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Neurotuberculosis and HIV Infection

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1. Introduction

The incidence and mortality of tuberculosis (TB), the most common opportunistic infection in HIV patients has drastically increased with the emergence of the HIV pandemic

The HIV infection supported the re-emergence of TB as well as two major changes in the natural history of TB, namely it has increased the frequency of extrapulmonary TB and the mycobacterial multidrug resistance. The extrapulmonary TB involvement is present in up to 40% of the HIV cases and includes respiratory, digestive, lymphatic and neurologic localizations. Of these neurotuberculosis (NTB) is probably the most devastating extrapulmonary form of TB. The risk of acquiring NTB in HIV patients has been reported as 10 times higher than in non-HIV individuals and its related mortality exceeds 50%. The prognosis is further worsened by the HIV related progressive immunodeficiency which leads to the reactivation of opportunistic infections and the development of malignancies. The early diagnosis of NTB in HIV positive patients improves the short and long term prognosis of these patients and increases their life expectancy. Unfortunately the complexity of the clinical presentation and the variability of the bacteriological results accounts for significant difficulties in the diagnostic confirmation of NTB. Therefore treatment in these patients is often empirical. Moreover the antituberculous treatment is of long duration with serious adverse effects. Ensuing complications during treatment include the immune reconstitution inflammatory syndrome (IRIS) - a complication that is characteristic for HIV patients undergoing treatment for TB. Furthermore the multiple drug interactions between the antituberculous and antiretroviral treatment require close supervision of these patients.

This chapter summarizes the epidemiological, pathogenic, clinic and therapeutic challenges of NTB in HIV patients.

This chapter summarizes the epidemiological, pathogenic, clinic and therapeutic challenges of NTB in HIV patients.

2. Epidemiological data on the HIV/TB co-infection

TB is preventable and curable and its eradication was considered possible before the spread of the HIV pandemic. Since then the pathogenic mechanisms of HIV and TB have been closely entwined. Such is the complementary evolution of HIV and TB that the HIV/TB co-infection has been referred to as a ''syndemic'' by some authors [1]. The term ''syndemic'' reflects the similar social, epidemiological and pathological settings of both diseases. The close interrelation between HIV and tuberculosis overcomes by far the interactions between other community acquired infections. Thus epidemiological studies suggest that as many as 50% of the HIV patients develop mycobacterial infections. The rate of extrapulmonary TB could account for more than 50% of cases presenting with HIV and TB coinfection. In the pre-AIDS era the immunodeficiency status incriminated in the pathogenesis of extrapulmonary TB was induced by autoimmune diseases, aging, diabetes, alcoholism, malnutrition, malignancies or immunosuppressive chemotherapy. However the total amount of extrapulmonary TB in non-HIV immunosupressed patients did not exceed 15% of all TB cases. In addition meningitis and other forms of NTB represented less than 1% of all TB cases in non-HIV patients [2,3] but presently account for 10% of all TB cases in HIV patients [4]. Tuberculous meningitis (TBM) occurs in 5%-8% of the HIV patients [5,6] but tuberculomas and abscesses are also a common finding in late stages of AIDS [7]. Regarding the CNS infection with non-tuberculous mycobacteria one of the most important risk factors is the progressive immunodeficiency induced by HIV infection.

Co-infection with HIV not only increases the risk for central nervous system (CNS) TB [17] but also alters the clinical signs, delays the diagnosis and worsens the prognosis [8]. Thus the mortality of HIV patients with TBM is as high as 63% and nearly half of deaths occur in the first 21 days [9].

3. Pathogenic mechanisms of NTB

TB is a respiratory infection with a generally latent course. The immunodeficiency status favors the extrapulmonary dissemination of mycobacteria leading to inflammatory granulomas with diverse localisations. Some granulomas arise adjacent to the meninges or to the brain parenchyma and become the last station before the CNS invasion. Disruption of these granulomas into the subarachnoid space is followed by the cerebrospinal fluid (CSF) invasion with mycobacteria and meningeal infection.Release of mycobacteria from these granulomas is mainly associated with the severe depletion of macrophages and lymphocytes along with the imbalance of local cytokines. The CSF inflammatory reaction induced by mycobacteria antigens leads to a lymphocyte and fibrin-rich subarachnoid exudate which progressively envelops the blood vessels and cranial nerves. The expansion and intensity of this inflammatory exudate induces multiple complications including: the obliterative vasculitis followed by cerebral infarctions, the CSF obstruction and emerging hydrocephalus and the spinal extension of TB and chronic arachnoiditis. Some of the CNS granulomas could evolve as cerebral or spinal

masses further developing into tuberculomas or tuberculous abscesses [10,11,12]. In addition HIV patients characteristically present several TB cerebral lesions evolving simultaneously.

Below we enlisted the factors involved in the clinical progression and persistent CNS invasion with mycobacteria in HIV patients.

1.   *The cellular immunosuppression in TB and HIV infection.*

The site of extrapulmonary mycobacterial infections and especially the CNS invasion depend on the efficacy of cell-mediated immunity. Both the HIV infection and TB trigger complex mechanisms which increase the cellular immunosuppresion.

On the other hand humoral immnity is increased but inefficient. The high titres of antimyco-bacterial antibodies are not protective and could instead result in numerous complications. The most important mechanism behind the cellular immunosuppression in the HIV-TB co-infection is the severe depletion of macrophage and lymphocyte cells.

Macrophage and lymphocyte cells. Macrophages play a crucial role in both HIV and mycobac-terial infections. As phagocytes of the innate immunity they are considered the main cells involved in the immune response against mycobacteria.Infected macrophages recruit addi-tional immune cells such as dendritic cells and T cell lymphocytes and release numerous chemokines and cytokines to form granulomas. The latter are specific stable inflammatory structures limiting the growth of mycobacteria. At the same time mycobacteria could devel-op inside macrophages from granulomas thus ensuring their persistence. In addition macro-phages infected with Mycobacterium tuberculosis (M. tbc) augment the expression of the C-C chemokine receptor type 5, also known as CCR5, the most important HIV coreceptor [13]. Therefore infected macrophages perform a significant role in the protection and transport of mycobacteria and HIV to other tissues including the brain.

With the passing of time some of the macrophages infected with mycobacteria suffer apoptosis leading to a numeric decrease of the most important cells involved in the defence against mycobacteria invasion. Moreover HIV is directly responsible for the depletion of CD4+ T lymphocytes through its cytopathic effect and anti-gp120 antibodies. The depletion of CD4+ T lymphocytes raises the susceptibility to TB and most notably towards neurologic forms of TB [14]. In this respect the decreasing CD4+ T cell count was proven to vary inversely with the incidence of NTB. Most patients with HIV and NTB display a CD4+ T cell count below 200 cells/ mm^3 unlike patients with pulmonary TB who commonly present with a CD4+T cell count, between 250 and 550 cells/ mm^3. In conclusion in the late stages of infection the main pathogenic mechanisms of invasion with mycobacteria and HIV are closely interwined.

The Cytokine dysregulation. Both HIV and mycobacteria are intracellular pathogens. Their presence stimulates the release of cytokines by macrophages and Th1 cells which in turn regulate the cells involved in the immune response. The stability of the granuloma is usually ensured by a high number of CD4+ T and CD8+ lymphocytes along with a Th1 cytokine profile represent-ed by IFN -γ and TNF-α. [15].TNF-α is a pro-inflammatory cytokine released at high levels by CD4+T cells and macrophages coinfected with mycobacteria and HIV. The role of TNF-α in the clinical outcome of the 2 diseases is contradictory. Regarding its role in the control of tuberculo-

sis a high level of TNF-α stimulates the apoptosis of infected macrophages and the cellular activation [16,17]. On the other hand the use of TNF-α neutralizing antibodies in inflammatory diseases has been associated with an increased risk of extrapulmonary TB including TBM [18].CD4-T-cell deficient mice [19] as well as mice able to neutralize endogenous TNf-α [20] or the gene for IFN-γ [21] are subjected to fatal TB. Nevertheless an in vitro experiment on human monocytes noted that higher levels of TNF-α could be associated with more virulent or faster growing mycobacterial strains [22].The contradictory effect of TNF-α was also observed in the HIV infection. Studies conducted by Lane and Osborn proved that TNF-α is a potent inhibitor over the primary HIV infection of the macrophages but enhances the HIV replication in latent HIV infections [23,24]. This finding could explain why mycobacteria infections which promote the synthesis of TNF-α could also augment HIV replication in chronic infected individuals. The level of TNF-α in the blood of patients infected with mycobacteria and HIV was documented to be 3 to 10 times higher than in non-HIV patients [25] showing a major imbalance in the release of this proinflammatory cytokine. TNF-α also plays a central role in the CNS localizations of mycobacteria. The excessive amount of TNF-α could accelerate the disruption of rich tuberculous foci adjacent to the CNS. Increased levels of TNF-α as well as IFN-γ were found in the CSF of patients with TBM at the disease onset [26] as well as several months after the acute episode [27] Experimental studies on rabbits proved that the excess of TNF-α acts as a persistent trigger of the inflammatory response and as a procoagulant factor associated with both the mycobacteria CNS invasion as well as cerebral vascular complications. [28]. The therapeutic use of TNF-α inhibitors in severe forms of TBM, tuberculoma and cerebral tuberculous abscesses was linked to a decreased inflammatory response and noticeable clinical recovery [29-31]. The major role of TNF-α in the progression of TBM was also proved in murine models by Tsenova as well [28,33]. Studies on HIV patients with TBM also emphasized the significance of increased levels of CSF TNF-α and of IFN-γ in advanced TBM stages [34].

