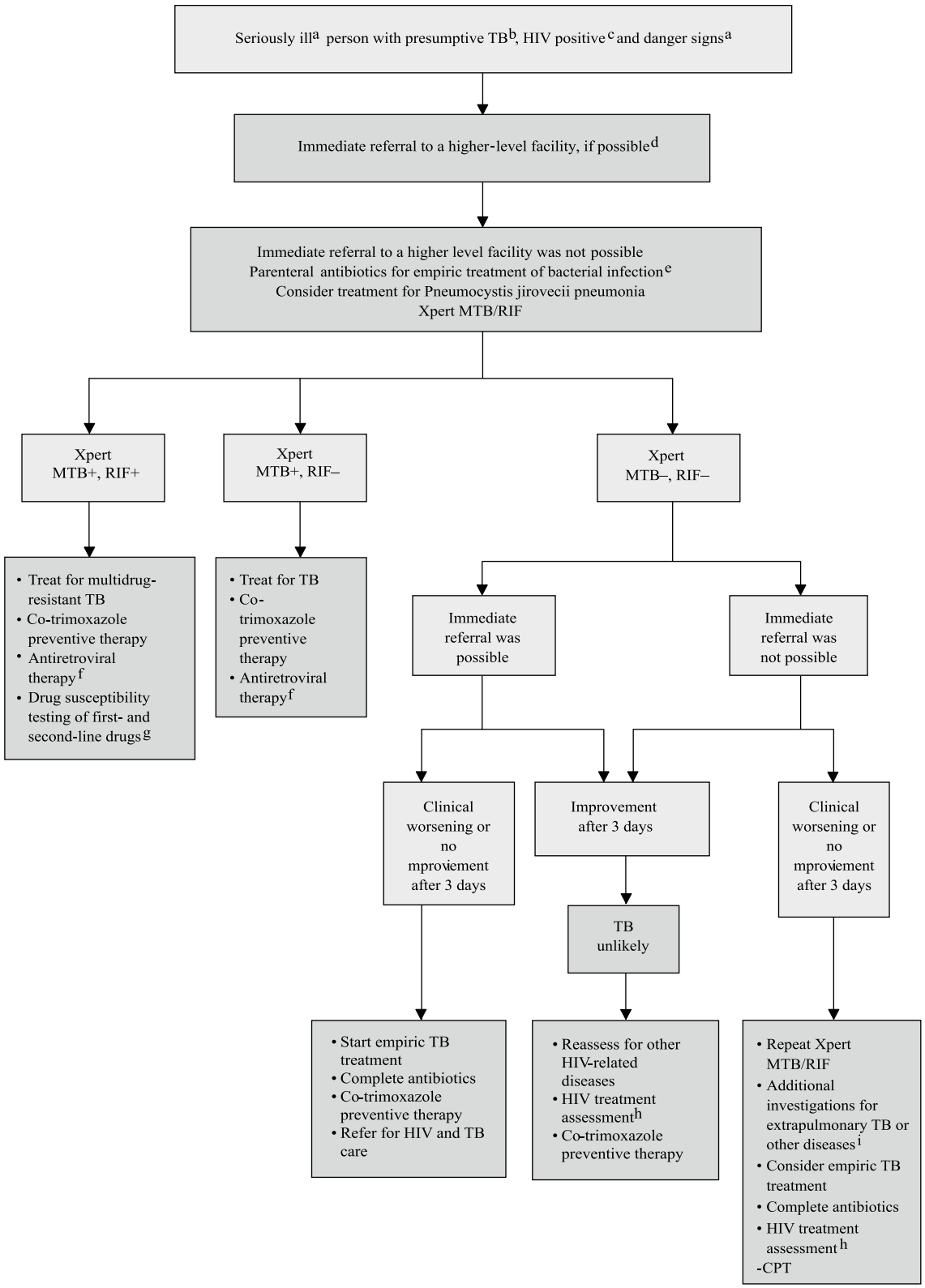
[e] *In settings with a low prevalence of multidrug-resistant TB, a confirmatory test for rifampicin resistance should be performed. See the algorithm for multidrug-resistant TB and Xpert MTB/RIF.*

[f] *A chest X-ray can assist in diagnosing extrapulmonary TB (such as pleural or pericardial) and in assessing for other causes of respiratory illness. It should only be performed in settings in which the quality of the film and its interpretation are assured.*

[g] *Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.*

[h] *HIV treatment assessment includes WHO clinical staging and/or CD4/mm^3 count to assess eligibility for ART. See the guidelines on ART.*

Fig 3. Algorithm for managing people with HIV and presumptive TB who are seriously ill



[a] *Seriously ill refers to the presence of danger signs, including: respiratory rate >30/minute, temperature >39°C, heart rate >120/minute and unable to walk unaided.*

[b] *Among adults and adolescents living with HIV, a person with presumptive TB is defined as a person who reports any of the following: current cough, fever, weight loss or night sweats. Among children living with HIV, a person suspected of having TB is defined as a child who reports any of the following: poor weight gain, fever, current cough or history of contact with a TB case.*

[c] *Among all people with unknown HIV status, HIV testing should be performed according to the national guidelines. In settings with a high prevalence of HIV infection, seriously ill people should be tested using Xpert MTB/RIF as the primary diagnostic test regardless of HIV status.*

[d] *The highest priority should be to provide life-sustaining supportive therapy, such as oxygen and parenteral antibiotics. If life-sustaining therapy is not available at the initial point of care, the person should be transferred immediately to a higher-level facility before further diagnostic testing.*

[e] *Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.*

[f] *All people with TB and HIV are eligible for ART irrespective of CD4/mm^3 count. Start TB treatment first, followed by ART as soon as possible within the first eight weeks of TB treatment. See the guidelines on ART.*

[g] *In settings with a low prevalence of multidrug-resistant TB, a confirmatory test for rifampicin resistance should be performed. See the algorithm for multidrug-resistant TB.*

[h] *HIV treatment assessment includes WHO clinical staging and/or CD4/mm^3 count to assess eligibility for ART. See the guidelines on ART.*

[i] *Additional investigations for TB may include chest X-ray, liquid culture of sputum, lymph node aspiration for acid-fast bacilli microscopy and culture and abdominal ultrasound. Non-TB mycobacterial infection should be considered in the differential diagnosis of people who have a negative Xpert test but a sputum or extrapulmonary specimen with acid-fast bacilli.*

1.5 Diagnosing HIV among people with TB or presumptive TB

Recommendations

1. Routine HIV testing should be offered to all people with presumptive or diagnosed TB (*strong recommendation, A*).
2. The national TB programme should ensure active HIV detection, further evaluation and management of HIV infection among people with TB or presumptive TB in close collaboration with the national HIV programme (*strong recommendation, C*).

Provider-initiated HIV testing and counselling should be a routine procedure in all health care settings dealing with individuals with presumptive and diagnosed TB *(53)*[4]. Health care providers should explain the reasons for offering the test and the importance of knowing the results for correct clinical management. HIV testing should be conditional to informed consent of the person being tested and the freedom to refuse it, with adequate pretest and post-test counselling, protection of confidentiality and effective access to services for treatment and care. The assessment of a person's HIV status should include:

- HIV pretest information;
- serological tests (typically, enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, followed by a confirmatory test according to national guidelines; and

[4] Infections the presence of which define AIDS among PLHIV include pulmonary or extrapulmonary M. tuberculosis, disseminated or extrapulmonary M. avium complex or M. kansasii, other disseminated or extrapulmonary species of Mycobacterium or unidentified species. HIV testing is strongly recommended among these people as an essential diagnostic test.

