HIV-Associated Tuberculosis: A sub-Saharan African Perspective

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ABSTRACT

The sub-Saharan Africa bears the brunt of being the region with the highest burden of both Human Immunodefiency Virus (HIV) infection and of tuberculosis (TB). While only 10% of immunocompetent individuals infected with M. tuberculosis go on to develop active disease in their lifetime, 50% of those co-infected with HIV develop active TB. Qualitative and quantitative defects of CD4+ T-lymphocytes explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Similarly, TB also accelerates the progression of HIV infection. The clinical and radiological presentation of TB in patients infected with the HIV virus may be different and atypical posing significant diagnostic challenges. This is compounded by the dearth of diagnostic facilities in sub-Saharan Africa. The initiation of antiretroviral therapy (ART) during anti-TB therapy (ATT) significantly improves survival of TB/HIV co-infected persons. There are challenges in treatment of HIV associated TB because of overlapping drug toxicities, pill burden and suboptimal adherence, drug-drug interactions between ART and ATT as well as timing of ART. Of particular importance are the immune reconstitution inflammatory syndrome (IRIS) and the emergence of multi-drug resistant (MD-R) and extensively drug resistant (X-DR) TB. Centre’s for tuberculosis diagnosis and treatment and for HIV care and treatment need to be integrated. This has not been so successful in sub-Saharan Africa. In spite of sustained support by donor organizations, a substantial number of HIV-TB co-infected individuals remain undiagnosed and are poorly managed. This review focuses on the epidemiology and pathogenesis of HIV-TB co-infection and the special areas of difficulty in the diagnosis and treatment of the dual infection. Emphasis is placed on the peculiarities of management in sub-Saharan Africa, the region with the highest burden of both infections.

Keywords: Africa, HIV, sub-Saharan, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is the most common cause of infectious disease-related morbidity and mortality worldwide after the human immunodeficiency virus (HIV) and the global burden of HIV has had a dramatic impact on the epidemiology of TB.[1] It was considered to be on the brink of elimination in the developed world until the late 1980s, when new HIV related TB cases and multidrug-resistant TB (MDR-TB) surfaced. However, in developing countries, TB has remained an important public health problem, exacerbated in the last decade by poverty, war, demographic changes and the rapid spread of HIV with case rates increasing by an average of 7% per year after 1985 in 20 sub-Saharan African countries.[2] HIV is the single most important factor determining the increased incidence of TB in the past years, underlining the synergy between the progress of HIV and TB. In sub-Saharan Africa, the resurgence of TB has also been fueled by the HIV pandemic[3,4] and the WHO African region bears the highest burden of disease worldwide accounting for 82% of HIV-positive incident TB cases in 2010 [Figure 1].

Sub-Saharan Africa remains the region most heavily affected by HIV. In 2010, about 68% of all people living with HIV resided in sub-Saharan Africa, a region with
only 12% of the global population. South Africa’s HIV epidemic remains the largest in the world and with an estimated 5.6 million people living with HIV while Nigeria continues to have the second largest number of people living with HIV in sub-Saharan Africa. Both countries are listed among the 22 high TB burden countries.

TB can occur at any stage of HIV disease and its manifestations depend largely on the level of immunosuppression. Early during HIV disease, symptoms and signs are similar to those in HIV-uninfected persons: the lungs are most commonly affected, with cough, fever and respiratory signs along with radiographic lesions, often with cavitation. In patients with more severe immunosuppression however, extra-pulmonary sites are more often involved in addition to lung disease where it resembles primary pulmonary TB with lymph node enlargement, miliary disease and minimal parenchymal lesions.

Diagnosis is difficult and/or delayed because of the poor performance of sputum smear microscopy in HIV-infected patients with disproportionate amount of smear-negative disease in sub-Saharan Africa. More sensitive tests are being investigated to improve both latent and active TB case detection in the setting of HIV infection. With respect to treatment, antiretroviral therapy has a profound effect on lowering the risk of TB in HIV-infected persons, but it can also be associated with immune reconstitution inflammatory syndrome (IRIS) and unmasking of previously subclinical disease. Differences also exist in treatment of HIV and TB co-infection because of overlapping drug toxicities and drug-drug interactions between antiretroviral therapy and anti-TB therapy.

The full cost of the TB epidemic in sub-Saharan Africa is rarely appreciated. The direct monetary costs of diagnosis and treatment are borne by health services and by patients and their families. Added to these are the indirect costs of lost income and production, incurred when TB patients are too sick to work and when young adults—often parents and household heads, die prematurely. Beyond these losses, enormous psychological and social costs are associated with TB. These extra costs are less easily quantified, but they are nonetheless real. In this review, the epidemiology, clinical features, diagnosis, treatment and challenges in the management of HIV and TB co-infection as seen in sub-Saharan Africa is presented.

