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From Basic Science  
to Patient Care



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## Chapter 17: Tuberculosis and HIV/AIDS

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### 17.1. Epidemiological background

Tuberculosis (TB) – known in the past as the “White Plague” – is an ancient and often neglected disease. Recent genetic evidence suggests that even our remote hominid ancestors, who lived three million years ago, may have suffered from TB (Gutierrez 2005). Paradoxically, the disease re-emerged in the late '80s fueled by the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) pandemic. In a few years TB became – and continues to be – a leading cause of illness and death among people with HIV/AIDS in resource-poor areas of the world (Moore 2007, Quy 2007). This unexpected encounter between the ancient and the new plague is an intriguing biological issue (Heney 2006).

Taking a turn for the worse, the AIDS pandemic further promoted the emergence of multidrug-resistant TB (MDR-TB). The first AIDS-associated MDR-TB outbreaks were reported in the United States (US) in the early '90s (Frieden 1996). These were the first alarm signals of the decline of the TB control programs that were prevalent at that time not only in the US, but also in several other parts of the world. Indeed, a third epidemic has resulted from the interaction of TB and AIDS epidemics, i.e. the MDR-TB epidemic, which not only affects immunodepressed hosts, but also extends globally (Neville 1994). This is partly due to the airborne nature of TB transmission, which is so difficult to prevent, as well as to the growing waves of human migration from high to low TB prevalence areas. Today, drug-resistant TB is still threatening the efforts towards effective control of the disease worldwide (see the WHO Global tuberculosis control 2006 on the internet at [http://www.who.int/tb/publications/global\\_report/2006/en/index.html](http://www.who.int/tb/publications/global_report/2006/en/index.html)).

An estimated 38.6 million people worldwide were living with HIV at the end of 2005. At that time, 4.1 million persons became newly infected with HIV, and 2.8 million lost their lives because of AIDS. Africa continues to be the global epicenter of the AIDS pandemic. South Africa's AIDS epidemic — one of the worst in the world — shows no evidence of declining. In this country, an estimated 5.5 million people were living with HIV in 2004 and almost one in every three pregnant women attending public antenatal clinics were HIV positive, with increasing prevalence trends. The epidemic also looks rampant in South-East Asian, East European and other Sub-Saharan African countries (see UNAIDS 2006 global

report on the internet, [http://www.unaids.org/en/HIV\\_data/2006GlobalReport/default.asp](http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp)).

A comparison between TB and HIV/AIDS statistics worldwide shows an overlap between both epidemics, mainly in Sub-Saharan Africa and South-East Asia, where a devastating synergy is observed between the kinetic of both diseases (see Chapter 7). Among all opportunistic diseases associated with HIV/AIDS, the distinctive feature of TB lies mainly in its airborne dissemination to other patients, to health-care workers and to the entire community (Pape 2004, Putong 2002, Sharma 2005). Poverty, social inequities, difficult access to public health systems, and lack of sanitary education leads to a critical public health situation that is hampering the international efforts aimed at controlling both diseases. The response of public and private health organizations to this burdensome association currently focuses on the reinforcement of TB and HIV/AIDS control activities, including a considerable increase in their budgets and in the interaction/partnership between both programs.

From the point of view of TB control, the emergence of MDR-TB, and especially of extensively drug-resistant TB (XDR-TB), has mobilized a strong partnership between public and private sectors on the international level. Global efforts brought together by an initiative of the World Health Organization (WHO) are currently being focused on the procurement of first quality drugs, the supervision of their administration and the development of new drugs (see the Stop TB Strategy on the internet at <http://www.who.int/tb/strategy/en/>).

## 17.2. Interactions between *M. tuberculosis* and HIV infection

A complex biological interplay occurs between *M. tuberculosis* and HIV in the co-infected host that results in the worsening of both pathologies. HIV promotes progression of *M. tuberculosis* latent infection to disease and, in turn, *M. tuberculosis* enhances HIV replication, accelerating the natural evolution of HIV infection (Goletti 1996, Mariani 2001, Nakata 1997, Rosas-Taraco 2006). HIV infection impairs *Mycobacterium tuberculosis*-specific IFN-gamma production, and this impairment is not reversed by anti-retroviral treatment (Sutherland 2006).

TB develops in HIV-infected hosts at a yearly rate of 8 % by either of the two pathogenic mechanisms: endogenous reactivation or exogenous reinfection (Small 1993, van Rie 1999). Eventually, both mechanisms can coexist. Indeed, it was shown that a single patient can be infected and/or re-infected with more than one strain of *M. tuberculosis* even during a single TB episode (van Rie 1999, van Rie 2005).

Unlike most other opportunistic diseases, which usually appear in the late stages of AIDS upon severe immunological impairment, TB can occur anytime during HIV infection. The clinical presentation of TB, however, differs according to the severity of the immunodepression associated with the HIV infection. Localized pulmonary disease is the most common presentation in the early stages of HIV infection. On the other hand, disseminated forms of TB, in particular TB meningitis, are more frequent in severely immunodepressed AIDS patients and, obviously, mortality in these cases is significantly higher (Whalen 1997).

### 17.3. Clinical characteristics

As mentioned above, the clinical presentations of TB in an HIV/AIDS patient is clearly related to the patient's degree of immunodepression, which is measured as the blood level of CD4+ T lymphocytes (Jones 1993). A level of 200 CD4+ T cells per  $\mu\text{L}$  represents an approximate threshold for severe immunodepression. Above this level, a complete TB granuloma is produced in response to *M. tuberculosis* infection, including multinucleated giant cells, macrophages, CD4+ and CD8+ T lymphocytes and a central caseous necrosis. On chest X-ray, the typical pulmonary localizations can be observed, often with images of lung cavitation (Figure 17-1). As in the immunocompetent host, the clinical presentation of the disease involves fever, night sweats and weight loss accompanied by productive cough with mucopurulent or hemoptoic sputum or even hemoptysis. In these early stages of HIV immunodepression, pleural and lymph node TB are the most frequent extrapulmonary localizations of the disease, whereas disseminated TB and meningitis are rarely seen.

With the decline of CD4+ T cell counts to below 200/ $\mu\text{L}$ , the formation of the granuloma is progressively impaired, the hematogenous and lymphatic dissemination of the disease is more frequent and the clinical picture changes drastically. The skin reaction to intradermal injection of Protein Purified Derivative (PPD) –, which is based on the cellular immune response, – is usually negative. Even in these cases with severe immunodepression, pulmonary localization is most common. However, the frequency of extrapulmonary and disseminated presentation scales up to near 50 % of cases and extrapulmonary involvement disease often coexists with pulmonary disease. The so-called “atypical” presentations are frequently observed in the chest X-ray (Figures 17-2, 17-3, 17-4) (Daley 1995). These include basal opacities, absence of cavitation, micronodular (miliary) patterns, hilar and mediastinal adenopathy, pleural and/or pericardial effusion. Still, up to 10 % of cases may present

with a normal chest X-ray, even with positive sputum acid fast bacilli (AFB) smear microscopy (Aaron 2004).



