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The changing landscape of diagnosing HIV-associated tuberculosis

G Maartens, MB ChB, FCP(SA), MMed

Division of Clinical Pharmacology, Department of Medicine, University of Cape Town

***Corresponding author**: G Maartens (gary.maartens@uct.ac.za)*

Tuberculosis is the most common cause of hospitalisation and death globally among people with HIV (PWH), even in the antiretroviral therapy era. Diagnosis of tuberculosis is challenging in PWH as bacillary load is lower in sputum and a high proportion have extrapulmonary or disseminated tuberculosis. The clinical features of tuberculosis in PWH are nonspecific and there is a wide differential diagnosis of other opportunistic infections. Tuberculosis progresses rapidly in people with advanced HIV disease, necessitating rapid diagnosis. In this narrative review, key changes are described in the diagnosis of HIV-associated tuberculosis in adults from 1990 until the present. Smear microscopy was the only rapid diagnostic test for tuberculosis until 2011, but its sensitivity is lower in PWH. Algorithms for diagnosing smear-negative tuberculosis had poor diagnostic accuracy, resulting in both underdiagnosis, which increased tuberculosis deaths, and overdiagnosis, leading to missed or delayed diagnosis of the opportunistic infections causing the symptoms. The evidence base for screening for HIV-associated tuberculosis is strong among ambulatory PWH, but screening algorithms have lower sensitivity in people on antiretroviral therapy. The development of novel rapid diagnostic tests (nucleic acid amplification tests and urine lipoarabinomannan lateral flow assay) for tuberculosis and the advent of antiretroviral therapy have dramatically changed the landscape of diagnosing HIV-associated tuberculosis, resulting in reductions in both tuberculosis incidence and deaths. Diagnostic challenges persist as none of the currently available rapid diagnostic tests have sensitivities that are ideal, and only one test (urine lipoarabinomannan detection) is both affordable and simple to perform at the point of care. Therefore, there is still a need for the development of novel, accurate and affordable point-of-care tests to improve the rapid diagnosis of HIV-associated tuberculosis.

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The focus of this article is on how the diagnosis of HIV-associated tuberculosis in adults has changed from 1990 until the present day. During this period, the diagnosis of HIV-associated tuberculosis markedly improved due to the development and roll-out of novel rapid diagnostic tests with improved diagnostic accuracy. In addition, the advent of antiretroviral therapy (ART) has dramatically altered the epidemiology of HIV-associated tuberculosis. The evidence base underlying the major diagnostic advances, together with their limitations, is briefly summarised.

Epidemiology of HIV-associated tuberculosis

The epicentre of the global HIV pandemic is in sub-Saharan Africa. Southern African countries have the highest HIV prevalence. South Africa has the highest number of people with HIV (PWH) globally. HIV infection markedly increases the risk of tuberculosis, which increases exponentially as immunity declines.[1] ART reduces the incidence of tuberculosis by 67%, but the incidence remains higher than in HIV-negative people, even among those who respond well to ART with CD4 lymphocyte counts returning to normal.[2] Tuberculosis is the most common cause of death and hospitalisation globally, even in the ART era, in PWH.[1]

Tuberculosis incidence in South Africa increased rapidly during the 1990s, peaking at an approximately threefold higher incidence in 2005 than in 1990.[1] For most of the last three decades, more than half of South African adults with tuberculosis have been PWH. The roll-out of ART dramatically reduced the incidence of tuberculosis and associated mortality, but tuberculosis incidence remains substantially higher than in 1990. ART has resulted in an increase in the prevalence of HIV as the life expectancy of PWH has improved; therefore, the pool of people at increased risk of tuberculosis remains high.