**Epidemiology of Tuberculosis and HIV in Sub-Saharan Africa**

TB is a major public-health problem and patients with PTB whose sputum is smear-positive for *M. tuberculosis*...
form the main source of infection in communities. It is estimated that around two billion people around the world are currently infected with the bacillus but yet only 10% of infected immunocompetent individuals are likely to develop symptomatic TB during their lifetime when compared to 50% in individuals that are immunologically weakened by concurrent HIV infection.\(^{[18]}\) The risk of developing the clinical manifestations of the disease is greatly increased by HIV co-infection.\(^{[3,4,19-21]}\) This strong association between HIV and TB in sub-Saharan Africa is responsible for the massive increase in the incidence of TB observed in the region in the last 20 years. This higher risk of HIV patients developing TB could be related to the fact that macrophages that are not activated by CD4+ T-lymphocytes are unable to restrict the growth of *M. tuberculosis*.\(^{[21]}\)

The WHO global TB control report estimated that 8.8 million incident or new TB cases occurred in the world in 2010.\(^{[22]}\) The worldwide TB incidence rates are estimated to have peaked in 2004 and to have decreased at a rate of less than 1.3% per year since that time. However, the overall worldwide burden continues to rise as a result of the rapid growth of the world population.\(^{[22]}\) The highest incidence rate was seen in the WHO Asian and African regions with 9 sub-Saharan African countries listed among the 22 high burden TB countries [Figure 2]. These countries include Democratic Republic of Congo, Ethiopia, Kenya, Mozambique, Nigeria, South Africa, Uganda, United Republic of Tanzania and Zimbabwe. While 13% of all new infections worldwide were attributable to HIV, in sub-Saharan Africa alone, approximately 39% of all new TB infections were attributable to HIV.\(^{[22]}\)

The interaction between TB and HIV is also characterized by a high mortality rate in individuals co-infected with HIV and *M. tuberculosis*. In the year 2010, of an estimated 1.40 million deaths from TB, 0.35 million deaths i.e. 25% were attributable to HIV compared to 12% in the year 2000.\(^{[22]}\) There were an estimated 440,000 cases of MDR-TB in 2008\(^{[23]}\) and as at July 2010, 58 countries and territories had reported at least one case of extensively drug-resistant TB (XDR-TB). It is estimated that approximately one third of the 33.2 million people living with HIV or AIDS worldwide are co-infected with TB.\(^{[24]}\) The relative risk of TB among HIV-infected persons, compared with that among HIV-uninfected persons, ranges between 20- to 37-fold, depending on the stage of the HIV disease.\(^{[22]}\) The majority of HIV-infected persons do not know their HIV status and there are no global data to quantify the proportion of the population that knows their HIV status.\(^{[24]}\)

**Pathogenesis of Tuberculosis in HIV Infection**

The yearly probability of developing active clinical TB after inhalation of *M. tuberculosis* aerosol from an infectious patient with active tuberculosis is very small. Close contacts of infectious TB patients who become tuberculin positive (i.e. converters) have a 5-10% risk of developing active TB in the following 2-5 years and another 5-10% during their lifetime.\(^{[22]}\) The risk of transmission is highest within the first few years after infection, but decreases substantially thereafter. Most immunocompetent individuals (over 90% of those infected) either eliminate *M. tuberculosis* or contain it in a latent state.\(^{[22]}\) The so-called latent TB infection (LTBI) is a clinical state in individuals infected with *M. tuberculosis* in which the host immune system retains sufficient control over replication of the bacterium such that the individual remains free of tissue damage and symptoms.

Qualitative and quantitative defects of CD4+ T-lymphocytes explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Reactive CD4+ T-lymphocytes produce cytokines of the Th1 pattern and participate in MHC class II-restricted killing of cells infected with *M. tuberculosis*.\(^{[27,29]}\) Th1 CD4+ cells produce interferon (IFN)-γ and IL-2 and promote cell mediated immunity cell mediated immunity (CMI) while Th2 cells produce IL-4, IL-5 and IL-10 and promote humoral immunity.\(^{[29,30]}\) The interplay of these various cytokines and their cross-regulation determine the host’s response.\(^{[30]}\)

HIV promotes the progression of LTBI to disease and TB accelerates the progression of HIV disease. In healthy people previously exposed to and infected by TB, host cell mediated immunity keeps LTBI dormant. HIV infection interferes with CMI, increasing the risk of progression to active disease. In people with HIV infection, the risk of TB disease is influenced by the prevalence of TB in the local community, the person’s likelihood of exposure to infectious TB, the person’s degree of immunodeficiency

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**Figure 2**: Burden of HIV-associated tuberculosis in 9 sub-Saharan African countries. Reproduced from WHO’s global tuberculosis report 2011 (22) by permission of the World Health Organization.
and the use of preventive therapy for LTBI.\textsuperscript{[31,32]} HIV-positive patients have however been found to be less infective than HIV-negative patients and this may partly be explained by lower bacillary load in the sputum.\textsuperscript{[33]}

**Impact of HIV infection on pathogenesis of tuberculosis**

HIV infection increases the risk of reactivation of LTBI and causes progression of new infection and re-infection to active disease. These accelerate the natural course of the disease with a more rapid spread of strains, including those that are drug resistant, in the community.\textsuperscript{[34]} *M. tuberculosis* is an intracellular pathogen and macrophage activation, by the release of IFN-\(\gamma\) from activated CD4\(^+\) and CD8\(^+\) T-lymphocytes, is the primary mechanism by which *M. tuberculosis* replication is inhibited and by which *M. tuberculosis* is ultimately killed.\textsuperscript{[35]} HIV infects and kills CD4\(^+\) T-lymphocytes, the concentration of which declines as the HIV infection progresses increasing the risks of TB disease and disseminated mycobacterial infection.