Figure 17-1: Chest X-ray of a male patient with HIV co-infection and 427 CD4+ cells/ $\mu$ L showing cavity images in both upper lobes.



Figure 17-2: Chest X-ray of a male patient with 23 CD4+ cells/ $\mu$ L showing lower and medial lobe opacities with hilar and mediastinal lymph node compromise.



Figure 17-3: Chest X-ray of a 31 years old AIDS patient with 71 CD4+ cells/ $\mu$ L in blood and *M. tuberculosis* isolation from sputum: multiple pulmonary opacities in both lungs are typical of hematogenous dissemination of TB.



Figure 17-4: Chest X-ray showing bilateral opacities in a 27-year-old patient with AIDS and disseminated MDR-TB. On admission, he was severely ill with a CD4+ count of 23 cells/ $\mu$ L. The sputum smear microscopy was positive for acid fast bacilli, and *M. tuberculosis* resistant to isoniazid and rifampicin was identified in the culture.

The differential diagnosis of both typical and atypical presentations of pulmonary TB includes *Pneumocystis jirovecii* pneumonia and bacterial pneumonia. In particular, pulmonary nocardiosis closely resembles TB due to its subacute evolution and the presence of apical infiltrates with cavitation. The differential diagnosis in AIDS patients should also consider infrequent respiratory pathogens, such as *Rhodococcus equii*.

The cornerstone of TB diagnosis is the isolation of *M. tuberculosis* from tissues, fluids or secretions of the suspected patient. As pulmonary localization is the most frequent form of TB, even in severely immunodepressed AIDS patients, the respiratory secretions are the first target to examine when searching for tubercle bacilli. Sputum can be easily obtained by spontaneous cough, induced by hypertonic saline nebulization, or recovered through an early morning gastric washing after overnight fasting. Bronchoscopy is a technique that allows the visualization of the accessible respiratory tract, the obtention of bronchial washings, bronchoalveolar lavages and bronchial or transbronchial lung biopsies. Therefore, bronchoscopy offers the advantage of expanding the diagnostic spectrum to non-infectious diseases (sarcoidosis, lymphoma, endobronchial tumors).

In the advanced stages of AIDS, the most common extrapulmonary localizations of TB are serous effusions (pleurisy, pericarditis, ascites), lymphadenopathy, Pott's disease, osteomyelitis, arthritis and meningitis. Other organs may be involved, including the gastrointestinal tract, liver, kidneys, urinary tract, adrenal gland, larynx and genital (male and female) tract.

Serous effusions (pleural, pericardial and/or peritoneal) are quite frequent in HIV/AIDS patients and may be caused by various other etiological agents. TB pleurisy ranks among the most frequent cause of serous effusion, together with empyema, from which it has to be differentiated. In TB pleurisy, the aspirated fluid is exudative with a predominance of lymphocytes. Pleural biopsy and mycobacterial culture of the fluid are the most useful and specific diagnostic tools. Adenosine deaminase (ADA) levels above 50 U/L in non-purulent pleural fluid specimens have a high positive predictive value for the diagnosis of TB.

Cervical lymphadenitis is the second most frequent extrapulmonary localization of TB in AIDS patients, after pleurisy. Aspiration puncture of a swollen and fluctuant lymphadenopathy usually yields a purulent or caseous material with abundant AFB on microscopy examination (Figure 17-5).

Abdominal localizations of AIDS-associated TB (ileocecal area, peritoneum, mesenteric lymph node, liver) are the cause of unspecific presentations such as diarrhea, visceral enlargement, swollen abdomen and right lower quadrant pain. Diag-

nostic procedures such as peritoneal fluid aspiration, laparoscopy or fiber colonoscopy can be performed and provide samples for culture and biopsy.



Figure 17-5: Aspiration procedure of a cervical lymphadenopathy in an AIDS patient with disseminated TB. The aspirate had a caseous aspect and was AFB smear microscopy + (10 AFB/field). Other demonstrated localizations in this case were pulmonary and a bilateral psoas abscess.

Spinal TB (Pott's disease) is a notoriously severe extrapulmonary TB presentation in AIDS patients because it can result in an accelerated destruction of vertebral bodies and intervertebral discs (Figure 17-6). The most common localizations are the thoracic and lumbosacral vertebrae, where there is risk of spinal cord compression and subsequent paraplegia. Progression through the psoas muscle can produce a cold inguinal abscess. The characteristic pain and the radiographic findings contribute to the diagnosis. The specimen for bacteriological confirmation is obtained by aspiration and/or biopsy of the affected vertebral body.

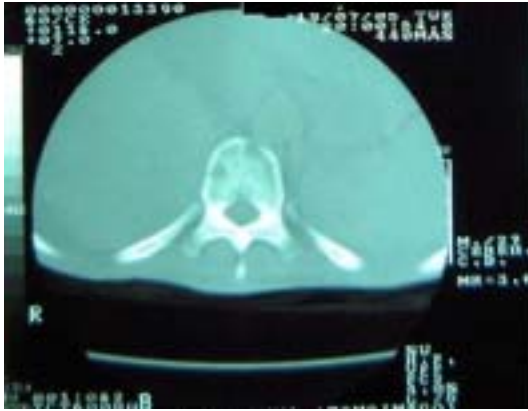


Figure 17-6: Computerized tomography scan showing an osteolytic lesion in the body of a thoracic vertebra in a patient with Pott's disease and AIDS.

TB meningitis has a more insidious clinical presentation and higher mortality in AIDS patients than in immunocompetent patients. Headaches and mental confusion may be the first symptoms to induce the suspicion of a meningeal involvement. The classical meningeal syndrome with the Kernig and Brudzinsky signs and cranial nerve palsies, usually appears late in its evolution (Figure 17-7). The basal meninges are usually involved and cranial palsies of the 3<sup>rd</sup> and 6<sup>th</sup> nerves are common. Mono-, hemi-, or paraparesis can occur, as well as seizures. In addition to the lumbar puncture, brain computed tomography imaging is needed to rule out or confirm the diagnosis of tuberculous meningitis. The central nervous system involvement may include intracranial tuberculomas and brain abscesses that require brain biopsy and/or aspiration for bacteriological and/or histopathological confirmation. The cerebrospinal fluid is hypertensive with an elevated protein content, low glucose levels and mononuclear pleocytosis.

