Review Article

Diagnostic Dilemma of Tuberculosis among HIV-positive patients: Challenges and Advances.

Sharma M,[1] Devnath S,[2] Ahmed SM,[3] Saleh AA,[4] *Anwar S,[5]

Abstract

HIV/TB co-infection presents a significant public health challenge due to the synergistic interaction between the two pathogens. HIV weakens the immune system, making individuals more susceptible to TB infection and reactivation of latent TB. Conversely, active TB accelerates the progression of HIV to AIDS by further compromising immune function, increasing viral replication, and promoting viral mutation. This interaction not only worsens clinical outcomes but also increases mortality rates among people living with HIV (PLWH). The mutual enhancement of these pathogens means that HIV infection increases the likelihood of TB infection and reactivation due to the compromised immune system. TB infection, in turn, accelerates the deterioration of immune function in PLWH, leading to faster progression to AIDS. Active TB is a leading cause of death among PLWH. In 2019, approximately 33% of the 690,000 AIDS-related deaths were attributable to HIV-associated TB.

Diagnosing TB in HIV-coinfected individuals is particularly challenging due to the reduced sensitivity of conventional diagnostic methods like sputum smear, sputum culture, tuberculin skin tests, and interferon-gamma release assays. The lower immune response in PLWH leads to lower detection rates with these methods. Emerging diagnostic approaches, such as micro RNAs, soluble inflammatory markers, and proteomic analysis, show promise for early detection of TB in HIV-coinfected individuals. However, these methods require further research and validation. Strengthening the integration of HIV and TB control programs can reduce diagnostic delays, improve early case detection, ensure prompt treatment initiation, and ultimately reduce transmission rates. This integration is crucial for managing co-infection and improving patient outcomes. To address these challenges, health systems need to focus on enhancing screening and diagnostic methods, developing and validating new diagnostic tools that are effective in immunocompromised individuals, and implementing coordinated care strategies that address both HIV and TB simultaneously.

Key words: HIV/TB co-infection, immune system, people living with HIV

Received on: 15.05.2024; Accepted on: 26.05.2024

Introduction

HIV is a primary global public health concern, having claimed around 40.4 million lives to date, and estimates place the number of people living with HIV at 39.0 million by the end of 2022.[1] Despite significant progress in TB control, tuberculosis (TB) remains the leading cause of death for adults worldwide, with 122 million cases being attributed to disease episodes and post-tuberculosis.[2] In 2022, the global incidence of tuberculosis (TB) was reported to be 7.5 million.[3]. In 2020, individuals diagnosed with HIV, commonly referred to as people living with HIV (PLHIV), constituted 8% of TB cases and were responsible for around 14% of TB-related mortalities.[4] The coinfection of HIV and TB infection presents a synergistic and potentially fatal combination, as each infection exacerbates the progression of the other.[5] Early detection through systematic screening of high-risk

Author's affiliation

1. Mukesh Sharma, MD Resident, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
2. Sourav Devnath, MD Resident, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
3. SM Ali Ahmed, Assistant Professor, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
4. Prof. Ahmed Abu Saleh, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
5. *Shaheda Anwar, Associate Professor, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Address of Correspondence: *Dr. Shaheda Anwar, Associate Professor, Department of Microbiology & Immunology, Shahbagh, Dhaka-1000, Bangladesh. E-mail: shahedaanwar17@gmail.com

groups is a crucial part of the WHO's interim milestone for the End TB strategy, set for 2035.[6] Standard diagnostic techniques in current active Tuberculosis diagnosis protocol in HIV-positive individuals include symptom-based diagnosis, X-ray chest, sputum smear microscopy, TST and IGRA, bacterial culture, GeneXpert MTB/RIF of sputum, LF-LAM, GeneXpert Ultra of sputum and granulomatous lesion in lung biopsy materials. However, current diagnostic methods for active TB in HIV-positive individuals have significant limitations.

