

CHAPTER 10

HIV infection and MDR-TB

10.1 Chapter objectives

This chapter addresses the management of MDR-TB in the presence of known or suspected HIV infection and provides guidance on recent developments in the approach to TB/HIV.¹ The chapter outlines:

- recommended collaborative MDR-TB/HIV activities;
- diagnostic and clinical guidelines for management of MDR-TB in HIV-infected patients;
- potential drug interactions, toxicities and monitoring requirements in the concomitant treatment of drug-resistant TB and HIV;
- implications of HIV for infection control.

10.2 General considerations

HIV coinfection is a significant challenge for the prevention, diagnosis and treatment of drug-resistant TB, especially in the case of MDR-TB. The local epidemiological prevalence of HIV, MDR-TB and HIV-associated MDR-TB is important in guiding strategies for treatment of HIV and drug-resistant TB. All DR-TB control programmes are therefore strongly encouraged to determine the extent of the overlap between MDR-TB and HIV epidemics.

10.3 Recommended collaborative activities for TB/HIV control

WHO recommends that certain collaborative activities are carried out to decrease the joint burden of TB and HIV (see Table 10.1) (1–3).

These activities are the backbone of the WHO TB/HIV collaborative strategy. Just as the basic DOTS programme should be in place before undertaking MDR-TB treatment strategies, these TB/HIV collaborative strategies should be in place before embarking on HIV/MDR-TB activities. It is not appropriate to carry out expensive HIV/MDR-TB activities if basic TB/HIV activities are not already in place.

¹ TB/HIV is the term used for the context of the overlapping of the two epidemics of TB and HIV/AIDS. It is often used to describe collaborative activities to control TB and HIV/AIDS. Patients with HIV-associated TB should be referred to as such.

TABLE 10.1 WHO-recommended collaborative activities for TB/HIV control^a

A. ESTABLISH THE MECHANISMS FOR COLLABORATION
A.1 Set up a coordinating body for TB/HIV activities effective at all levels
A.2 Conduct surveillance of HIV prevalence among TB patients
A.3 Carry out joint TB/HIV planning
A.4 Conduct monitoring and evaluation
B. DECREASE THE BURDEN OF TB IN PEOPLE LIVING WITH HIV/AIDS
B.1 Establish intensified TB case-finding
B.2 Introduce isoniazid preventive therapy
B.3 Ensure TB infection control in health-care and congregate settings
C. DECREASE THE BURDEN OF HIV IN TB PATIENTS
C.1 Provide HIV testing and counselling
C.2 Introduce HIV prevention methods
C.3 Introduce co-trimoxazole preventive therapy
C.4 Ensure HIV/AIDS care and support
C.5 Introduce antiretroviral therapy

^a A detailed description of each of the activities listed in Table 10.1 can be found in the WHO document *Interim policy on collaborative TB/HIV activities (1)*

When the activities listed in Table 10.1 are in progress, programmes may seek to add activities for HIV/MDR-TB. The activities a programme chooses to add often depend on the resources available. These guidelines recommend the highest standard of care whenever possible, which includes the following HIV/MDR-TB activities:

- **Determine the prevalence of TB drug resistance in patients with HIV.** Programmes should determine the extent of the overlap of the MDR-TB and HIV epidemics. This can be done in two ways: data from TB DRS can be linked with HIV testing of those TB patients included in TB DRS; and/or when HIV surveillance among TB patients is implemented (4), TB DST can be included for all patients or for an unbiased subset.
- **Perform routine HIV testing in all TB patients.** WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend that all patients with TB should be routinely offered an HIV test (5), and these data can be used as the basis for surveillance of HIV among TB patients. Priority should be given to those countries and administrative areas where the adult HIV prevalence is $\geq 1\%$, or where the HIV prevalence among patients with TB is $\geq 5\%$ (1).
- **Use mycobacterial culture.** Mycobacterial culture of sputum or other fluids and tissues is increasingly recommended and used to help in the diagnosis of sputum smear-negative TB. This is especially important for HIV-infected TB patients (see below).

