

## Review Article

### **Tuberculosis in Immunocompromised Patients: Review Article**

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**Abstract:** The purpose of these Studies have been published in the area of tuberculosis but much is not known in the area of interaction between HIV and tuberculosis, etiology, immunological mechanism involved, risk factors, diagnostic features, diagnostic tools, immunogenetics and complications involved. The recent results of Tuberculosis have been reported in people living with HIV indifferent parts of the world. Cases are unrecognized due inaccurate diagnosis and hence are treated as other diseases. However the most recent studies have shown that tuberculosis and HIV coexist together especially extrapulmonary tuberculosis and that there are other highly sensitive and quick to yield results. In conclusion The Tuberculosis in HIV is as a result of complex interactions between the host-pathogen and the immune mechanisms involved in the protection. Overall, this review has expanded our understanding of the mechanism involved in the pathogenesis and the relationship between tuberculosis and kidney disease. It has opened new line of investigations that will ultimately result in a better clinical practice.

**Keywords:** HIV, extrapulmonary tuberculosis.

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#### **INTRODUCTION**

Co-infection between HIV and tuberculosis is the leading cause of death in patients infected with HIV living in resource limited countries accessing antiretroviral treatment (ART) programmes. In 2010, there were 350,000 tuberculosis-related deaths in HIV-infected people, most of them in developing countries, and 22.5 million people were estimated to be living with HIV in sub-Saharan Africa [1]. During the same year, 2.8 million new cases of tuberculosis were reported in Africa, the majority in the sub-Saharan area; and 37% of tuberculosis episodes were diagnosed among HIV infected patients. A major challenge to diagnosing pulmonary tuberculosis (PTB) is alteration of the presentation of PTB due to HIV infection [2]; [3]. HIV infection increases the risk of developing tuberculosis but also modifies the clinical presentation of the disease [4]. HIV-infected patients are twice as likely to experience sputum smear-negative pulmonary tuberculosis (PTB) than HIV-uninfected patients and extra pulmonary tuberculosis (EPTB) is also more common in HIV-positive patients [5] which contributes to delayed tuberculosis diagnosis, leading to high mortality, and represents an important burden for health systems. The problem is increased in resource-limited settings without routine access to mycobacterial culture or other highly sensitive diagnostic tests [6]; [7]. Alteration in the clinical and radiographic presentation

of PTB among HIV-infected persons has long been recognized [8]; [9]. Direct smears can be used but they are often negative and do not differentiate mycobacterium tuberculosis from non-tuberculous mycobacterium [10, 11]. Culture, which is more sensitive, may take 2 to 8 weeks due to the slow growth rate of mycobacterium while liquid culture may take 7-10 days [12]. There is a great need for implementing new diagnostic methods for tuberculosis to increase the sensitivity and speed of diagnosis in these patient groups especially in view of their high mortality and the risk of nosocomial transmission [13]. A range of new diagnostics for TB is now emerging, employing various different technologies [14]. One area of renewed interest has focused on the potential for TB diagnosis to be made from analysis of urine samples [15]; [16]; [17]). Urine has many characteristics which make it a potentially useful specimen for TB diagnosis as it is simple to obtain, even from very ill patients who may not be able to produce sputum. Urine sampling does not generate hazardous infectious aerosols and is relatively clean and easy to handle in the laboratory. Urine may be cultured, tested by polymerase chain reaction (PCR) for mycobacterial transrenal DNA or tested for specific mycobacterial antigens such as lipo arabinomannan (LAM) [18]. Recent studies have shown that urine LAM may have diagnostic value in HIV-infected patients with low CD4+ counts [19]. Currently there is

no data on the diagnostic utility when a sputum sample is compared to a urine sample [20].

Recently, the Gene Xpert MTB/RIF rapid molecular assay [21] has been endorsed by the Scientific and Technical Advisory Board of the World Health Organization (WHO) as the most sensitive fast test for TB diagnosis in paucibacillary respiratory samples [22]. However there are also reports of this diagnostic platform being used to diagnose TB by testing a range of extrapulmonary samples, including urine. Diagnostic accuracy will be assessed by comparison with mycobacterial urine culture results. This technology may be a promising tool for rapid detection of tuberculosis in urine samples in individuals with mycobacterium tuberculosis (active TB) prior to starting antiretroviral therapy (ART).