Clinical features of HIV-associated tuberculosis

The degree of immune suppression is critical in determining the clinical picture of HIV-associated tuberculosis. In PWH with mild immune suppression, tuberculosis presents in a similar way to people without HIV – most disease is pulmonary. Chest radiographs typically show predominant involvement of the upper zones and cavities are frequently present.[1]

By contrast, people with advanced HIV disease (AHD) (defined as CD4 lymphocyte count of ≤200 cells/μL or World Health Organization (WHO) clinical stage 3/4) often present with extrapulmonary or disseminated tuberculosis.[1] Pulmonary tuberculosis is atypical in people with AHD – chest radiographs usually show nonspecific infiltrates without cavitation or upper lobe predominance, and may even be normal despite respiratory symptoms and positive sputum cultures for *Mycobacterium tuberculosis*.[1] Tuberculosis progresses more rapidly in people with AHD, often presenting with features of severe sepsis in inpatients.[1]

Most inpatients with tuberculosis have AHD. Because studies are typically performed either in ambulatory PWH or in inpatients, it is more practical to approach diagnosing HIV-associated tuberculosis by healthcare setting rather than by presence or absence of AHD.

Diagnostic challenges of HIV-associated tuberculosis

A pooled analysis of autopsy studies reported that about half of PWH who died of tuberculosis were undiagnosed before death,[3] which starkly illustrates the need for improved diagnosis.

Major tuberculosis diagnostic challenges occur in people with AHD. Because the course of tuberculosis in people with AHD is subacute or acute, rapid diagnosis of tuberculosis is essential to reduce morbidity and mortality.[1] However, several factors make the rapid diagnosis of tuberculosis difficult in AHD. First, there is a wide differential diagnosis of other opportunistic infections with similar clinical presentation in people with AHD. Second, concomitant pulmonary bacterial infections are frequently found in people with AHD[4]; therefore, responses to trials of antibiotic therapy can be misleading. Third, sputum smears are often negative, as pulmonary cavities are uncommon in AHD.[1] Finally, inpatients with AHD are often unable to produce sputum samples, even with confirmed pulmonary tuberculosis.[1] Sputum induction with ultrasonic nebulisation of hypertonic saline is successful in obtaining sputum samples in most inpatients,[5] but this is underutilised.

Diagnosing tuberculosis in the smear microscopy era

The only rapid diagnostic test for tuberculosis was smear microscopy for acid-fast bacilli until the introduction of rapid diagnostic tests in 2011. HIV highlighted the limitations of smear microscopy.[6] National tuberculosis programmes focused on sputum smear-positive tuberculosis, as these patients are responsible for most of the transmission. Algorithms were developed for diagnosing sputum smear-negative pulmonary tuberculosis based on multiple sputum smear samples, trials of antibiotic therapy and chest radiography.[6] However, these algorithms were ill-suited to PWH and had a poor evidence base. Furthermore, no widely accepted algorithms existed for diagnosing smear-negative extrapulmonary tuberculosis. Clinical case definitions of smear-negative pulmonary and extrapulmonary tuberculosis, developed from clinical experience, had high positive predictive values in an inpatient cohort of PWH in Cape Town.[7] The WHO's algorithm for diagnosing HIV-associated smear-negative tuberculosis had only modest diagnostic accuracy, with a sensitivity of 80% and a specificity of 44% in a study of ambulatory symptomatic patients in Pietermaritzburg.[8]

Patients with sputum smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis (which is often smear negative, irrespective of HIV status) should ideally have mycobacterial cultures performed to guide therapy; however, most tuberculosis-endemic regions have no or minimal access to mycobacterial culture. Even if mycobacterial cultures are accessible, tuberculosis in people with AHD progresses over days and culture results take weeks.

Monitoring response to trials of antituberculosis therapy in PWH and suspected tuberculosis was often the only way to make a rapid diagnosis. Few studies were performed to define responses to empirical antituberculosis therapy – reduction in C-reactive protein (CRP) was the most sensitive parameter tested in a cohort of inpatients in Cape Town with smear-negative tuberculosis.[7]

In high-burden settings, national tuberculosis programmes were perceived as rigid – changes were seldom required as there were minimal treatment and diagnostic advances. By contrast, HIV programmes had to respond rapidly to a myriad of new developments. The differing cultures of the two programmes were particularly detrimental to PWH, as the policies of the tuberculosis programmes delayed or impeded access to therapy in people with smear-negative tuberculosis.[9] Combined tuberculosis and HIV clinics were set up by Médecins Sans Frontières in Khayelitsha, Cape Town and subsequently adopted in the South African public sector – combined clinics have improved holistic patient care.