The differential diagnosis between meningitis caused by *M. tuberculosis* and *Cryptococcus neoformans* is extremely important in order to establish adequate treatment. Both etiological agents produce a subacute meningeal syndrome and very similar abnormalities in the cerebrospinal fluid. In most cases, however, a direct India ink coloration of the spinal fluid allows the immediate identification of the typically capsulated *Cryptococcus* cells. The culture for mycobacteria is frequently negative in tuberculous meningitis and the value of other diagnostic methods, such as adenosine deaminase dosage or PCR, is questionable. Therefore, many patients are empirically treated upon clinical suspicion of TB meningitis in view of its somber prognosis. Sequels, including cranial nerve palsy, deafness, hydro-

cephalus, altered mental status and paresis or paralysis are common in AIDS patients who survive to develop tuberculous meningitis.

Enlargement of the liver and spleen is often indicative of hematogenous dissemination of *M. tuberculosis*. Multiple nodular lesions (microabscesses) in both organs can be detected as hypoechoic images on the ultrasound ecography (Figure 17-8) and also on computed tomography scans. Another consequence of the hematogenous spread is the above-mentioned meningeal involvement, which has a poor survival prognosis (Berenguer 1992, Sanchez Portocarrero 1996, Cecchini 2007). Retroperitoneal, multiple adenopathies and psoas abscesses can be diagnosed by ultrasonography or computed tomography guided aspirate.



Figure 17-7: Kernig's sign positive appears late in the evolution of TB meningitis. In this particular case, the spinal fluid was positive for *M. tuberculosis* culture.

Polyserositis (pleural-pericardial-peritoneal involvement) is another manifestation of disseminated TB in AIDS patients, where *M. tuberculosis* can be recovered from any of the various serous effusions. The clinical presentation of this form of disseminated TB is unspecific: fever of unknown origin, anemia and wasting are usual manifestations in AIDS patients, common to several other co-morbidities and also to the HIV infection itself. In these cases, several bodily sources in addition to respiratory secretions are useful for *M. tuberculosis* isolation: blood, bone marrow, abscess punctures, urine and cerebrospinal fluid. In the pre-AIDS era, specimens such as blood or bone marrow aspirate specimens were unthinkable sources of *M. tuberculosis* isolation. In severely immunodepressed AIDS patients, however, they offer a considerable diagnostic yield ranging from 10 % to 20 % (Biron 1988,

Khandekar 2005). Figures 17-4, 17-6, 17-7, and 17-8 illustrate the case of a transvestite male sex worker with AIDS and disseminated MDR-TB with pulmonary, vertebral, liver, spleen, psoas muscle, and finally meningeal involvement.

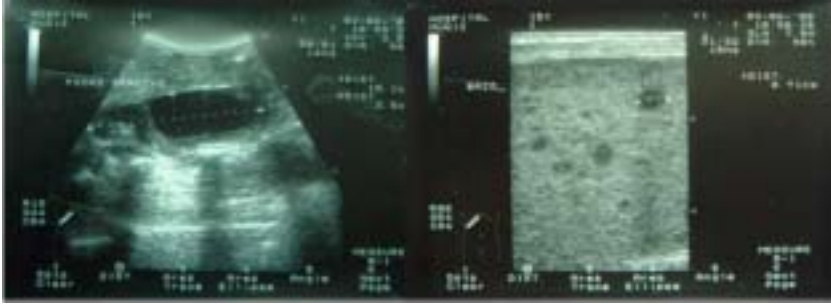


Figure 17-8: Abdominal ultrasonography showing a psoas muscle abscess and multiple hypo-echoic lesions in spleen, suggestive of TB microabscesses in the same patient as in Figure 17-7.

The clinical manifestations of disseminated TB are very similar to those of disease caused by nontuberculous mycobacteria, mainly *M. avium*. For this reason, the presence of AFB in the smear microscopy examination is not enough for the diagnosis: the specimen must be submitted to cultivation, species identification and drug susceptibility testing. In addition to disease due to mycobacteria other than *M. tuberculosis*, the differential diagnosis includes disseminated cryptococcal disease, disseminated histoplasmosis and lymphoma.

## 17.4. Multidrug-resistant tuberculosis and HIV/AIDS

### 17.4.1. Definitions

A case of TB is more or less manageable according to the drugs to which the patient's isolate is resistant. In this respect, the disease can be classified as:

- **Monoresistant TB:** caused by *M. tuberculosis* resistant to a single drug
- **Polyresistant TB:** caused by *M. tuberculosis* resistant to at least two drugs, but not involving isoniazid (INH) and rifampicin (RIF) simultaneously
- **Multidrug-resistant TB (MDR-TB):** caused by *M. tuberculosis* resistant to at least two drugs, always involving INH and RIF

- **Extensively drug resistant TB (XDR-TB):** defined as MDR-TB with additional resistance to any fluoroquinolone, and to at least one of the three following injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin (Raviglione 2007)

The most frequent drugs involved in mono-resistance are INH and streptomycin (SM) (see Chapter 19). Nowadays, SM is not regularly used in the standard therapeutic schemes, and resistance to INH has limited clinical or epidemiological relevance (Nardell 2005). Likewise, poly-resistance is relatively easy to overcome as long as susceptibility to RIF is preserved. In contrast, the standard antituberculosis chemotherapy often fails in patients with RIF-resistant TB, which are therefore at an increased risk of developing added INH resistance, that is, to become MDR. In many settings, resistance to RIF is a strong predictor of MDR-TB (Traore 2000) (see chapter 19). Furthermore, poor outcome and death are associated with resistance to RIF alone or in combination with resistance to other drugs (Espinal 2000). Monoresistance to RIF is rather unusual and occurs mainly in association with HIV/AIDS. The reasons for this association appear to be multiple, including mal-absorption, drug interaction and previous administration of a related rifamycin (rifabutin) as a prophylactic treatment for *M. avium* disease (Ridzon 1998).

As for the epidemiological mode of *M. tuberculosis* resistance development, drug resistant TB is classified in two subgroups:

- **drug resistance in patients without previous treatment for TB** (formerly “primary” or “initial” drug resistance)
- **drug resistance in patients with previous TB treatment** (formerly “secondary” or “acquired” drug resistance)

Assumedly, a case of MDR-TB in a person without a previous history of TB treatment has been contracted from a source MDR-TB case (see Chapter 19). This kind of resistance is rather frequent in HIV/AIDS cases, in which MDR-TB may acquire epidemic dimensions (Frieden 1996). On the other hand, MDR-TB in a patient with previous TB treatment is usually the result of a prolonged history of inadequate treatment due to erroneous prescriptions, inadequate quality of medicines or irregular treatment compliance. Erratic behavior of certain populations with TB and HIV/AIDS co-infection is often associated with poor treatment compliance and acquisition of antituberculosis drug resistance. However, the distinction between “initial” and “acquired” drug resistance is not always clear in HIV/AIDS patients, who may become infected with a drug resistant strain in the same healthcare environment where they are being treated for pansusceptible TB. In fact, in certain settings, with a high incidence of both TB and HIV/AIDS, the relative contribution

of transmission to the burden of drug-resistant tuberculosis seems to be much higher than previously expected (Gandhi 2006, van Rie 2000).

