HIV-Associated TB Syndemic: A Growing Clinical Challenge Worldwide

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The association of tuberculosis (TB) with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome over the past several years has become an emerging syndemic. Approximately 10% of people living with HIV (PLHIV) with latent TB infection will develop active TB disease each year. In this review, we highlight that this phenomenon is not limited to high endemic regions, such as Afro-Asian nations, but globalization/migration is causing increased case detection even in developed nations, such as the United States. Active screening should be performed for TB in PLHIV. A high degree of clinical suspicion for TB is warranted in PLHIV presenting with fever, cough, and unintentional weight loss. HIV–Mycobacterium tuberculosis (MTB) coinfection is often paucibacillary, precluding diagnosis by conventional diagnostics and/or smear microscopy/culture. Improved detection of pulmonary and extrapulmonary TB is now possible by incorporation of the GeneXPERT MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA). The World Health Organization recommends instituting immediate therapy for MTB, in conjunction with ongoing or newly introduced anti-retroviral therapy. Vigilance is required to detect drug-induced organ injuries, and early-treatment-induced immune reconstitution inflammatory syndrome. Collaborating MTB and HIV activities in concentrated HIV epidemic settings should become a high public health priority.

Keywords: coinfections, extrapulmonary tuberculosis, HIV, TB, diagnosis, GeneXpert, AFB

INTRODUCTION

Mycobacterium tuberculosis (MTB) coinfection in patients pre-infected with human immunodeficiency virus (HIV) and/or with full-blown acquired immune deficiency syndrome (AIDS) is an emergent pandemic (1–3). Due to increased recognition of the morbidity and mortality associated with this coinfection, the World Health Organization (WHO) recommends aggressive approaches for MTB screening during primary visits related to HIV screening and treatment (2). While this state of coinfection is a major public health challenge in resource-constrained settings with a high burden of both diseases, such as those in African and Asian nations (1, 4, 5), it is being increasingly recognized in the settings of developed nations, including the United States (U.S.) (6–9). WHO estimated 1.5 million tuberculosis (TB) deaths in approximately 70% HIV-negative and 30% HIV-positive individuals, which makes MTB the second leading cause of death from an infectious disease and the leading cause of death in the setting of AIDS worldwide (10). This review presents the key
clinical aspects of HIV–MTB coinfection, including the uncom-
mon presentations, diagnostic issues, and management strategies,
and emphasizes the continued need for increased vigilance for
intensified case finding.

Per WHO guidelines, all clients attending HIV testing centers
and people living with HIV (PLHIV) attending anti-retroviral
therapy (ART) centers should be clinically screened for TB
symptoms at every ambulatory encounter (2). Although the
initiation rates of HIV-positive TB patients to ART are improving
case fatality continues to be steep compared to HIV-negative TB
patients (2). The chief rationale for this difference may include
delays in bacteriological detection of HIV-associated TB, enroll-
ment into ART care or immediacy of ART initiation (2).

Different populations pose group-specific challenges in
response to detection and treatment. These populations include
pediatric patients, antenatal HIV-infected patients, truckers,
female sex workers, and men who have sex with men, refugees,
and displaced populations (2). Other challenges exist in over-
crowded settings such as mines, prisons, homeless shelters, and
opioid substitution therapy centers (2). Social issues, including
poverty, are warped into the fabric of clinical course of HIV–MTB
coinfection (2). In this review, we emphasize early detection by
effective implementation of provider-initiated HIV testing and
counseling in TB patients as well as intensified TB case finding
among PLHIV and initiation of prompt treatment to minimize
morbidity and mortality (2).

**DEMOGRAPHIC FACTORS RELATED TO MYCOBACTERIUM TUBERCULOSIS COINFECTION IN HIV PATIENTS**

Gender, age, socioeconomic status, marital status, and educa-
tional level are factors that impact the likelihood of HIV–MTB
coinfection. Male gender is reported to be positively correlated
with MTB infection at a ratio of 2:1 (11). HIV–MTB coinfection
is more common in adults with an average age of 33–45 years
(2). Single status, low socioeconomic and income status, and lack
of education are associated with disadvantaged living conditions.
Compromised sanitation and poor access to healthcare negatively
impact outcomes, which may explain the higher incidence and
mortality in this group of patients (2).