### ETIOLOGY

Tuberculosis is caused by a group of bacteria species known as the mycobacterium tuberculosis complex. These include: *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microtyis* and *M. Canetti*. *M. tuberculosis* is responsible for the majority of TB cases [23].

### PATHOGENESIS

Tuberculosis is spread by one person by the aerosol route. The lung is the first *M. tuberculosis* site of infection. Most infection resolve with local scarring and is known as the primary complex. However, infection may disseminate from the primary focus throughout the body which is referred to as Millitary spread. Millitary spread may resolve spontaneously or developed into localized infection. Resistance to tuberculosis depends on T cell function. The disease may reactivate once the immunity falls. HIV patients are likely to develop asymptomatic disease [24].

*Mycobacterium tuberculosis* is ingested by macrophages but escapes from phagolysosome and hence multiplies in the cytoplasm. In response, the immune system causes local tissue destruction which is referred to as cavitation and cytokine-mediated immune effects which are systemic causing fever and weight loss. Many antigens have been identified as possible virulence determinants. For example: Lipoarabinomannan which stimulate cytokine production, superoxide dismutase which in turn promotes intramacrophages survival [25].

Clinical features include; may affect several organs of the body causing both inflammatory and malignant conditions. For the case of pulmonary tuberculosis, it may present persistent cough, hemoptysis, fever and weight loss and sometimes as a recurrent bacterial pneumonia. If untreated, the infection becomes chronic causing tuberculous meningitis which is characterized by fever and

deteriorating level of consciousness. Kidney infection can result to local infection, fever and weight loss. This can be complicated by the presence of ureteric fibrosis and hydronephrosis. The infection can also affect the lumbosacral spine which is the most common site of infection, causing vertebral collapse and nerve compression. Also pus may be present causing psoas abscess. If the infection affects the joints, it may cause destructive arthritis. Mesenteric lymphadenopathy and chronic peritonitis may be present in case of abdominal infection. Abdominal infection may appear as fever, weight loss ascites and intestinal malabsorption. Disseminated tuberculosis may occur without evidence of active lung infection.

### IMMUNOLOGICAL MECHANISM

Both TB and HIV influence the progression of each. They have a strong effect on the immune system. In HIV infection, there is a reduction of CD4+ T cells which has a major role in providing immunity to tuberculosis [26]; [27]. This is reflected in the integrity of the cellular immune response known as the granuloma. It has also been associated with the presence of functional abnormalities of CD4+ and CD8+ cells. Likewise, TB infection has been associated with progression of HIV infection to AIDS the disease [28]; [29]. Tumor necrosis factor-Alpha has been associated with replication of HIV. The Tumor necrosis factor-Alpha is produced by the activated macrophages within granuloma as a response to tubercle infection [30]. HIV infection also down regulates the TH1 and does not affect the TH2 response in anyway. HIV-TB co-infected patients have suppressed levels of IFN- $\gamma$ , IL-2 and IL-4 in PBMCs but the IL-10 levels are not affected hence do not differ from patients with HIV infection only [31]. Various lines of evidence indicate that inborn errors of immunity, as well as genetic polymorphisms, have an impact on susceptibility to TB and HIV. Susceptibility to intracellular infections is as a result of suppressed TH1. A decline in Natural killer cells activity has also been associated with HIV progression [32]. When treated for TB, HIV patients respond very well. However, they develop other opportunistic infections rapidly. Furthermore recurrence of TB is more often than in immunocompetent cell population due to both endogenous reactivation and exogenous reinfection.

### Evasion of host immune response by *M. tuberculosis*

The majority of individuals in the general population who become infected with *M. tuberculosis* never develop clinical disease [33]. This demonstrates that the innate and adaptive immune response of the host in controlling TB infection is effective. Mycobacterial and host factors that adversely affect these two arms of the immune system contribute to latent tuberculosis infection (LTBI) and active disease. *M. tuberculosis* evade the immune system through

various means which include; avoiding elimination by T cell which is made possible by modulation of antigen presenting cells.

### **Innate immune response**

The pathophysiology of innate immunity early in the course of infection is uncertain. In the average human alveolus there are more than 28,000 epithelial cells (pneumocytes) and about 50 macrophages [34]; [35]. Mouse studies have shown that after about 14 days of infection, the predominant cell type infected with *M. tuberculosis* is the myeloid dendritic cell rather than the alveolar macrophage [36]. Thus, in the very early phase of lung infection, the interaction of *M. tuberculosis* with epithelial cells may influence clinical outcomes. Little is known about what happens during this early phase.