#### 17.4.2. The development of drug resistance

The mechanisms driving *M. tuberculosis* resistance to antituberculosis drugs are genetically controlled (see Chapter 18). A proportion of mutants resistant to a single drug are generated spontaneously in any bacilli population, even if not exposed to any antituberculosis drug. In *M. tuberculosis*, the average spontaneous mutation rate for resistance to RIF, INH, SM, and ethambutol (EMB) is  $2.25 \times 10^{-10}$ ,  $2.56 \times 10^{-8}$ ,  $2.95 \times 10^{-8}$  and  $1.0 \times 10^{-7}$  mutations per bacterium per generation, respectively. The probability of occurrence of simultaneous resistance to both INH and RIF (MDR-TB) is obtained by multiplying both mutation rates:  $(2.25 \times 10^{-10}) \times (2.56 \times 10^{-8}) = 5.76 \times 10^{-18}$  (Canetti 1965). Thus, it is highly improbable that a patient with a pulmonary cavity lesion containing approximately  $10^9$  bacilli can be spontaneously multidrug-resistant.

Drug resistance emerges a result of a selection process that occurs within the lesions of a TB patient undergoing inadequate therapy. Usually, drug resistance is acquired stepwise through successive inadequate treatments. This is consistent with the finding of higher rates of drug resistance in previously treated TB cases. The selection process of *M. tuberculosis* resistant mutants requires an important bacillary load within the patient's lesions. This is the reason why drug resistance occurs mainly in cases of pulmonary TB and, in turn, is rare in latent TB infection and extrapulmonary localizations that usually have low bacillary loads (Centers for Disease Control and Prevention 1994).

For a long time, drug resistant strains were thought to be less fit than pansusceptible strains and therefore less likely to be transmitted. In particular, large mutations in the *M. tuberculosis* catalase-peroxidase (*katG*) gene have been associated to both an INH-resistant phenotype and a reduced virulence. Actually, mutations leading to antibiotic resistance may or may not have an effect on the fitness of drug-resistant tuberculosis strains (Cohen 2003) (see Chapter 18). The results from different studies are controversial regarding the risk of infection among contacts exposed to resistant bacilli (Burgos 2003, Snider 1985, van Soolingen 1999). Certain MDR *M. tuberculosis* strains, at least those bearing the most commonly occurring *katG* mutation S315T, are to be considered as infectious as wild pansusceptible strains (Gagneux 2006, Pym 2002, van Doorn 2006). In any case, the occurrence of drug-resistance in patients without previous treatment and the very occurrence of MDR-TB outbreaks undeniably denote ongoing transmission of drug resistant strains.

### 17.4.3. Early suspicion of drug-resistance in the HIV or TB clinic

The first outline of a probable case of drug resistant TB can be drawn in the clinical interview. Such is the case of treatment failure, which almost certainly denotes a case of drug-resistant TB or MDR-TB. Treatment **failure** is defined as the finding of a positive *M. tuberculosis* sputum culture at the end of the fourth month of chemotherapy in a patient under standard therapy in a DOTS regimen (World Health Organization 2003). A persistently positive AFB sputum smear microscopy result in a patient under a strict DOTS regimen can also predict treatment failure and consequently MDR-TB. Treatment **default** (interruption of the treatment for longer than a two-month period) and **relapse** (defined by a positive culture after the end of treatment) may also be suggestive of drug resistant TB. A history of one (or more) previous treatment(s) with several failing or discontinued regimen(s) is indeed a much stronger predictor of drug-resistant TB.

The exposure to a known source of drug resistant TB is another situation in which the investigation of drug resistant TB is mandatory. The risk of exposure is enhanced if the patient has a history of previous hospitalizations, stays in shelters or imprisonment. Once the patient's informed consent has been obtained, HIV testing should be indicated to all TB patients at the initiation of treatment (Caminero 2005) and conversely, antituberculosis drug susceptibility testing should be routinely performed on all HIV/AIDS patients in whom TB is suspected.

### 17.4.4. AIDS-associated multidrug-resistant tuberculosis outbreaks

The initial reports on MDR-TB outbreaks among HIV/AIDS patients were communicated in the early '90s in Florida (Pitchenik 1990) and New York City (Edlin 1992, Pearson 1992, Frieden 1993). A common feature in these and later publications was the hospital exposure of highly susceptible HIV/AIDS patients to infectious chronic MDR-TB cases. When seeking assistance repeatedly in health centers for infectious diseases, AIDS patients with progressive immunodepression shared waiting rooms, wards and other hospital facilities with infectious MDR-TB patients. At that time, MDR-TB strains were considered of low infectivity and adequate biosafety measures were not in force. This erroneous concept – combined with the previous dismantling of TB control programs and TB clinics – paved the way for the early AIDS-associated MDR-TB outbreaks.

The most spectacular MDR-TB outbreak was caused by the so-called W strain, belonging to the *M. tuberculosis* Beijing family. This strain is resistant to multiple

drugs, and was identified as the main source of clustered MDR-TB cases in New York City throughout the first half of that decade (Ikeda 1995). The W strain is an eloquent example of the pathogenic potential of the Beijing lineage of *M. tuberculosis*. Evidence has been gathered supporting the idea that some Beijing strains, which are highly prevalent in East Asia and former Soviet Union Republics, have an increased potential for spontaneous mutation – which increases the possibility of selection for drug-resistant clones – and apparently an increased virulence, too (European Concerted Action 2006).

Analogous nosocomial outbreaks were described in other countries. A conspicuous example occurred in Argentina and was due to an MDR *M. tuberculosis* strain of the Haarlem lineage: the M strain (Ritacco 1997). In a single reference treatment center for infectious diseases, located in Buenos Aires, more than 800 cases were assisted with the association MDR-TB-AIDS from 1992 to 2005. In the early stages of the outbreak, most patients died before culture and drug susceptibility testing confirmed the diagnosis. Later on, methods for speeding up the diagnosis were implemented, adequate second-line drug treatment could be instituted promptly, and survival was substantially elongated. Also, the implementation of internationally recognized hospital infection control measures helped to contain the outbreak (Waisman 2005). Yet, the outbreak strain managed to disseminate in a large urban area not only among AIDS patients but also among HIV-negative patients, both with and without a history of TB treatment (Palmero 2005).

*M. bovis*, another member of the *M. tuberculosis* complex, was also involved in similar MDR-TB outbreaks. The *M. bovis* strain named B – resistant to 11 antituberculosis drugs – affected mainly hospitalized AIDS patients with advanced immunodepression in two big health centers in central Spain between 1993 and 1995 (Guerrero 1997). Afterwards, the outbreak spread to other cities in the country and even to Canada (Samper 1997, Long 1999, Rivero 2001). Sporadic cases in HIV-negative patients were also described (Palenque 1998, Robles Ruiz 2002). It has been hypothesized that the original strain developed INH resistance in the natural host as a consequence of the use of this drug as a growth promoter in cattle, which was once common practice in Spain. The treatment of the first human case with the standard antituberculosis therapy, which in addition to INH and RIF included pyrazinamide (PZA) – to which *M. bovis* is naturally resistant – would have been in fact a monotherapy with RIF that led to multidrug resistance (Romero 2006).