It is important to outline some exceptions here. For example,
young people may also be afflicted with the coinfection. Pediatric
populations may particularly be at high risk, especially those who
acquired infections by vertical transmission (12). Interestingly,
certain geographic regions such as the Pakistan–Afghanistan
border areas report more incidence in females than males (13).
According to the WHO 2013 Global TB Report, Afghanistan is
a high burden country for TB with a male to female ratio for
TB of 0.5, so that in contrast to many other countries, Afghan
women are more likely to be infected with TB than men. The
estimated incidence of HIV–TB coinfections is relatively low
(1 in 100,000) in this group and concentrated mostly among
injection drug users (according to the World Bank). If there was
a higher HIV–MTB coinfection incidence in Afghan women
refugees, the observations would likely be due to the higher
TB incidence in Afghan women or due to a small sample size
of HIV–MTB coinfection in a refugee camp. Furthermore,
immunocompromised states, such as those receiving anti-tumor
necrosis factor treatment, corticosteroids, dialysis, organ, or
hematologic transplantation or those with silicosis, may be more
predisposed to HIV–MTB coinfection due to activation of latent
TB infection (14).

**PATHOGENESIS OF MYCOBACTERIUM TUBERCULOSIS–HIV COINFECTION**

The details of immune responses to TB, HIV, and coinfections
have been described in recent reviews (1, 15). It is important
to note that MTB occurs earlier in HIV patients than other
opportunistic infections (OIs) due to increased susceptibility
of MTB-specific CD4+ T-cells to HIV infection (16). We present the
immune pathogenesis in relation to the intensity of the clinical
presentation of TB with pre-existing HIV infection.

Tuberculosis infection is a result of the interplay between bact-
erial virulence and host resistance (17, 18). The infection begins
through inhalation of air droplets containing approximately
1–200 bacilli from an individual with active MTB (pulmonary)
disease (18). The bacilli are rapidly phagocytosed by resident
macrophages in the alveoli. This triggers an inflammatory cas-
cade, followed by development of granuloma. Furthermore, cell-
mediated immunity through activation of CD4–T lymphocytes
is important in the prevention of MTB disease’s acceleration and
reactivation (1, 15, 17, 18).

On the other hand, HIV transmitted primarily through genital
fluids, blood, and mucosa interacts with different cells in the
body and tends to escape the host immune response against it,
resulting in full-blown AIDS disease (19). Progression of HIV
infection is a result of a combination of CD4+ T lymphocytes
depletion and a chronic state of immune inactivation. The repres-
sion of CD4+ T cells and impairment of macrophages’ activity
in HIV/AIDS results in down-regulation of the body’s immune
response to infections, such as MTB. *Mycobacteria* are contained
within granulomas; however, their disruption leads to MTB
bacterial growth and systemic dissemination to multiple organs
(1, 15). MTB has a negative impact on the immune response of
the body to HIV by up-regulating the immune response of the
host by activating T-cells. Studies have demonstrated that MTB
enhances HIV viral replication by increasing the expression of
receptors (e.g., CXCR4), which favors viral growth (15, 19). The
immune response is responsible for the vigor of TB infection in a
HIV-coinfected host and is responsible for miliary and extrapul-
monary presentations and its associated diagnostic dilemma (1,
15, 20, 21).

Studies aiming to obtain direct evidence of disease progres-
sion have been limited due to economic reasons of HIV viral
load estimation, especially in countries where the incidence/
prevalence of HIV–MTB coinfection is high but has the short-
coming of resource constraints (22). As pointed out, the impact of
MTB on HIV disease progression primarily involves upregulated
HIV-1 viral load, including the development of new OIs (22–28). Interestingly, TB was found to exert significant effect on diminishing survival rates in subjects with more preserved immunological status (i.e., CD4 cell counts >200 cells/µL) (27, 28). Enhanced HIV-1 production has been demonstrated at local sites of MTB infection, for example, in bronchoalveolar lavage (BAL) fluid from TB involved, compared with uninvolved, lungs of patients with HIV-1/TB coinfection (29). A clinical presentation of TB that is particularly observed in HIV-1-infected patients is pleural TB, a common presentation in African coinfected patients (30, 31). These sites of active MTB infection act as foci of HIV replication and evolution of quasi-species, independent of systemic HIV-1 activity, and may be responsible for disseminated MTB infection in HIV-1 coinfected hosts.