The tubercle bacillus ultimately gets taken up by macrophages and has evolved several strategies to evade early intracellular killing mechanisms inside these target cells. Some of the mechanisms previously thought to contribute to these strategies include: Resistance to reactive oxygen intermediates (ROIs), Inhibition of phagosome-lysosome fusion, Inhibition of phagosome acidification and Escape from the phagosomal compartment into the cytoplasmic space.

During the initial stages of infection, tubercle bacilli stimulate the migration of neutrophils and mononuclear phagocytes to the site of infection. *M. tuberculosis* possesses a variety of products that enable it to constitutively resist ROIs produced by these cells, which are usually toxic to other pathogens. Lipo arabinomannan (LAM) serves as a scavenger for oxygen intermediates [37]. Entry of the organism into macrophages via complement receptors (CR1 and CR3) does not stimulate ROI production [38]. Cyclopropanated mycolic acids of the cell wall may help the organism resist hydrogen peroxide [39].

### **Toll-like receptors**

The Toll-like receptors (TLR) is a family of transmembrane proteins in mammalian cells that mediate immune response against infectious agents by activating the NF- $\kappa$ B pathway, which elicits a pro-inflammatory response[40].

TLR is a mammalian homologue of the Toll receptor in the insect *Drosophila* that plays a role in conferring immunity of the insect against yeast infections [41]. TLRs exhibit pattern recognition of organism group characteristic molecules, such as the lipopolysaccharide of gram-negative organisms, peptidoglycan of gram-positive organisms, double-stranded RNA of viruses, and lipoteichoic acids of yeasts [42]; [43]; [44]. TLR2 and TLR4 are important for the recognition of *M. tuberculosis* products [45]. *M. tuberculosis* was killed by activation of the TLR2 by the

bacterial lipoprotein (19-kD) in both mouse and human macrophages [46]. However, the killing in the mouse macrophage was dependent on the intracellular nitric oxide pathway, while in the human macrophage, it was independent of this pathway. That is, the human TLR2 activation by the 19-kD lipoprotein killed *M. tuberculosis*, but no nitric oxide production could be demonstrated.

Further characterization of the mechanism of killing of *M. tuberculosis* in human macrophages has identified that TLR1/2 activation up-regulates expression of the vitamin D receptor, as well as vitamin D-1-hydroxylase [47].

TLR2 and TLR4 require MyD88, an intracellular adapter protein required for inducing early innate immune response to pathogens[48]. However, in murine macrophages, *M. tuberculosis* can activate macrophages via a MyD88-independent pathway[49]. Furthermore, *M. tuberculosis* infection of MyD88-deficient C57BL/6 mouse is fatal despite an intact adaptive immune response [50].

### **Humoral immune response**

The role of the humoral immune response in protection against *M. tuberculosis* is controversial. The range of findings can be illustrated by the following observations: Passive transfer experiments of serum from BCG-vaccinated animals or *M. tuberculosis*-infected animals and humans to other animals have provided conflicting evidence of protection. Antibodies against a variety of mycobacterial antigens, including lipid and carbohydrate products, can be demonstrated in both asymptomatic PPD-positive persons and in patients who develop active disease. *M. tuberculosis* strains incubated with an antibody raised against BCG promoted phagosome-lysosome fusion, but the viability of such strains inside macrophages was not affected. Transgenic mice unable to make IgM become more susceptible to *M. tuberculosis* [51]. Thus, unequivocal evidence for the protective role of humoral immunity against TB does not exist. In the absence of detailed studies, it is difficult to conclude how much of the protective response against TB, if any, is mediated by humoral immunity.

### **Cellular immune response**

Demonstrated clinically by the development of a delayed-type hypersensitivity (DTH) response to intradermally injected tuberculin or PPD. One study of T cell responses in persistently anergic patients with documented pulmonary TB demonstrated that T cells produced interleukin (IL)-10 but not IFN-gamma and failed to proliferate in vitro following stimulation with PPD [52].

The DTH response per dose does not correlate with protection against TB, since numerous BCG vaccination trials have demonstrated that disease can occur in those who mount a DTH response [53]. Hence protective T cell response must be distinguished from the T cell response associated with DTH.