- post-test counselling, including information on reducing high-risk behaviour, irrespective of the results of the HIV test.

Decisions on whether to use HIV rapid tests or traditional assays should take into account all advantages and disadvantages, including the cost and availability of the HIV test kits, reagents and equipment, health care personnel, resources, infrastructure, laboratory expertise and personnel as well as considerations on the number of samples to be tested, sample collection and transport methods, testing setting, convenience and people's ability to return for results *(54)*.

If a confirmatory HIV test is positive, further evaluation and clinical management of a person with HIV and TB, including selection of anti-TB and antiretroviral drugs, should be provided according to the national TB and HIV guidelines.

For more detailed information, see HIV/AIDS Treatment and Care – Clinical Protocols for the WHO European Region (2012 revision): Protocol 1 (55).

2. Treatment of TB and HIV among adults and adolescents

All people with TB who are living with HIV need treatment for TB and HIV irrespective of the CD4/mm^3 cell count.

In general, treating TB among PLHIV should be considered a priority and start as soon as possible after TB diagnosis while awaiting the results of drug susceptibility testing. Treating TB promptly reduces the TB-related mortality and interrupts TB transmission, including to other PLHIV *(40,56)*. Treatment of TB and multidrug-resistant TB consists of a standard regimen comprising various combinations of 4–5 effective anti-TB drugs (Annex 1) given during an intensive phase and fewer drugs given during a continuation phase.

Active TB among PLHIV indicates the need to initiate ART as soon as possible and regardless of CD4/mm^3 cell count or HIV viral load. ART can comprise various combinations of antiretroviral drugs (Annex 2). It should be considered part of HIV and TB treatment and prevention, which prolongs and enhances the quality of life, preserves and improves immune function and reduces the risk of HIV transmission among PLHIV. Because HIV is a chronic lifelong infection that currently cannot be cured, PLHIV have to be followed medically for the rest of their lives, and ART is a core component of their treatment and care.

Standardized, simplified ART regimens are used to support HIV treatment programmes so they can reach as many PLHIV as possible. The first-line ART regimen should contain two nucleoside reverse-transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse-transcriptase inhibitor (NNRTI). These are efficacious, relatively less expensive, have generic and fixed-dose combination formulations, do not require a cold chain and preserve a potent new class of agents (protease inhibitors (PIs)) for second-line regimens.

The treatment of active TB disease among PLHIV should be carefully designed to consider their anti-TB drug susceptibility, the need for antiretroviral drugs that may interfere with anti-TB drugs and the presence of specific conditions such as pregnancy, use of injecting drugs and kidney or liver disease.

2.1 Treatment of drug-susceptible TB and HIV

2.1.1 Treatment of TB

Recommendations

1. People with TB who are living with HIV should receive at least the same duration of TB treatment as HIV-negative people with TB (*strong recommendation, A*).
2. People with TB who are living with HIV should receive daily TB treatment during the intensive and the continuation phases (*strong recommendation, A*).
3. During the continuation phase, if a daily dose of anti-TB drugs is not possible, three times weekly dosing is an acceptable alternative (*moderate recommendation, B*).
4. In populations with known or presumed high levels of isoniazid resistance, people newly acquiring TB may receive isoniazid-rifampicin-ethambutol combined therapy in the continuation phase as an acceptable alternative to isoniazid-rifampicin (*optional recommendation, C*).
5. Rifabutin is preferred to rifampicin among PLHIV who require an ART regimen containing a boosted PI (*strong recommendation, A*).

New TB patients[5] coinfected with HIV can be treated with a rifampicin-based regimen consisting of isoniazid, rifampicin, pirazinamide and ethambutol daily for the first two months (intensive phase) and isoniazid and rifampicin daily for four months (continuation phase). Three times weekly dosing of isoniazid and rifampicin during the continuation phase is an acceptable alternative where it is not possible to adopt the daily dosing.

A rifabutin-based regimen is equally effective as a rifampicin-based regimen, such as two months of isoniazid, rifabutin, pirazinamide and ethambutol followed by four months of isoniazid and rifampicin.

Because of bidirectional drug–drug interactions, the blood levels of rifabutin increase when this drug is taken along with antiretroviral PIs. The recommended dose of rifabutin therefore becomes 150 mg daily (or 300 mg every other day) instead of the usual standard dose of 300 mg daily *(57)*.

Whenever TB develops among PLHIV who are already taking ART, it should be continued (if there is no evidence of failure) and the TB regimen selected according to the antiretroviral drugs in use.

Table 1 summarizes the recommended standard regimens for treating TB among PLHIV.

[5] New TB patients are defined as people with TB who have never had treatment for TB or have taken anti-TB drugs for less than one month. New TB patients may have positive or negative bacteriology and may have disease at any anatomical site.

Table 1. Recommended standard TB regimens for people with TB and HIV

Treatment regimen	Comments
2 H + R + Z + E 4 (H + R)	Standard treatment for new TB patients
2 H + Rfb + Z + E 4 H + Rfb	Alternative standard treatment for new TB patients
2 H + R + Z + E 4 H_3 + R_3	Alternative standard treatment for new TB patients when daily dosing is difficult to arrange
2 H + R + Z + E 4 (H + R) + E	Alternative standard treatment for new TB patients in settings with high levels of isoniazid resistance and awaiting the results of drug susceptibility testing
2 H + R + Z + E + S 1 (H + R) + Z + E 5 (H + R) + E	Preferred standard treatment for people lost to follow-up or relapsing from previous TB treatment in settings with low or medium levels of isoniazid resistance
Empirical multidrug-resistant TB regimen	Empirical treatment based on the country's drug resistance susceptibility profile: for people for whom previous TB treatment had failed in settings with low or medium levels of isoniazid resistance all previously treated people with TB in settings with high levels of isoniazid resistance and awaiting the results of drug susceptibility testing

The number before a phase of treatment is the duration of that phase in months. A subscript number (such as $_3$) after a letter or letters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, the dose is daily. The letters in parentheses indicate a fixed-dose combination of those drugs.

H: isoniazid; R: rifampicin; Z: pirazinamide; E: ethambutol; Rfb: rifabutin; S: streptomycin.

2.1.2 Treatment of HIV

Recommendations

1. ART should be started among all people with TB living with HIV irrespective of their CD4/mm^3 counts (*strong recommendation, A*).
2. Anti-TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of treatment. The people with TB who are living with HIV with profound immunosuppression (such as CD4/mm^3 counts less than 50 cells/mm^3) should receive ART immediately within the first two weeks of initiating TB treatment (*strong recommendation, A*).
3. In case of TB meningitis, the initiation of ART should be deferred until after the intensive phase of TB treatment is completed (*strong recommendation, A*).
4. Efavirenz, in association with two NRTIs, should be used as the preferred NNRTI among people starting ART while receiving anti-TB treatment (*strong recommendation, A*).

Antiretroviral and anti-TB medications have drug–drug interactions that affect the clinical management of PLHIV and TB. This is especially true for rifampicin, which reduces the levels of both NNRTIs and PIs by inducing the cytochrome P450 liver enzyme system *(58–61)*. Rifabutin is a much less potent inducer of the cytochrome P450 system than rifampicin *(62)*. Annex 3 summarizes the major interactions between rifampicin and rifabutin and antiretroviral drugs and provides recommendations for their clinical management.