*Mycobacterium tuberculosis* breaches the alveolar epithelium during the first phase of extrapulmonary dissemination. Molecular mechanisms for this cytolytic have been reported. For example, heparin-binding hemagglutinin adselin (HBHA) facilitates MTB to bind to sulfated glycoconjugates on epithelial cells. Two gene products of the MTB RD1 gene, early secretory antigenic target 6 kDa (ESAT-6) and culture filtrate protein 10 kDa (CFP-10), have been causally linked to the cell lysis and extrapulmonary mycobacterial spread (32). The trafficking of mycobacteria to the regional lymph nodes, while essential for the development of a protective T-cell-mediated immune response, is the first extrapulmonary site of migration of MTB. Bacteria thereafter disseminated through the bloodstream and lymphatics lead to extrapulmonary tuberculosis (EPTB). Lung granulomas from MTB/HIV-1 coinfected patients release lower levels of *in situ* TNF production (33). Additionally, MTB–HIV-1 coinfected hosts have low circulating mannose-binding lectin levels (34). The complex interactions that take place between host T cells, Tregs, cytokine production, and overall impaired Th1 responses predispose to extrapulmonary infections in HIV-coinfected hosts (35, 36). Several primary immunodeficiencies, including Mendelian susceptibility to mycobacterial infections, enhance the overall risk of EPTB (37). These aspects merit detailed studies in the future.

**SCREENING FOR MYCOBACTERIUM TUBERCULOSIS–HIV COINFECTION**

World Health Organization formulated a policy on collaborative MTB/HIV activities with the chief aim to reduce the dual burden of MTB and HIV (2). WHO recommends MTB screening among HIV-positive patients at the time of diagnosis and before the initiation of ART. The screening for MTB should also be extended to the household contacts of HIV-positive patients (2). The screening tool utilizes a clinical symptom-based algorithm that consists of the absence or presence of current cough, fever, weight loss, or night sweats at the time of initial presentation and at every visit to health clinics. This tool can be used to identify patients who need further medical attention and those who need MTB chemoprophylaxis intended to prevent active TB disease (rather than prevention of TB infection *per se*).

**DIAGNOSIS OF MYCOBACTERIUM TUBERCULOSIS INFECTION IN HIV-COINFECTED PATIENTS**

A high degree of clinical suspicion and the need for obtaining a focused and detailed history merits emphasis. Numerous diseases may mimic presentations of TB, but TB should be high up on the differential for pneumatic presentations and HIV-associated thoracic diseases (7, 38). Initial screening with a tuberculin skin test (TST) or interferon-gamma release assays (IGRA) is recommended. TST, which can be affected by bacillus Calmette–Guérin (BCG) vaccination, and/or IGRA, which is unaffected by BCG vaccination, are routinely used screening methods for TB in asymptomatic, non-HIV-infected individuals in low TB prevalence nations. However, it may be noted that these tests have a “low specificity” (TST) or “have false positive and false negative results” (IGRA) and are of low diagnostic values in TB endemic areas, especially when there is coinfection with HIV. When there is a high degree of clinical suspicion or pneumatic presentations, the standard diagnosis of TB in symptomatic patients is typically not a TST or IGRA, but rather achieved with sputum smear microscopy. This is inexpensive, rapid, and easy to perform in a field setting but has a lower sensitivity in MTB–HIV coinfection. The sputum smear sample has the advantage of being used for culture of MTB and drug susceptibility testing. Because coinfection lowers microscopy sensitivity, several current diagnostic techniques are more sensitive than the conventional sputum smear microscopy in detecting MTB in HIV-positive individuals. A growth-based detection of MTB, in cultures and molecular techniques, such as nucleic acid amplification testing (NAAT), has been shown to be more sensitive and allows strain characterization and drug susceptibility tests (39, 40).