Active TB has been associated with a higher HIV viral load, which might be expected to accelerate the loss of CD4\(^+\) T-lymphocytes and promote HIV/AIDS disease progression.\textsuperscript{[36-38]} Granulomas are absent or poorly formed in people with poor immune responses, particularly those infected with HIV.\textsuperscript{[39]} Through several mechanisms, HIV-1 co-infection leads to functional and numeric depletion of *M. tuberculosis*-specific CD4\(^+\) T-lymphocytes and Th1 cytokine production.\textsuperscript{[36]} The resulting dysfunction of the CD4\(^+\) T-lymphocyte-macrophage immune axis impairs the host’s ability to orchestrate CMI responses and form immunologically competent granulomas. As a result, histological examination of tissue specimens might reveal uncontrolled *M. tuberculosis* replication with little evidence of a host cellular response. Sites of TB disease and granulomas themselves provide the ideal microenvironment for the propagation of HIV-1, thereby maximizing the adverse consequences of HIV-1 at the crucial interface between *M. tuberculosis* and the host.\textsuperscript{[35]}

**Impact of tuberculosis infection on the pathogenesis of HIV**

In the lungs, a synergistic immune dysregulation with perturbation in cytokine expression has been described.\textsuperscript{[39]} High levels of TNF-\(\alpha\) which are known to increase HIV replication in T-lymphocyte clones have been demonstrated in both HIV-1 seropositive and seronegative TB cases.\textsuperscript{[40,41]} Moreover, investigators have shown that *M. tuberculosis* or purified protein derivative (PPD) can also increase viral replication in infected T-lymphocytes and monocytes. Gray et al., demonstrated that in asymptomatic HIV infected highly active antiretroviral therapy (HAART) naïve children, isoniazid prophylaxis showed a marked reduction in TB incidence and death when compared to a placebo group.\textsuperscript{[42]} Thus, preventing TB infection and disease in HIV-infected patients, it is potentially an important public health intervention.

**Clinical Features of HIV-Associated Tuberculosis**

### Latent TB infection

As noted earlier, primary infection with *M. tuberculosis* leads to clinical disease in only ~10% of individuals. In the remaining cases, the ensuing immune response arrests further growth of *M. tuberculosis*. However, the pathogen is completely eradicated in only ~90% people,\textsuperscript{[26]} while the immune response in the remaining ~10% individuals only succeeds in containment of infection as some bacilli escape killing by blunting the microbicidal mechanisms of immune cells (such as phagosome-lysosome fusion, antigen presentation by MHC class I, class II and CD1 molecules, production of nitric oxide and other reactive nitrogen intermediates) and remain in non-replicating (dormant or latent) state in old lesions.\textsuperscript{[26]} The clinical state is termed as latent tuberculosis infection (LTBI) and the dormant bacilli retain the ability to resuscitate and to cause active TB if a disruption of immune response (as in HIV infection) occurs. It is hypothesized that HIV co-infection has a fundamental impact on the spectrum of the host-pathogen relationship with a general shift towards poor immune control, high bacillary numbers and subsequent development of active infection and symptomatic disease.\textsuperscript{[26,42]} Recurrent exogenous re-exposure to *M. tuberculosis* in high TB prevalence settings is also very likely to play an important role, further increasing bacillary numbers and increasing the likelihood of progression to disease.\textsuperscript{[25,43]}

### Active TB infection

Active infection and disease with *M. tuberculosis* can occur at any CD4\(^+\) count. The nature, clinical presentation and investigative features of TB depend on the degree of HIV-related immunosuppression. In patients with early HIV disease and a well-maintained CD4\(^+\) count, the clinical picture is essentially very similar to that in the HIV-negative population and the classical presentation of cough, fever and weight loss is common.\textsuperscript{[3,4,21]} As the degree of immunosuppression increases, the clinical presentation becomes increasingly atypical and non-specific particularly in the late stage of HIV infection, with non-cavitary disease, lower lobe infiltrates, hilar lymphadenopathy and pleural effusion and other extra-pulmonary manifestations of the disease.\textsuperscript{[44]} The difficulty with diagnosis is compounded by the fact that fever and weight loss can be common symptoms of HIV disease alone or other opportunistic infections.\textsuperscript{[45]} The risks of disseminated disease become higher as the CD4\(^+\) count falls. A clear association has been reported between low CD4\(^+\) count and an increased frequency of extrapulmonary TB (EPTB), positive
blood cultures for *M. tuberculosis* and intrathoracic adenopathy on chest X-ray.[21] Common EPTB forms include lymph nodes, pleura, pericardium, abdomen (spleen, liver and peritoneum), meninges, genitourinary system and disseminated disease.[3,21] Infectiousness and transmission are less in TB-HIV co-infected patients compared to HIV-negative patients.[46]