In conclusion all these studies proved that important variations of the Th1 cytokine profile and especially of those involving the release of TNF-α represent one of the pathogenic mechanisms that aggravate the outcome of NTB in the HIV infection. Understanding these changes could be the first step towards the development of efficient complementary therapies in NTB to reduce the excessive inflammatory response. Thus TNF-α inhibition could be used as an antiinflammatory therapy in NTB with severe complications but should not be recommended in other forms of TB.

2. *The persistent activation of microglial cells.*

A significant role in the pathogenic mechanisms of CNS infections was assigned to the activation of microglial cells, the resident macrophages of the CNS. Microglial cells are involved in the local phagocytosis and play a central role in the pathogenesis of infections and inflammatory diseases [35]. These cells also represent the main target of both HIV and mycobacteria infection [36,37]. Thus the activation of microglial cells by mycobacteria induces the release of proinflammatory cytokines, some of which are able to add to the stability of cerebral granulomas. A moderate level of CXCL9 and CXCL10 chemokines released by microglial cells regulates the influx of inflammatory cells to the brain and interferes with the chemotaxis of monocytes/macrophages and T cells thus assisting the

formation of granulomas. However since microglial cells are the main source of cerebral TNF-α these could also induce an aggresive inflammatory response with severe meningeal inflammation, brain edema, protein accumulation, endarteritis and intracranial hypertension accounting for most of the complications described in NTB [28,38]. Therefore a balanced activation of microglial cells is critical against the CNS mycobacterial invasion. On the other hand the intracellular HIV replication in microglial cells leads to their activation, neuroinflammation and release of neurotoxins that cause AIDS associated neural dysfunctions. The complex role of the microglia in cerebral HIV/TB co-infection is explained by the rich number of HIV receptors and co-receptors expressed by these cells such as CD4, CCR5, CXCR4 as well as other receptors involved in the inflammatory response including IFN-γ, TNF-α,CD14 and MHC class I and II receptors [39].The CD14 receptor promotes the uptake of both HIV and nonopsonized M.tbc strains in microglial cells [40] while CD4 and CCR5/CXCR4 co-receptors interfere with HIV cell attachment. As a result microgial cells are the main target of HIV and mycobacteria once these enter the CNS. Therapies directed towards reducing the inflammatory response in the HIV/TB co-infection include the blockage of certain receptors (such as CD14), the use of CCR5 antagonists and TNF-α blockers (as thalidomide). Another alternative is dexametasone recommended in most forms of CNS TB. The clinical benefits of dexametazone were inspired by in vitro studies proving a potent inhibitory effect on the release of cytokines from microglia [39].

In conclusion simultaneous infection of the microglia with HIV and mycobacteria increases the meningeal inflammatory response, the fundamental pathogenic step in all forms of CNS TB. The synthesis of excessive inflammatory infiltrate is responsible for the clinical findings and possibly irreversible complications in NTB, such as hydrocephalus and vasculitis [41]. Moreover the excessive inflammatory response triggered in the HIV/TB co-infection could induce the immune reconstitution inflammatory syndrome – a complication that is specific for this patient category.

4. Pathogenesis of the immune reconstitution inflammatory syndrome

The Immune Reconstitution Inflammatory Syndrome (IRIS) is an uncommon inflammatory response encountered in those cases of severe immunosuppression in which the rapid administration of specific treatment abruptly restores the immune response. The HIV infection is the most frequent cause of immunodeficiency predisposing to IRIS. In addition TB is the most common opportunistic infection related to HIV-associated IRIS. The antiretroviral and antituberculous treatments rapidly restore the immune response. Such a rapid treatment response may sometimes lead to an aggressive lymphoproliferative reaction and massive release of proinflammatory cytokines. There are 2 clinical presentations of IRIS known as the paradoxical IRIS and unmasking IRIS. IRIS manifestations in HIV patients with NTB follow two possible scenarios:

a. A paradoxical reaction emerging in patients with NTB correctly diagnosed and appropriately treated in which HIV infection is subsequently detected and also treated but new severe neurological manifestations arise during treatment (paradoxical NeuroIRIS-TB).

b. An unmasking reaction appears in patients with HIV and latent unknown NTB in which the successful antiretroviral treatment unexpectedly induces neurological manifestations of TB (unmasked NeuroIRIS-TB)

The neurologic manifestation of IRIS-TB are rare (19% of the total cases) but with a mortality risk that is three times higher than other IRIS localisations [42]. The specific features related to NeuroIRIS-TB reside in the excessive CNS inflammatory reactions generated by the activation of microglia. The excessive inflammatory response is linked to the abundance of mycobacterial antigens and their high immunogenicity. Various studies have approached the immunologic mechanisms and risk factors for IRIS in HIV-TB patients.

The observations below on the pathogenesis of IRIS-TB were selected according to the potential clinical application.

- The release of multiple mycobacterial antigens in the first 2 months of antituberculous therapy and concurrent wide distribution of sequestered CD45RO memory lymphocytes in the bloodstream during HIV antiretroviral treatment are the principal mechanisms inducing an excessive inflammatory response. To avoid the overlap of these events the current WHO recommendations advocate an initial antituberculous treatment followed at a minimum interval of 2 weeks by the antiretroviral treatment in patients with a low level of Th CD4+ cells [43]

- The pathological overproduction of Th1 cytokines particularly IFN-γ was noticed in IRIS-TB/ HIV co-infection [44,45].Taking into account the experimentally increased levels of IFN-γ in IRIS the blood interferon-gamma (IFN-γ) release assays (IGRA) could be implemented to monitor IRIS evolution in the future. In addition the pathological overproduction of chemokines CXCL9 and CXCL10 induced by IFN-γ was observed in IRIS-TB/HIV co-infection [46]. The development of therapeutic strategies which could reduce the intracerebral level of these chemokines are essential to prevent and decrease ensuing granulomas thus protecting against IRIS.[47,48]

- The excessive release of IgG antibodies to PPD was observed in patients with IRIS-TB/HIV co-infection [45] Nonetheless the level of antibodies against the phenolic glycolipid antigen (PGL-TB1) was lower in IRIS hosts. The IgG anti PPD and especially the intrathecal synthesis of IgG/PPD could provide additional information on the humoral immune response in NeuroIRIS – TB [49].

- The restoration of a delayed type of hypersensitivity to mycobacterial antigens was reported in HIV patients with latent TB after starting the antiretroviral therapy [50,51]. All the same recent studies cast doubt on the tuberculin-specific Th1-responses in prompting IRIS [52]

- The profile of cytokines differs between the 2 types of IRIS as well as between TB infection and IRIS-TB. Hence certain cytokines (IFN-γ,TNF-α and IL-6) are more elevated in IRIS-TB than compared with patients presenting only TB. [53,54]. This finding could help distinguish

TB from IRIS-TB. Other studies have also investigated different profiles of immunological markers which could aid in the above distinction. Conradie et al. have identified a profile of makers including IL8, active NK cells, C reactive protein and lymphocyte count that is related to unmasking IRIS-TB. This profile could be further used in the differential diagnosis of the 2 manifestations or as a prediction of unmasking IRIS-TB [55].

5. Etiological data on the mycobacterial strains in HIV/TB co-infection

HIV patients are frequently infected by virulent strains of M.tbc. The virulence of a particular strain depends on the genetic composition of M.tbc. Thus the Beijing genotype of M.tbc mostly found in Asia is considered the most aggressive genotype and has been associated with CSF dissemination and multidrug resistance to antituberculous agents in HIV patients [56]. Infections with M. bovis are rare and occur mostly in HIV Hispanic patients. Despite the high environmental exposure to nontuberculous mycobacteria CNS involvement is rare even in AIDS patients and usually occurs at a CD4+ count under 10 cells/mm3. The pathogenic mechanisms behind the interactions established between the host and virulent mycobacteria are less documented. The infection with Mycobacterium avium complex (MAC) remains the most studied and most frequent nontuberculous mycobacteria accounting for the atypical tuberculous manifestations in the advanced stages of AIDS infection [57]. The Mycobacterium avium intracellulare (MAI) serotypes 4 and 8 are the most prevalent in AIDS patients [58].