The recommended first-line ART regimen for people with TB contains the NRTI class lamivudine (3TC) or emtricitabine (FTC) and tenofovir (TDF) associated with the NNRTI class efavirenz (EFV), since interactions with anti-TB drugs are minimal. In several cohort studies, such standard ART regimens were well tolerated and highly efficacious in achieving complete viral suppression among people receiving concomitant rifampicin-based TB treatment *(63–65)*.

Regarding the risks and benefits of pregnant women and women who want to conceive while using EFV, evidence supports the benefits of EFV against the known risks and complexities of alternatives such as nevirapine (NVP) *(66,67)*. In particular, the current data review of the safety of EFV, including the risk of teratogenicity, is reassuring.

Based on currently available evidence, programmatic considerations and a careful weighing of risks and benefits, EFV should be considered part of the preferred first-line treatment option, including among women of reproductive age and those in the early stages of pregnancy. Global and national guidelines need to carefully consider the impact of recommending avoiding EFV among pregnant women or women of childbearing age.

People with TB requiring an ART regimen containing a boosted PI should receive a rifabutin-based TB treatment regimen, whenever this drug is available. Because rifabutin is a much less potent inducer of the cytochrome P450 system than rifampicin, the dose of PI remains unchanged (Annex 3). Rifabutin, however, is also a substrate of the cytochrome P450 enzyme system, PIs affect its metabolism and its dose needs to be reduced (see above).

If rifabutin is not available, PIs should not be used with rifampicin because highly variable and mainly subtherapeutic plasma concentrations of PIs are observed, even in the presence of boosted doses of ritonavir. The use of a boosted ART containing lopinavir (LPV) or saquinavir (SQV) with additional ritonavir (LPV/r or SQV/r) dosing is not recommended because of its toxicity *(68)*.

Where rifabutin is not available, a triple nucleoside or nucleotide regimen of 3TC [FTC] + ZDV + ABC [TDF] is recommended for people with TB and HIV who cannot take EFV. However, such a triple nucleoside or nucleotide regimen is significantly less potent than the other ART regimens.

Table 2 presents the recommended first-line ART for people with TB treated with rifampicin or rifabutin.

Table 2. Recommended antiretroviral standard regimens for people with TB and HIV

Treatment regimen	Comments
Recommended ART regimen for PLHIV being treated with rifampicin	
3TC [FTC] + TDF + EFV	Two NRTIs + EFV is the preferred first-line standard ART among people treated with rifampicin-based anti-TB treatment
3TC + ZDV + ABC 3TC [FTC] + ZDV + TDF	Three NRTIs is the alternative first-line standard ART for people treated with anti-TB rifampicin and unable to take EFV. This is less effective than first-line ART options
Recommended ART regimen for PLHIV being treated with rifabutin	
TDF + 3TC [FTC] + ATV/r TDF + 3TC [FTC] + LPV/r	Two NRTIs + one PI/r[a] is the preferred alternative first-line standard ART for people treated with rifabutin-based anti-TB treatment
3TC [FTC] + ABC [ZDV] + DRV/r	Two NRTIs + one PI/r[a] is the second-choice alternative first-line standard ART for people treated with rifabutin-based anti-TB treatment
3TC [FTC] + ABC [ZDV] + FPV/r 3TC [FTC] + ABC [ZDV] + SQV/r	Two NRTIs + one PI/r[a] is the third-choice alternative first-line standard ART for people treated with rifabutin-based anti-TB treatment

[a] *PI/r: ritonavir-boosted protease inhibitor.*

2.2 Treatment of drug-resistant TB and HIV

Recommendations

1. In the treatment of people with multidrug-resistant TB, a fluoroquinolone should be used (*strong recommendation, C*).
2. In the treatment of people with multidrug-resistant TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (*moderate recommendation, C*).
3. In the treatment of people with multidrug-resistant TB, ethionamide (or prothionamide) should be used (*strong recommendation, C*).
4. In the treatment of people with multidrug-resistant TB, four second-line anti-TB drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (*moderate recommendation, C*).
5. In the treatment of people with multidrug-resistant TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and either cycloserine or para-aminosalicylic acid (PAS) if cycloserine cannot be used (*moderate recommendation, C*).
6. The use of thioacetazone is not recommended for PLHIV (*strong recommendation, A*).
7. ART should be started as soon as possible (within eight weeks of TB treatment) among all people with multidrug-resistant TB living with HIV irrespective of their CD4/mm^3 counts (*strong recommendation, A*).

A person with multidrug-resistant TB requires anti-TB treatment with an intensive phase of at least 8 months and a continuation phase of at least 12 months. Widely available WHO guidelines *(8,11,69)* provide more details on the treatment.

Subjects with an Xpert MTB-positive and RIF-positive result should be treated for multidrug-resistant TB *(20)*. In settings with a low prevalence of multidrug-resistant TB, a confirmatory test for rifampicin resistance should be performed. People who are likely to have multidrug-resistant TB can also start a second-line regimen while awaiting the results of drug susceptibility testing. Candidates for an empirical multidrug-resistant TB treatment regimen include people for whom a Category I treatment regimen has failed and those exposed to a person with multidrug-resistant TB, especially if they present with severe disease.

An empirical multidrug-resistant TB regimen should be based on an anti-TB drug resistance profile identified from an anti-TB drug resistance survey or surveillance representative for the country. Widely available WHO guidelines provide more details on the TB treatment using second-line drugs *(8,11,69)*.

Whenever the results of drug susceptibility testing become available, people can have an individually tailored multidrug-resistant TB regimen still based on a few important principles (similar to that among people without HIV): at least four effective second-line anti-TB drugs to be given daily and under direct observation (DOT) and including a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide) and either cycloserine or PAS if cycloserine cannot be used. A later-generation fluoroquinolone is preferred to an earlier-generation fluoroquinolone. The first-line anti-TB drug pyrazinamide should also be included. Some experts recommend using high-dose isoniazid (defined as 16–20 mg/kg per day) in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 µg/ml but susceptible to 1 µg/ml of isoniazid), whereas isoniazid is not recommended for high dose resistance (>1% of bacilli resistant to 1 µg/ml of isoniazid). Thioacetazone should not be used among PLHIV because it causes severe cutaneous hypersensitivity reactions *(70)*.

Evidence from several studies (including two European cohorts) of PLHIV treated with second-line TB drugs suggests a lower risk of death and a higher likelihood of curing TB when they are also treated with ART *(71,72)*. Based on this evidence, it is recommended that, among people with multidrug-resistant TB, ART start as soon as possible (within the first eight weeks) after anti-TB treatment starts, irrespective of the CD4/mm^3 cell count *(69)*.

Systematic assessment of serious adverse events, treatment adherence, drug interactions and the incidence of immune reconstitution inflammatory syndrome associated with second-line TB drugs among PLHIV who have multidrug-resistant TB is rather scarce and needs to be improved.

Some interactions between the drugs used to treat HIV and TB are summarized below.