Interferon-gamma release assays have been developed; these are *in vitro*, whole blood-based tests to measure T cell activation. The assays are an alternative to the tuberculin skin test (TST) for detection of latent *M. tuberculosis* infection in human hosts [54]; [55]; [56]. The test measures interferon-gamma released into blood from T cells when they are activated by *M. tuberculosis* antigens *in vitro*. The tests use antigens specific to *M. tuberculosis* including the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10).

The importance of T cells in the protective immune response against TB was first demonstrated in mice; adoptive transfer of T cells from BCG-immunized mice protected irradiated recipient mice from infection [57, 58]. Other animal studies showed that this protective response was mediated by CD4-bearing T cells [59]. If it is assumed that the DTH response is mediated by CD4+ Th1 cells, the wide range of protection (0 to 80 percent) demonstrated by numerous BCG trials suggest that CD4+ T cells are not sufficient for protection, and that other cells must be involved. However, the greatly increased risk of TB with HIV infection, in which CD4+ T cells become depleted, suggests that these cells are important for protection against TB in humans. CD4+ T cells exert their effector function by producing IFN-gamma, which activates macrophages. This response is important, particularly during early phase of an infection. In one study, in CD4-disrupted mice, levels of IFN-gamma in the lungs, while diminished early in infection, reached levels found in wild type mice after about three weeks, suggesting that other cell types (CD8+ cells), can compensate for the decreased cytokine expression by CD4 T cells [60]. Finally, in addition to the role of cytokines produced by CD4+ cells, apoptosis of infected cells by CD4+ T cells may contribute to controlling infection. However, published reports on the role of apoptosis in *M. tuberculosis* infection control remain equivocal [61]; [62].

Cytotoxic T lymphocytes (CTLs) have been implicated in protection against *M. tuberculosis*, and active investigation into the details of this mechanism is ongoing. Mice with disruption of the  $\beta$ 2-microglobulin gene fail to control infection with a virulent strain of *M. tuberculosis* (Erdman) despite having intact CD4+ and cytolytic gamma-delta T cells [63]. This gene inhibits expression of functional class I major histocompatibility

complex (MHC-I) molecules which is a feature of CD8+ CTLs.

Another study using different strains of gene-disrupted mice found: perforin contributed only partially to the protective ability of CTLs; there were  $\beta$ 2-microglobulin-dependent T cells which exerted a protective effect distinct from CTLs; and transporter associated with antigen processing (TAP) pathways were predominant in mediating protection against *M. tuberculosis*, but TAP-independent mechanisms also played a role [64]. Mice immunized with *Mycobacterium vaccae* can generate CD8+ T cells that express IFN-gamma and that are lytic to macrophages infected with *M. tuberculosis* [65]. Live mycobacteria activate more CD8+ T cells than dead organisms or PPD [66].

Antigen-presenting pathways other than MHC class I or class II that stimulate this type of CTL response have been explored. One such pathway, CD1-restricted CTL stimulation, involves MHC-like cell surface molecules that process and present nonpeptide antigens to T cells [67]. In patients with active TB, two types of T cells that recognize *M. tuberculosis* lipid and lipo glycan antigens presented by CD1b-bearing cells were found, "double negative" (DN) CD4-/CD8- T cells and CD8+ T cells [68]. These cells were both capable of lysing macrophages (CD-1 bearing cells) infected with *M. tuberculosis*. However, cell lysis would not necessarily lead to protection in the absence of bacterial killing. CTL-mediated cell lysis involves two pathways: a degranulation pathway that generates perforin and granzymes; and a Fas-FasL-dependent pathway that induces apoptosis of the target cell [68, 69]. Studies with perforin gene-disrupted mice showed that this pathway was not essential for early protection against *M. tuberculosis* infection [70]. Another study showed that perforin-disrupted mice eventually did succumb to infection at a later time point, suggesting that the protection is partially dependent on perforin. Culturing DN and CD8+ T cell lines with CD1 cells infected with *M. tuberculosis* revealed that DN CD1-restricted cells had no effect on the viability of the organism, while CD8+ CD1-restricted T cells reduced the number of colony forming units (CFU) by 35 to 50 percent.