Sporadic cases of NTB with other mycobacteria have also been recorded in AIDS patients following disseminated infection [59]. MAC is an ubiquitary environmental mycobacteria which colonizes the gastrointestinal and respiratory tract but is also able to invade the epithelial cells and the intestinal wall [60]. Virulent strains isolated from AIDS patients are able to penetrate the mucosal barriers and resist intracellular killing by macrophages resulting in a disseminated infection. Further studies on the interaction between M. avium and the HIV-infected cells confirmed the inhibition of several cytokines secreted by the Th_1 CD4+cells, natural killer cells and macrophages.These ultimately favour the intracellular survival of M. avium and even accelerate its growth rate [61,62]. The neurologic involvement due to MAC in advanced stages of AIDS generally presents as TBM following a disseminated infection with prolonged bacteremia [63-66]. The comparative aspects of the CNS invasions with M.tbc and nontuberculous mycobacteria in HIV hosts are presented in table 1

6. Clinical data on NTB in HIV patients

NTB is frequent in HIV patients compared with non-HIV patients. Reactivation of latent forms of TB is accelerated in HIV patients with a 10% annual risk of progression to active infection compared with 10-20% lifetime risk of developing TB in non-HIV patients. Literature data is contradictory as to the role of HIV on the clinical presentation or evolution of NTB. Although some studies found significant differences between HIV and non-HIV NTB [67-69] others

	M. tbc	Nontuberculous mycobacteria
Mycobacteria strain	M tbc, rarely M bovis	98% MAC, rarely other mycobacteria
Primary infection	Usually respiratory	Gastrointestinal or respiratory
Frequency	Moderate	Low/very low
CD4+ T cell count	< 200 cells/mm3	<10% cells/mm3 (usually)
Clinical forms	Meningitis, Tuberculoma, Abscess	Disseminated, Abscess
Diagnosis	Established diagnosis criteria	No standard diagnosis criteria
CSF mycobacteria detection	Essential to diagnosis confirmation	Not essential to diagnosis confirmation
Mycobacteria detection (other than CSF)	In blood	In faeces (frequently), in blood (if disseminated infections)
Prognosis	Reserved	Terminal infections (frequently)

Table 1. Comparative aspects of the CNS invasions with M. tbc and nontuberculous mycobacteria in HIV hosts

argued that the HIV co-infection does not influence the clinical evolution [70]. Nevertheless the differential diagnosis between NTB and numerous systemic and neurologic nontuberculous complications emerging in AIDS is difficult. Thus the clinical presentation of NTB in HIV patients could be influenced by numerous factors such as:

- various neurological manifestations caused by HIV itself;

- other opportunistic infections with CNS tropism, mainly toxoplasma, criptococcus, papilloma or herpes viruses infections;

- concurrent cerebral tumors : non-Hodkin cerebral lymphoma, Kaposi sarcoma;

- simultaneous evolution of various forms of NTB (meningitis, tuberculoma)- a characteristic finding in HIV patients;

- extra-neurological infections or malignancies related to HIV.

All these interfering factors could explain the variable descriptions of the clinical presentation, CSF manifestations or imaging aspects in the numerous studies on NTB in HIV patients.

NTB in HIV patients encompasses the following forms: TBM, disseminated TB of the nevrax, tuberculoma, and tuberculous abcess. En plaque tuberculoma, chronic spinal pahymeningitis and serous TBM are rare forms of TB not described in HIV patients.

6.1. Tuberculous meningitis in HIV patients

The real frequency of TBM in HIV patients is hard to assess as the various clinical presentations related to immunodepression could be confused with other neurologic manifestations. The epidemiological data on the subject is contradictory. Current statistics in areas with an increased prevalence of TB disclose M. tbc as the most frequent etiologic agent of meningitis in HIV patients [71]. Moreover TBM was recorded as the

initial presentation of AIDS in 42% of cases. A study performed in Kenya, a state with an increasing incidence of TB and HIV, revealed that 80% of the necropsies performed on HIV patients exhibited disseminated TB and 26% of these also displayed meningeal involvement [72].On the other hand the frequency of disseminated tuberculosis based on clinical and bacteriological criteria only did not exceed 14,5% of cases [73-74]. The conclusion arising from these studies is that the extent of the CNS invasion is highly variable and a large number of disseminated TB in AIDS probably remains undiagnosed.

Neurological presentation. TBM is the most frequent form of NTB in HIV patients. The neurological manifestations differ according to the degree of immunodeficiency.

• *TBM in the early stages of HIV immunodepression.* The onset of TBM is insidious. Fever and meningeal signs develop progressively (7-30 days) paralleling the changes in the cognitive status and mental state. Once the meningeal syndrome is established the evolution is rapid. The meningeal syndrome is intense and progressive. Under such circumstances the diagnosis could be aided by recognizing the paralysis of certain cranial nerves (mostly involving the sixth cranial nerve but also the second, third, fourth and eighth nerves) as well as the signs of hydrocephalus or cerebral edema (headache, convulsions, pyramidal or cerebellar signs). Encephalitic forms display an altered level of consciousness with progressive evolution to coma. In forms with major spinal involvement (TB spinal meningitis, spinal arachnoiditis) the inflammatory exudate surrounds the spinal cord and induces radicular compression. As a result radicular pains develop along with sings of transverse mielitis (paraplegia and urine retention).

• *TBM in advanced stage of HIV immunodepression*. In advanced stage of immunodepression the inflammatory exudate is decreased and the clinical presentation is atypical. Fever could be absent in these patients. The meningeal sings are discrete or missing [75]. Hydrocephalus is delayed. Tuberculous vasculopathy prompts frequent complications following thrombosis, or hemorrhagic infarcts. Focal lesions related to the vasculopathy are common. The cognitive dysfunction is severe [76] with a rapid evolution to profound coma [8].In this advanced stage of AIDS NTB rarely evolves as a solitary finding. Usually other infections or tumors are also associated with NTB and the wide spectrum of clinical manifestations implies various *neurological patterns with focal, perypheral or central nervous signs.*

CSF data. The aspect of the initial CSF could be suggestive disclosing lymphocytic pleocytosis, elevated proteins and low glucose levels. Nevertheless the etiologic confirmation is based on bacteriological criteria only. In patients with severe immunodeficiency the CSF white cell count is usually only slightly increased but could also be normal [67] The low number of lymphocytes in HIV could modify the differential count in the CSF to a predominant number of neutrophils [67] causing confusion with bacterial meningitis. Elevated proteins are a typical finding in TBM in non-HIV patients. However 43% of the HIV reported cases presented low or even normal protein values [5,8]. The most difficult cases are those in which the CSF is reported as normal, a common finding in patients with severe immunodeficiency. In the absence of a strong inflammatory response acid-fast bacilli smear retrieves positive results [67] in up to 67% of cases and the cultures are positive in 40 – 87,9% of cases [76,77].High rates of smear and culture

positivity facilitate the diagnosis in patients with an atypical clinical presentation and normal CSF exam.

Neuroradiological findings. The classic CT neuroradiological findings in TBM include basal meningeal enhancement, hydrocephalus, and infarctions in the supratentorial brain paren-chyma and brainstem [78]. The concurrent finding of basal meningeal enhancement, tubercu-loma or both on CT scans could disclose a sensitivity of 89% and 100% specificity for TBM in non-HIV patients [79]. In HIV patients contrast-enhanced MRI is generally considered superior to CT results [78]. Some MRI studies indicated that meningeal enhancement and cerebral infarctions were more common in HIV-infected individuals with TBM by comparison with non-HIV patients [5,70]. However the basal meningeal enhancement and hydrocephalus rarely occur in advanced stages of AIDS with reduced inflammatory response [76]. On the other hand cerebral infarctions and focal mass lesions are frequently encountered in late stages of AIDS [80-82]. In addition to the previous aspects imaging studies also disclose cerebral atrophy due to HIV infection. Tubeculomas also were reported in 15-24% of cases [5].

6.1.1. The diagnosis of TBM in HIV infected patients

The diagnosis is urgent and extensive including all tuberculous lesions, HIV status and other HIV associated lesions, bacteriological confirmation and neurological complications. It is based on clinical features, CSF analysis and MRI imaging. (table 2). A belated diagnosis increases the mortality, complications and the risk of relapse.

Clinical diagnostic criteria. Clinical features in HIV patients with TBM reflect the atypical inflammatory response and the extensive vasculopathy. The meningeal sings are inconstant and discrete especially in patients with severe immunodepression. The signs of encephalitis emerge from the onset and could be the first significant manifestation of the disease. The gravity of the altered level of consciousness parallels the increased mortality [8].Cerebral nerve paralysis is a common finding but could be also induced by other associated conditions such as HIV neurotoxicity, the cerebral reactivation of opportunistic infections (toxoplasma, JS virus, Herpes simplex virus) or cerebral malignancies (Non-Hodgkin lymphoma, Kaposi sarcoma). These patients particularly exhibit multiple extraneurologic manifestations. The presence of other active lesions like pulmonary TB or other extrameningeal sites of TB is highly suggestive for the CNS TB diagnosis [5,67,81]. Thus the presentation of HIV patients unlike non-HIV patients often includes peripheral, intrathoracic and intraabdominal adenopathies. The etiology of these adenopathies does not always imply a diagnosis of TB. The differential diagnosis for adenopathies should always include other lymphotropic opportunistic infections with neurologic manifestations (toxoplasma, CMV, syphilis). The tuberculous origin of adenopathies could be overestimated in the clinical diagnosis if the histological confirmation is not obtained. The histological examination is thus a prerequisite for a correct diagnosis of these adenopathies. Hepatosplenomegaly is commonly reported but could also occur as a result of other HIV associated infections (B or C hepatitis, CMV infections).To conclude no clinical criteria is highly suggestive for CNS TB in HIV patients. Moreover any neurologic or extraneurologic finding should prompt a thorough differential diagnosis that includes any other HIV related affections.