Beyond smear microscopy – advances in rapid diagnostic tests

The diagnostic challenges of HIV-associated tuberculosis spurred funding for improved diagnostic tests. The development of two key rapid diagnostic tests for tuberculosis has facilitated a rapid diagnosis. Both tests have been implemented widely in high HIV prevalence settings, in part due to humanitarian funding.

The Xpert MTB/RIF test (Cepheid, USA) is a polymerase chain reaction assay that simultaneously detects *Mycobacterium tuberculosis* DNA and rifampicin resistance. The ability to rapidly detect rifampicin resistance has major benefits, as this is a risk factor for death in hospitalised PWH and tuberculosis.[10] This assay can be carried out at the point of care with a 2-hour turnaround time, but in practice the turnaround time is usually a few days, as very few health facilities in South Africa perform the assay on site. The Xpert MTB/RIF test is more sensitive than smear microscopy in sputum (74.9% v. 22.0-43.0% for smear in single sputum samples) and extrapulmonary specimens, and has specificity approaching 100%.[1] Xpert MTB/RIF testing was shown to reduce mortality among PWH by 20% when compared with smear microscopy.[11] South Africa was the first high-burden tuberculosis country to scale up Xpert MTB/RIF testing, commencing in 2011. The Xpert MTB/RIF Ultra test has improved sensitivity at the cost of modestly reduced specificity (92.8% v. 99.7% in sputum in PWH).[1] A number of similar rapid molecular diagnostic tests have recently been developed.

The urine lipoarabinomannan (LAM) test (Alere Determine™ TB LAM Ag) is an affordable point-of-care lateral flow assay that detects the presence of LAM, which is a component of mycobacterial cell walls. Urine LAM has a specificity of 91% in PWH,[1] partly due to false-positive tests in people with non-tuberculous mycobacteria. A randomised controlled trial conducted in four African countries showed that use of urine LAM in hospitalised PWH with suspected tuberculosis reduced mortality by 17%.[12] A positive urine LAM test indicates the presence of disseminated tuberculosis, which explains why it has a higher sensitivity in people with AHD. Other rapid diagnostic tests for disseminated tuberculosis in hospitalised PWH are Xpert MTB/RIF on urine,[10] and Xpert MTB/RIF Ultra performed on blood, which has a similar yield to mycobacterial blood culture.[13]

In a Cape Town inpatient cohort, mycobacterial culture added only minimal additional confirmed cases of tuberculosis compared with Xpert MTB/RIF, on induced or spontaneous sputum plus urine LAM.[14]

Implementation of urine LAM and rapid molecular diagnostic tests have completely changed the diagnosis of tuberculosis in PWH. In HIV-negative people, rapid molecular diagnostic tests capable of detecting rifampicin resistance are now used as the initial rapid diagnostic test of choice. However, currently available urine LAM assays are not sensitive enough to be used in HIV-negative people.

Clinical and radiological diagnosis in the post smear microscopy era

Clinical and radiological features were used to diagnose tuberculosis that was smear negative in the era when smear microscopy was the only rapid diagnostic test.[15] Clinical diagnosis remains important in the era of the urine LAM and Xpert MTB/RIF assays because neither

of them has a sensitivity of 100% using culture as the reference standard.[1] Even if they had sensitivities of 100%, not all patients with tuberculosis are culture positive.

The need for clinical diagnosis is greatest in inpatients, who have high mortality even when tuberculosis is diagnosed and treated – especially among those with disseminated tuberculosis.[10] A clinical prediction rule was developed in two secondary hospitals in Cape Town for diagnosing tuberculosis in HIV-positive inpatients fulfilling the WHO criteria of cough and danger signs.[5] The strongest clinical predictor of tuberculosis was anaemia – the classic tuberculosis symptoms of night sweats and weight loss were not independent predictors of tuberculosis.[5]

Chest radiographs have been used to detect tuberculosis for many years, but most high-burden countries have moved away from this strategy in favour of microbiological tests as the main screening strategy. However, digital radiographic facilities are becoming more affordable and more widely available. Digital radiographs can be interpreted by computer-aided detection software, which was more accurate than clinicians at diagnosing HIV-associated pulmonary tuberculosis in two Cape Town cohorts of inpatients and emergency-centre patients.[16] Computer-aided detection software will be particularly useful in countries with limited access to radiologists.