Clinical presentation of Tuberculosis in HIV-coinfected individuals

According to current WHO standards, every adult or adolescent with HIV should be screened for TB based on symptoms at each medical visit. The WHO four-symptom screen assesses the presence of fever, night sweats, cough, or weight loss.[7] HIV-positive individuals may experience a range of TB signs and symptoms, depending on their level of immunosuppression. Although less immunocompromised persons are more likely to experience pulmonary manifestations, patients with severe immunosuppression are more susceptible to extrapulmonary tuberculosis, which can appear as a variety of signs and symptoms, most notably lymphadenopathy and pleural effusion.[8] The pooled sensitivity of symptom-based diagnosis among all PLHIV was 83% (95%CI: 74–89%), and the specificity was 38% (95%CI: 25–53%) when compared to a culture reference standard according to a meta-analysis conducted by WHO including 23 studies.[7] Any organ in the body can be affected by extrapulmonary TB, which frequently affects the pericardium, central nervous system, pleura, lymph nodes, abdominal organs, and bone. It frequently manifests as disseminated TB.[9]

Conventional Diagnostic Methods and Their Limitations

While many conditions can mimic TB symptoms, HIV-associated pulmonary diseases, and pneumonic presentations should put TB at the top of the differential diagnosis list.[10] Patients with coinfection of HIV and TB present with more unusual clinical and imaging manifestations due to reduced immunity and decreased bacterial load in sputum. TB screening tools are intended to differentiate individuals with a higher risk of getting tuberculosis from those with a lower risk. To confirm or rule out tuberculosis, diagnostic testing must be conducted after screening and be provided as part of a thorough clinical evaluation.[11] For many years, the primary methods used for diagnosing and validating active TB were bacterial culture and smear microscopy to check for acid-fast bacilli. A more recent improvement to the diagnostic toolkit is the nucleic acid amplification of Mtb via tests like GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra. While smear-positive cases can be diagnosed with high sensitivity and specificity using culture and GeneXpert, smear-negative patients, children, PLHIV, and extrapulmonary tuberculosis (EPTB) have lower diagnostic accuracy.[12]

In an MTB-HIV coinfection, sputum microscopy is less sensitive, but it is quick, cheap, and simple to use in the field setting.[13] Sputum bacillary load is typically low in HIV-positive individuals, which reduces the sensitivity of bacteriological tests.[8,14] Between 24% and 61% of patients with HIV coinfected are smear-negative.[15] MTB culture in liquid or on solid agar is still a crucial conventional test for TB diagnosis. The cost of solid culture is lower than that of liquid culture. However, liquid culture is more sensitive and quicker.[16]

Interferon-gamma release assays (IGRA) or the tuberculin skin test (TST) are advised for initial screening.[7] In countries with low TB prevalence, asymptomatic, non-HIV-infected people are routinely screened for TB using TST, which is influenced by the bacillus Calmette-Guérin (BCG) vaccination, and IGRA, which is not. Current blood-based assays, like IFN-γ release assays (IGRAs), are specific to Mtb infection and measure IFN-γ production in response to stimulation with Mtb-specific antigens, such as ESAT6 and CFP10.[17,18] However, IGRAs (like QuantiFERON or T-SPOT.TB) are not good enough to track treatment response,[19] and they cannot distinguish between latent Mtb infection (LTBI) and ATB.[20,21] A multicenter prospective study evaluating the diagnostic qualities of the TST, QuantiFERON Gold In-Tube (QFT), and T-SPOT-TB (TSPOT) was carried out in the United States, involving 1510 people living with HIV (PLWH). This study discovered that TSPOT was more applicable to PLWH with high CD4+ counts and low risk for tuberculosis exposure, as it had a significantly higher positive predictive value (90.0%) than the TST (45.4%) or QFT (50.7%).[22] C-reactive protein (CRP) has been added as a screening marker for ambulatory PLHIV in the most recent version of the WHO guidelines on TB.[7] The WHO-recommended four-symptom screen alone had a lower specificity and a similar sensitivity to high CRP, according to a meta-analysis that supported the recommendation.[23] The benefit of CRP is that it is an inexpensive point-of-care test that can be performed on capillary blood. Additional infectious agents that are in circulation have the potential to decrease the specificity of CRP.

Molecular diagnostic tests

Gene-Xpert MTB/RIF and Gene-Xpert Ultra

It is not possible to use GeneXpert MTB/RIF analysis to identify treatment effects, even though it has significantly improved diagnostic capability and reduced accuracy in the PLHIV group.[24] Furthermore, sputum specimens, which are challenging to obtain in adults following symptomatic improvement in pediatric patients or patients with extrapulmonary TB, are another requirement for GeneXpert MTB/RIF.[25] Though the GeneXpert MTB/RIF fast molecular assay provides

improved diagnostic capabilities, its estimated sensitivity for smear-negative cases is just 55% in PLWH, whereas it is 67% in HIV-negative people (Theron et al., 2011). The purpose of Xpert MTB/RIF Ultra (Xpert Ultra) is to increase rifampicin resistance identification and improve the sensitivity of tuberculosis diagnosis. Two distinct multicopy amplification targets (IS6110 and IS1081) and a bigger reaction chamber are intended to lessen the limit at which bacterial colony-forming units can be detected. In adults with pulmonary tuberculosis, prospective multicenter research revealed that Xpert Ultra had a greater diagnostic sensitivity than Xpert: 90% versus 77% in culture-positive sputum samples from HIV-coinfected persons and 63% versus 46% in smear-negative, culture-positive sputum samples.[6]