Laboratory diagnostic criteria. The degree of immunodeficiency in HIV patients with NTB could be assessed using the CD4+T cell count. Most studies on TBM disclose a CD4+T cell count between 32-200 /mm^3 [5,81,82].Other findings including a lower hematocrit, peripheral low neutrophils, lower plasma sodium level [76] and moderate to severe anemia Hb < 8 gm/dl [69] were not constantly present in all studies and could be mostly related to the HIV infection than to TB. Moreover hyponatremia in patients with HIV-TB co-infection could arise due to the following: a) cerebral salt wasting syndrome observed in 65% of patients with numerous cerebral lesions, including patients with TBM [83]; b) the syndrome of inappropriate release of antidiuretic hormone secretion; c) hypothalamus pituitary-adrenal axis suppresion. Hyponatremia is a marker of the disease severity and the mortality in this patient group is significantly higher than that of patients with normal sodium levels (36,5% versus 19.7%) [84].

The CSF exam is decisive for the diagnosis. The specificity of the bacteriological diagnosis is 100% but its implication in the final diagnosis is quite low since the Ziehl-Neelsen stain is positive in less than 20% of cases and Lowenstein culture confirmation although positive in 73% of cases is tardy [85]. Methods of improving the sensibility of Ziehl-Neelsen stain have been described [86] but are less implemented. Tuberculin skin test and Interferon-gamma release assays if positive do not distinguish between latent TB and active disease. As well negative results should be evaluated with caution in severely immunodepressed patients. Several complementary diagnostic tools were explored in certain studies like specific antigens and antibodies detection, adenosine deaminase detection, PCR techniques, detection of tuberculostearic acid or IFN-γ levels in the CSF. However their use is limited due to discordant results or other inconveniences related to the cost, cross-reactivity, specificity or sensibility [87-90]. Recently the improvement of nucleic acid amplification assay techniques, particularly polymerase chain reaction (PCR) assay (especially nested PCR assay technique) increased the diagnostic sensitivity and specificity but its use in AIDS related CNS TB is still unconfirmed [91]. All in all the bacteriological confirmation is difficult and belated but remains the only diagnostic tool in AIDS related CNS TB.

Imaging diagnostic criteria. Imaging studies are required in the evaluation of neurological complications of TBM, in the treatment follow-up and differential diagnosis. Contrast enhanced MRI and Positron emission computed tomography – computed tomography (PET-CT) display the highest sensibility. Unfortunately most literature studies are based on the more inexpensive CT scans. No aspects are definitely characteristic to CNS TB in HIV patients. Atypical results showing the absence or minimal meningeal enhancement [8] or the absence of communicating hydrocephalus were reported on the CT scan in 69% of AIDS cases [5,8]. Nevertheless other studies found no significant radiological differences between HIV and non-HIV patients.

*In addition to the clinical, CSF and radiologic criteria, a medical history of TB and positive tuberculin skin test could help raise the diagnostic suspicion of a tuberculous infection.

Neurotuberculosis suspicion
Clinical investigations (assessing the risk of tuberculosis, neurological manifestations, other manifestations)
History of tuberculosis (TB antecedents, risk of exposure)
Physical examination disclosing:
1. Signs of menigeal irritation (suggesting meningitis or a meningeal reaction to localized cerebral lesions)
2. Neurologic examination (mental status, sensory and motor exam, focal signs, intracranial hypertension)
3. Other manifestations suggesting TB and nontuberculous lesions induced by HIV activity, opportunistic infections or malignancies like lymphadenopathy (given attention to lymphoma, syphilis, toxoplasmosis), pleural or pericardial effusion (given attention to Kaposi sarcoma), pulmonary lesion (given attention to pneumocystosis, Kaposi sarcoma, fungal pneumonia,CMV pneumonia, lymphocytic interstitial pneumonitis), skin lesions (given attention to Kaposi sarcoma, Moluscum contagiosum, fungal lesions, meningococcal purpura)
Laboratory data assessing the immune status, HIV activity, risk of opportunistic infections or malignancies
Complete blood count (pancytopenia suggests medullar invasion with mycobacteria but also invasive malignancies or drug toxicities)
Biochemical evaluation of liver and renal function; indicate associated co-morbidities; important for drug regimen recomandation,
Serum sodium level (hyponatremia is linked to disseminated mycobacteriosis and cerebral lesions/ it corelates with the mortality risk)
Immune status: CD4+ T cell count (CD4<200 cells/mm^3 is related to the risk of NTB and major HIV-related opportunistic infections; CD4< 50 cells/mm^3 is related to the risk of nontuberculous mycobacteriosis or to the risk of IRIS)
HIV viral status: blood/CSF RNA HIV viral load (if positive it point to the antiretroviral failure and needing to swich the regimen)
Serologic assays: serum specific antibodies IgG and IgM related to other HIV-opportunistic infections,mainly toxoplasma, CMV, syphilis.
Imaging studies: cerebral or spinal CT/MRI; (important in localized NTB and other cerebral opportunistic infections or malignancies
Eye fundus examination : shows choroid tubercles in disseminated tuberculosis
Neurotuberculosis confirmation
Lumbar puncture (if the MRI does not indicate mass lesions!): CSF analysis: cytochemistry, stains*, culture **, or complementary exams ***!
Other specimens analysis: sputum, pleural fluid, blood, urine, tissue specimens (lymph node, hepatic or cerebral biopsy): stains*, culture** other examination***

, human immunodeficiency virus; CSF, cerebrospinal fluid; TB, tuberculosis; NTB, neurotuberculosis; MRI, magnetic resonance imaging;CMV, citomegalvirus; * stains: Ziehl Neelsen (acid-fast bacilli), India ink (fungi), Gram smear (bacteria); ** culture on specific media: Lowestein or Bactec(mycobacteria), Sabourraud (fungi), blood agar (bacteria); *** PCR,polymerase chain reaction, detection of ADA activity, detection of antigens/ antibodies for toxoplasma, CMV, criptococcus, meningococcus, pneumococcus

Table 2. Neurotuberculosis diagnosis in HIV patients

6.1.2. The evolution of TBM in HIV patients

In the HIV-TB co-infection TBM is frequently associated with pulmonary TB or tuberculous lymphadenopathies. *The risk of a relapse* is considered 23%. The most important risk of relapse is the lack of adherence to the antituberculous and antiretroviral treatment. CSF blood glucose ratio and the presence of pulmonary TB could also be linked with the risk of relapse according to a study performed in Vietnam [92]. *The mortality rate* is high; the survival rate is difficult to evaluate taking into account the increased mortality of HIV patients due to other opportunistic infections or specific complications. Risk factors for death during hospitalization for TBM included: a) the CD4+ count lower than 50 cells/mm^3; b) the presence of advanced neurologic signs or hydrocephalus on admission; c) a diagnosis and treatment delay with more than 3 days [80];d) the absence of the antiretroviral treatment or failure of the highly active antiretroviral therapy (HAART) [93].TBM relapsing forms and multidrug resistant mycobacteria are linked to a high mortality rate. IRIS prognosis is generally good.

6.1.3. Conclusion

TBM comprises variable manifestations in HIV patients. Early stages of immunodepression in HIV patients usually set the same diagnostic difficulties as in non-HIV patients as a result of the variable clinical presentations and delayed bacteriological results. In the advanced stages of HIV the clinical presentation is atypical and the CSF cytochemical profile could be within normal parameters. Other concurrent lesions of active TB could ease the diagnosis. The differential diagnosis should always include other HIV-associated manifestations, other opportunistic infections or malignancies. The bacteriological exam is still the only tool able to confirm the diagnosis. The prognosis of TBM in HIV patients is shadowed by numerous diagnostic difficulties, increased risk of relapse and associated HIV pathology.