A deadly outbreak occurred more recently in Tugela Ferry, a rural district in Kwala Zulu-Natal province, South Africa. MDR-TB was diagnosed in 221 out of 1,539 patients recruited within a 15-month period (2005-2006). Of these 221, 53 had

extensively drug resistant TB (XDR-TB), an especially serious condition. Fifty-five percent of the patients had never been treated for TB and 67 % had had a recent hospital admission. All 44 patients with XDR-TB, who were tested for HIV, were co-infected and 52 of 53 patients with XDR-TB died, with a median survival of 16 days from the time of diagnosis. Genotyping of isolates showed that 85 % of patients with XDR-TB had similar strains (Gandhi 2006).

This South African outbreak underlined the severity and urgency of the current situation of MDR-TB in a number of developing countries. Hospital transmission between AIDS patients in the absence of adequate biosafety measures reproduces the major features of previous MDR-TB outbreaks. The risk of transmission of these highly resistant strains to healthcare workers and to the general population jeopardizes the efforts to control TB. As described later in the treatment section of this chapter, the current treatment of MDR-TB includes “injectable” compounds (aminoglycosides or capreomycin) and quinolones. Precisely these dangerous XDR *M. tuberculosis* strains are resistant to at least to one drug of either class.

In the course of an international survey, XDR-TB cases were identified in six continents and their treatment outcome was found to be significantly worse than that of other MDR-TB cases (Sarita Shah 2007). TB organizations worldwide are nowadays focusing their efforts on diagnosing, treating, and controlling this new enemy (see the WHO Global Task Force Report on XDR-TB 2006 on the internet [http://www.who.int/tb/xdr/globaltaskforcereport\\_oct06.pdf](http://www.who.int/tb/xdr/globaltaskforcereport_oct06.pdf)).

The prevention of institutional transmission of TB and MDR-TB is outlined in the guidelines released by the US Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 1994, Centers for Disease Control and Prevention 2005) and in the 1999 WHO guide for resource-limited settings. The classification of control measures in administrative, environmental and personal respiratory protection described in Chapter 11 is widely accepted and efficacy-proven. Basically, the first steps are:

- the prompt identification of the infectious TB case
- the adequate isolation and treatment of the patient
- the protection and control of personnel at risk of infection and disease

Paradoxically, in many developing countries, where TB is an important public health problem, airborne infection control measures are often neglected in view of many other more immediate sanitary problems, such as cholera, malaria, war and disaster. This allows the perpetuation of chains of transmission involving inpatients, outpatients, healthcare workers and community members.

## 17.5. Treatment of tuberculosis in HIV/AIDS patients

### 17.5.1. Special considerations

The application of Directly-Observed Treatment, Short-course (DOTS), the universally accepted intervention for TB treatment, is crucial in AIDS cases. In fact, the DOTS strategy recreates the sound idea of a supervised TB treatment that was delineated in the '70s by the eminent bacteriologist Wallace Fox. However, the DOTS strategy includes not only the observation of the patient's medicine intake but also other important issues that constitute a strategy launched in 1996 by the WHO (World Health Organization 2006). Its five essential elements are: 1) sustained political commitment, 2) access to quality-assured TB sputum microscopy, 3) standardized short-course chemotherapy, supervised, 4) adequate and continuous supply of quality assured drugs, and 5) a recording and reporting system with outcome assessment of patients (see Chapter 7).

TB clinics are excellent sites to detect HIV infection and also to apply the same directly observed therapy strategy to the initial antiretroviral therapy. There is an urgent need to complement the TB and the HIV programs worldwide in order to reinforce detection and control activities of both diseases.

Many patients with HIV/AIDS disease and TB have severe immunodepression and high plasmatic viral loads. The instauration of antituberculosis treatment is critical in these patients (Quy 2007). Indeed, if not treated promptly, an AIDS patient with disseminated TB will die from it in the short term. In turn, HAART substantially improves the prognosis of patients with *M. tuberculosis* co-infection by helping to restore the immune system. Nevertheless, the efficacy of HAART in these cases is often jeopardized by drug toxicity, pharmacological interactions, impaired drug absorption and paradoxical reactions. HAART has to be frequently combined with treatments for TB and other opportunistic infections caused by agents such as *Candida*, *Pneumocystis*, mycobacteria other than *M. tuberculosis*, Cytomegalovirus, *Toxoplasma*, herpes, fungus, etc.

Strong evidence has been gathered on the high efficiency of RIF in reducing the mortality of TB/AIDS patients (Wallis 1996). Consequently, RIF is considered an essential drug in the treatment of HIV/AIDS-associated TB. Unfortunately, this drug is a potent inducer of hepatic cytochrome P-450 (isozyme CYP3A) and as such, it interacts with two classes of antiretroviral drugs: protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Within the family of rifamycins, rifabutin is a less potent activator of CYP3A and therefore can be used safely as a

surrogate for RIF in combination with protease inhibitors such as nelfinavir. All HIV infected patients with TB should be treated with a rifamycin-based combination regimen i.e., rifabutin reducing the dose to half (150 mg/d).

TB caused by fully susceptible strains of *M. tuberculosis* can be treated with a six-month standard scheme (2 months of INH, RIF, PZA, and EMB plus 4 months of INH and RIF) as recommended by international organizations, with the exception of meningeal, miliary or spinal TB, which should receive a nine-month treatment regimen (2 months of INH, RIF, PZA, and EMB plus 7 months of INH and RIF) (ATS/Centers for Disease Control and Prevention/IDSA 2003, World Health Organization 2004). Some authors have reported higher rates of relapse with standard treatment in HIV/AIDS patients and therefore recommend prolonging the second phase of TB treatment to seven months (Pulido 1997).

SM is seldom used in the initial phase due to both the discomfort caused by its application and the risk inherent to the handling of syringes and needles. In the continuation phase, drugs can be administered daily or intermittently, but this latter option is reserved for patients with a CD4+ T cell count above 100/ $\mu$ L. The risk of resistance to rifamycins increases when they are administered intermittently, especially in regimens consisting of rifapentin plus INH once weekly or RIF plus INH twice weekly. When intermittent therapy is indicated, regimens administered thrice weekly that include INH (10 mg/kg/d) plus RIF (usual dosage) are preferable (World Health Organization 2004, American Thoracic Society/Centers of Disease Control/Infectious Disease Society of America 2003). If the CD4+ T cell count is not available, intermittent therapy should not be used in HIV/AIDS patients.