The most common manifestation of TB is pulmonary (Koch’s) disease manifesting as prolonged cough for more than 2 weeks, haemoptysis, fever, weight loss and night sweats.[21] Among HIV-infected patients not on antiretroviral therapy, TB was the commonest cause of adult hospitalization, accounting for 29% of HIV admissions in Zaria, Nigeria and 44% in Chennai, India.[44,47]

Clinical course may be complicated in profoundly immunosuppressed HIV infected patients after starting anti-TB treatment. Though initiation of ART during anti-TB treatment reduces mortality, the actual time for commencing ART during anti-TB treatment remains controversial.[3] Early initiation of ART restores pathogen-specific immunity, but also significantly increases the risk of the TB-associated immune reconstitution inflammatory syndrome (TB-IRIS). Conversely, a delay in initiation of ART may allow additional AIDS-defining illnesses to manifest. Other reasons for clinical deterioration during anti-TB treatment include antimicrobial resistance, suboptimal anti-TB drug concentrations, drug reactions and other opportunistic illnesses.[48] In a study in South Africa by Pepper et al., 40% of patients experienced clinical deterioration due to co-morbid illness, TB-related illness, non AIDS-defining HIV-1 related infection and AIDS-defining illnesses.[49] HIV-1 infection and a low CD4+ count at TB diagnosis were significant risk factors for clinical deterioration and death. The initiation of ART at a CD4+ count of 350cells/μL will likely reduce the high burden of clinical deterioration.

**Diagnosis of HIV-Associated Tuberculosis**

Although of recent there are promising advances in the microbiological diagnosis of TB, the diagnosis of HIV-associated TB remains difficult because of more frequent atypical presentation as sputum negative or extrapulmonary disease. In sub-Saharan Africa, the diagnosis of TB still relies heavily on sputum smear microscopy and chest radiography. These techniques are often unsatisfactory and unavailable at patients’ first point of contact with the health care system and underperform in the setting of TB/HIV co-infection. There is a great need for rapid point-of-care tests that can be readily used at all levels of the health system and in the community.[35]

**Diagnosis of LTBI in HIV**

The usual method used to diagnose latent tuberculosis infection is the tuberculin skin test (TST). This clearly shows, after injecting a purified protein derivative (PPD), a state of prior hypersensitivity when the body is challenged with this substance.[50] The TST measures CMI in the form of a delayed-type hypersensitivity (DTH) to a complex cocktail of >200 *M. tuberculosis* antigens, known as PPD and the test result is usually read as induration (in mm) recorded 48 to 72 h after intradermal injection of PPD. The criteria for a positive TST vary considerably and depend on the dose of inoculum and type of PPD preparation used in the test. In general, 5 tuberculin units (TUs) are used and an induration of ≥5 mm in HIV-seropositive patient is considered as positive.[1,51] This criterion does not take into account the role of prior sensitization by Bacille Calmette Guerin vaccine (BCG) and infection with environmental mycobacteria in developing countries where >80% of the global TB cases occur. Furthermore, sensitivity of TST is limited in immunocompromised individuals due to anergy.[31] These factors have compromised the sensitivity and specificity of tuberculin skin test for the diagnosis of LTBI. It is important to keep in mind that a negative TST does not exclude infection or active disease and testing with tuberculin PPD is dependent on the presence of an intact CMI response. In the setting of HIV infection, reduced CMI and decreasing CD4+ T-lymphocyte counts can lead to decreased DTH responsiveness, resulting in false-negative skin tests.[52]

More recently, several immunodiagnostic assays have been developed for diagnosing *M. tuberculosis* infection. These assays, referred to as IFN-γ release assays (IGRAs), have been specifically designed to overcome the problem of low specificity of the TST. In fact, they detect cellular immune response to antigens which are absent in BCG and most environmental mycobacteria and specifically present in *M. tuberculosis*. Two such antigens, early-secreted antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10 are encoded in the mycobacterial genomic region of difference (RD)-1.[53,54] A limitation to IGRA use in developing countries is their relatively high cost and need for laboratory infrastructure.[55] IGRA performance will also have to be evaluated in large scale longitudinal studies conducted in low resource, high TB prevalence settings like sub-Saharan Africa where the burden of immunosuppression due to the HIV pandemic is high.[52] However, current evidence suggest that the IGRA perform similarly to the TST in identifying HIV-infected individuals with LTBI and the decision to use either test should be based on country guidelines, resource and logistical considerations.[56]

**Diagnosis of Active TB in HIV**

**Microscopic detection**

Since Koch’s discovery of TB bacilli in 1882, microscopic detection of the acid-fast bacilli in clinical specimens has remained the gold standard for the diagnosis of
TB disease. Microscopy has the advantage of being inexpensive, relatively easy to perform and specific in most settings.[4] However, to be smear positive a specimen needs to contain 10^{6} mycobacteria/ml or more; the sensitivity of sputum microscopy in HIV infection is less than 60%.[37] Methods that improve speed or sensitivity include fluorescence microscopy and alternative specimen processing methods, such as concentration and bleach sedimentation. Any procedure for digestion or liquefaction followed by centrifugation, prolonged gravity sedimentation, or filtration increases sensitivity by 13% to 33% over direct microscopy when culture is used as the reference standard.[4] Equipment costs limit the wider use of fluorescence microscopes in resource-limited settings. Alternative technologies using light-emitting diode (LED) bulbs allow fluorescence microscopes at a much lower cost; field-level evaluation has shown promising results.[9,35,36,59]