Below are NTB diagnosis criteria (table 2) and imaging aspects found in our clinical practice in patients with HIV and NTB: meningoencephalitis (figure 1), cerebral tuberculoma (figure 2) and cerebral tuberculoma in context of IRIS (figure 3)

6.2. CNS disseminated TB

CNS disseminated TB (CNS milliary TB, cerebrospinal granulia) is a form of cerebral milliary frequently associated with disseminated TB. It is rarely limited to the CNS. The diagnosis is usually based on findings at the necropsy or MRI results. *Constitutional symptoms develop progressively even in the absence of neurologic signs; mycobacteria could also be isolated in other pathological products than the CSF (most frequently from the blood). The eye fundus exam could disclose characteristic choroid tubercles.* A classical miliary pattern on chest radiograph frequently complements the aspects of cerebral miliary. Postconstrast MR brain images reveal intense nodular enhancing granulomas located at cortico-medulary junction and throughout the brain parenchyma. The differential diagnosis of cerebral military should include other opportunistic disseminated infections or secondary metastatic lesions. It is possible to underestimate this form of CNS TB as a result of the diagnostic difficulties and required expensive imaging studies.
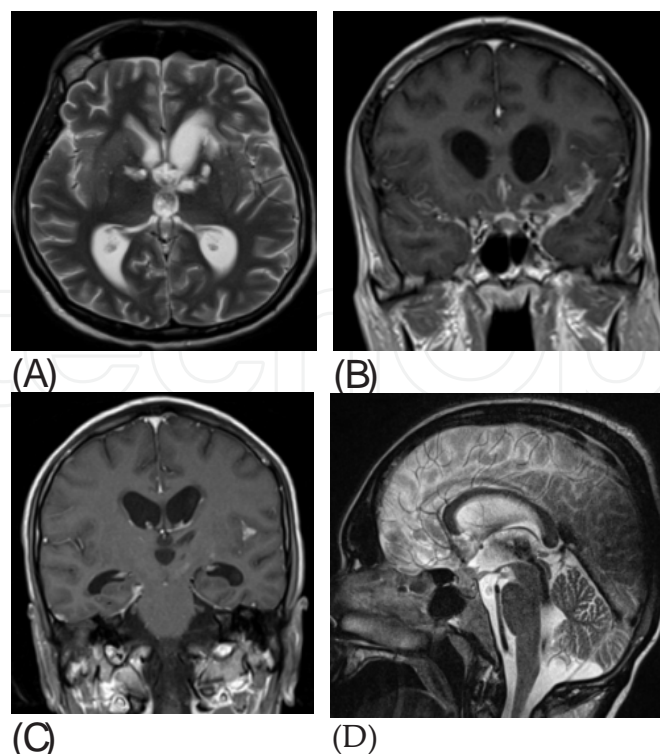
Figure 1. A-D. Cranio-cerebral MR: axial (A), coronal (B and C), and saggital (D) images showing tuberculous meningitis, cerebral thrombosis and hidrocephalus in a 23-year-old patient with AIDS. He had been receiving antiretroviral treatment for 3 months prior to the present hospitalization. He was admitted with milliary TB and meningoencephalitis associated with oral HCV infection, candidiosis and reactivated CMV infection. The clinical evolution was complicated by toxic hepatitis due to antituberculous treatment and cerebral thrombosis. On admission the CD4 count was 244/mm^3 and the RNA HIV load was 239 copies/ml. Contrast MRI before and after the administration of intravenous gadolinium and angioMRI(sag 3D PC phlebography) show: hyperintense lesions on FLAIR sequences and T2 weighted images, appearing hypointense on T1 with no contrast enhancement, located in the medial part of the lentiform nucleus and the head of the caudate nucleus; contrast filling of the basal cisterns extending to the sylvian fissure (more proeminent on the left side), the floor of the third ventricule and the infundibular area (involving the optic nerves, chiasm and optic tracts); asymmetric profound venous system with bilateral amputation of the superios talamostriate veins without the visualisation of the anterior left vein of the pellucid septum; enlargement of the ventricular system with no median shift or transependimar resorbtion. *Conclusions*: post ischemic sequelae, thrombosis of the profound venous system, basal meningeal contrast enhancement suggestive for meningitis and dilation of the ventricular system.

6.3. Intracranial mass lesions in HIV patients with CNS TB

6.3.1. Tuberculoma

CNS tuberculomas develop insidiously in the cerebral parenchyma following either the reactivation of local granulomas [94] or a paradoxical response to the antituberculous therapy (figure 2,3). The lesions could be solitary or multiple and their localisations are diverse. Cerebral localisations are more frequent than spinal ones. Data on HIV patients presenting tuberculomas is scarce [95,96]. The diagnosis is probably underestimated in low income countries taking into account the expensive CT/MRI importance in the confirmation. The clinical presentation is pseudotumoral with fever and headaches. The neurologic signs vary according to localisation and may be absent. HIV patients rarely present signs of intracranial hypertension or convulsions. On the other hand tuberculomas could be associated with other
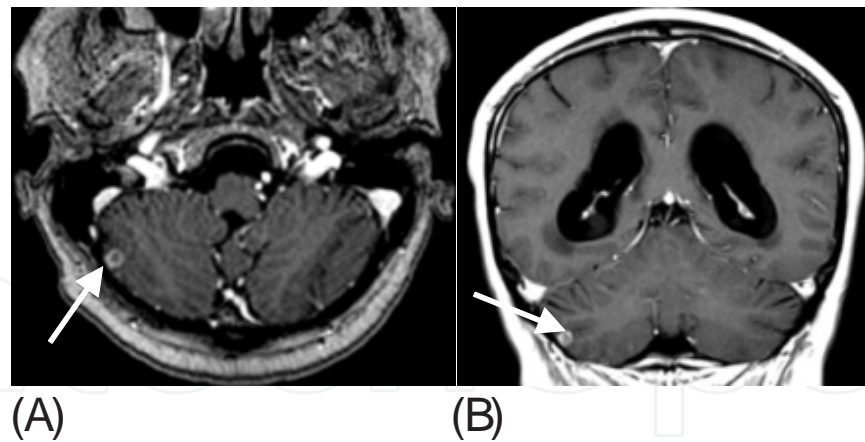
(A)   (B)

Figure 2. Cranio-cerebral *MR images* showing cerebelous tuberculoma in a 41 year-old patient with a 5 year history of HIV infection nonadherent to the antiretroviral treatment.The patient was admitted with a cerebellous tuberculoma and acute ischemic stroke.The laboratory data on admission disclosed a CD4 count of 145cells/mm^3 and RNA HIV load 240000 copies/ml.*Axial T1 weighted images shows (A)*: Focal enchancing triangular lesion in the anterolateral right-side of the pons of 5×9 mm with FLAIR hyperintensity, difussion restriction, no significant changes in the apparent diffusion coefficient (ADC) and no contrast enhancement (the aspect is suggestive for acute ischemia); a right focal cortico-subcortical cerebellous lesion with peripheral ring enhancement on T1 weighted images and mass effect (the aspect is compatible with a tuberculoma). *Coronal T1 weighted images shows (B)*: symmetrical enlargement of the ventricular system with no midline shift; transependimar circumferential resorbtion edema is present adjacent to the ventricular wall; no intraventricular obstruction or contrast enhancement. *Conclusions*: acute ischemic stroke in the anterolateral right side of the pons; focalinferolateral parenchymal lesion suggestive for a tuberculoma; significant hydrocephalus with no intraventricular obstruction.