In 2013, the Food and Drug Administration (FDA) in the U.S. approved the GeneXpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA), a NAAT-based diagnostic platform. WHO endorsed the use of this assay as the initial test for TB diagnosis in PLHIV or who are suspected of multidrug-resistant TB (MDR-TB) and has since been extensively used (41–44). The cost of the test, despite being subsidized, has been a barrier in many TB endemic countries to be used as a first line diagnostic tool.

Additionally, low thresholds should be exercised when performing standard chest X rays and computerized tomography scans for diagnostic suspicion of miliary TB and detecting lesions during extrapulmonary manifestations (38). The pleomorphic manifestations of radiographic appearances in HIV–MTB coinfection is depicted in Figure 1.

A critical caveat in the diagnosis of MTB relates to the context of latent TB. The low specificity of TST and the issues of false positive and false negative detection with IGRA’s [QuantiFERON®-TB Gold In-Tube (QFT-G-IT) assay (Cellestis Ltd., Carnegie, VIC, Australia) or T-SPOT®TB assay (Oxford Immunotec Inc., Marlborough, MA, USA)] pose significant challenges in HIV–coinfected patients. The critical aspects and unmet needs in diagnosing latent TB have been recently reviewed (39). Due to very high risk of activation of latent TB in HIV coinfection,
these cohorts (immunocompromised subjects, immigrants from
countries with high disease burden, homeless subjects, prison-
ers, illicit drug users, healthcare workers taking care of high risk
group populations, and adult contacts of persons with TB) need
careful identification and evaluation to be considered for follow-
up, preventive therapy, and prompt institution of treatment upon
detection of active lesions.

**CLINICAL MANAGEMENT OF MYCOBACTERIUM TUBERCULOSIS–HIV COINFECTION**

Delay in the diagnosis of MTB in HIV-positive patients and
inadequate initial treatment may lead to multidrug resistant TB
(MDR-TB). MDR-TB is a growing concern not only because of
its longer treatment duration but also because of its associated
increased transmission risk among contacts and increased mort-
ality rates in HIV-coinfected patients (45).

Considerations in the management of HIV–MTB coinfection
include adjustment in the duration, dosage, and frequency of
anti-TB drug administration as well as optimal timing of initia-
tion of highly active anti-retroviral therapy (HAART) treatment.
The standard therapeutic regimen for TB consists of isoniazid
(INH), a rifamycin (rifampin-RIF or rifabutin-RFB), pyrazina-
mide (PZA), and ethambutol (EMB) given for 2 months, followed
by INH plus rifamycin for 4–7 months (46). Treatment of active
TB infection is the priority due to the risk of transmitting TB
to other people. However, when CD4+ T cell count is extremely
low (<50 cells/mm³), an appropriate treatment plan should be
formulated wherein prompt initiation of HAART is necessary.
Randomized controlled trials such as SAPIT (47), CAMELIA
(48), and STRIDE (49) suggested and have provided evidence
for immediate institution of ART within 2 weeks of starting anti-
mycobacterial therapy.

There are several debates on the ideal timing of HAART initia-
tion and concomitant administration with anti-TB medications.
Advantages of early HAART administration include higher cure
rates, reduced risk of relapse, reduced risk of infection with other HIV-associated OIs, and lower mortality rates. On the other hand, disadvantages include potential drug interactions of HAART with rifampicin, thus limiting co-administration of selected protease inhibitors (PIs), cumulative toxicity, therapeutic failure, and the risk of immune reconstitution inflammatory syndrome (IRIS), which affect the long-term adherence to HAART in MTB-infected patients (50). Furthermore, non-compliance due to pill burden, side effects of medications, accessibility of treatment centers for HIV and TB, fears of stigmatization, cost of healthcare, and lack of proper health education are also major problems that need to be addressed to successfully treat MTB patients (51). In general, the priority should be to provide directly observed therapy (DOT) for these patients to ensure compliance and treatment success (10). Two recently published trials have re-emphasized the importance of early initiation of ART. The TEMPRANO study from the Ivory Coast showed that early ART initiation in subjects with CD4+ cell count of ≥500 cells/mm³ was associated with a 44% lower risk of death or severe HIV-related illness than when ART was initiated according to prevailing WHO criteria (52). Furthermore, patients who received INH prophylaxis had a 35% lower risk of death or severe HIV-related illness than patients who did not receive it. In the START study involving 215 sites in 35 countries, the risk of death, a serious AIDS-related event, or a serious non-AIDS-related event was 57% less among the subjects treated than among those treated when the CD4+ cell count decreased to 350 cells/mm³ (53). In both trials, a reduced rate of TB after early rather than deferred ART was the most significant contributor to the overall benefits. Early initiation of ART possesses the added benefits of reducing the risk of sexual transmission of HIV and HSV2 infections (54). However, the public health challenges concerning the cost and global health motivation for implementation of these recent evidence-based guidelines remains a major challenge that needs to be overcome (54).