Furthermore, it has been demonstrated that 2 specimens collected on the same day (so-called front loading) give results equivalent to the traditional 3 specimens[60] increasing convenience for the patient and potentially increasing the proportion of patients treated appropriately. Frequent smear-negative disease exacerbates the difficulty of detecting HIV-associated TB, leading to additional delays while diagnostic testing or antibiotic treatment trials are being carried out.[7] Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy may be useful in the evaluation of an abnormal chest radiograph when sputum smears are negative in these groups of patients.

Under diagnosis and delayed diagnosis of TB contribute to excess mortality among people living with HIV and development of a standardized screening tool for TB in people living with HIV in resource-constrained settings have been proposed using the symptoms of cough (any duration), fever, night sweats, or weight loss.[61] The overall sensitivity of this rule was 78.9% and specificity was 49.6%; negative predictive value was 97.7% and abnormal chest radiographic findings increased the sensitivity of the rule by 11.7% to 90.6%.

In high HIV-prevalent and resource-constrained settings, algorithms [Figure 3] have been proposed by the WHO[62] aimed at minimizing delays in diagnosis and treatment of smear-negative PTB, thereby increasing the survival of people living with HIV/AID.[63,64]

**Culture-based detection**

Mycobacterial culture on selective media remains the most sensitive method for detecting *M. tuberculosis* bacilli in clinical specimens and allows subsequent strain characterization, including drug sensitivity testing (DST). The slow replication time of *M. tuberculosis* requires that solid media cultures be incubated for 2-8 weeks (depending on the inoculated bacterial concentration) for the growth of the millions of organisms necessary to generate visible colonies. This process can be accelerated by microscopically detecting immature colonies, detecting products of bacterial replication, or using bacteriophages as markers of mycobacterial viability.

Automated liquid culture systems have been developed as alternatives to conventional solid media culture. These systems detect bacterial carbon dioxide production or oxygen consumption with radiometric sensors (BACTEC 460 TB; Becton Dickinson Diagnostic Instruments Systems), fluorescent sensors (BACTEC Mycobacteria Growth Indicator Tube [MGIT] 960), or redox reagents, such as Alamar blue.[65] These techniques are now the gold standard for the diagnosis of tuberculosis; they are substantially faster, have a 10% greater yield than solid media[35] and allow continuous monitoring of growth, obviating the need for mature colony formation compared with Löwenstein-Jensen culture.

Due to cost of the above procedures, alternative inexpensive noncommercial culture and DST methods were endorsed by WHO in 2009 for use as an interim solution in resource constrained settings. The microscopic observation drug-susceptibility (MODS) assay is a simple, rapid, low-cost method for diagnosis of TB and MDR-TB and among predominantly HIV-infected TB suspects in South Africa; MODS provided high sensitivity and specificity for rapid diagnosis of TB and MDR-TB.[66] With the exception of Brazil, the Russian Federation and South Africa, culture facilities are not readily available in countries with a high TB burden.

**Molecular detection**

Aside from microscopy and culture, the only proven method for detection of *M. tuberculosis* that has been successfully developed as a clinical diagnostic tool is nucleic acid amplification testing (NAAT). These tests use oligonucleotide primers and enzymes to catalyze reiterative reactions that amplify a target, probe or signal, yielding a result within minutes to hours.[37] NAAT provides a reliable way of increasing the specificity of diagnosis (ruling in disease), but sensitivity is variable, especially in paucibacillary disease. Despite the clear advantages of NAAT over existing tests, their use in diagnosis is limited in TB-endemic settings, primarily because of their cost and complexity.[37] However, a molecular line probe assay (LPA) is being scaled up by TB programs for rapid detection of rifampicin and isoniazid resistance and, in combination with liquid culture, is expected to provide timely results that confirm TB and the presence of drug resistance.[35]

A sensitive and specific fully automated and commercially
available NAAT assay has now been developed for use outside reference laboratory centres. This Xpert MTB/RIF assay uses a series of molecular probes and real-time PCR technology to detect *M. tuberculosis* and the rpoB rifampicin resistance mutation. The cartridge-based system dispenses with the need for the sputum to be processed in advance, needs minimum laboratory expertise and results are available in less than 2 h, which permits a specific TB diagnosis and rapid detection of rifampicin resistance. A large multicountry assessment found excellent performance characteristics. In culture-positive patients, a single direct Xpert MTB/RIF assay identified 551 of 561 patients (98%) with sputum smear-positive tuberculosis. The sensitivities were 72.5%, 85.1%, 90.2% when processing one, two and three sputum specimens for smear-negative disease respectively while specificity was 99.2%. If these results are replicated under field conditions at points of care and the price of introducing the Xpert MTB/RIF assay to points of care in resource-poor countries is brought down, it will represent a major breakthrough in rapid TB diagnostics and for rifampicin resistance screening. These tests showed a moderate sensitivity and high specificity for TB in a predominantly HIV-seropositive population with negative sputum smears in Kampala, Uganda.