- **Use DST at the start of TB therapy when antituberculosis drug resistance is known to be a significant problem in the area.** Unrecognized MDR-TB in an HIV patient carries a high risk of mortality. However, the exact prevalence at which TB drug resistance becomes a significant mortality risk, necessitating DST at the start of antituberculosis treatment in all HIV-infected patients, is not well defined. Analysis of DRS data and the available resources will guide a country's decisions on whether DST is warranted at the outset of TB therapy or whether only HIV-infected patients identified with risk factors for MDR-TB (see Chapter 5) need DST. For example, in most countries in Africa where MDR-TB rates are low and technical capacity is limited, the circumstances do not warrant DST in all cases of active TB in HIV-infected individuals, but DST will be indicated in patients with risk factors for MDR-TB or in areas where high rates of MDR-TB have been identified.
- **Introduce antiretroviral therapy (ART) promptly in MDR-TB/HIV patients.** TB is an indicator disease for ART, irrespective of CD4 cell count. If CD4 cell counts are available, they can guide the decision on when to start ART (6). ART is similarly recommended for MDR-TB/HIV-infected cases, given the elevated mortality in these coinfecting patients. In general, ART should not be delayed for fear of giving the patient too many medicines. The usual protocols to prevent immune-reconstitution syndrome should be followed (6).
- **Arrange close treatment follow-up by a specialized team.** The team should be familiar with the treatment of both MDR-TB and HIV, with close monitoring of potential additive adverse effects, prophylaxis and treatment of opportunistic infections, general primary care, vaccinations and nutritional support.
- **Provide additional socioeconomic support.** Patients with MDR-TB and HIV are often at very high risk for inability to adhere to treatment. Additional socioeconomic support should be in place for such patients.
- **Ensure strict infection control.** TB infection control should be ensured in health care and congregate settings for both drug-susceptible and drug-resistant TB (1). Administrative measures include early recognition, diagnosis and treatment of TB suspects, particularly those with pulmonary TB, and separation from others, particularly those with HIV infection, until a diagnosis is excluded or the patient adequately treated. Environmental and personal protection measures should also be considered.
- **Involve the TB/HIV coordinating body.** This board should be involved in the planning and monitoring of HIV/MDR-TB activities and programmes.

10.4 Clinical features and diagnosis of MDR-TB in HIV-infected patients

The presentation of MDR-TB in the HIV-infected patient does not differ from that of drug-susceptible TB in the HIV-infected patient (7).

The diagnosis of TB in HIV-positive people is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extrapulmonary or sputum smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality. The use of X-ray and/or culture improves the ability to diagnose TB in HIV patients and is recommended where available.

In areas where MDR-TB is known to be a problem in HIV-positive patients, and where resources permit, all HIV patients with TB should be screened for MDR-TB with DST. Rapid diagnostic techniques for MDR-TB should be employed when possible since HIV-infected patients with TB on inadequate antituberculosis treatment, or no treatment, for even short periods of time are at a high risk of death.

10.5 Concomitant treatment of drug-resistant TB and HIV

The recommended treatment of TB, whether drug-susceptible or -resistant, is the same for HIV-infected and non-HIV-infected patients, except for the use of thioacetazone, which should not be used in HIV-infected patients (8). However, treatment is much more difficult and adverse events more common. Deaths during treatment, caused by TB itself or by other HIV-related diseases, are more frequent in HIV-infected patients, particularly in the advanced stages of immunodeficiency.

The use of ART in HIV-infected patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-infected patients with drug-susceptible or drug-resistant TB is often associated with adverse events that may lead to the interruption of both TB and/or HIV therapy. Information on when and how to design regimens for HIV treatment is available in other WHO publications (6). However, given the large amount of pills that need to be ingested and the potential of overlying toxicities, the following issues should be considered.

10.5.1 Potential drug interactions in the treatment of drug-resistant TB and HIV

There are several known interactions between drugs used to treat TB and HIV. Rifamycins (rifampicin, rifabutin), while not used in MDR-TB treatment, are needed in the treatment of many poly- and mono-resistant cases. Rifamycins may lower the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, contributing to the development of resistance to these drugs. In this regard, rifabutin has the least effect of all the rifamycins.

Antiretroviral drugs increase the level of rifampicin and the risk of toxicity. The interactions between rifamycins and antiretroviral drugs are described elsewhere in detail (10).

Other interactions include those between fluoroquinolones and didanosine. Nonenteric-coated didanosine contains an aluminium/magnesium-based antacid that, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should therefore be given six hours before or two hours after fluoroquinolone administration. Clarithromycin, a drug not routinely recommended for MDR-TB by WHO but used by some programmes, has several interactions with HIV medications (11–12).

10.5.2 Potential drug toxicity in the treatment of drug-resistant TB and HIV

In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications (13–14). Known adverse effects of increased severity in coinfecting patients include peripheral neuropathy (15) (stavudine, aminoglycosides, cycloserine, pyrazinamide), cutaneous and hypersensitivity reactions (thioacetazone) (16), gastrointestinal adverse effects (17), renal toxicity (injectables) and neuropsychiatric effects (cycloserine, efavirenz).

10.5.3 Monitoring of drug-resistant TB and HIV therapy in coinfecting patients

Unlike MDR-TB treatment, which can be omitted on one day of the week, HIV medicines must be given every day. While the treatment of MDR-TB is being administered, DOT of ART should be included.

The complexity of antiretroviral regimens and treatment of drug-resistant TB, each with its specific toxicity profiles – some of which may be potentiated by concomitant therapy – demands rigorous monitoring in this particular group of patients (18). Ideally, ART should be initiated and monitored in collaboration with a health-care provider knowledgeable in both drug-resistant TB and HIV. Chapter 11 describes the monitoring requirements for treatment of drug-resistant TB and also indicates where monitoring in HIV-infected individuals is required with increased frequency. Standard monitoring procedures for those on ART should be followed.