manifestations of TB such as TBM, pulmonary TB or other signs suggestive for CNS TB such as tuberculous vasculitis. The CSF usually displays no changes or few cytochemical abnormal findings (low glucose, elevated proteins); the acid-fast bacilli smear and culture are frequently negative. The aspect on the CT suggestive for a tuberculoma presents as isodense or lightly hypodense lesions with annular contrast enhancement and the ''target sign'' as a result of central calcifications. Nevertheless these aspects are not pathognomonic and the diagnosis requires a cerebral biopsy with histological and bacteriological confirmation. The histopathological examination usually discloses a central region of caseous necrosis surrounded by a capsule with a granulomatous structure. This aspect evolves dynamically as follows: 1) noncaseating granuloma; 2) caseating granuloma with a solid center; 3) caseating granuloma with a liquid center. This dynamics could also be detected at the contrast enhanced MRI or MRI spectroscopy as opposed to the images induced by a cerebral abscess. The MRI examination indicates a correspondent evolution with the histopatological examination as: 1) hypointense lesions on T1-weighted images (T1W) and hyperintense T2W lesions with nodular enhancemen postgadolinium administration; 2) hypointense lesions on T1W and T2W with peripheral rim enhancement postgadolinium ;3) hypointense T1W and hyperintense T2W with hypointense rim postgadolinium. Difussion weigthed images indicate diffusion restriction within the tuberculoma. The lesions are surrounded by edema. The lesions in HIV patients often appear as ring-enhancement lesions under 1 cm and the mass effect is rarely seen [97]. The CT/MRI aspect should be distinguished from other ring-enhancing lesions including bacterial cerebral abscesses, cerebral toxoplasmosis, CNS cryptococcosis, neurocysticercosis or CNS lymphomas.
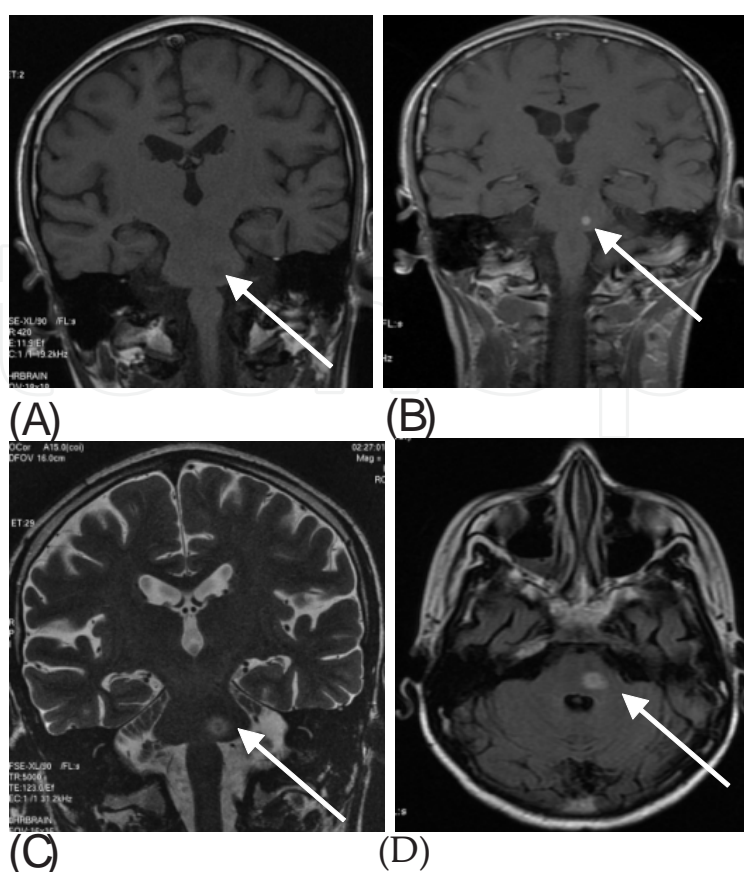
Figure 3. Cranio-cerebral *MRI,* showing left pontine tuberculoma in a 16 year-old patient previously diagnosed and undergoing treated for lymph node TB for the past 2 months and recently diagnosed with HIV infection.The patient also associated HBV and CMV infection and oral candidiosis.On admission the patient was in coma. The laboratory data displayed a CD4 count of 24 cells/mm^3 and RNA HIV 1064973copies/ml. Final diagnosis was NeuroIRIS TB (tuberculoma).The CSF disclosed no changes.The clinical evolution was favourable. *A:* coronal T$_1$ weighted image demonstrating left pontine paramedian nodular lesion of 4 mm surrounded by perilesional edema (discrete hyposignal). *B:* coronal section T$_1$ postcontrast shows hypersignal; C- coronal section T$_2$ and D- axial FLAIR section show intense contrast uptake and no diffusion restriction.

6.3.2.Tuberculous abscess

The tuberculous abscess represents a purulent collection delineated by a capsule with a granulomatous structure. This is a rare finding in immunocompetent patients as well as in the early stages of AIDS but common in severe immunodeficiency states with CD4+T cell count under 100/mm^3 [96]. The tuberculous abscess results from the liquefaction of tuberculomas [13] or from the necrotic evolution of granulomas in the setting of severe immunodeficiency [98].The necrotic centre is invaded by mycobacteria. The CSF is unchanged. The evolution is more acute than tuberculomas with neurologic deficit, fever and headaches [96, 99-100]. The CT/MRI aspect resembles the images in caseous tuberculomas but the lesion is larger (>3cm), multilobulated, surrounded by a thick capsule and ring enhancement. The perilesional edema and the mass effect are the most important features. The histological and bacteriological exam the cerebral biopsy confirm the diagnosis. The differential diagnosis includes other intracranial

space-occupying lesions especially cerebral toxoplasmosis and lymphoma [19].In such cases PCR techniques could increase the diagnostic yield [101,102].

7. Infections with non-tuberculous mycobacteria in HIV patients

Nontuberculous mycobacteria induce CNS lesions especially in AIDS patients with advanced stages of immunodepression. Sporadic cases triggered by M. avium, M. kanssasi, M. fortuitum, M gordonae, M. genavense and M. terrae were reported [105,106]. As a rule CNS infections with non-tuberculous mycobacteria are the result of MAC infection. Nevertheless infection with MAC shows no predilection for the CNS as it frequently colonises the respiratory and gastrointestinal tract. Disseminated infections occur as a result of a severe immune dysfunction at a CD4 count under 60 cells/mm^3 [57]. Under 10 cells/ mm^3 the neurological dissemination is also possible [107]. However a case study reported by Fletcher disclosed a cerebral abscess with a double etiology involving M tbc and MAC in an AIDS patient with a CD+4 count of 140 cells/mm^3 [108]. Higher values of the CD4+ count were also found in cases of MAC–related IRIS in the absence of a systemic infection [109]. Most MAC neurologic manifestations in HIV infected patients are cerebral abscesses and meningoencephalitis. Localized mass lesions (including single or multiple abscesses) contain a large number of mycobacteria in the absence of the typical granulomatous structure. These findings are frequently accompanied by pleocytosis and an occasionally high protein level on CSF examination. The diagnosis should be confirmed by a histological exam (in cerebral localized forms) or by using minimum 2 hemocultures (in disseminated forms). MAC was also isolated in the CSF in disseminated forms. NeuroIRIS-MAC associated manifestations were sporadically reported in HIV patients [110].

8. The treatment of NTB in HIV patients

The treatment of NTB in HIV patients should be combined, controlled and individualized.

1. The antituberculous and antiretroviral medication must be *combined* according to the synergistic drug interactions; the doses in the combined scheme must be adjusted to prevent treatment resistance.

2. The drug regimen must be *controlled* for adherence, drug interactions, toxicities, clinical response and treatment resistance

3. Treatment must be *individualized* and adapted to other co-morbidities, associated therapies and hypersensitivity reactions of the patient

The main antituberculous and antiretroviral classes, their corresponding representative drugs, pharmacological interactions, adverse reactions and treatment efficacy are shown in table 3. The NTB treatment principles in HIV patients are presented in accordance with the European AIDS Clinical Society guidelines, CDC and American Thoracic Society recomandations [111-113].

8.1. The antituberculous treatment

Treatment of tuberculous meningitis. TBM is a curable disease. Response to treatment in patients with NTB and HIV is similar to patients diagnosed with TB only. The elevated mortality is a result of the belated diagnosis, resistant mycobacteria and severe immunodeficiency

- **The main characteristics of the antituberculous treatment in HIV patients with NTB**

1. Treatment should be urgently started based on clinical and biological data, CSF modifications, the history of TB, other tuberculous lesions and imaging studies. The CSF specimens should be collected for culture and for resistance detection before treatment starting. The bacteriological confirmation should not delay the treatment as the treatment delay accounts for a poor prognosis. Advanced stages of the disease with irreversible complications (hydrocephalia, adherences, cerebral infarcts) are related to high mortality rates.

2. The antituberculous therapy must have increased CSF penetration (table 3) [114-120].

3. Corticosteroid therapy should be initiated as early as possible and continued for 6–8 weeks.

4. A long course of therapy for a minimum of 12 months is strong recomended.

- **Factors to consider**

1. *Combined treatment* must include an *initial phase* of 2 months, with 4 first-line antituberculous drugs having high CSF penetration (ussualy isoniazid, rifampicin, pyrazinamide, ethambutol) administered daily; the initial phase is followed by a *second phase* of another 10 months with only 2 first-line antituberculous drugs (isoniazid, rifampicin) administered 3 times per week [121]

2. *Controlled treatment* should approach:

- treatment adherence

- drug interactions and toxicities taking into consideration the followings (see table 3):a) the side effects to the antituberculous treatment are three times more frequent in HIV than non HIV patients; b) the interactions between the antituberculous and antiretroviral therapy may impede the administration of the most efficient regimen or a simultaneous therapy; the most important interaction involves the protease inhibitors (important class of antiretrovirals) and rifampicin (first line antituberculous drug). Rifampicin accelerates the hepatic metabolism of protease inhibitors decreasing their blood levels and increasing the risk of HIVdrug resistance. In addition protease inhibitors delay the metabolism of rifampicin increasing its serum concentration and toxicity. Izoniazid and rifampicin also decrease the concentration of fluconazole, an antifungal frequently used in the HIV patients. Additionally there are many other interactions between rifampicin and antiretrovirals, corticosteroids or trimetoprim/sulfamethoxazole (table 3). For this reason rifabutin is preferred to rifampicin in HIV patients along with a prolonged treatment.

• neurological/extraneurological complications

Monitoring for ensuing complications includes a complete physical examination, laboratory data, CSF aspects and imaging studies. It is important to consider the followings: a) neurological complications are more frequent in HIV patients (mostly due to immune exacerbation as tuberculous vasculopathy or IRIS); b) neurological complications may occur during treatment: hydrocephalus and arachnoiditis could sometimes occur even in the presence of a correct treatment; c) complications are frequently associated with other undetected TB localizations.