**Radiographic features of HIV-associated tuberculosis**

The radiographic appearance of TB in AIDS differs from that in immune competent hosts and depends largely on the level of immunosuppression. In early HIV disease where patients have relatively high CD4+ T-lymphocyte counts (>200 cells/μL), the typical pattern of pulmonary reactivation occurs with the chest x-ray revealing cavitary apical disease of the upper lobes. In advanced disease where patients present with lower CD4+ T-lymphocyte counts (<200 cells/μL), disseminated disease is more common. In these patients, the chest x-ray may reveal diffuse or lower lobe bilateral reticulonodular infiltrates consistent with primary TB i.e. hilar spread, pleural effusions and hilar and/or mediastinal adenopathy.

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**Figure 3: Algorithm for the diagnosis of TB in seriously ill patient in HIV-prevalent settings.** Reproduced from WHO’s Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents 2007 (62) by permission of the World Health Organization
The chest x-ray may also be normal in appearance in some patients with HIV and TB co-infection. Yusuph and colleagues in Maiduguri, North-Eastern Nigeria reported normal chest radiographic appearance in 25% of patients in contrast to Awoyemi and colleagues who reported 11% in Ibadan, South-Western Nigeria.

This may be related to the presence of more advanced immune suppression in the former group and as such, absence of changes on chest radiographs should not exclude the diagnosis of PTB in this group of patients.

### Treatment of HIV-Associated Tuberculosis

Several aspects of HIV-associated TB and its treatment differs from those of TB in HIV-uninfected persons. The risk of TB and the clinical and radiographic manifestations of disease are primary examples. The initiation of antiretroviral therapy (ART) during anti-TB therapy (ATT) significantly improved survival of TB/HIV co-infected persons. There are also differences in treatment of HIV associated TB because of overlapping drug toxicities, pill burden and suboptimal adherence, drug-drug interactions between ART and ATT as well as timing of ART. Patients already on ART may also develop TB and this has numerous implications including ART failure.

These challenges in the management notwithstanding, the principles of TB treatment in HIV-infected individuals are the same as those in HIV-negative individuals and consensus is developing that ART should be provided as soon as practicable after starting TB treatment in HIV-co-infected persons. This has the consequence of increasing the frequency of IRIS and unmasking of previously subclinical disease, the pathogenesis and management of which remains poorly defined.

### Anti-tuberculosis therapy

The standard recommendation for the treatment of TB is a 6-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol, irrespective of HIV status. However, the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) guidelines recommend extending treatment beyond 6 months to 9 months in HIV-infected patients, especially when there is delayed sputum conversion or evidence of dissemination and low CD4+ cell count. They also recommend the routine use of mycobacterial culture and DST which are not routinely available in most sub-Saharan African settings.

The WHO revised international guidelines for the treatment of tuberculosis in 2010 attempted to address the growing problem of drug resistance and discourages the empirical use of blind therapy for retreatment cases, which combined with poor adherence to treatment might have inadvertently fuelled the emergence of multidrug-resistant strains. It recommends that rifampicin should now always be given throughout the 6 months duration of the first-line regimen with the use of directly observed treatment short course (DOTS).

New emphasis is placed on the crucial role of DST for guiding the individual management of patients who have previously received treatment for TB. For settings where this is not routinely possible, national TB programmes are strongly encouraged to assess country-specific drug resistance data for patients with treatment failure, relapse and default to inform local policy on empirical use of either retreatment or MDR-TB treatment regimens. TB patients returning after defaulting or relapsing from their first treatment course can receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are not available. Although no trials have directly compared daily and thrice-weekly treatment among co-infected patients, the current recommendation is to use daily treatment at least in the intensive phase for patients with CD4+ cell counts <100 cells/μl.

### Anti-retroviral therapy

Timely access to ART minimizes immune deterioration and improves TB outcomes. The first line ART regimen that is most widely available and that are recommended by the WHO for the treatment of HIV disease include: combinations of 3 drugs: 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 non-nucleoside reverse-transcriptase inhibitor (NNRTI).