At least in settings with a high prevalence of MDR-TB, antituberculosis drug susceptibility testing should always be performed upon isolation of *M. tuberculosis* from an HIV/AIDS patient. The early detection of resistance to RIF and INH prompts switching to a drug scheme containing second-line drugs. This often extends a patient's survival, even in the case of disseminated TB. If standard TB program guidelines were to be followed strictly, severely immunodepressed patients with MDR-TB would most probably die under a standard antituberculosis drug scheme before treatment failure is suspected and/or confirmed.

Treatment regimens for MDR-TB should preferably be tailored on the basis of the results of susceptibility testing. The initial phase of two to six months includes three or four drugs given orally together with an injectable drug such as an aminoglycosides (SM, kanamycin or amikacin) or capreomycin. In the second phase, the injectable drug is discontinued. The patient is discharged as cured after 18 to 24

months of uninterrupted therapy, only when five sequential cultures yield negative results.

There is a great deal of controversy on case management of MDR-TB in resource-limited high burden countries and simplified regimens have neither been evaluated nor standardized (Caminero 2006). TB control programs without adequate bacteriological support are compelled to apply empirical re-treatment schemes based on previous local susceptibility testing surveys. Prospective studies of this kind of approach evidenced poor treatment outcomes when compared with regimens tailored according to drug susceptibility test results (Mitnick 2003).

In the medical management of MDR-TB cases, some degree of empiricism associated with expertise is necessary for the design of the re-treatment regimens. Actually, most of the currently available rapid drug susceptibility methods only produce results for first-line drugs (SM, INH, RIF, EMB and PZA). Testing for second-line drugs is usually not available – or results only become available after a considerable delay because the tests are performed on traditional solid media. In addition, the results are less reliable than those of the first line drugs due to insufficient standardization and external quality control. In most cases, there is no control at all. Often, the specialist physician is constrained to select a drug scheme merely on the basis of the pattern of resistance to the first-line drugs.

### **17.5.2. Adverse reactions in HIV/AIDS patients**

The HIV/AIDS patient with low CD4+ T cell counts is usually a multi-etiological case. Several opportunistic infectious and noninfectious agents coexist in addition to the HIV itself, which puts into action its own pathogenic mechanisms. Organs in the gastrointestinal tract, mainly the esophagus, are affected by pathogens, including *Candida sp*, cytomegalovirus, herpes virus, *Cryptosporidium*, etc. These infections contribute to the wasting of the patient and hamper the ingestion, tolerance and absorption of oral medicines. In such conditions, the gastric intolerance to antituberculosis drugs such as RIF or PAS, which itself is fairly frequent, is exacerbated. It should be highlighted that parenteral formulations of first-line drugs exist but are not currently available in any TB control program worldwide.

The potential hepatotoxicity of drugs such as INH, RIF, PZA, and ethionamide increases when administered to patients with concomitant hepatitis C or B.

The impairment of the renal function in an HIV/AIDS patient under treatment with aminoglycosides or capreomycin may be due either to drug toxicity or to an AIDS-associated kidney disease.

The involvement of the central and the peripheral nervous system is frequent in AIDS and may be caused by the HIV itself and/or by various opportunistic infections, including toxoplasmosis and cryptococcosis. Thus, the neurotoxicity of drugs, for example INH, cycloserine/terizidone or fluorquinolones, often aggravates a previous condition and the exact contribution of the drug adverse effect to the clinical picture is difficult to discern.

Moreover, the multiple treatments simultaneously required for different pathologies contribute to drug-drug interactions. RIF, a key drug for TB treatment, interacts with the protease inhibitor class of antiretroviral drugs and its surrogate, rifabutin, is not always available for TB treatment in developing countries.

The same general principles of antituberculosis drug toxicity applied to the general population are valid for HIV-positive patients with some peculiarities. For instance, RIF-induced gastrointestinal intolerance and toxic hepatitis are more frequent in HIV/AIDS patients. Also, skin reactions in HIV/AIDS patients have been attributed to the association of INH plus RIF (Pitche 2005).

In the heavily treated AIDS patient, it is difficult to accurately identify which drug is causing an adverse drug reaction. In view of this, a first-line antituberculosis drug should never be discontinued in the absence of solid evidence of such a drug being the cause of an adverse reaction (American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America 2003).

Thiacetazone is an antituberculosis drug widely used in developing countries, mainly in Africa. This drug frequently produces serious adverse events in the skin, including Stevens-Johnson and Lyell syndrome, and its use is very dangerous in AIDS patients (Lawn 1999).

The first- and second-line drugs used in TB treatment, dose and toxicity in HIV/AIDS patients are summarized in Table 17-2 (see also Chapter 18).

Table 17-2: Drugs used in the TB treatment and re-treatment (see also Chapter 18)

Drug	Daily dose	Toxicity in HIV/AIDS
Rifampicin	10 mg/kg	Gastric intolerance, hepatitis, rash, hemolytic anemia, acute nephritis, purpura, epidermolysis, potent inducer of CYP3A (drug interactions)
Rifabutin	5 mg/kg	Similar to RIF, less potent inducer of CYP3A
Isoniazid	5 mg/kg	Hepatitis, polyneuropathy
Pyrazinamide	25 mg/kg	Hepatitis, hyperuricemia
Ethambutol	20 mg/kg	Optical neuropathy
Aminoglycosides*	15 mg/kg	Renal and 8 <sup>th</sup> cranial nerve
Capreomycin	15 mg/kg	Renal and 8 <sup>th</sup> cranial nerve
Para-aminosalicylic acid	100 mg/kg	Gastric intolerance
Cycloserine/ Terizidon	10-15 mg/kg	Central nervous system (seizures, psychosis)
Ethionamide/ Prothionamide	15 mg/kg	Hepatitis
Levofloxacin	500 mg	Tendonitis, neurotoxicity, arrhythmia
Moxifloxacin	400 mg	Tendonitis, neurotoxicity, arrhythmia
Linezolid	600 mg**	Last chance drug, optical neuritis, bone marrow depression
Thiacetazone	Not recommended	Epidermolysis (Lyell syndrome)

\* Streptomycin, Kanamycin, Amikacin

\*\*Half of the recommended dose for bacterial infections (1,200 mg/d) seems to be effective in TB

### 17.5.3. When to start antiretroviral therapy in patients with tuberculosis

When TB and HIV/AIDS are diagnosed simultaneously, the treatment for TB should be started immediately. In principle, antiretroviral therapy should be started as early as possible in patients with low CD4<sup>+</sup> cell counts. However, the simultaneous implementation of both treatment regimens conveys an elevated risk of adverse effects. There is neither consensus on a CD4<sup>+</sup> cell count threshold below which therapy should be postponed nor on an optimal time-interval for the delay in the start of antiretroviral therapy. The issue is particularly controversial in the case of severely immunodepressed patients (CD4<sup>+</sup> cell count below 100/ $\mu$ L) with TB. In one study, adverse events occurred in 54 % of 183 patients, one third of who changed or interrupted HIV and/or TB medication. Most of the adverse events occurred in the first two months and consisted of peripheral neuropathy, rash, hepatitis, and gastrointestinal upset (Dean 2002). In 2006, the International AIDS Society recommended starting HAART after the first month of antituberculosis therapy in patients with less than 100 CD4<sup>+</sup> cells/ $\mu$ L, and after the initial phase of TB treatment (end of the second month) when the CD4 + T cell level is above 100/ $\mu$ L (Hammer 2006).