- Quinolones and didanosine. Buffered didanosine contains an aluminium- or magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone is administered. The enteric-coated formulation of didanosine can be used concomitantly without this precaution.
- Ethionamide/protionamide. Based on limited existing information on the metabolism of the thiamides (ethionamide and protionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/protionamide is thought to be metabolized by the cytochrome P450 system, although it is not known which of the cytochrome P enzymes are

responsible. Whether doses of ethionamide/protionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of multidrug-resistant TB and HIV is currently unknown.
- Clarithromycin is a substrate and inhibitor of cytochrome P3A and has multiple drug interactions with PIs and NNRTIs. If possible, the use of clarithromycin should be avoided among people with multidrug-resistant TB and HIV because of both its weak efficacy against multidrug-resistant TB and multiple drug interactions.

Because of the potential nephrotoxicity of the anti-TB injectable drugs and the antiretroviral TDF, these drugs should be used together with caution, and renal function tests should be performed frequently.

2.3 Adherence to anti-TB treatment and ART

Adherence is crucial for the success of both anti-TB and ART. People with poor adherence are at very high risk of developing drug-resistant strains of TB and HIV. Drug-resistant TB and HIV generate high costs, are difficult to treat and can be transmitted to other people.

Direct observation of drug intake (DOT) is strongly recommended to reinforce adherence to TB treatment, combined with context-specific and patient-centred support *(73)*. Although DOT is very demanding for health services, implementing appropriate DOT strategies should receive the utmost priority and should specifically target high-risk groups and people with multidrug-resistant TB.

Unlike TB treatment, HIV therapy is lifelong and DOT is not usually an option. However, the need to prevent the selection and spread of drug-resistant viral strains is not less important: for ART, more than 95% adherence is required to achieve optimal HIV suppression and treatment outcome *(74)*. The people receiving treatment should fully understand the importance of adhering to treatment and the consequences of poor adherence, and this should be properly addressed during counselling *(75)*. Some European countries have experienced DOT being applied to ART at TB services during TB treatment, possibly resulting in better understanding of the importance of adhering to treatment.

Adherence to treatment of TB and HIV should be closely monitored and explored at every visit. Effectively managing adverse reactions to drugs is very important and considered an essential condition for ensuring adherence to treatment.

For both TB and ART, adherence may be challenging among special population groups, such as people who inject drugs and prisoners. People who inject drugs, in particular, have an increased risk of poor adherence to ART and to TB treatment. Barriers to adherence vary between settings, so services should consult with users and their representatives first to find the most effective ways to overcome them and the best local solutions. In general, abstaining from treating people who inject drugs because of adherence issues is not justified. With adequate support, stable care and experienced personnel, drug users can adhere to long-term treatment and can have clinical outcomes comparable to those of people who do not use drugs. Evidence indicates the effectiveness of adherence reminders, adherence counselling, contingency management, supervised therapy and ancillary services. Adherence support has a special role in the provision of anti-TB and ART in services providing OST with methadone or buprenorphine. Co-location of multiple services, especially for people who inject drugs, has been shown to result in im-

proved health outcomes. Social support has been associated with improved outcomes in DOT programmes for treating TB.

For detailed information about factors influencing adherence in people who inject drugs, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users (76)*.

For more information on adherence, please see the sections on adherence to ART and monitoring adherence in *Patient evaluation and antiretroviral treatment for adults and adolescents (55)*.

2.4 Adverse treatment events and managing them

It is recommended that, during the initial 2–4 weeks of TB treatment, a complete clinical evaluation be done at least weekly. Serum glutamic pyruvate transaminase (SGPT) must be assessed at least once at the end of the first month.

Hepatotoxicity may be observed among up to 13% of people with TB and HIV *(77,78)*. Three TB drugs used in the intensive phase are hepatotoxic (rifampicin, isoniazid and pyrazinamide), and some HIV drugs are hepatotoxic as well (NNRTIs). If there are signs of significant liver injury (SGPT levels five times higher than the upper normal value for the test), all TB and HIV drugs should be changed to less toxic ones and interaction between anti-TB and antiretroviral drugs should be considered. If the person is severely ill with TB and stopping TB treatment is considered unsafe, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started. If TB treatment has been stopped, liver function tests must revert to normal and clinical symptoms (nausea and abdominal pain) must resolve before the anti-TB drugs are reintroduced. Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Rifampicin is less likely than isoniazid or pyrazinamide to cause hepatotoxicity, is the most effective agent and should be preserved in treatment as far as possible.

A skin rash is also a common side effect of combined TB and HIV therapy. The recommended approach is to try symptomatic treatment with antihistamines and skin moisturizing and to continue treatment while closely observing the person receiving treatment. If the skin rash worsens, however, all anti-TB and anti-HIV drugs must be stopped. Once the reaction has resolved, anti-TB drugs are reintroduced first, one by one, followed by HIV drugs.

The second-line TB drugs have many more adverse effects than the first-line anti-TB drugs, but these adverse effects can be managed even in resource-limited settings. Timely and intensive monitoring for and management of adverse effects caused by second-line drugs are essential for treating multidrug-resistant TB. It is essential for the people receiving treatment to be aware of possible side effects, to know their nature and to have access to clinical and laboratory services to help detect side effects and medications to treat adverse effects when they occur. Details on managing the side effects of second-line TB drugs are available elsewhere *(8)*.

2.5 Treatment of TB and HIV in special conditions

2.5.1 Renal insufficiency

Isoniazid, rifampicin and ethionamide/prothionamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds; consequently, these drugs can be given in normal dosage to people with renal failure. For people with severe renal failure, with creatinine clearance <30 ml/min or receiving dialysis, isoniazid can cause peripheral neuropathy, which can be prevented by prescribing pyridoxine.

Ethambutol, pyrazinamide, cycloserine, injectables and fluoroquinolones are excreted by the kidney and should be given in reduced doses or prolonged intervals (Table 3) under close monitoring of renal functioning by checking creatinine levels monthly. Formulations of PAS that do not use sodium salt can be used without the hazard of retaining sodium.

Such antiretroviral drugs as TDF and indinavir should be avoided because of their known renal toxicity.

Table 3. Adjusting anti-TB drugs in renal insufficiencya (8)

Drug	Change in frequency?	Recommended dose[b] and frequency for people with creatinine clearance <30 ml/min or for people receiving haemodialysis
Isoniazid	No change	300 mg once daily or 900 mg three times per week
Rifampicin	No change	600 mg once daily or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg once daily or 500 mg/dose three times per week[c]
Terizidone	–	Recommendations not available
Protionamide	No change	250–500 mg per dose daily
Ethionamide	No change	250–500 mg per dose daily
Para-aminosalicylic acid[d]	No change	4 g/dose, twice daily

Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[e]
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[e]
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[e]
Amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[d]

[a] *For Group 5 drugs, see the manufacturers' recommendations on adjustment in renal insufficiency.*

[b] *To take advantage of the concentration-dependent bactericidal effect of many antiTB drugs, standard doses are given unless there is intolerance.*

[c] *The appropriateness of 250-mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible, measure serum concentrations and adjust accordingly).*

[d] *Sodium salt formulations of para-aminosalicylic acid may result in an excessive sodium load and should be avoided among people with renal insufficiency. Formulations of para-aminosalicylic acid that do not use the sodium salt can be used without the hazard of sodium retention.*

[e] *Caution should be used with the injectable agents among people with impaired renal functioning because of the increased risk of both ototoxicity and nephrotoxicity.*

2.5.2 Liver disorders

Pyrazinamide, isoniazid and rifampicin or rifabutin can induce an inflammatory process in the liver. Pyrazinamide is the most hepatotoxic, followed by isoniazid. Rifampicin is less likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Among the second-line anti-TB drugs, ethionamide/prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

People carrying the hepatitis virus or with a past history of acute hepatitis or current excessive alcohol consumption can receive the usual TB regimens. However, hepatotoxic reactions to anti-TB drugs may be more common among these people and should therefore be anticipated.

