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Review Article

Advances in technology for the laboratory diagnosis of individuals with HIV/AIDS coinfected with *Mycobacterium tuberculosis*

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ABSTRACT

The high morbidity and mortality rate of individuals with human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS) coinfected with *Mycobacterium tuberculosis* (MTB) is a tough challenge for current global tuberculosis prevention and control efforts. HIV/MTB coinfection is more complex than a single infection, and the interaction between the two diseases aggravates the deterioration caused by the disease, resulting in increased hospitalizations and deaths. Rapid screening and early diagnosis facilitate the timely initiation of anti-tuberculosis treatment in HIV/MTB coinfected individuals, thereby reducing transmission and the incidence of adverse prognoses. To date, pathogenic detection has remained the gold standard for diagnosing tuberculosis, but its sensitivity and specificity are greatly affected by the body's immune status, which limits its application in the diagnosis of HIV/MTB coinfection. Recently, immunology and molecular detection technology has developed rapidly. New detection technologies, such as interferon-γ release assays, interferon-gamma inducible protein 10, and GeneXpert MTB/RIF assay have overcome the limitations of traditional detection methods, significantly improved the sensitivity and specificity of tuberculosis diagnosis, and brought new hope to the detection of HIV/MTB coinfection. In this article, the principle, scope of application, and latest research progress of relevant detection methods are reviewed to provide a reference for the early diagnosis of HIV/MTB coinfection.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a chronic infectious disease caused by human immunodeficiency virus (HIV), which has an insidious onset and high morbidity and mortality rates and seriously threatens human health. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) [1], by the end of 2022, there were 39 million people living with HIV (PLWH) worldwide, including 1.3 million new HIV-infected individuals and 630,000 deaths from AIDS-related diseases, dramatically challenging global public health. HIV-infected individuals are susceptible to coinfection of bacterial, fungal and other pathogens due to their weakened immune function [2]. Tuberculosis (TB) is one of the most common opportunistic infections in the population with HIV/AIDS and the leading cause of death among HIV/AIDS patients, accounting for approximately one-third of AIDS-related deaths. *Mycobacterium tuberculosis* (MTB) infection can facilitate HIV replication and increase viral diversity in HIV-infected individuals. And the co-infected state promotes immune activation of the infected individuals, thus accelerates the progression of AIDS [3,4]. Meanwhile, HIV infection is an important independent risk factor for MTB infection and can increase the chances of endogenous relapse and exogenous reinfection of MTB [5]. Due to impaired cellular immune function and inflammatory cytokine secretion such as tumor necrosis factor α (TNF-α) and interferon-γ (IFN-γ) [6], HIV-infected individuals have increased susceptibility to TB and are prone to developing systemic disseminated lesions after infection [7,8], thus increasing the morbidity, hospitalization, and mortality rates of HIV/MTB-coinfected individuals. Compared with single infection, HIV/MTB coinfection is more complicated, and its clinical symp-

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toms are primarily atypical and often combined with other opportunistic infections, which greatly complicates clinical diagnosis and treatment [9]. Although antiretroviral therapy (ART) has greatly extended the lifespan of patients, TB still seriously threatens the life and health of HIV-infected individuals. Epidemiological data show that in 2020, approximately 1.5 million people died of TB worldwide, and approximately 214,000 were infected with HIV. An autopsy study among HIV-infected individuals showed that up to 45.8% of TB cases were undiagnosed at the time of death [10]. The current data on deaths from HIV/MTB coinfection are likely to be significantly lower than reality, so timely, accurate, and feasible screening and diagnosis strategies can ensure timely interventions for HIV/MTB-coinfected populations and effectively reduce hospitalization and mortality rates. Currently, the gold standard for diagnosing TB remains the positive culture of MTB. However, due to various factors, such as the complexity of HIV/MTB coinfection and the difficulty of obtaining biopsy specimens, traditional TB detection methods may lead to underdiagnosis and misdiagnosis of HIV/MTB-coinfected individuals, delaying diagnosis and treatment. Therefore, this paper reviewed the characteristics and recent advances in HIV/MTB coinfection-related detection technologies (Table 1), intending to provide a better understanding for achieving a rapid and accurate diagnosis.