In specific patients, such as HIV-infected pregnant women with active TB, the recommendation is to start on ART as early as feasible, both for maternal health and to prevent perinatal transmission of HIV (55). The choice of ART should be based on efficacy and safety in pregnancy and take into account potential drug interactions between anti-retrovirals and rifampycin (50). In HIV-infected patients with latent tuberculosis infection (LTBI), isoniazid preventive therapy (IPT) has been reported to reduce reactivation of latent TB infection in the context of both industrialized and developing countries (56).

COMPLICATIONS ARISING OUT OF THERAPY FOR HIV–MTB COINFECTION

Immune Reconstitution Inflammatory Syndrome

Transient exacerbation of respiratory signs and symptoms despite reduction in viral load and/or radiological deterioration may develop in HIV–MTB coinfected patients who are treated with anti-TB medications concomitantly with HAART (19). IRIS has a dimorphic presentation: unmasking and paradoxical (57, 58). Restoration of immune competence by administration of ART results in hyperimmune host response to TB bacilli and/or antigens. Unmasking IRIS presents with active TB soon after ART is started. Paradoxical IRIS refers to the worsening of TB symptoms after ART is initiated in patients who are receiving TB treatment. Anti-inflammatory drugs and steroids are the mainstay therapy for IRIS. Discontinuation of HAART is not warranted in most cases. Delaying initiation of ART for 2–8 weeks may reduce the incidence and severity of IRIS. However, this possible advantage of delayed ART must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality. Importantly, immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive IGRA for MTB-specific proteins) (44). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, this situation should be clinically recognized, especially in high risk groups.

Anti-Tuberculosis and Anti-Retroviral Drug Interaction

Rifamycins are potent inducers of the hepatic cytochrome P (CYP) 450 enzyme. They are associated with significant interactions with all PIs, some non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL) (50, 58–61), leading to enhanced drug clearance and significant lowering in circulating anti-retroviral drugs. However, good virological, immunological, and clinical outcomes may be achieved with standard doses of efavirenz (EFV) and nevirapine (NVP) when combined with rifampin (61). Suboptimal HIV suppression or suboptimal response to TB treatment should prompt immediate assessment of drug adherence, sub-therapeutic drug levels (with consideration for therapeutic drug monitoring), and acquired drug resistance.

Other Known Side Effects

Hepatotoxicity potentially arises from co-administration of antiretroviral and anti-mycobacterial agents; therefore, continuous monitoring of liver function should be exercised. Symptoms of abdominal pain, jaundice, loss of appetite, fever, and nausea merit urgent clinical attention (39). Additionally, many of these patients may need additional treatment, for example, for drug dependence or HCV coinfection, which presents additional risk for coexisting liver diseases (62). Peripheral neuropathy, on the other hand, can occur with administration of INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of the native HIV infection per se. All patients receiving INH should be administered supplemental pyridoxine to reduce peripheral neuropathy (61). Other coexisting medical and behavioral conditions, such as tobacco smoking, alcoholism, malnutrition, and diabetes mellitus, may significantly impact disease management and outcomes (63).

CONCLUSION

Coinfection with the HIV is an important contributing factor to TB mortality not only in many countries, mainly those of
sub-Saharan Africa, but also in developed countries such as the U.S. Today, caring for TB patients and controlling the spread of TB are complicated by the emergence of MDR-TB.

Globalization and migration from endemic zones continues to be a major force in global spread of this coinfection.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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