With regard to the optimal antiretroviral regimen in patients without previous antiretroviral treatment (initial treatment), two approaches yielded comparable performances: one included boosted protease inhibitors (not recommended in association with RIF) plus two nucleoside or nucleotide reverse transcriptase inhibitors, and the other included a non-nucleoside reverse transcriptase inhibitor such as efavirenz associated with two nucleoside or nucleotide inhibitors of reverse transcriptase (zidovudine plus lamivudine or tenofovir plus emtricitabine).

Rifabutin should be used instead of RIF in combination with protease inhibitors to minimize drug interactions. As RIF also interacts with non-nucleoside reverse transcriptase inhibitors, its association with nevirapine is not recommended. Efavirenz, however, can still be associated with RIF, preferably in a higher dosage i.e. 800 mg instead of 600 mg/d (Corti 2005). Fusion inhibitors such as enfuvirtide belong to a new class of antiretroviral drugs that has no interactions with RIF (Manfredi 2006).

## 17.6. Immune reconstitution inflammatory syndrome

This syndrome, also known as IRIS, was recognized early in the modern antituberculosis therapy era and consists of a paradoxical worsening of clinical disease shortly after the initiation of drug treatment. Irrespective of the HIV status, the

immune system is impaired in the advanced stages of TB as shown by low levels of circulating CD4+ T lymphocytes. Once the treatment starts to produce an effect, an “immune restoration” occurs that reflects the reconstituted immunity to *M. tuberculosis*. The syndrome includes an enlargement of the affected lymph nodes and of the lung lesions accompanied by an exacerbation of the general symptoms. This condition resolves spontaneously during the course of antituberculosis therapy.

Since the beginning of the HAART era, the immune reconstitution inflammatory syndrome has been observed with increasing frequency in AIDS. Although HIV/AIDS-related IRIS can be associated with other opportunistic infections – namely mycobacterioses and mycoses – TB accounts for one third of the cases, at least in settings with a high prevalence of HIV-TB co-infection (Colebunders 2006). This syndrome is observed most frequently when the treatment of both infections is started in close temporal proximity. The reactions usually occur in the first four to eight weeks after initiation of the antiretroviral therapy and do not differ from those associated with the classical TB immune restoration syndrome. They may include systemic manifestations, such as fever and malaise and/or local reactions in lymph nodes, lungs, pleura and the central nervous system, depending on the localization of the TB lesions (Narita 1998). New infections and other reactions to therapy must be taken into account in the differential diagnosis of this syndrome. As a consensus has not been reached on its clinical definition, the syndrome is probably being over-diagnosed (Lipman 2006).

In AIDS patients, the immune reconstitution inflammatory reactions are best managed with anti-inflammatory agents, including corticosteroids such as prednisone 20-40 mg/d, if necessary. Both antituberculosis and antiretroviral therapy should be continued during the entire reconstitution syndrome.

### 17.7. Treatment of latent tuberculosis infection in HIV/AIDS patients

The classical method for detection of TB infection is the skin test reaction with PPD RT23 2 UT or PPDS 5 UT. In HIV-infected persons, a nodule of 5 mm or more is considered positive. Particularly in this population, the reliability of the method of detection of latent infection is highly dependent on the level of immunosuppression. Quantiferon is a whole blood assay for the detection of interferon gamma produced by peripheral lymphocytes in response to specific *M. tuberculosis* antigens. This test often yields negative or indeterminate results in severely immunosuppressed AIDS patients (Brock 2006). On the other hand, preliminary results

suggest that the performance of ELISPOT – a test that enumerates *Mycobacterium tuberculosis* antigen-specific IFN- $\gamma$ -secreting T cells test – is not affected by HIV-associated immunosuppression (Dhedra 2005). Further studies on improved versions of these tests are needed to fully assess the value of this kind of approach for the detection of latent TB in severely immunodepressed AIDS patients (see Chapter 13).

When latent TB infection is detected in an HIV-positive person, he/she should receive chemoprophylaxis. The treatment consists of a course of at least six months – preferable nine months – of INH. Alternatively, a four-month course of RIF may be indicated. Both drugs are administered in their usual dosages (Centers for Disease Control and Prevention 2000).

The protective effect of a number of TB chemoprophylaxis regimens in HIV-positive, PPD-positive persons has been sufficiently proven (Whalen 1997, Lim 2006). An interesting option is to administer TB chemoprophylaxis to AIDS patients with CD4<sup>+</sup> counts below 100 cells/ $\mu$ L. The risk exists, however, of overlooking a sub-clinical TB, thus selecting INH resistant, or worse, RIF resistant mutants – depending on the drug used in chemoprophylaxis.

At the turn of the millennium, a simple and ingenious solution was evaluated for the treatment of latent TB infection in HIV/AIDS patients, consisting of a two-month course of RIF plus PZA. The use of two drugs was expected to prevent the development of resistance, while the short-course treatment would grant a better adherence. Indeed, this chemoprophylaxis regimen was successfully used in HIV infected persons (Gordin 2000). Unfortunately this regimen proved unsafe for the general population due to the high incidence of severe liver toxicity associated with its use (Centers for Disease Control and Prevention 2001).

## 17.8. Mycobacteriosis in AIDS patients

### 17.8.1. Non-tuberculous mycobacteria and AIDS

Mycobacteriosis is a term generally reserved for the disease caused by any mycobacteria other than *M. leprae* and those belonging to the *M. tuberculosis* complex. Non-tuberculous mycobacteria (NTM) – also called atypical or environmental mycobacteria – are ubiquitous organisms commonly found in soil and water. They are infrequent agents of human disease in patients other than HIV/AIDS. When present, they affect mainly predisposed hosts and produce disease in organs with underlying conditions. For instance, organisms in the *Mycobacterium avium* com-

plex, *M. kansasii* and other mycobacteria may cause a pulmonary disease resembling TB in patients with lung disorders, including bronchiectasis, chronic obstructive pulmonary disease, or residual granulomatous lesions produced by TB and mycoses.