Rifampicin is a potent inducer of many genes controlling drug metabolism and transport, including cytochrome P450 isoenzymes (CYP3A4) and the drug efflux pump p-glycoprotein. Rifampicin may therefore reduce plasma concentrations of concomitantly administered NNRTIs and protease inhibitors (PIs), potentially resulting in inadequate ART plasma concentrations and inferior ART outcomes. Although rifampicin, through its induction of the cytochrome enzyme system, lowers levels of both the NNRTIs-efavirenz and nevirapine, the former is less affected. Efavirenz is therefore the NNRTI of choice for patients with TB and HIV co-infection at the recommended dose of 600mg, which achieves adequate blood levels and is associated with good outcomes, despite high intra-individual and inter-individual variability. In an Indian study, the efavirenz dose (600 vs 800mg) with concurrent rifampicin administration was shown to have less impact on efavirenz drug levels but a polymorphism in the CYP2B6 gene (G-to-T mutation) was shown to have a stronger influence on efavirenz levels with significantly higher blood levels of the drug.
In a randomized control trial, CPT substantially showed that a 36-month INH as an alternative to rifampicin in the Starting Isoniazid preventive therapy but not in those with a negative count, deferral of ART to the end of treatment for TB is optimum time to start ART in such patients. The decision regarding when to start ART during TB treatment needs to balance several considerations. The two most important variables in the decision are the incidence and mortality associated with TB-IRIS and the excess mortality associated with delaying ART and the development of other opportunistic infections. Data are now emerging from controlled clinical trials of the optimum time to start ART in such patients. These studies have shown that irrespective of the CD4+ cell count, deferral of ART to the end of treatment for TB is associated with high mortality risk and that mortality was reduced by 34% in patients in the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) trial with very low CD4+ cell counts (median 25cells/μL) who are started on ART within the first 2 weeks of treatment rather than after 2 months. The Starting Antiretrovirals at Three Points in TB Therapy (SAPIT) trial in South Africa observed 56% lower mortality rates among patients who started ART during TB treatment, compared with patients who waited until ATT had been completed. Reasons to delay the initiation of ART until after 2 months of ATT include drug interactions between rifampicin and NNRTIs, cumulative drug toxic effects (especially hepatotoxicity), pill burden and IRIS. The current WHO guidelines recommend that all HIV-infected individuals with active TB (regardless of CD4+ cell count) receive ART as soon as TB treatment is tolerated, generally within 2-8 weeks.

Co-trimoxazole preventive therapy
In all HIV-positive TB patients, co-trimoxazole preventive therapy (CPT) should be initiated as soon as possible and given throughout TB treatment irrespective of CD4+ T-cell count but barriers to implementing CPT still exist in TB/HIV programs. CPT substantially reduces hospitalization and mortality in HIV-positive TB patients.

Preventing active TB in HIV patients
As part of core HIV and TB prevention, care and treatment strategies to reduce the morbidity and mortality from TB in people living with HIV, the WHO recommends provision of combination ART (ART) and the Three I’s for HIV/TB: intensified case-finding of TB (ICF), infection control (IC) and isoniazid preventive therapy (IPT) for TB. Isoniazid preventive therapy significantly reduces tuberculosis in these patients who have a positive TST but not in those with a negative test. Such preventive therapy, administered to patients who are positive on TST and infected with HIV, in areas of high incidence also provides around 60% protection, although the duration of protection is limited.

The WHO recommended a 6-month course of isoniazid for people with HIV infection and a positive TST after excluding active TB and extended this recommendation to patients living in areas where tuberculin skin testing was not feasible if the prevalence of latent tuberculosis infection was high. In a randomized control trial, Samandari et al., showed that a 36-month INH prophylaxis was more effective for prevention of TB
than a 6-month prophylaxis in individuals with HIV infection.

The major challenges to uptake of IPT in TB/HIV programs in sub-Saharan Africa have been the issue of lack of resources to identify and exclude active TB, high dropout rate and side effects especially hepatotoxicity and the risk for INH-resistant TB after IPT. Strengthening TB/HIV programs should overcome these obstacles to make the 3 I’s universally available.

**TB-associated IRIS**

The immune reconstitution inflammatory syndrome (IRIS) has emerged as an important early complication of ART in resource-limited settings, especially in patients with TB. The condition results from rapid restoration of pathogen-specific immune responses to opportunistic infections, causing either the deterioration of a treated infection or the new presentation of a previously subclinical infection.

In TB-IRIS, transient worsening of symptoms and signs of TB after the initiation of antiretroviral treatment, despite a reduction in HIV viral load (1 log10 copies/mL) and immunological recovery of CD4+ T-lymphocytes occurs. There are 2 types of presentation: unmasking of undiagnosed TB and a paradoxical deterioration of existing TB lesions or appearance of new lesions after initial improvement. Manifestations include fever, lymph node enlargement, worsening respiratory symptoms and signs, cold abscess, psoas abscesses, central nervous system (CNS) lesions; tuberculoma and/or meningitis and radiological deterioration. Incident of active TB occurs most often during the first 3 months after ART initiation and can be considerably reduced by efficient screening for TB before ART.