• drug resistance.

The risk of resistance is increased in non-adherent patients, large bacillary load and patients who start less efficient regimens. The glucocorticoid therapy reestablishes the low permeability of the blood-brain barrier and could therefore decrease the CSF diffusion of antibiotics. Inadequate doses of antituberculous therapy or low CSF antituberculous concentration may induce drug resistance. An unfavourable clinical evolution and decreasing CD4+T cell count require repeated CSF collection for culture and drug resistance. Close surveillance for drug resistance is essential throughout the entire course of therapy.

3. *Individualized treatment*. The patient's co-morbidities (like viral hepatitis or other risk factors for hepatotoxicity, ocular diseases, renal failure, allergic reactions,other medications and pregnancy) must be investigated before establishing the drug regimen and should continue to be closely monitored.

Treatment of tuberculomas. Cerebral tuberculomas are potentially curable tumor-like masses. There is a low number of tuberculoma cases reported in HIV patients [94- 95, 122-125]. Treatment is based on the same principles as TBM but with the following mentions:

• The perilesional granulomatous vasculitis decreases the penetration of antituberculous drugs; the lesions heal progressively and require 12 to 30 months of antituberculous treatment, or even longer;

• The recommended regimen is based on rifampicin, izoniazid and pirazinamide for 4 to 5 months and then rifampicin and izoniazid for 12 to 16 additional months. Other active drugs include rifabutin, fluoroquinolones, kanamycin, ethionamide;

• Surgical treatment is rarely needed; it is indicated in tuberculomas with mass effect, increased intracranial hypertension and hydrocephalus. The antituberculous treatment should be started before surgery. The recurrence after surgical ablation is unsual.

• Glucocorticoid therapy is an important part of the treatment regimen as it reduces the edema and improves the clinical manifestations. It should be maintained for at least 4 to 8 weeks.

Treatment monitoring requires the clinical and radiological follow-up on the long term. The evolution of other tuberculous localizations if present should also remain under observation. Response to therapy is favorable despite large lesions or immunodeficiency.

Treatment of tuberculous abscesses requires surgical and pharmacological treatment similar to the regimen recommended in tuberculoma but for an interval of 18 months to 2 years. The *prognosis* is unfavourable due to severe imunodeficiency and large lesions [99, 101].

Treatment of NTB with resistant strains of M.tbc. The risk of resistance is higher in geographic areas with high prevalence of resistant mycobacteria and in the case of recent TB improperly treated. Resistance could occur against one or more antituberculous drugs. The association between HIV and multidrug resistance (MDR-TB) or extensive drug resistance (XDR-TB) is not well documented [126,127].The antituberculous treatment should be undertaken according to the advice of an experienced specialist only and should include at least 4 antituberculous drugs with an increased diffusion in the CSF [128].

Treatment of CNS TB with nontuberculous myobacteria. Data related to infections with nontuberculous mycobacteria is scarce and insufficient for establishing definite treatment guidelines. Therefore treatment regimens are largely undefined and the subsequent outcome remains disappointing. The severity of the evolution appears to be related to the variable sensitivity to the antituberculous antibiotics and the advanced stages of immunodeficiency which predispose to a disseminated disease. Therapeutic regimens should be individualized to include complex drug associations (5-6 drugs) on longer periods of time. A close consultation with an experienced specialist is required. Mycobacteria belonging to the MAC display increased resistance against most antituberculous drugs and therefore a large variety of therapeutic regimens was evaluated. The repeated therapeutic failure is apparently linked to the diverse sensitivity to antituberculous drugs associated with M. avium species. Moreover there is the alternative that some HIV patients could be simultaneously infected with more than one species of M avium. Macrolides proved efficient but cannot penetrate to the CSF. Chlaritromycin is involved in several drug interactions with the antiretroviral therapy. Considering the increased risk for disseminated forms induced by the MAC it is recommended to add azithromycin, ethambutol and rifabutin to therapy. Other drugs that could be associated in such cases include fluoroquinolones, streptomycin, amikacin. Treatment should always be based on the results of susceptibility testing. After 12 months of treatment, prophylaxis with macrolides is recommended until the CD4+ count raises above 100/mm3.M. scrofulaceum, M. simiae, M. malmoense reveal the same sensitivity pattern as MAC. In the case of M. kansasii recommended drugs include: rifabutin, streptomycin, HIN, ethambutol, amikacin.

Treatment during Pregnancy. The antituberculous treatment is urgently instituted according to classic treatment regimens. Among prohibited drugs are streptomycin, fluoroquinolones and ethionamide.

Treatment of NeuroIRIS-TB. Neurologic TB-IRIS is a rare manifestation of TB-IRIS. It generally occurs within 2-3 months after initiating the combination of antiretroviral and the antituberculous therapy [42].The risk of IRIS increases with the early starting and high efficacy of antiretroviral therapy. Delaying the antiretroviral therapy with a minimum of 2 weeks after antituberculous therapy is recommended to avoid IRIS complication. Usually IRIS is self-limited and requires symptomatic or anti-inflammatory treatment without stopping the antiretroviral treatment. Severe forms benefit from treatment with prednisone or methylpred-nisolone 1 mg/g gradually tapered within the 2 following weeks [129,130]

8.2. The antiretroviral therapy

The antiretroviral (ARV) treatment ought to be started as soon as possible after the antituber-culous treatment. The urgency of the ARV therapy increases with the degree of immunodefi-ciency. Three important studies (CAMELIA performed in Cambodgia, SAPiT conducted in South Africa and STRIDE a multinational study) established that an earlier start of the ARV therapy significantly decreases the mortality in AIDS patients and especially in patients in which the CD4+ cell count is below <50 cells /mm^3. Although the development of IRIS is more frequent if the ARV treatment is more precocious, the gravity of the IRIS manifestations in the 3 studies above cannot justify a longer delay of the antiretroviral therapy. Most guidelines recommended that HIV patients start the antiretroviral treatment at least 2 weeks after the antituberculous treatment if the CD4+ count is below 50 cells per mm^3 ; the antiretroviral treatment can be delayed until 4 weeks if the CD4+ count > 50 cells/mm^3. Note that NTB in HIV patients could be shadowed by the possible reactivation of other neurotropic agents (cytomegalovirus, toxoplasma, JV virus) or cerebral tumors (cerebral lymphoma, Kaposi sarcoma).The diagnosis in these cases could be difficult and if these associations are not excluded from diagnosis, treatment should also address these conditions with the risk of multiple drug interactions. Such is the case of cerebral toxoplasmosis.

• **The main characteristics of antiretroviral treatment in HIV patients with NTB**

  ○ Therapeutic regimens must contain antiretroviral drugs with a high penetration in the CSF. The main ARV drugs used in the co-infection with TB are listed in table 3 along with their adverse reacions.

  ○ The antiretroviral therapy in NTB is based on reverse transcriptase inhibitors represented by 2 important classes: nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The highest drug penetration into the CSF is assigned to zidovudine, abacavir, nevirapine, delavirdine. Although efavirenz (a NNRTI) does not display high levels in the CSF some studies advocate a very good response in the treated adults [131]. Protease inhibitors should not be used due to their interaction with rifampicin and low diffusion in the CSF. If their use is required (as a result of resistance or toxicity to other antiretrovirals) rifampicin is to be replaced with rifabutin with similar results.

  ○ The doses of antiretrovirals should be changed according to the antituberculous drug interference.

• **Factors to consider**

1. *Combined treatment* includes 3 NNRTIs with a preferred option for trizivir (combination of zidovudine, abacavir and lamivudine) or 2 NRTIs + 1 NNRTI (ussualy efavirenz).

2. *Controlled treatment* should approach:

• The adherence (especially if a large number of drugs are introduced at the same time) [132]. Nevertheless adherence to trizivir is high (the number of capsules is low, there are few adverse reactions).

- Drug interactions and toxicities (see table 3). The clinician should recognize the overlapping toxicities, drug interactions and also the occurrence of IRIS (paradoxical reactions) [133].The interactions between NNRTI or NRTI and antituberculous drugs are few. The risk of toxicity is minimal but adverse reactions are possible with some NRTIs (see table 3). Regarding the toxicity the ARV could interfere not only with antituberculous drugs but also with other drugs used in the prophylaxis or treatment of other opportunistic infections (such as fluconazol for Candida or Criptococcus neoformans or sulphametoxazole/trimethoprim for Penumocystis jirovecii).

- The efficiency and complications of treatment. The efficiency is to be monitored on a clinical, virologic and immunological basis. The best control in HIV infections is the virologic (RNA HIV viral load) and immunologic control (CD4+ cell count).Treatment control could be undertaken at 14 days, one month, three and six months respectively. If the HIV RNA load does not become undetectable after 3 months of treatment virologic failure should be considered. If this is the case investigations on the underlying cause should focus on the lack of adherence, acquired resistance (especially to NNRTIs) or a wrong treatment regimen (doses, antagonistic associations or the lack of drug penetration to the CSF). Nevertheless the intracerebral load of HIV could be hard to evaluate since the viral load detection in the serum does not always reflect the intracerebral levels of HIV.