Mycobacterioses became particularly relevant in relation to the global emergence of HIV/AIDS. *M. avium* is the most frequent etiological agent of NTM disease associated with AIDS, as shown by an early study where it accounted for 96 % of 2,269 NTM-AIDS cases (Horsburgh 1989). Indeed, early in the AIDS pandemic, *M. avium* was recognized to cause disseminated disease and death in advanced stages of immunodepression with blood CD4+ counts below 50 cells/ $\mu$ L (Chaisson 1992). In the course of HIV infection, the progression of this NTM disease seems to undergo several stages from mucosal entry, passing through early transient dissemination and tissue colonization, before the persistent and deadly bacteremia. *M. avium*-specific T cell responses apparently develop and still persist during disseminated disease. Yet, they are dysfunctional or insufficient to prevent persistence (MacGregor 2005).

Specific and effective therapeutic and prophylactic therapeutic schemes have been developed for AIDS-associated *M. avium* disease. In addition, the introduction of HAART and the subsequent improvement in the survival of AIDS patients lowered the incidence of most opportunistic associated diseases, including NTM. In the US, NTM diseases have fallen from 16 % before 1996 to 4 % soon after HAART implementation (Palella 1998). Nevertheless, the risk of these opportunistic infections remains high in undiagnosed HIV-infected patients and in patients who either have no access to, or do not adhere to HAART.

*M. xenopi* and *M. kansasii* are the next most frequent NTM producing opportunistic infections associated with AIDS. Several other mycobacterial species can cause local and/or disseminated disease in these patients, including *M. fortuitum*, *M. genavese*, and *M. chelonae* (Shaffer 1992). As the infection with NTM is acquired from the environment and interhuman transmission has not yet been demonstrated, the isolation of these patients is not necessary.

### 17.8.2. Clinical presentations

Disseminated *M. avium* disease usually appears with fever, malaise, weight loss (over 10 % of body weight), nocturnal sweats, abdominal pain, and diarrhea. Peripheral lymphadenitis with frequent abscesses as well as liver and spleen enlargement are frequently observed. Either abdominal ultrasonography or computed to-

mography scans reveal visceral enlargement with multiple focal hypoechoic or hypodense images, and retroperitoneal lymph node enlargement. Psoas abscess and vertebral compromise can also be observed. The laboratory results show anemia and leucopenia, reflecting bone marrow invasion by *M. avium*. Hepatic alkaline phosphatase is consistently elevated.

The immune reconstitution inflammatory syndrome or IRIS is frequently associated with *M. avium* disease in AIDS patients who start HAART (Karakousis 2004). In a study of 51 patients with mycobacterial disease (mainly *M. avium*), the incidence of nontuberculous mycobacterial immune reconstitution syndrome was 3.5 % among patients initiating HAART with a baseline CD4+ cell count of < 100 cells/ $\mu$ L. The main clinical presentations were peripheral lymphadenitis, pulmonary disease and intra-abdominal disease (Phillips 2005).

### 17.8.3. Diagnosis

The diagnosis of *M. avium* disease should be born in mind in all AIDS patients presenting with fever of unknown origin. The isolation of the agent from stool does not necessarily indicate disseminated *M. avium* disease but merely gastrointestinal colonization (Jacobson 1991). Similarly, the finding of *M. avium* in sputum requires repeated positive sputum cultures together with radiological and clinical manifestations to confirm its pathological involvement in progressive pulmonary disease. On the other hand, a positive culture from a sterile source, such as blood or bone marrow, is enough to confirm the diagnosis of disseminated *M. avium* disease (MacGregor 2005).

### 17.8.4. Treatment

With few exceptions, *M. avium* is resistant to the usual antituberculosis drugs. As is the case in TB, the treatment of *M. avium* disease is a combination therapy to avoid resistance due to selective pressure. The results of drug susceptibility testing often have a poor correlation with the clinical evolution and empirical treatment has to be used.

Empirical treatment schemes for *M. avium* disease are:

- clarithromycin (or azithromycin), EMB and rifabutin or
- clarithromycin (or azithromycin), EMB, fluoroquinolone and amikacin

These schemes are applied at least during the initial 6 to 12 weeks (Benson 2003, Gordin 1999, Katoch 2004). The treatment is generally prolonged for about one year, depending on the clinical evolution and CD4+ cell counts. As is the case in TB, the early initiation of HAART is of crucial importance in these severely immunodepressed patients. After finishing treatment of *M. avium* disease, secondary prophylaxis should be administered until the CD4+ cell count reaches 100 CD4+ cells/ $\mu$ L; this may consist of azithromycin 1,200 mg/once weekly or clarithromycin 1,000 mg/day. Paradoxically, secondary prophylaxis may ultimately not be necessary if the patient suffered IRIS during treatment. Indeed, together with a dramatic deterioration of the clinical status, this syndrome induces an inflammatory response that is often accompanied by a restoration of the immune response (Shelburne 2003).

Several pharmacological interactions should be considered: the macrolide clarithromycin interacts with RIF and rifabutin, increasing their serum concentration by 25 %. In turn, these rifamycins reduce serum concentrations of clarithromycin by 50 %. In addition, clarithromycin interacts with protease inhibitors, in particular with atazanavir, which increases its concentration by 95 %. Thus, the recommendation is to halve the macrolide dose.

Rifabutin can be discontinued after several weeks of treatment when clinical improvement is observed. The clarithromycin dose should not exceed 1,000 mg/d because high doses were found to be significantly associated with high rates of death (Cohn 1999).

Azithromycin has less drug-drug interactions and therefore can be used more safely in place of clarithromycin. It has been proven to have comparable efficacy in combination with ethambutol (Ward 1998). A promising new macrolide named thelitromycin has been proven to have activity against *M. avium* in vitro as well as in animal models (Bermudez 2004).

*M. xenopi* and *M. kansasii* are susceptible to INH, RIF, and EMB, with or without the addition of SM (Katoch 2004). A one year therapeutical scheme, similar to that used in TB can be applied with the exception of pyrazinamide, a drug to which these mycobacterial species are naturally resistant.

### 17.8.5. Primary prophylaxis

All AIDS cases with a CD4+ count below 50 cells/ $\mu$ L are at high risk of developing disseminated *M. avium* disease and must receive prophylaxis (Kaplan 2002). Before the introduction of effective prophylactic therapy, *M. avium* disease ap-

peared in more than 40 % of AIDS patients in developed countries with a low TB incidence. Large placebo-controlled clinical trials have shown that rifabutin, as well as the macrolides clarithromycin and azithromycin, significantly reduce the incidence of *M. avium* when used for primary prophylaxis in severely immunocompromised patients (Havlir 1996, Pierce 1996). There are substantial arguments against the use of rifabutin, a drug rich in pharmacological interactions with the additional disadvantage of selecting rifamycin monoresistant *M. tuberculosis* clones. Clarithromycin has also several drug-drug interactions. The safest drug for primary chemoprophylaxis of *M. avium* infection in AIDS patients is azithromycin, which has fewer interactions, and can be administered weekly at a dose of 1,200 mg, alternative to the conventional dose of 500 mg daily. Prophylaxis must be continued until the CD4+ count reaches levels above 100/ $\mu$ L sustained over time (Kirk 2002).

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