This bacterial killing is mediated by granulysin, a protein found in the granules of human CTLs and natural killer (NK) cells, but not in murine cells. Granulysin is present in CD1-restricted CD8+ T cells but not in CD1-restricted DN T cells. Granulysin, a member of the saposin-like protein family, induce blister-like lesions on the surface of *M. tuberculosis*[71]. There also appears to be a role for CD8+ alpha beta TCR+ cells which recognize antigens bound to MHC class I. In one study, for example, two human TCR alpha beta+ CD8+ T cell lines specific for

*M. tuberculosis* antigens recognized lipid antigens when presented by CD1a or CD1c antigen-presenting cells and displayed both cytotoxicity and cytokine responses [72]. 5'-adenosine phosphosulfate reductase (CysH), an enzyme essential for the production of reduced-sulfur-containing metabolites, has been shown to be important for *M. tuberculosis* during the chronic infection phase [73]. Resistance to nitrosative and oxidative stress (RNI and ROI) may be the mechanism of this protection.

### Granuloma formation

In addition to the specific cell-mediated protective response involved in *M. tuberculosis* elimination, granuloma formation is an important mechanism of the host to control infection. Granuloma formation requires balanced expression of cytokines and chemokines, including RANTES, MIP1-alpha, MIP1-beta, MCP-1, MCP-3, MCP-5, and IP10 [74, 75]. Chemokine receptors also determine proper formation of granulomas, and with *M. tuberculosis* infection, the expression of CCR5 (receptor for RANTES, MIP1-alpha, and MIP1-beta) increases in macrophages [76]. CCR2-disrupted mice are more susceptible to *M. tuberculosis* than the wild type mice [77]. CCR2 is a receptor for MCP-1, 3, and 5. MCP-1-disrupted mice, however, are not susceptible [78]. These observations suggested that alteration in the cell wall lipid composition or its remodeling can greatly affect host immune response, and that a certain level of proinflammatory response induced by *M. tuberculosis* itself is necessary for proper granuloma formation, that is protective both to the host and the bacterium. Thus, the role of the granuloma as a host protective factor needs a revision in thinking as it may also play a role in protecting the tubercle bacilli for its long-term survival in the host.

### PULMONARY TUBERCULOSIS

Patients with TB and early HIV disease present in similar ways to HIV-seronegative patients, with cavitation in apical pulmonary areas. Symptoms of pulmonary TB include fever, cough, weight loss, night sweats and malaise. As an immunity decline, the frequency of pulmonary cavitation, which is the hallmark of pulmonary TB in adults, becomes progressively less common [79, 80]. One consequence of the lower frequency of pulmonary cavitation in HIV infection is that hemoptysis occurs with lower frequency.

### EXTRAPULMONARY TUBERCULOSIS (EPTB) AND HIV-COINFECTION

EPTB is TB disease affecting organs other than the lungs, and the most common forms include body cavity (pleural, pericardial and abdominal), lymph node, and meningeal [81]. EPTB is responsible for 10-20% of global TB cases and has increased substantial in

areas of high HIV prevalence as the incidence of EPTB and disseminated forms of TB increase with worsening immunosuppression [82, 83]. The diagnosis of EPTB is particularly difficult and is the most important obstacle to improved management due to a wide range of presentation of the disease. Both conventional and novel sputum-based diagnostic tools such as smear microscopy, Xpert MTB/RIF and *M. tuberculosis* culture have reduced diagnostic accuracy [83, 84]. Consequently, diagnosis often requires invasive, expensive tissue sampling for histological diagnosis and to improve the likelihood of microbiological confirmation. Empiric treatment based on clinical and radiological screening is commonplace in the management of EPTB, and novel non-sputum based diagnostics and diagnostic strategies are urgently required [85].

#### 1. RISK FACTORS

Predisposing factors to TB include exposure to active TB, recent tuberculin skin test conversion, and immigration from high prevalence country, homelessness, living in institutions, infancy and old age. Other factors include; HIV infection, silicosis, diabetes, renal insufficiency, malignant lung tumors, post gastrectomy, alcoholism, massive weight loss, steroid and immunosuppressive therapy [86].

#### 2. DIAGNOSIS

Tuberculosis diagnosis has not been easy especially in HIV patients. However, specimen is stained by Ziehl-Nelsen's method, cultured on lipid-rich medium with malachite green to suppress other organism. Growth can be detected more quickly in broth culture by radiometric or fluorescence methods. Susceptibility tested on slopes of L-J medium or in radiometric broth polymerase chain reaction and Southern hybridization are helpful in the rapid diagnosis of mycobacterial infection. However new molecular methods for rapid susceptibility testing are now available. *M. tuberculosis* can now be typed using Gene Xpert MTB/RIF which is our main focus.