Among people with unstable or advanced liver disease, liver functioning should be tested when treatment starts, if possible. If the serum alanine aminotransferase level is more than three times the normal range before treatment is initiated, people may receive a treatment regimen without pyrazinamide: in this case, however, a nine-month treatment regimen with rifampicin, isoniazid and ethambutol (intensive phase only) is recommended. Close monitoring of liver enzymes is advised.

2.5.3 Pregnant women

Active TB has been diagnosed at rates up to 10 times higher among pregnant women living with HIV than among women without HIV infection *(79)*. Untreated maternal TB is associated with a 2.5-fold increased risk of vertical transmission of HIV infection to the unborn child *(80)*. Similarly, HIV infection is a risk factor for active TB disease among infants and children. More severe forms of TB disease and higher mortality rates are reported among children living with HIV *(81)*. Treating TB and HIV coinfection among pregnant women is therefore a crucial intervention for both the mother and her child. The frequent and severe drug reactions require that the risks and benefits of anti-TB treatment be carefully considered, with the primary goal

of smear conversion to protect the health of the mother and child, both before and after birth. Consider the following general recommendations.

- Use of first-line ART in non-pregnant women. Review of the available data and programmatic experience provides reassurance that exposure to EFV in early pregnancy has not resulted in increased birth defects or other significant forms of toxicity *(66)*. For drug-susceptible TB, use standard first-line anti-TB treatment.
- For drug-resistant TB:
  - Avoid injectable anti-TB drugs, which are particularly toxic to the developing fetal ear. Capreomycin may also carry a risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.
  - Avoid ethionamide/prothionamide, which can increase the risk of nausea and vomiting associated with pregnancy and have teratogenic effects.

2.5.4. People who inject drugs

WHO has produced specific guidelines on providing collaborative HIV and TB services for people who inject drugs *(6)*.

People who inject drugs have a higher risk of TB *(82,83)* in addition to the high burden of HIV *(84)* and hepatitis C *(85)* infections in this population. However, alcohol dependence, active drug use and mental health problems should not be used as reasons to withhold TB and HIV treatment. The following factors require special approaches in their clinical management.

- The interaction of illicit drugs and OST with anti-TB and antiretroviral drugs results in increased hepatotoxicity *(86)*. This requires careful selection and dosage of anti-TB and antiretroviral drugs and closer monitoring of liver functioning. Cycloserine causes a high incidence of adverse effects, including seizures, among people dependent on alcohol or other substances and should possibly not be included in the treatment of multidrug-resistant TB.
- Rifampicin substantially reduces the concentration and effect of methadone: the dose of methadone has to be adjusted (increased) to maintain the substitution effect (11). As an alternative, rifampicin could be replaced by rifabutin, since rifabutin and methadone have not been reported to interact.
- Antiretroviral drugs and methadone may commonly interact, because of the latter opioid-induced effects on gastric emptying and the metabolism of cytochrome P450 isoenzymes 2B6, 3A4 and 2D6. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity and/or decreased efficacy of antiretroviral drugs. EFV, NVP and LPV/r have been associated with significant decreases in methadone levels. The people receiving treatment and the drug dependence treatment facilities should be informed of the likelihood of this interaction. The clinical effect is usually seen after seven days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved *(87)*.
- Limited information is currently available about interactions between buprenorphine and antiretroviral drugs. The findings from available studies show that the drug interaction profile of buprenorphine is more favourable than that of methadone *(88)*.
- Naltrexone is not metabolized via the cytochrome P450 enzyme system and is not expected to interact with PIs or NNRTIs *(89)*.
- Frequent coinfection with hepatitis C virus and/or hepatitis B virus and the interactions with drugs used for the treatment of hepatitis require special approaches *(90–92)*. Viral hepatitis infections should not contraindicate HIV or TB treatment but require closer monitoring of liver functioning. Treatment of HIV and hepatitis B virus coinfection should include the antiretroviral drugs TDF and FTC [3TC]. In general, peg-interferon and ribavirin treatment of hepatitis C virus infection should be deferred until TB treatment is completed; however,

in the presence of severe liver fibrosis or cirrhosis, a decision on treatment should be taken individually.

- Treatment adherence is important, considering that comparable treatment outcomes can be achieved with adequate support *(75,93)*. OST supports the adherence to TB and HIV treatment *(94,95)*. OST has to be integrated into the provision of TB and HIV inpatient and outpatient treatment services.
- Poor access to the health care system is a special consideration. Collaboration with harm-reduction programmes is essential in organizing effective outreach services such as education, HIV testing, TB screening and preventive treatment, DOT and tracing people lost to follow-up on TB treatment *(6,96,97)*.

2.5.5 Children

For recommendations on managing TB and HIV infection among children, see clinical protocol 11, *HIV treatment and care for children* (revision 2012) *(98)*.

2.6 Tuberculosis preventive treatment

Recommendations

1. PLHIV who have a positive TST or interferon-gamma release assay result benefit most from TB preventive treatment; however, TST is not a requirement for initiating TB preventive treatment among PLHIV (*strong recommendation, B*).
2. Eligible adults and adolescents living with HIV, irrespective of their degree of immunosuppression and including people receiving ART who were previously treated for TB as well as pregnant women, should receive at least six months of isoniazid preventive therapy (*strong recommendation, A*).
3. Isoniazid preventive therapy for 36 months increases protection in settings with high TB prevalence and transmission (*optional recommendation, C*).
4. The use of isoniazid alone for TB preventive treatment does not increase the risk of developing isoniazid-resistant TB. Concerns regarding the development of isoniazid resistance should therefore not be a barrier to providing isoniazid preventive therapy (*strong recommendation, B*).
5. Providing TB preventive treatment to PLHIV is a core component of HIV preventive care, and national HIV programmes and HIV service providers should take responsibility for this (strong *recommendations, C*).

PLHIV with latent TB infection are at a higher risk of developing active TB disease. Treatment for preventing TB should therefore be initiated among the PLHIV for whom active TB has been ruled out and who are presumed to or confirmed to have latent TB infection based on test results and/or history of TB exposure (Fig. 1).

2.6.1 Eligibility

PLHIV with a positive TST or interferon-gamma release assay benefit more from TB preventive therapy than those testing negative *(99)*. In addition, the use of TST and the interferon-gamma release assay can reduce the number of PLHIV who receive unnecessary TB preventive therapy.

In such settings as the WHO European Region, TST has been found to be cost-effective and beneficial in identifying the PLHIV most in need of TB preventive treatment, overcoming its related costs (procurement, distribution, cold chain, training, etc.). The interferon-gamma release assay may represent an alternative or a complement to TST in some settings, as described in section 1.3.

TB preventive treatment should therefore be initiated among the PLHIV among whom active TB disease has been excluded and who are confirmed or presumed to have latent TB infection based on test results or the prevalence of latent TB infection, respectively.