Urine Lateral Flow Lipo-arabino-mannan (LF-LAM)

For a subset of HIV-positive individuals who are thought to be co-infected with active tuberculosis, the urine LF-LAM assay is an immunocapture test that finds the mycobacterial LAM antigen in urine. The assay can be used as a rapid bedside rule-in test for HIV-positive individuals despite its limited sensitivity, particularly in emergency scenarios where the patient's survival depends on a prompt TB diagnosis.[26] For HIV-positive adults, adolescents, and children with TB signs and symptoms (pulmonary or extrapulmonary), who have advanced HIV disease or are critically ill, or who have a CD4 cell count of less than 200 cells/mm3, LF-LAM is advised in inpatient settings to assist in the diagnosis of active tuberculosis. In outpatient settings, the World Health Organization advises using LF-LAM to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children who exhibit pulmonary or extrapulmonary TB signs and symptoms, are critically ill, or have a CD4 cell count of less than 100 cells/mm3, regardless of TB signs and symptoms.

Prospects of tuberculosis diagnosis in HIV/TB coinfected individuals

MicroRNAs: MicroRNAs (miRNAs) hold promise as diagnostic biomarkers for TB in HIV-coinfected individuals due to their ability to provide early, specific, and non-invasive detection. miRNAs can differentiate between latent and active TB and reflect disease activity and treatment responses, improving monitoring and management. Essential in HIV-positive patients where conventional diagnostic techniques might not work is the ability of these tiny, persistent RNA molecules to discriminate between latent and active tuberculosis.[27] Furthermore, miRNAs have the ability to reflect disease activity and treatment responses, which facilitates efficient disease monitoring.[28] Their application in blood-based testing improves patient accessibility and compliance, particularly in environments with limited resources.[29] In general, miRNAs have the potential to transform the identification and treatment of tuberculosis in individuals who also have HIV, leading to better clinical results and improved public health.[30]

Immuno-activation markers of tuberculosis

Immune activation markers may hold significant promise for diagnosing TB in HIV-coinfected patients, where traditional methods often fail due to overlapping symptoms and reduced sensitivity. Macrophage and T-cell-specific soluble cellular markers of immune activation, sCD27, sCD163, and sCD14, are found at increased levels in pleural fluid versus plasma and even higher in TB patients coinfected with HIV-1.[31] Higher levels of circulating soluble CD14 (sCD14), a marker of macrophage activation, were found in HIV/TB coinfected patients with pulmonary TB compared to CD4-matched HIV-1 infected healthy subjects, regardless of their CD4 T cell count.[32] Moreover, studies indicate that markers such as CD38, HLA-DR, and CD69 on T-cells may help identify TB in these patients by reflecting immune system activation specific to TB.[33] CD69 is recognized as a costimulatory receptor and an early activation marker.[34] Elevated levels of CD4+ CD69+ IFNγ+ T cells are linked to early active tuberculosis or recent TB infection.[31] By using CD38, an immune activation marker, and CD27, a maturation marker, Ahmed et al. showed that active TB was associated with increased frequency of CD38+ CD27low, while LTBI was associated with CD38-CD27 high.[34] By week nine, following the commencement of anti-TB therapy, the expression of immune activation markers such as CD38 and HLA-DR on T cells had significantly decreased. So, these markers can be used to see the treatment response in TB. So, incorporating these markers into diagnostic protocols can enhance the accuracy and timeliness of TB diagnosis, improving outcomes for HIV-infected individuals.