- Drug resistance. In case of virologic failure drug-resistance testing should be obtained during treatment with the failing ARV regimen or within 4 weeks of treatment discontinuation. Resistance to antiretrovirals generally applies to most compounds in the same class.A new regimen with other fully active drugs preferably from other new classes must be restarted.

3. *Individualized treatment*: the treatment options should address other opportunistic infections and the patient's medical history. A CD4+ count under 200 cells/mm^3 urges the prophylaxis against fungal infections (cryptococcus, pneumocytsis). Prophylaxis against toxoplasmosis should be started at a CD4+ cell count under 100 cells/mm^3 due to an increased risk of reactivation. Pregnant patients require urgent ARV treatment after 14 days of antituberculous treatment.

9. Conclusion

The failure of the antituberculous/antiretroviral treatment is generally a result of the low compliance, inadequate treatment regimen (length, doses, low penetration into the CSF, adverse reactions impeding the use of certain efficacious drugs), delays in the diagnosis or treatment resistance. Any changes in the clinical examination, imaging studies and CSF aspect during treatment or at follow-up require further investigations. Despite the immunodeficiency the prognosis of CNS TB in HIV patients resembles that of non-HIV patients.

ANTITUBERCULOUS DRUGS		
Drug	Pharmacologic aspects	Drug interactions/Adverse reactions
Isoniazid (NIH)*** (first-line agent)	Interferes with mycolic acids synthesis. Bactericidal to rapidly-dividing extracellular mycobacteria, bacteriostatic against the slow-growing intracellular mycobacteria. CSF peak concentrations exceed 30 times the minimal inhibitory concentration	Peripheral neuropathy (requires pyridoxine supplementation). Hepatotoxicity (reversible) depending on the dose and association with rifampicin and alcohol consumption. Rare cases of fulminant hepatitis. Rare allergic reactions.
Rifampicin* (first-line agent) Associations of rifampicin: rifamate, rifater Rifabutin* Rifapentine is a semi-synthetic rifamycin derivate with longer half-time (not recommended in HIV patients)	Rifampicin acts against intra and extracellular bacilli, especially on slow-growing mycobacteria (bactericidal). The metabolism is primarily hepatic; because of its ability to induce certain microsomal hepatic enzymes (CYP3A4) it interferes with the metabolism of other drugs. Poorly penetrates the CSF in the absence of meningeal inflammation. In meningitis CSF level is up to 10-20% of the serum levels. Rapid emergence of resistant mycobacteria. Rifabutin is bactericidal.The level of rifabutin in the serum is 7-10 times lower than the concentration of rifampicin. It easily diffuses through the uninflammed meninges.	Renal failure. Digestive and allergic reactions. Hepatotoxicity (cholestatic hepatitis) especially in drug associations. Hemorrhagic manifestations due to thrombocytopenia. Sulfamethoxazole/ trimethoprim enhances the effect of rifampicin and could increase its toxicity. Corticosteroids decrease the level of rifampicin. Rifampicin could singnificantly reduce the plasma concentrations of most PIs and some NNRTIs; it could be associated with NRTI and some NNRTIs. Adverse reactions to rifabutin mirror those of rifampicin; in addition rifabutin could induce uveitis, arthralgias, leucopenia, asymptomatic hepatitis. Rifabutin does not interact with PIs. Because rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampicin. Doses should be adjusted in the coadministration with an PI ; underdosing of rifabutin can result in selection of rifamycin resistance, whereas overdosing of rifabutin might result in toxicities.
Pyrazinamide*** (first-line agent)	Active against intracellular bacilli only at acid pH. Bactericidal/bacteriostatic (dose dependent). Is well absorbed and crosses the blood-brain barrier leading to CSF concentrations almost as high as those in the blood	Hepatotoxicity Hypersensitivity reactions
Ethambutol* (first-line agent)	Bactericidal with low activity. Ethambutol could increase the activity of other antituberculous drugs affecting the cellular permeability of MAC strains and possibly of multiresistant M.tbc strain. Low CSF level (moderate rise above the minimum bactericidal concentration)	Optic neuropathy especially after prolonged treatments. Rarely triggers allergic reactions and hyperuricemia. No hepatotoxicity reactions.
Streptomycin* (second-line drug)	Belongs to aminoglycosides class. Bactericidal. Active only on replicating extracellular bacilli. Poor CSF level even in patients with meningitis. High rate of resistance	Nephrotoxicity. Neurotoxicity. Ototoxicity. Contraindicated in pregnancy. No recorded hepatotoxic reactions
Amikacin* (second-line drug)	Belongs to the class of aminoglycosides. The same characteristics as streptomycin. Low CSF concentrations	Less toxic than streptomycin.Contraindicated in pregnancy

ANTITUBERCULOUS DRUGS		
Drug	Pharmacologic aspects	Drug interactions/Adverse reactions
Ofloxacin** Levofloxacin** Moxifloxacin** Ciprofloxacin *	Belongs to fluorochinolones class. Bactericidal. Active on rapidly multiplying bacilli. Acts on nontuberculous mycobacteria. Good CSF penetrations. except for ciprofloxacin	Rare adverse reactions. To be avoided in pregnancy. Interferes with antiacids
Azithromycin Clarithromycin	Belongs to macrolides class. Bacteriostatic. Active on nontuberculous mycobacteria. High intracellular levels Do not cross the blood brain barrier.	Clarithromycin interfers with PIs and efavirenz; azithromicin does not display these interferences.
Ethionamide*** (second-line drug)	Bacteriostatic/bactericidal (dose depending). Effect on extra/intra cellular bacilli. Good CSF penetration (equal to those in serum).Active on resistant mycobacteria.	Allergic reactions. Digestive reactions. Hepatotoxicity. Neurotoxicity. Teratogenic effects
Cycloserine*** (second-line drug)	Bactericidal/bacteriostatic (dose depending). Effect on intra and extracellular bacilli, including resistant mycobacteria. Good CSF penetration	Neuropsy-chic reactions. Rash. Not recommended with efavirenz. No hepatotoxicity; indicated in patients with acute hepatitis in combination with other nonhepatotoxic drugs.
CCR5 antagonist: maraviroc (MVC) **	Belongs to the entry inhibitor class (chemokine receptor antagonist); it blocks HIV entry into the host cell. Substrate of CYP3A enzymes.	Hepatotoxicity. Rash. Caution and dose adjustment is necessary when MVC is used in combination with CYP3A inducers agents (such as EFV or rifampin).
Fusion inhibitor: enfuvirtide (EFV) *	Belongs to the entry inhibitor class. It is not affected by the CYP enzymes	Hypersensitivity reactions. Can be used with the rifamycins
Integrase inhibitor: RAL**	HIV-1 integrase inhibitor. Blood-brain-barrier restrict RAL entry; meningeal inflammation enhances drug entry.	Hypersensitivity reactions. Rifampin and rifabutin can significantly reduce the concentration of RAL.
Protease inhibitors (PI): SQV*;ATV***;DRV*;FPV***; AMP ***; IDV***; LPV***; NFV*;RTV*; TPV*	Interfere with the protease enzyme that HIV uses to produce infectious viral particles. PI are CYP P450 inducer and substrate	Hepatotoxicity (requires monitoring of hepatic enzymes). Rash. Prolonged QT interval. PIs are not recommended with rifampicin. Adjust the dose of PIs when combined with rifabutin
Non-nucleoside reverse transcriptase inhibitors (NNRTI): EFV**;NVP*** ETV; DVR***	NNRTI bind to revers transcriptase, interfering with its ability to convert the HIV RNA into HIV DNA The NNRTIs are also substrates of CYP3A4 and can act as an inducer/inhibitor or mixt NNRTIs are related with an increased risk of resistance if the therapeutic regimen is not respected.	Hepatotoxicity. Hypersensitivity reactions. Fewer interactions with RIF; nevirapine does not affect the levels of RIF; efavirenz or nevirapine-based regimen are preffered when using associated therapy with RIF; etravirine not recommended with RIF. Adjust the doses in the combination of EFV and rifabutin /rifampicine
Nucleos(t)ide reverse transcriptase inhibitors (NRTI): ZDV***; 3TC** ABC ***; d4T ** ddI* ; FTC**TDF*; ZAL*	Interfere with reverse transcription and conversion of HIV RNA to HIV-DNA. Do not use the CYP metabolic pathway. No significant interaction with rifampicin or rifabutin	Hepatitis. Neuropathy (only stavudine, didanosine). Optic neuritis (didanosine)

***very good ability to cross the blood-brain barrier; ** moderate ability to cross the blood-brain barrier; * low ability to cross the blood-brain barrier

Table 3. The most important antituberculous and antiretroviral drugs used in the treatment of CNS tuberculosis [113-118]

Acknowledgements

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