PLHIV should be treated for latent TB infection regardless of latent TB infection test and age if they have no evidence of active TB and exhibit the following characteristics:
- are close contacts of people with infectious pulmonary TB; and
- have a history of untreated or inadequately treated healed TB (old fibrotic lesions on chest radiography).

In some settings, for example in prisons, PLHIV with negative tests for latent TB infection and/or a negative history of TB may still benefit from TB preventive treatment because of a high TB prevalence among the prison population and the specifically high risk of progression from latent infection to disease *(82)*.

It is not recommended to use the CD4/mm^3 cell count (for example below 500 cells/mm^3) as a criterion for implementing TB preventive therapy. Past history of TB, current pregnancy and current ART should not contraindicate starting TB preventive treatment. In the presence of hepatitis (acute or chronic), regular and heavy alcohol consumption or symptoms of peripheral neuropathy, closer treatment supervision is warranted because the risk of severe side effects is higher.

2.6.2 Choice of regimen and doses

TB preventive treatment is most commonly based on isoniazid preventive therapy. The existing evidence *(99)* demonstrates that isoniazid preventive therapy reduces the risk of active TB among PLHIV by 33% overall and by 64% when targeting PLHIV who had a positive TST.

Evidence demonstrates that administering isoniazid preventive therapy does not increase the development of drug resistance to isoniazid *(100–103)*. The concern that isoniazid preventive therapy could further amplify existing isoniazid resistance is disputed by the fact that the number of bacilli in latent TB infection is very low, preventing the selection of pre-existent genetic mutations that confer drug resistance.

In countries with high resistance to isoniazid, although isoniazid preventive therapy does not amplify drug resistance, its efficacy in preventing TB is reduced proportionally to the extent of background isoniazid resistance. Even considering this shortfall, delivering isoniazid preventive therapy to PLHIV will still benefit a significant proportion of PLHIV living in areas with a high prevalence of isoniazid resistance and should be recommended.

Isoniazid preventive therapy should be prescribed regardless of the concomitant use of ART. Two observational studies from Brazil *(40)* and South Africa *(104)* and a subanalysis of data from a randomized clinical trial from Botswana *(105)* demonstrated additional protective benefits of the concomitant use of isoniazid preventive therapy with ART.

The recommended dose of isoniazid for TB preventive treatment is 5 mg/kg (300 mg maximum dose) once daily *(13)*. Isoniazid does not have clinically significant interactions with HIV drugs (Annex 3).

There is no currently accepted substitute for isoniazid for TB preventive treatment. The use of short-course multi-drug regimens has been advocated for countries with a high prevalence of isoniazid-resistant *M. tuberculosis*. A combination of rifampicin and pyrazinamide for two months is as effective as six months of isoniazid *(106)*, but this regimen is no longer recommended because it increases the risk of severe liver injury *(107)*. Regimens using ethambutol and pyrazinamide have undocumented efficacy and are likely to require discontinuation of treatment because of adverse effects *(99)*. A combination of isoniazid and rifampicin for three months reduces the risk of acquiring TB by 32–64% *(99)*, but such a regimen may cause drug–drug interactions with HIV drugs; in addition, the risks and benefits of using rifampicin for treating latent TB infection is a matter of debate. A recent study from South Africa found that a three-month regimen of isoniazid in association with rifapentine was not superior to standard six-month isoniazid treatment *(108)*.

More operational research is required on candidate regimens for treating latent TB infection in countries with a high prevalence of isoniazid resistance.

2.6.3 Duration of treatment

Isoniazid preventive therapy should be given at least for six months. This duration of treatment is consistent with evidence from low TB incidence areas that extending duration to 12 months (or 9 months) increases protection but only marginally *(99)*.

In settings with a high incidence of TB, isoniazid preventive therapy among PLHIV appears to have a short-lasting effect (1–2.5 years) because the drug cannot protect against reinfection.

One large recent trial conducted in Botswana suggests that a 36-month isoniazid preventive therapy regimen is more effective in preventing TB among PLHIV *(106)*. However, another trial from South Africa did not confirm the superiority of a 36-month regimen over the 6-month one *(108)*. A likely explanation is that longer courses of isoniazid are more efficacious but discontinuation of treatment and adverse events may compromise the extra benefit.

The possibility exists that continuous treatment with isoniazid, or cycles of six-month courses of isoniazid given intermittently (that is, every two years) may be more effective than standard isoniazid preventive therapy in preventing the reactivation of and reinfection with *M. tuberculosis* in high-incidence areas, but this hypothesis has not yet been investigated in clinical trials. Additional research to explore these and other options is urgently required.

It has been shown that one year of isoniazid prophylaxis given at the end of TB treatment reduces the risk of recurrence of TB among PLHIV in Africa and Haiti *(109,110)*. There is no experience on such a strategy in European countries to support recommending it as the standard of care in the European Region.

2.6.4 Adverse effects and managing them

Isoniazid preventive therapy has a low risk of adverse effects *(111)*. Isoniazid may cause drug-induced hepatitis, which is mostly mild to moderate in intensity, and peripheral neuropathy.

Routine monitoring of liver functioning is not generally necessary, except among PLHIV who have concomitant risk factors for liver injury (concomitant viral hepatitis, addition to alcohol and drugs, etc.). However, all individuals taking isoniazid should be instructed on how to recognize and immediately report clinical symptoms of liver injury (nausea, vomiting, jaundice, etc.).

Peripheral neuropathy occurs more commonly among PLHIV with concomitant conditions such as pregnancy, alcohol dependence, malnutrition, diabetes, chronic liver disease and renal failure. Pyridoxine should be prescribed for prevention (10 mg/day) and treatment (50–70 mg/day).

Isoniazid may rarely cause drowsiness. In this case, the drug may be administered before bedtime.

2.6.5 Treatment delivery and adherence

In settings in which different health care facilities manage people with TB and PLHIV, HIV health care providers should administer isoniazid preventive therapy with the assistance of social workers and peer supporters.

The adherence rates for isoniazid preventive therapy may vary widely: from 34% to 98% *(13)*. Lack of adherence to isoniazid preventive therapy does not promote drug resistance, and isoniazid preventive therapy therefore does not strictly require DOT. However, adherence to isoniazid preventive therapy is important for its effectiveness and could be promoted by integrating services: for example, staff of HIV and drug dependence services counselling people with TB and delivering isoniazid preventive therapy, ensuring coordinated clinical management of side effects, etc. The role of outreach and other harm reduction activities, such as needle and syringe programmes, should be explored in the effective delivery of isoniazid preventive therapy. Although DOT is not required for isoniazid preventive therapy, isoniazid may be given under supervision in specific settings such as prisons, shelters and outreach services for people who inject drugs.

In general, concerns regarding adherence should not be a barrier to implementing isoniazid preventive therapy.

2.7 Co-trimoxazole preventive therapy

Recommendations
1. Routine co-trimoxazole preventive therapy should be administered to all PLHIV who have active TB disease regardless of CD4/mm^3 counts (*strong recommendation, A*).

People with TB and HIV may die soon after treatment starts, especially if ART is started late and at a stage of HIV infection that is too advanced. 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 or *Toxoplasma gondii* encephalitis. Evidence indicates that co-trimoxazole (trimethoprim-sulfamethoxazole) is effective in preventing *P. jirovecii* pneumonia and *T. gondii* encephalitis and probably affects a range of other bacterial infections among people with HIV and TB *(112–114)*. There is no significant increase in adverse events among PLHIV with active TB disease regardless of their CD4/mm^{3}counts *(112,115)*.