Integrative multiomics approach

An integrative multi-omics approach, utilizing data from genomics, transcriptomics, proteomics, metabolomics, microbiomics, and epigenomics, offers a comprehensive view of TB in HIV-coinfected individuals. This approach can improve biomarker discovery, diagnostic accuracy, and personalized treatment options.[35] In a study including active tuberculosis patients with HIV coinfection and healthy controls, greater MDC/CCL22 in controls ($p=0.0072$) and greater TNFα and IP-10/CXCL10 in cases ($p=0.011$, $p=0.0005$) were observed. Gamma-glutamyl threonine and hsa-miR 215-5p were shown to be the best variables by a decision-tree method for classifying incident TB cases (AUC 0.965; 95% CI 0.925-1.000).

Conclusion

In HIV-positive patients, early TB testing improves the management of both conditions and lowers morbidity and mortality rates. Timely and accurate diagnosis of TB in HIV-positive individuals is crucial, as coinfection exacerbates the progression of both diseases. Early TB

testing improves management, reduces morbidity and mortality, and enhances public health outcomes by limiting disease transmission. Enhancing diagnostic capacities is essential to improving survival rates and quality of life for individuals coinfected with HIV and TB.

Author Contribution

MS and DS wrote the manuscript and performed the literature search. SMA and AAS modified the literature search and revised the manuscript. SA conceptualized the idea of the article, modified the search and revised the manuscript.

Declaration of interests

The authors declare no conflict of interest.

Reference

1. World Health Organization. People living with HIV People acquiring HIV People dying from HIV-related causes. Who [Internet]. 2023;1–8. Available from: https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/j0294-who-hiv-epi-factsheet-v7.pdf
2. Natarajan A, Beena PM, Devnikar A V., Mali S. A systemic review on tuberculosis. Indian J Tuberc [Internet]. 2020;67(3):295–311. Available from: https://doi.org/10.1016/j.ijtb.2020.02.005
3. Organization WH. Global Tuberculosis Report [Internet]. Vol. t/malaria/, January. Geneva; 2023. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports
4. World Health Organization. Global tuberculosis report 2021: supplementary material. Global tuberculosis report 2021: supplementary material. 2021. 153 p.
5. Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. Int J Tuberc Lung Dis [Internet]. 2001 Mar;5(3):225–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11326821
6. Donovan J, Thu DDA, Phu NH, Dung VTM, Quang TP, Nghia HDT, et al. Xpert MTB/RIF Ultra versus Xpert MTB/RIF for the diagnosis of tuberculous meningitis: a prospective, randomised, diagnostic accuracy study. Lancet Infect Dis [Internet]. 2020;20(3):299–307. Available from: http://dx.doi.org/10.1016/S1473-3099(19)30649-8
7. World Health Organization. Consolidated Guidelines on Tuberculosis Treatment. Who. 2024. 99 p.
8. Hamada Y, Getahun H, Tadesse BT, Ford N. HIV-associated tuberculosis. Int J STD AIDS. 2021;32(9):780–90.
9. Naing C, Mak JW, Maung M, Wong SF, Kassim AIBM. Meta-analysis: The association between HIV infection and extrapulmonary tuberculosis. Lung. 2013;191(1):27–34.
10. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-research that is available on the COVID-19 resource centre - including this for unrestricted research re-use a. 2020;(January):19–21.
11. World Health Organization. Consolidated Guidelines on Tuberculosis Treatment. Who. 2020. 99 p.
12. Tiamiyu AB, Iliyasu G, Dayyab FM, Habib ZG, Tambuwal SH, Animashaun AO, et al. A descriptive study of smear negative pulmonary tuberculosis in a high HIV burden patient's population in North Central Nigeria. PLoS One [Internet]. 2020;15(9 September 2020):1–9. Available from: http://dx.doi.org/10.1371/journal.pone.0238007
13. Montales MT, Chaudhury A, Beebe A, Patil S, Patil N. HIV-Associated TB Syndemic: A Growing Clinical Challenge Worldwide. Front Public Heal. 2015;3(December):1–7.
14. Luetkemeyer AF, Kendall MA, Wu X, Lourenço MC, Jentsch U, Swindells S, et al. Evaluation of two line probe assays for rapid detection of mycobacterium tuberculosis, tuberculosis (TB) drug resistance, and non-TB mycobacteria in HIV-infected individuals with suspected TB. J Clin Microbiol. 2014;52(4):1052–9.
15. 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):2042–9.
16. Murphy ME. A comparison of solid and liquid culture in tuberculosis diagnosis and treatment monitoring. 2015;(January).
17. Thillai M, Pollock K, Pareek M, Lalvani A. Interferon-gamma release assays for tuberculosis: Current and future applications. Expert Rev Respir Med. 2014;8(1):67–78.
18. Nyendak MR, Lewinsohn DA, Lewinsohn DM. New diagnostic methods for tuberculosis. Curr Opin Infect Dis. 2009;22(2):174–82.
19. Meier T, Eulenbruch HP, Wrighton-Smith P, Enders G, Regnath T. Sensitivity of a new commercial enzyme-linked immunospot assay