Monitoring of chest X-rays, smears and cultures in the coinfecting patient is the same as for HIV-negative MDR-TB patients. If the patient shows signs of treatment failure, the same evaluation as described in Chapter 13 is warranted. In addition, the ART regimen should be re-evaluated as described above.

Patients with HIV-associated MDR-TB will usually require special socio-economic support. The regimens together are particularly difficult to tolerate, the stigma of both diseases can result in serious discrimination and the risk of mortality is very high.

10.6 Implications of HIV for MDR-TB infection control

MDR-TB outbreaks have overwhelmingly involved HIV-positive patient populations and nosocomial transmission. Delay in recognition of MDR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission. These practices have contributed to MDR-TB outbreaks that affect both HIV-positive and HIV-negative patients.

Implementation of adequate infection control precautions significantly reduces nosocomial transmission. Home-based measures of separate living quarters, masks for visitors and adequate ventilation can also be effective. Infection control measures for MDR-TB are described in Chapter 15.

10.7 Coordination of HIV and TB care: involvement of the TB/HIV board

The national TB and HIV/AIDS control programmes need a joint strategic plan to collaborate successfully and systematically on carrying out the recommended joint activities. A joint plan can be made to treat patients in whom drug-resistant TB and HIV infection have been diagnosed. Alternatively, components can be introduced in their respective programmes to ensure adequate diagnosis, care, treatment and referral of patients with HIV-associated drug-resistant TB. Coordinated training activities should focus on developing a group of providers in a specialized multidisciplinary team with adequate expertise in both areas. The roles and responsibilities of each programme at national and district levels must be clearly defined, as well as the roles of individual team members.

10.8 Summary

Understanding the regional prevalence of HIV, MDR-TB and MDR/HIV coinfection is the first step in guiding the strategies for MDR-TB/HIV activities. In some areas, MDR-TB is an important potential problem for HIV-infected patients. Before programmes embark on MDR-TB/HIV control strategies, the activities listed in Table 10.1 should be implemented. The patient with drug-resistant TB disease and HIV will require intensive medical care to decrease the high level of mortality. Rigorous infection control measures should be part of the planning. Coordination between the team treating drug-resistant TB and the HIV control programme for training, care and treatment is an essential component. MDR-TB/HIV coinfection has the potential to increase rapidly. All drug-resistant TB and HIV control programmes should coordinate the collaborative activities described in this chapter, which are an integral element of both HIV/AIDS and TB control, aimed at avoiding epidemics of HIV-associated MDR-TB.

References

1. *Interim policy on collaborative TB/HIV activities*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.330; WHO/HTM/HIV/2004.1).
2. *Strategic framework to decrease the burden of TB/HIV*. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.296; WHO/HIV_AIDS/2002.2).
3. *Guidelines for implementing collaborative TB and HIV programme activities*. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.319; WHO/HIV/2003.01).
4. *Guidelines for surveillance of drug resistance in tuberculosis*. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003/320; WHO/CDS/CSR/RMD/2003.3).
5. *UNAIDS/WHO policy statement on HIV testing*. Geneva, World Health Organization/Joint United Nations Programme on HIV/AIDS, 2004.
6. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. 2003 revision*. Geneva, World Health Organization, 2004.
7. *TB/HIV: a clinical manual*. Geneva, World Health Organization, 2003 (WHO/HTM/TB/2004.329).
8. Nunn P et al. Thiacetazone commonly causes cutaneous hypersensitivity reactions in HIV positive patients treated for tuberculosis. *Lancet*, 1991, 337:627–630.
9. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report*, 2004, 53(2):37.
10. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report*, 2000, 49(9):185–189.
11. *The PIH guide to medical management of multidrug-resistant tuberculosis*. Boston, MA, Partners In Health, Program in Infectious Disease and Social Change, Harvard Medical School, Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, 2003.
12. Bartlett JG. *The Johns Hopkins Hospital 2003 guide to medical care of patients with HIV infection*, 11th ed. Philadelphia, Lippincott Williams & Wilkins, 2003.
13. Chaisson RE et al. Tuberculosis in patients with the acquired immunodeficiency syndrome. Clinical features, response to therapy, and survival. *American Review of Respiratory Disease*, 1987, 136(3):570–574.

14. Soriano E et al. Characteristics of tuberculosis in HIV-infected patients: a case-control study. *AIDS*, 1988, 2(6):429–432.
15. Breen RA, Lipman MC, Johnson MA. Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. *AIDS*, 2000, 14(5):615.
16. Watkins WM et al. Cutaneous hypersensitivity reactions to thiacetazone, HIV infection and thiacetazone concentrations in plasma. *British Journal of Clinical Pharmacology*, 1996, 41(2):160–162.
17. Dean GL et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS*, 2002, 16(1):75–83.
18. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. *Morbidity and Mortality Weekly Report*, 2002, 51(RR07).