The recommended dose for co-trimoxazole preventive therapy among adults and adolescents is one double-strength tablet: 160 + 800 mg daily.

Adherence to co-trimoxazole is critical, and direct observation of its administration, together with the anti-TB drugs, may be useful, especially among very ill people. HIV and TB prevention and care programmes should establish a system to provide co-trimoxazole preventive therapy to all eligible PLHIV. Several possible obstacles that may reduce the coverage of co-trimoxazole preventive therapy need to be addressed and solved at the programme level *(116)*, including the following:

- erratic supply and lack of stocks (stock-outs) of co-trimoxazole at health-care facilities;
- insufficient awareness among health care workers because of lack of training and supervision;
- perceived low priority of co-trimoxazole because of the absence of a reporting requirement;
- lack of integration of TB and HIV services; and
- fear that co-trimoxazole prescription would identify people as being infected with HIV.

Discontinuation of co-trimoxazole prophylaxis should be considered among all people with TB and HIV when TB therapy ends: discontinuation is possible when the CD4/mm^3 cell count is above 200 cells/mm^3 for more than three months after initiating ART.

2.8 Delivering TB and HIV treatment services

HIV and TB prevention and care programmes need to define the best model for delivering integrated services that enables the provision of quality-assured comprehensive services at the same time, as soon and as close as possible to where PLHIV and TB and their families reside. The best treatment and care for TB and HIV coinfection is based on a multidisciplinary approach *(117)*.

The basic treatment and care requirements should consider the needs of the person with HIV and TB and his or her comorbid conditions. Care is provided by a multidisciplinary team comprised of one or more physicians (in many countries being one specialist in infectious diseases and HIV and one specialist in pulmonology and TB), a nurse and a social worker or non-medical service provider. Each team member has a distinct role in providing treatment and care, and

their services should be complementary. It is essential that team members collaborate regularly in planning, implementing and monitoring all activities related to case management. A network of other specialists and self-help groups should be available to support people with TB and HIV, including providing OST for people who inject drugs *(118)*.

Hospitalization is essential for people who are severely ill or with associated conditions requiring closer clinical monitoring. However, in all cases of hospitalization, it is imperative to ensure that the other health care services the person is receiving are not disrupted, by providing them in the same place where the person is hospitalized (such as providing HIV treatment and OST in TB facilities for people who inject drugs).

Hospitalization of people with non-severe and/or non-infectious cases could be unnecessarily expensive compared with outpatient care, unethical from a patient perspective and even dangerous by exposing these people to multidrug-resistant TB superinfections if airborne infection control measures are poor. Most of the people with TB may effectively receive their TB treatment on an ambulatory basis, especially during the continuation phase of treatment. Integration with general services in primary health care is recommendable.

From the perspective of delivering TB and HIV collaborative treatment services, an HIV-experienced physician should initiate ART as soon as TB treatment is tolerated, usually between the first 2–8 weeks (the duration of the intensive phase of TB treatment). A TB specialist should monitor ART and its effectiveness in coordination with an HIV expert.

The risk of acquired *M. tuberculosis* drug resistance appears to be similar among people with and without HIV. However, the risk of primary disease after infection with drug-resistant strains is substantial among PLHIV, as demonstrated by the outbreaks of multidrug-resistant TB among hospitalized PLHIV and health care workers in Europe and the United States of America *(119)*. Strategies for infection control based on administrative measures, environmental control and respiratory protection must be regarded as a priority in countries in which both multidrug-resistant TB and HIV are prevalent.

The decision on how TB and HIV treatment should be delivered after hospital discharge and during the continuation phase of TB treatment should be taken by considering what the most convenient option is for the person receiving treatment to ensure adherence to treatment. Including lay workers, such as social workers and nongovernmental actors and communities, can effectively provide patient support and directly observed TB treatment (DOT), which enhances the completion of treatment and is so important for a successful outcome and in preventing the development of drug-resistant *M. tuberculosis (120,121)*.

3. Monitoring anti-TB treatment and ART

3.1 Monitoring anti-TB treatment

All people with TB should be monitored to evaluate their response to treatment, to identify and manage adverse drug reactions and to facilitate treatment adherence.

Follow-up procedures do not differ from those recommended for people with TB who are HIV-negative (69). Briefly, the response to treatment is followed up by monitoring weight and clinical conditions and by microbiological monitoring of sputum samples (Table 4). A symptom-based approach is recommended for managing most common side effects of TB drugs. Adherence to treatment should be ensured by continuous and careful registration of drug intake. All people with TB, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions or treatment interruptions.

3.2 Monitoring ART

Monitoring people with TB receiving ART should include clinical signs and symptoms, immunological and virological criteria and the toxicity and side effects of antiretroviral drugs. A systematic review reported that 16% of the patients develop immune reconstitution inflammatory syndrome *(122)*[6]. Immune reconstitution inflammatory syndrome can occur with any CD4/mm^3 count, but the highest incidence is among people with CD4/mm^3 counts <50 cells/mm^3 who received early ART *(123–125)*. It generally presents within three months from the start of ART.

Immune reconstitution inflammatory syndrome appears to comprise two distinct syndromes: (1) paradoxical immune reconstitution inflammatory syndrome, comprising worsening of TB despite effective TB treatment, often observed in the context of initiating ART; (2) unmasking immune reconstitution inflammatory syndrome, comprising a new presentation of TB (or other opportunistic infection) after initiating ART, often with an atypical or exaggerated presentation. Serum inflammatory biomarkers can predict and characterize TB-associated immune reconstitution inflammatory syndrome: people with unmasking immune reconstitution inflammatory syndrome had higher pre-ART levels of plasma interferon-gamma and C-reactive protein consistent with pre-existing subclinical TB; paradoxical immune reconstitution inflammatory syndrome is associated with lower levels of biomarkers of monocyte and regulatory T-cell activity and higher C-reactive protein *(126)*. Immune reconstitution inflammatory syndrome should be diagnosed only after thorough evaluation has already excluded other causes, especially failure of the TB treatment.

Most cases resolve without any intervention, and ART can be safely continued without interruption. Steroids can be given to reduce morbidity and hospital stay among everyone with immune reconstitution inflammatory syndrome who has moderate to severe symptoms and signs. Prednisone may be given at the dose of 1.5 mg/kg per day for at least two weeks, gradually decreasing in dose over at least one month *(127)*.

[6] Immune reconstitution inflammatory syndrome is defined as a clinical picture characterized by new or progressive signs, symptoms or radiographic anomalies temporally linked to the initiation of antiretroviral therapy in the presence of an increased CD4 count, decreased HIV-1 RNA and exclusion of multidrug-resistant TB, antiretroviral therapy failure, adverse events, non-adherence to medications and new opportunistic infections. The most common clinical manifestations are respiratory symptoms and pulmonary infiltrates.

For information about antiretroviral drug toxicity and its management please refer to the section on management of antiretroviral toxicity and side effects in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents, 2012 revision (55).*

People treated for TB and HIV should be followed regularly to clinically evaluate whether they can tolerate treatment. Table 4 summarizes the tests to be performed.