An individual participant data meta-analysis in ambulatory PWH being screened for tuberculosis found that chest radiograph findings suggestive of tuberculosis had a sensitivity of 63% and a specificity of 78%.[17]

Considerably less research has been carried out on the diagnostic accuracy of affordable imaging among inpatients with AHD. Chest radiographic features interpreted as 'likely tuberculosis' were the strongest predictors of tuberculosis in the Cape Town clinical prediction rule study of inpatients.[5] An interesting finding in that study was that pulmonary cavities were not associated with confirmed tuberculosis. The likely explanations for this finding are that people with AHD seldom produce pulmonary cavities and that almost half the cohort had had a previous episode of tuberculosis, which was the likely cause of the cavities. Abdominal ultrasound is widely used among inpatients with HIV to detect features of extrapulmonary or disseminated tuberculosis (abdominal lymph node enlargement, splenic hypodensities and effusions). However, abdominal ultrasound had only moderate sensitivity and specificity (63% and 68%, respectively) in a systematic review.[18] Among inpatients, chest radiographs are more specific but less sensitive than abdominal ultrasound.[19]

Screening for tuberculosis

Simple screening tools for tuberculosis in PWH are needed to facilitate the diagnosis of tuberculosis earlier in the disease course, to reduce morbidity and mortality, reduce transmission and rule out tuberculosis before starting tuberculosis preventive therapy. Individual participant data meta-analyses of studies evaluating screening for tuberculosis in PWH have recently been conducted among ambulatory people and inpatients.[17,20] In ambulatory PWH, elevated CRP concentrations had the best performance characteristics (high sensitivity with moderate specificity) to predict tuberculosis.[17] CRP testing is available as an affordable point-of-care test. However, CRP had a higher specificity but lower sensitivity among PWH on ART, making it less attractive as a screening test in this setting. In inpatients, none of the screening tests evaluated had desirable test characteristics – although sensitivities were higher than in ambulatory PWH, specificities were much lower. These findings resulted in the WHO recommending rapid molecular diagnostic tests for all inpatients with HIV in settings with a high tuberculosis prevalence.[20]

Conclusion

The dramatic advances in the diagnosis of tuberculosis were accelerated by global funding increases in response to the devastating effect the HIV pandemic was having on tuberculosis outcomes, which benefited all people with tuberculosis. The diagnostic challenges of HIV-associated tuberculosis persist, as none of the currently available rapid diagnostic tests have sensitivities that are 100%, and only one test (urine LAM) is both affordable and simple to perform at the point of care. The evidence base for screening for HIV-associated tuberculosis is strong among ambulatory PWH, but screening algorithms are less sensitive in people on ART.