(T SPOT-TB) for diagnosis of tuberculosis in clinical practice. Eur J Clin Microbiol Infect Dis. 2005;24(8):529–36.
20. Denkinger CM, Pai M, Patel M, Menzies D. Gamma interferon release assay for monitoring of treatment response for active tuberculosis: An explosion in the spaghetti factory. J Clin Microbiol. 2013;51(2):607–10.
21. Janssens JP, Roux-Lombard P, Perneger T, Metzger M, Vivien R, Rochat T. Quantitative scoring of an interferon-γ assay for differentiating active from latent tuberculosis. Eur Respir J. 2007;30(4):722–7.
22. Pettit AC, Stout JE, Belknap R, Benson CA, Séraphin MN, Lauzardo M, et al. Optimal Testing Choice and Diagnostic Strategies for Latent Tuberculosis Infection Among US-Born People Living with Human Immunodeficiency Virus (HIV). Clin Infect Dis. 2021;73(7):E2278–84.
23. Dhana A, Hamada Y, Kengne AP, Kerkhoff AD, Rangaka MX, Kredo T, 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):507–18.
24. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert ® MTB / RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review) Xpert ® MTB / RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Libr. 2014;(1):1–3.
25. Sweeney TE, Braviak L, Tato CM, Khatri P. Tuberculosis: a Multicohort Analysis. Lancet Respir Med. 2017;4(3):213–24.
26. Ketema W, Woubishet K, Tesfaye S, Gutema S, Taye K, Shibeshi MS, et al. A Breakthrough in the Challenges of Tuberculosis Diagnosis: Lateral Flow Urine Lipoarabinomannan (LAM) Assay for the Diagnosis of Active Tuberculosis in a Subset of Human Immuno Deficiency Virus (HIV) Patients at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia. Int Med Case Rep J. 2022;15(August):393–7.
27. Sabir N, Hussain T, Shah SZA, Peramo A, Zhao D, Zhou X. miRNAs in tuberculosis: New avenues for diagnosis and host-directed therapy. Front Microbiol. 2018;9(MAR):1–14.
28. Sessa R, Hata A. Role of microRNAs in lung development and pulmonary diseases. Pulm Circ. 2013;3(2):315–28.
29. Witwer KW, Halushka MK. Toward the promise of microRNAs – Enhancing reproducibility and rigor in microRNA research. RNA Biol [Internet]. 2016;13(11):1103–16. Available from: http://dx.doi.org/10.1080/15476286.2016.1236172
30. Fu Y, Yi Z, Wu X, Li J, Xu F. Circulating microRNAs in patients with active pulmonary tuberculosis. J Clin Microbiol. 2011;49(12):4246–51.
31. Nikolova M, Markova R, Drenska R, Muhtarova M, Todorova Y, Dimitrov V et al. Antigen-specific CD4- and CD8-positive signatures in different phases of Mycobacterium tuberculosis infection. Diagn Microbiol Infect Dis [Internet]. 2013;75(3):277–81. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2012.11.023
32. Toossi Z, Funderburg NT, Sirdeshmuk S, Whalen CC, Nanteza MW, Johnson DF, et al. Systemic immune activation and microbial translocation in dual HIV/tuberculosis-infected subjects. J Infect Dis. 2013;207(12):1841–9.
33. ong YK, Tan HY, Saeidi A, Wong WF, Vignesh R, Velu V, et al. Immune Biomarkers for Diagnosis and Treatment Monitoring of Tuberculosis: Current Developments and Future Prospects. Front Microbiol. 2019;10(December).
34. Ahmed MIM, Ntinginya NE, Kibiki G, Mtafya BA, Semvua H, Mpagama S, et al. Phenotypic Changes on Mycobacterium Tuberculosis-Specific CD4 T Cells as Surrogate Markers for Tuberculosis Treatment Efficacy. Front Immunol. 2018;9(September).
35. Qiu S, Cai Y, Yao H, Lin C, Xie Y, Tang S, et al. Small molecule metabolites: discovery of biomarkers and therapeutic targets. Signal