Table 4. Monitoring people receiving anti-TB treatment and ART

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
Comorbid conditions	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			X			X
CD4/mm^3 count	X		(X)		(X)			(X)			(X)			X
Viral load (if available)	X		(X)		(X)			X			X			X
Chest X-ray	X							X						X
Pregnancy test	X													X
Sputum-smear examination[a]	X			X	X		X	X		X				
Adherence (both TB treatment and ART)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X: required; (X): optional.

[a] *Required at the end of the third and eighth month only when on an eight-month TB treatment regimen. For people with multidrug-resistant TB, sputum-smear examination is required monthly.*

4. Minimum patient data to be collected at the service delivery level

The following indicators should be collected regularly to improve the clinical management of people with TB and HIV and to monitor the implementation of collaborative TB and HIV activities *(128–130)*:

- adults and children enrolled in HIV care who had their TB status assessed and recorded during their last visit among all adults and children enrolled in HIV care (on pre-ART and ART registries) and seen for care in the reporting period (number and percentage) (TB/HIV-1);
- adults and children enrolled in HIV care who started TB treatment among all adults and children in HIV care during the reporting period (number and percentage) (TB/HIV-2);
- proportion of people with TB with known HIV status [C.1.1];
- proportion of people with TB with known HIV status who are HIV positive [C.1.1];
- estimated HIV-positive incident TB cases who received treatment for TB and HIV (percentage) (B.1.2.2.);
- adults and children newly enrolled in HIV care (on the pre-ART and ART registries) who started treatment for latent TB infection (isoniazid preventive therapy) among the total number of adults and children newly enrolled in HIV care during the reporting period (number and percentage) (TB/HIV-4);
- people with TB registered over the reported period who had an HIV test result recorded in the TB registry among the total number of people with TB registered during the reported period (number and percentage) (TB/HIV-3);
- HIV-positive people with TB, registered over the reported period, starting or continuing co-trimoxazole preventive therapy treatment during their TB treatment among all HIV-positive people with TB registered during the reported period (number and percentage);
- HIV-positive people with TB who started on or continued previously initiated ART, during or at the end of TB treatment, among all HIV-positive people with TB registered during a given time period (number and percentage);
- percentage of sites providing services for people who inject drugs that contributed to case detection or provided TB preventive therapy;
- percentage of people who inject drugs with their TB status assessed;
- percentage of people who inject drugs completing TB preventive therapy;
- percentage of people who inject drugs diagnosed with TB and starting treatment in the past 12 months (129);
- percentage of people who inject drugs completing treatment for TB; and
- reduced TB-related morbidity and mortality among people who inject drugs.

Annex 1. Anti-TB drugs most commonly used (8)

Group	Drug (abbreviation)
Group 1: First-line oral agents	isoniazid (H) rifampicin (R) ethambutol (E) pyrazinamide (Z) rifabutin (Rfb)
Group 2: First- and second-line injectable agents	streptomycin (S) kanamycin (Km) amikacin (Am) capreomycin (Cm)
Group 3: Fluoroquinolones: second-line agents	levofloxacin (Lfx) moxifloxacin (Mfx) ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	ethionamide (Eto) protionamide (Pto) cycloserine (Cs) terizidone (Trd) para-aminosalicylic acid (PAS)
Group 5: Agents with an unclear role in the treatment of drug resistant-TB	clofazimine (Cfz) linezolid (lzd) amoxicillin/clavulanate (Amx/Clv) thioacetazone (Thz) clarithromycin (Clr) imipenem (Ipm)

Annex 2. Antiretroviral drugs most commonly used (55)

Group	Drug (abbreviation)
Nucleoside reverse-transcriptase inhibitors (NRTIs)	abacavir (ABC) didanosine (ddl) emtricitabine (FTC) lamivudine (3TC) tenofovir (TDF) zidovudine (ZDV) ABC + 3TC TDF + FTC ZDV + 3TC ZDV + 3TC + ABV
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	efavirenz (EFV) nevirapine (NVP) etravirine (ETV)
NRTIs + NNRTI	TDF + FTC + EFV (Atripla)
PIs	atazanavir (ATV) darunavir (DRV) fosamprenavir (FPV) ritonavir (RTV) lopinavir boosted with low-dose RTV in a fixed combination (LPV/r) saquinavir (SQV) tipranavir (TPV)
Integrase inhibitors	raltegravir (RAL)
Entry inhibitors	maraviroc (MRV) enfuvirtide (ENF)

Annex 3. Managing interactions among anti-TB and antiretroviral drugs (57)

HIV infection treatment	TB treatment	Interaction	Recommendation
PIs, un-boosted (no ritonavir)			
Atazanavir	Rifampicin	Rifampicin reduces C_{max}, AUC and C_{min} by 180%	Do not coadminister
Atazanavir	Rifabutin	Increased concentrations of rifabutin with no effects on PI exposure	Rifabutin 150 mg daily or 300 mg three times a week
PIs, boosted (with ritonavir)			
Lopinavir, fosamprenavir, atazanavir, darunavir, and tipranavir	Rifampicin	Rifampicin reduces C_{max}, AUC and C_{min} >75%	Do not administer rifampicin and PIs The use of LPV/r 400 + 100 mg twice daily plus RTV 300 mg twice daily is toxic and may not overcome interaction
	Rifabutin	Significant increase in rifabutin and rifabutin metabolite exposure, potentially resulting in toxicity	Rifabutin 150 mg once daily or 300 mg three times a week. PI doses unchanged
Non-nucleoside reverse-transcriptase inhibitors			
Efavirenz	Rifampicin	Efavirenz exposure reduced by ~26%	Administer both drugs at usual doses; some recommend increasing the efavirenz dose to 800 mg if weight >60 kg
	Rifabutin	Rifabutin exposure reduced by ~38%	Rifabutin 450–600 mg once daily or 600 mg three times a week
Nevirapine	Rifampicin	Nevirapine AUC reduced by 20–58%	Do not coadminister
	Rifabutin	Minimal interactions	May be coadministered safely at the usual doses

Etravirine	Rifampicin	Significant interaction of rifampicin on etravirine exposure	Do not coadminister
	Rifabutin	Etravirine exposure reduced by ~37%	Rifabutin 300 mg once daily if ETR is not coadministered with an RTV-boosted PI If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered
Integrase inhibitors			
Raltegravir	Rifampicin	Rifampicin reduces C_{max}, AUC and C_{min} levels by 60–70%;	Increase raltegravir dose to 800 mg twice daily. Consider rifabutin with raltegravir coadministration.
	Rifabutin	RAL AUC increased by 20%, C_{max} increasedby 40%, C_{min} reduced by 20%	No dosage adjustment necessary.
Coreceptor inhibitors			
Maraviroc	Rifampicin	Rifampicin reduces maraviroc exposure by 160%	Do not coadminister, or increase maraviroc dosage to 600 mg twice daily
	Rifabutin	Modest impact of rifabutin on maraviroc exposure likely	Administer maraviroc (300 mg twice daily) and rifabutin (300 mg daily)
Fusion inhibitors			
Enfuvritide	Rifampicin and rifabutin	No interactions	No dose adjustments necessary
Nucleoside analogues			
Zidovudine	Rifampicin	Rifampicin reduces the zidovudine AUC by 47%, but the effect on intracellular concentrations is unknown	Clinical significance unknown

AUC: area under the curve; C_{max}: maximum plasma concentration of drug; C_{min}: minimum concentration of drug; DRV/r: darunavir boosted with ritonavir; PI: protease inhibitor; SQV/r: saquinavir boosted with ritonavir.

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