### TUBERCULIN SKIN TESTING

The utility of a tuberculin skin test depends on the immune status of the patient. A negative tuberculin skin test in a patient with AIDS does not rule out the diagnosis due to the high prevalence of false negative tests in patients with advanced immunosuppression [73].

In an HIV-infected patient with relatively preserved CD4 cell counts (eg, CD4 count >350 cells/mm<sup>3</sup>) a positive skin test in a patient with compatible symptoms and signs of TB is strongly suggestive of the diagnosis pending further evaluation in low TB prevalence settings. However, tuberculin skin testing is not of value for diagnosing active TB in

adults in areas where TB prevalence is high because the prevalence of positive skin tests is also high. A positive tuberculin skin test is also an indication for preventive therapy once active TB has been excluded.

#### **SPUTUM SMEAR AND CULTURE**

Some studies show HIV-infected patients are more likely to have smear-negative pulmonary or extrapulmonary disease [73,75]. A wide range of acid-fast smear positivity has been reported (31 to 81 percent) [75]. In a study from South Africa among 584 HIV-infected patients, only one-third of the 116 positive cultures were smear-positive [76]. In a study from Tanzania, a minority of patients who required treatment for suspected TB had positive microbiology (eg, AFB smear or culture) [77]. Smear-negative pulmonary TB occurs more commonly in HIV-infected patients because of their lower prevalence of pulmonary cavities. The yield on sputum culture is substantially higher (85 to 100 percent), since culture can detect as few as ten bacteria per mL of sputum [73,78]. In patients infected with HIV, a positive smear for acid-fast bacilli (AFB) is very specific for *Mycobacterium tuberculosis*, even in a setting with a high incidence of *Mycobacterium avium* complex (MAC), which will stain similarly. At San Francisco General Hospital, for example, 248 of 271 (92 percent) expectorated sputum samples that were positive for AFB grew *M. tuberculosis* on culture. This value is comparable to that found in HIV-negative patients.

#### **FLUORESCENCE MICROSCOPY**

An alternative to Ziehl-Neelsen staining is examination with fluorescence microscopy, which has comparable specificity but has about 10 percent greater sensitivity. Studies in Kenya and Uganda demonstrated that the increased sensitivity of this test was cost-effective and expedited diagnosis [86, 87].

In resource-limited settings, innovative techniques have been investigated to determine if the utility of fluorescence microscopy may be improved by the use of low-cost light-emitting diode (LED), which has a lifespan of more than 50,000 hours.

#### **URINE ANTIGEN DETECTION**

Detection of the mycobacterial antigen lipoarabinomannan (LAM) in the urine may be a useful diagnostic assay. Urine LAM reflects disseminated TB and is more likely to be detected in HIV-infected patients with lower CD4 counts, especially inpatients [89, 90, 91]. In one meta-analysis of HIV-infected patients, use of a urine LAM detection assay had sensitivity and specificity of 56 and 95 percent, respectively. The sensitivity of the assay is low in HIV-negative patients. Further study of this assay is needed, including evaluation of the appropriate cut point for a positive result on point-of-care urine test strips.

#### **DRUG RESISTANCE TESTING**

For all patients, testing for susceptibility to first-line agents should be performed if this is affordable to optimize efficacy of the therapeutic regimen and to decrease transmission of drug-resistant TB.

#### **Xpert MTB/RIF**

Xpert MTB/RIF assay is a real-time PCR platform with excellent sensitivity, specificity and low indeterminate rate which can provide a result in less than two hours. It is the most exciting new TB diagnostic method developed in decades. The Xpert MTB/RIF assay integrates DNA extraction, genomic amplification, and semi-quantitative detection of *M. tuberculosis* complex and rifampicin (RIF) resistance into a fully automated system [92, 93].

#### **SENSITIVITY OF URINE BASED METHODS (XPRT MTB/RIF)**

There are limited published data about the performance of MTB/RIF using urine samples. In a selected laboratory cohort interrogating extrapulmonary samples found that MTB/RIF sensitivity was 100% in 6 culture-positive urine samples with unknown HIV status, while in HIV-infected out-patients pre-ARV initiation, report the overall sensitivity of urine MTB/RIF to be 19% [94]. It is likely that HIV-infected patients' with more advanced immunosuppression accounted for the higher urine MTB/RIF sensitivity. Studies have found a strong association between declining CD4 cell count, LAM in the urine, proteinuria, and increasing urine MTB/RIF positivity. This may reflect renal TB as part of disseminated TB, increased bacillary burden in those with the most advanced immunosuppression, a 'leaky' filtration mechanism or a combination of these. The sensitivity of urine MTB/RIF was markedly improved by the centrifugation and pelleting of ~ 2–10 mls urine.