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1. Meintjes G, Maartens G. HIV-associated tuberculosis. N Engl J Med 2024;391(4):343-355. https://doi.org/10.1056/nejmra2308181
2. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. Lancet Infect Dis 2010;10(7):489-498. https://doi.org/10.1016/s1473-3099(10)70078-5
3. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: A systematic review and meta-analysis. AIDS 2015;29(15):1987-2002. https://doi.org/10.1097/qad.0000000000000802
4. Maartens G, Griesel R, Dube F, Nicol M, Mendelson M. Etiology of pulmonary infections in human immunodeficiency virus-infected inpatients using sputum multiplex real-time polymerase chain reaction. Clin Infect Dis 2020;70(6):1147-1152. https://doi.org/10.1093/cid/ciz332
5. Griesel R, Stewart A, van der Plas H, al. Optimizing tuberculosis diagnosis in human immunodeficiency virus-infected inpatients meeting the criteria of seriously ill in the World Health Organization algorithm. Clin Infect Dis 2018;66(9):1419-1426. https://doi.org/10.1093/cid/cix988
6. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: Informing urgent policy changes. Lancet 2007;369(9578):2042-2049. https://doi.org/10.1016/s0140-6736(07)60284-0
7. Wilson D, Nachega J, Morroni C, Chaisson R, Maartens G. Diagnosing smear-negative tuberculosis using case definitions and treatment response in HIV-infected adults. Int J Tuberc Lung Dis 2006;10(1):31-38.
8. Wilson D, Mbhele L, Badri M, et al. Evaluation of the World Health Organization algorithm for the diagnosis of HIV-associated sputum smear-negative tuberculosis. Int J Tuberc Lung Dis 2011;15(7):919-924. https://doi.org/10.5588/ijtld.10.0440
9. Mandavilli A. A clash of cultures. Nat Med 2007;13(3):268-270. https://doi.org/10.1038/nm0307-268
10. Schutz C, Barr D, Andrade BB, et al. Clinical, microbiologic, and immunologic determinants of mortality in hospitalized patients with HIV-associated tuberculosis: A prospective cohort study. PLoS Med 2019;16(7):e1002840. https://doi.org/10.1371/journal.pmed.1002840
11. Haraka F, Kakolwa M, Schumacher SG, et al. Impact of the diagnostic test Xpert MTB/RIF on patient outcomes for tuberculosis. Cochrane Database Syst Rev 2021;5(5):Cd012972. https://doi.org/10.1002/14651858.cd012972.pub2
12. Peter JG, Zijenah LS, Chanda D, et al. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: A pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. Lancet 2016;387(10024):1187-1197. https://doi.org/10.1016/s0140-6736(15)01092-2
13. Boloko L, Schutz C, Sibiya N, et al. Xpert Ultra testing of blood in severe HIV-associated tuberculosis to detect and measure Mycobacterium tuberculosis blood stream infection: a diagnostic and disease biomarker cohort study. Lancet Microbe 2022;3(7):e521-e532. https://doi.org/10.1016/s2666-5247(22)00062-3
14. Boyles TH, Griesel R, Stewart A, Mendelson M, Maartens G. Incremental yield and cost of urine Determine TB-LAM and sputum induction in seriously ill adults with HIV. Int J Infect Dis 2018;75:67-73. https://doi.org/10.1016/j.ijid.2018.08.005
15. Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. Lancet Infect Dis 2003;3(5):288-296. https://doi.org/10.1016/s1473-3099(03)00609-1
16. Rajpurkar P, O'Connell C, Schechter A, et al. CheXaid: Deep learning assistance for physician diagnosis of tuberculosis using chest x-rays in patients with HIV. NPJ Digit Med 2020;3:115. https://doi.org/10.1038/s41746-020-00322-2
17. Dhana A, Hamada Y, Kengne AP, et al. Tuberculosis screening among ambulatory people living with HIV: A systematic review and individual participant data meta-analysis. Lancet Infect Dis 2022;22(4):507-518. https://doi.org/10.1016/s1473-3099(21)00387-x
18. Van Hoving DJ, Griesel R, Meintjes G, Takwoingi Y, Maartens G, Ochodo EA. Abdominal ultrasound for diagnosing abdominal tuberculosis or disseminated tuberculosis with abdominal involvement in HIV-positive individuals. Cochrane Database Syst Rev. 2019;9(9):Cd012777. https://doi.org/10.1002/14651858.cd012777.pub2
19. Griesel R, Cohen K, Mendelson M, Maartens G. Abdominal ultrasound for the diagnosis of tuberculosis among human immunodeficiency virus-positive inpatients with World Health Organization danger signs. Open Forum Infect Dis 2019;6(4):ofz094. https://doi.org/10.1093/ofid/ofz094
20. Dhana A, Hamada Y, Kengne AP, et al. Tuberculosis screening among HIV-positive inpatients: A systematic review and individual participant data meta-analysis. Lancet HIV 2022;9(4):e233-e241. https://doi.org/10.1016/s2352-3018(22)00002-9

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