2. Traditional microbiological assays

Microbiological detection technology provides strong evidence for the diagnosis of TB. However, the difficulty of draining sputum, the high incidence of extrapulmonary tuberculosis (EPTB), concurrent infections in HIV/AIDS patients, and a dramatic increase in false-positive indications of pathogen tests severely limit the application of pathogen diagnosis in these groups.

2.1. Sputum smear examination

The anti-acid sputum smear method is the most basic and widely used test to diagnose TB. Currently, there are two common methods of sputum smear detection: Ziehl-Neelsen microscopy and fluorescence microscopy. The most commonly used method is Ziehl-Neelsen microscopy. This method is simple, rapid, inexpensive, and highly specific [11] but has low sensitivity, requires prolonged microscopic observation by the detector, imposes a heavy workload, and is prone to false positives [12]. Therefore, it may be more suitable for application in countries with a low burden of TB. Fluorescence microscopy has been widely used in various clinical diagnostics and basic research in recent years, although it is still unfit to distinguish MTB from nontuberculous mycobacteria (NTM). Compared with conventional light microscopy, fluorescence microscopy has improved the sensitivity of TB detection and the efficiency of the surveyor. One report showed that the sensitivity of fluorescence staining was increased by approximately 10%, and the specificity was maintained [13]. Light-emitting diode fluorescence microscopy (LED-FM), which was further developed on this basis, has increased the sensitivity of detecting TB compared with conventional optical microscopy, thus has become an approved test by the World Health Organization (WHO) as an alternative to conventional optical microscopy for its rapid diagnosis of TB [14].

Table 1
Summary of detection techniques for *Mycobacterium tuberculosis* infection in HIV/AIDS individuals.

Detection techniques	Sample type	Detection principles	Major conclusion (s)	References
Sputum smear	Sputum, BALF, pleural fluid, ascites et al.	Microscopic observation after acid-fast staining or fluorescent staining	Lower applicability among HIV/AIDS patients	[12,15,16]
MTB culture	Sputum, BALF, pleural fluid, ascites et al.	Microscopic observation after cultivation on solid or liquid culture media	Lower applicability among HIV/AIDS patients	[8]
TST	Diameter of the skin nodule	Delayed-type hypersensitivity	Lower applicability among HIV/AIDS patients	[25]
TBST	Diameter of the skin nodule	Delayed-type hypersensitivity	Not influenced by the host's immune status and BCG vaccination	[27,28]
T-SPOT.TB	PBMCs	Elispot (detect the number of T cells in peripheral blood mononuclear cells producing IFN-γ after stimulation with MTB antigen)	Diagnosis of LTBI and ATB in HIV/AIDS patients	[40,42]
QFT-GIT/ QFT-Plus	Peripheral blood	ELISA (detect IFN-γ levels in plasma after stimulation with MTB-specific antigens)	Diagnosis of LTBI and ATB in HIV/AIDS patients	[42,48]
IP-10/IP10 mRNA	Peripheral blood, BALF, pleural fluid et al.	ELISA	Diagnosis of LTBI and ATB in HIV/AIDS patients; distinguishing ATB from LTBI	[50,51,54]
CRP	Peripheral blood	Inflammatory response	Increase the diagnosis rate of MTB in HIV-infected individuals	[56–58]
Novel biomarkers	Peripheral blood	Antigen-antibody reaction	Potential diagnostic biomarkers in HIV/MTB co-infection	[60,61]
Xpert MTB/RIF	Sputum, BALF, pleural fluid, ascites et al.	Fully automatic integrated semi-quantitative nested real-time PCR	Diagnosis of HIV/MTB co-infection; drug resistance	[29]
LPA	Sputum, BALF, pleural fluid, ascites et al.	DNA strip reverse hybridization technique	Initial testing for isoniazid/rifampin resistance in sputum smear/MTB culture-positive patients	[29,69]
LAM	Peripheral blood, urine	MTB antigen detection	HIV/TB co-infection with a $CD4^+$ T-cell count < 200 cells/μL	[72]
LAMP	Sputum, BALF, pleural fluid, ascites et al.	NAAT	Applicability among HIV/AIDS patients needs further validation	[83]
NGS	Peripheral blood, Sputum, BALF, CSF, pleural fluid, ascites et al.	High-throughput sequencing technology	Diagnosis of HIV/MTB co-infection	[88]