#### **THE RELEVANCE OF MTB DNA IN URINE TO TB DISEASE**

The Xpert MTB/RIF assay detects intact *Mycobacterium tuberculosis* bacilli. This is because the cartridge-based processing entails lysis, washing and deposition of whole mycobacteria on a filter membrane prior to ultrasonic disruption real-time PCR amplification and detection. Thus detection of *M. tuberculosis* in urine using Xpert indicates renal tract involvement with TB as the bacilli would otherwise be unable to enter the urine. Also it reflects lack of disease anatomic compartmentalization in patients with advanced immunodeficiency. Assessment of urine samples using Xpert provides a means of rapid assessment of disseminated TB.

### **URINE FOR TB DIAGNOSIS**

Urine as a biological sample for diagnostic testing is appealing. Urine is easy to collect, readily available and has a low infection risk to staff during collection [95]. Urine antigen detection is the most common diagnostic technique employed for infectious diseases, and TB diagnosis is no exception. A number of *M. tuberculosis* antigens have been evaluated in urine for the TB diagnosis. Of these 12 evaluated TB antigens, lipoarabinomannan (LAM) is the most extensively evaluated and promising [96].

### **DIAGNOSTICS GAPS**

Although MTB was identified as the causative organism for tuberculosis centuries ago, the detection of tuberculosis in the developing world is still a significant healthcare due to a number of challenges. Due to lack of reliable and validated biological markers from host or pathogen, hampers advances in TB diagnostic assay. Despite existing technologies and advances over the last few decades, development of new POC test is still challenging. There is need for a POC diagnostics that would be able to detect early infection, that has high specificity and sensitivity, quick to yield result, affordable, that would require a single visit, causes little or no pain at all to patients, has the ability of using specimens other than sputum e.g urine, CSF e.t.c., detect multiple biomarkers so as to be able to improve sensitivity and specificity, detect smear negative cases, assess drug susceptibility and be readily available specifically to remote regions with poor access to reference laboratories. An alternative strategy to develop should be employed so as to develop POC test is to minimize TB diagnosis by using on-chip micro fluidic technologies or by integrating novel nanotechnologies[97].

### **EFFECT OF HIV ON TB**

The risk of TB increases after HIV seroconversion, doubling within the first year [98], due to rapid depletion of TB-specific T helper cells, which occurs soon after HIV infection [99]. Thereafter, the risk of TB progressively increases with declining immunity[100, 101]. HIV-infected patients are at greatly increased risk of developing active TB from reactivated latent infection [102]. TB incidence has increased greatly in Africa driven by the HIV epidemic[103].

HIV infection is also a risk factor for accelerated progression of TB following exposure[104], which has resulted in outbreaks of multidrug-resistant and extensively drug-resistant (XDR) tuberculosis [105, 106, 107]. One study reported that the calculated duration of TB disease prior to diagnosis was three times shorter in HIV-infected patients than in HIV-seronegative patients. Clinicians therefore need to be aware that in HIV-infected patients, TB is a more

subacute than chronic illness, and that TB can progress rapidly while a diagnostic work up is being done. The shorter disease duration together with the higher proportion of sputum smear-negative TB saw with HIV infection results in a lower risk of TB transmission from HIV-infected patients with TB [108]. A positive HIV serostatus also confers risk of recurrent TB infection [109], often due to exogenous reinfection.

### **EFFECT OF TB ON HIV**

Likewise, TB seems to have a negative impact on HIV disease, increasing the risk of progression to AIDS or death following TB treatment [110, 111]. The acceleration of HIV diseases by TB may result from one or more of the following mechanisms: i).TB infection is associated with significant increase in plasma HIV viremia [112]. As is the case with other opportunistic infections, HIV viremia usually declines after initiation of successful TB treatment [113]. However, for reasons that remain unclear, persistently high levels of viremia have been observed in patients from Africa despite initiation of effective antitubercular therapy[114, 115]. ii). Generalized immune activation, due to TB infection, may increase the proportion of CD4 cells that are preferential targets for HIV [116]. iii). Increased expression of the HIV co receptors CCR5 and CXCR4 occurs in HIV-infected patients with TB co-infection [115].