In resource-constrained settings where diagnostic capacity is limited, a definition of TB-IRIS is suggested based on 3 criteria as recommended by the International Network for the Study of HIV-associated IRIS (INSHI) in 2006:

1. An initial clinical response to ATT, based on a combination of some of the following factors: Cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of meningeal signs (depending on presenting symptoms)
2. New persistent fevers without an identifiable source or reason (e.g., an allergic reaction, malaria) and/or worsening or emergence of dyspnea and/or stridor and/or increase in lymph node size and/or development of abscesses and/or development of abdominal pain with ultrasound evidence of abdominal adenopathies and/or unexplained CNS symptoms
3. Adequate adherence to ART and ATT

The incidence of paradoxical TB-IRIS ranges from 8% to 43% and in Africa, Baalwa and colleagues reported an incidence of 29% in Uganda while Abdoolkareem and colleagues reported 12.4% in South Africa. Risk factors include lower CD4+ T-cell count, higher viral load at start of treatment, rapidity of viral load decline, bacillary and antigen load (disseminated TB) at initiation, starting highly active ART closer to starting ATT and genetic predisposition (HLA B-44). Although the pathophysiology of TB-IRIS is incompletely understood, it is associated with an exuberant production of cytokines. Drug resistance, malignancies, drug reactions and other opportunistic infections need to be ruled out. TB-IRIS can be managed by anti-inflammatory drugs and steroids which have been found to reduce the need for hospitalization and therapeutic procedures and hastens improvements in symptoms, performance and quality of life.

**Drug-Resistant Tuberculosis in HIV**

Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient’s treatment. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin). These forms of TB do not respond to the standard six month treatment with first-line anti-TB drugs and can take up to two years or more to treat with drugs that are less potent, more toxic and much more expensive.

**MDR-TB and HIV**

Data from HIV-endemic countries show that the prevalence of MDR-TB in HIV is similar to that in the general population, however, localized mini epidemics tend to occur in settings where there is close congregation of HIV-infected persons. Although MDR-TB appears not to cause infection or disease more readily than drug-susceptible TB in HIV-infected persons, HIV infection may lead to malabsorption of anti-TB drugs and acquired rifamycin resistance which may contribute to resistance. Institutional outbreaks of MDR-TB have primarily affected HIV-infected persons and delayed diagnosis, inadequate initial treatment and prolonged infectiousness contribute to increased attack rates among contacts and high case fatality rates among patients. Lack of routine use of mycobacterial culture and DST as recommended by the WHO are the main impediments to MDR-TB diagnosis in sub-Saharan Africa. No large scale data is available but in two Nigerian studies, an MDR-TB incidence of 16% and 13% from all culture-positive isolates was described in Jos and Abuja respectively.
At least 4 effective drugs—including a fluoroquinolone, an injectable agent (capreomycin, kanamycin, or amikacin) and at least 2 agents from the remaining second-line anti-TB drug classes (cycloserine, thioamides [ethionamide or prothionamide] and p-aminosalicylic acid)—along with pyrazinamide and ethambutol, if still sensitive, should be used. Therapy may be individualized on the basis of drug susceptibility test results; however, many countries use standardized regimens that are based on surveillance of anti-TB drug resistance in the community as recommended by the WHO.[74]

XDR-TB and HIV
XDR-TB can develop when the second-line drugs for MDR-TB treatment are misused and therefore, become ineffective and lead to amplified resistance. With XDR-TB, the most effective first-line and second-line TB medications are no longer effective, thereby severely limiting the chance of treatment success. Treatment options are extremely limited and challenging, with high frequencies of adverse events and death.

The devastating interaction between XDR-TB and HIV infection was demonstrated in Tugela Ferry, KwaZulu-Natal province of South Africa in 2006 where 52 of 53 XDR-TB patients died on average within 16 days of presenting to the hospital.[102] Some of those who died were hospital staff and 67% had been hospitalized in the preceding two years, which led the team to believe that transmission of XDR-TB had likely occurred in the overcrowded wards of the hospital. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74-95) patients with XDR-TB had similar strains.[102]

Integrating TB and HIV Care
The mechanisms for collaboration between HIV and TB programmes have been clearly spelt out in the WHO intercom policy on collaborative tuberculosis and HIV activities.[103] However, this is presently sub-optimal in sub-Saharan African Countries[3] and efforts have to be made to strengthen collaboration between TB and HIV programs. Uptake of HIV counseling and testing in TB clinics is low and there is a heavy load and a large degree of cross-referrals between both services[104] and these are usually not located within the same facility.

Centre’s for TB diagnosis and treatment and for HIV care and treatment need to be located together, integrated, or better matched quantitatively and geographically.[104,105] Prognosis will greatly improve with provider-initiated HIV testing and counselling, the 3 I’S, co-trimoxazole preventive therapy and ART; and national tuberculosis programmes must show commitment and provide resources to overcome the logistical and operational hurdles of delivery of this package to all HIV-infected patients with tuberculosis.[105]

CONCLUSION
TB remains a major cause of morbidity and mortality in sub-Saharan Africa in the HAART era and control efforts so far have not adequately controlled the epidemic in many parts. Absence of a cheap point of care diagnostic test, the long duration of treatment, emergence of drug-resistant TB and weak health systems and the HIV pandemic are all factors that continue to retard the progress towards achieving TB control. The control of HIV associated tuberculosis will require efforts made at strengthening national control programs by optimizing the DOTS strategy and improving or integrating TB-HIV collaborative activities including the 3I’S, anti-retroviral therapy and co-trimoxazole preventive therapy. This must be matched by massive political commitment to provide adequate funding to ensure that the aims of the WHO Global Plan to STOP TB 2006-2015 are achieved.

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