### **HIV/TB AND THE KIDNEYS**

Patients with HIV are at risk for both acute kidney injury (AKI) and chronic kidney disease (CKD) secondary to medication nephrotoxicity, HIV-associated nephropathy, immune complex kidney diseases, and kidney disease in the setting of thrombotic microangiopathy. The incidence of AKI in HIV-infected patients is higher than it is in patients without HIV. Some risk factors for AKI among HIV-infected patients are similar to risk factors for AKI in the general population, such as older age, diabetes mellitus, preexisting CKD, and acute or f AKI increases the risk of death in patients with HIV. The most common types of AKI in HIV-infected patchronic liver disease. However, some risk factors are specific to HIV. Similar to the general population, the development oients are prerenal states and acute tubular necrosis, although other etiologies may also occur. Patients with HIV infection are at risk for nephrotoxicity from highly active antiretroviral therapy (HAART), as well as from medications used to treat opportunistic infections or hepatitis virus coinfection.

The prevalence and incidence of HIV-related CKD and end-stage renal disease (ESRD) are projected to increase as the prevalence of HIV infection continues to rise. The etiology of CKD in patients with HIV ranges from HIV-independent disorders (such as hypertension, diabetes, and incomplete recovery from

an episode of AKI) to HIV-related disorders (such as HIV-associated nephropathy [HIVAN]). Glomerular diseases which may occur more commonly in HIV-infected patients than in the general population include HIVAN, immune complex mediated glomerulonephritis, and glomerulonephritis secondary to hepatitis C virus coinfection. All HIV-infected patients should be screened for proteinuria and reduced kidney function. Identification of CKD in a patient with HIV should prompt nephrology referral and initiation of HAART.

### IMMUNOGENETICS OF TB

Immunogenetics of TB deals with immunology of TB and host genetics. Understanding the genetic markers such as Human leukocyte antigen (HLA) and their association to susceptibility tuberculosis will serve as a means to understanding predisposing factor to tuberculosis.

Tuberculosis is an opportunistic infection in people living with HIV. Tuberculosis has been reported to be leading cause of death in HIV patients. Genetic susceptibility to TB in HIV negative subjects is well documented. Since coinfections can influence the way in which immune system respond to different pathogens, genetic susceptibility to TB in HIV patients might also change. Studies from India and other parts of the world have shown that genetic susceptibility to TB is influenced by HIV infection. Polymorphisms in human leukocyte antigen (HLA), MBL2, CD209, vitamin D receptor, cytokine, chemokine and chemokine receptor genes have been shown to be associated with development of TB in HIV patients. There is need for conducting more studies on genomics so as to validate the reported data and their association. Despite the preliminary status of the reported associations, it is becoming clear that susceptibility to development of TB in HIV patients is influenced by both environmental and genetic components. Understanding the genetic and immunologic factors that influence susceptibility to TB in HIV patients could lead to novel insights for vaccine development as well as diagnostic advances to target treatment to those who are at risk for developing active disease.

### VACCINE DEVELOPMENT

The efficacy of BCG vaccination is limited; the development of new vaccines has been hampered by lack of good understanding of correlates of protection, and difficulty identifying surrogate endpoints of protective immunity against active disease that can be used in vaccine trials. Further more experimental animal models have not been reliable in predicting vaccine protection against human infection.

### CONCLUSION

Diagnosis of tuberculosis in HIV is based on clinical features and supported and laboratory investigations. Tuberculosis has been associated with renal disease in immunocompromised. Both protective and pathological response of host to M. tuberculosis is complex. Therefore it has become extremely difficult to identify the mechanism involved in protection. Both animal models and human subjects will be very helpful in understanding this pathogen (M.tuberculosis) in future. Further molecular biological and pathological studies are required to shed more light on the underlying mechanisms. The Xpert MTB/RIF assay is also an important tool for rapid diagnosis of tuberculosis in urine as well as presence of rifampin resistance. The risk of TB increases with progressive immunosuppression. Likewise, TB has a negative impact on HIV disease, increasing the risk of AIDS or death. The risk of extrapulmonary and disseminated TB is greater in HIV-infected patients with advanced immunosuppression.

### COMPETING INTEREST

Authors have declared that no competing interests exist.

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