Abbreviations: MTB, *Mycobacterium tuberculosis*; BALF, bronchoalveolar lavage fluid; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; TST, tuberculin skin test; TBST, *Mycobacterium tuberculosis* antigen-based skin test; BCG, Bacillus Calmette-Guérin; T-SPOT.TB, T-cell spot test; QFT-GIT, QuantiFERON-TB gold in-tube test; QFT-Plus, Quantiferon-TB gold plus; PBMCs, peripheral blood mononuclear cells; LTBI, latent tuberculosis infection; ATB, active tuberculosis infection; Elispot, enzyme-linked immunosorbent spot; ELISA, enzyme-linked immunosorbent assay; IP-10, interferon-gamma inducible protein 10; CRP: C-reactive protein; LPA, linear probe assays; PCR, polymerase chain reation; DNA, deoxyribonucleic acid; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; NAAT, nucleic acid amplification tests; NGS, next-generation sequencing; CSF, cerebrospinalfluid.

Among HIV/MTB-coinfected individuals, approximately 24% − 61% have a negative sputum smear result [15]. Sputum microscopy is highly insensitive in PLWH [16]. Although fluorescence staining and LED-FM tests developed in recent years have improved the sensitivity of TB detection, the test's sensitivity remains low in HIV/AIDS patients [12]. Therefore, the diagnosis of HIV/MTB coinfection by smear microscopy alone is insufficient.

2.2. *Mycobacterium tuberculosis* culture

To date, MTB culture is still an essential means of TB diagnosis, and the commonly used methods include solid culture and liquid culture, which are more sensitive than smear microscopy. Specimens with positive cultures can also be used for bacterial type identification and offer a better guide in clinical diagnosis [17].

Löwenstein–Jensen medium (L-J) is the most commonly used solid culture for MTB detection. It allows clear observation of colony growth, which facilitates bacterial type identification and drug resistance experiments, but the sensitivity is low, and the period is long (approximately 3–8 weeks) [18], which is not suitable for the early diagnosis of HIV/MTB coinfection. The liquid culture method determines whether there is MTB growth by measuring the oxygen consumption in the liquid medium, and the results are mostly available in approximately 1–2 weeks, which can effectively improve the efficiency and sensitivity of TB diagnosis [17]. Compared with L-J culture, the positive rate of liquid culture is less affected by $CD4^+$ T-cell counts [19]. Thus, the sensitivity is higher in diagnosing HIV/MTB coinfection, especially in individuals with low $CD4^+$ T-cell counts [20]. However, liquid culture requires a high level of biosafety and high laboratory costs, making it difficult to use in the primary stage. Thus, pathogenetic-based diagnosis of HIV infections is time-consuming and costly, leading to delayed clinical diagnosis and treatment.

3. Immunological diagnostic technologies

MTB invasion can trigger a series of immunopathologic changes. Immune cells, antibodies, cytokines, and chemokines involved in the anti-TB immune response can be used as potential targets for immunological detection, which is the basis of immunological detection techniques. Currently, the most widely used immunological tests are the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) [21].

3.1. Skin test

3.1.1. TST

The TST is an intradermal detection technique based on the principle of a delayed cellular hypersensitivity reaction. The test uses tuberculin pure protein derivative (PPD) as an antigen to induce a hypersensitivity reaction, leading to an increase in vascular permeability and local infiltration of macrophages to form a red, swollen induration. By detecting the size of the induration, we can determine whether there is an MTB infection. Because of its low cost and ease of use, the TST plays a vital role in routine screening in countries with a high burden of TB. The positive rate of TST is high in TB patients with normal immune level. However, this method cannot distinguish between latent and active TB infections, and the specificity is likely to be influenced by many factors, such as Bacillus Calmette-Guérin (BCG) vaccination or NTM infection [22,23]. As a result, sensitivity is lacking in HIV-infected individuals. The positivity rate of the TST for detecting TB was only 19.10%, with a sensitivity of 35.96% [24], HIV patients are more likely to have TST anergy due to the decreased $CD4^+$ T-cell counts [25]. Therefore, novel tests must be sought to detect TB infection in HIV/AIDS patients.

3.1.2. *Mycobacterium tuberculosis* antigen-based skin test (TBST)

TBST is similar to the TST. It is a skin test to detect MTB infection using MTB-specific antigens (early secreted antigenic target-6 [ESAT-6], and culture filter protein-10 [CFP-10]), which effectively avoids the influence of BCG vaccination and most NTM infections on the specificity of the skin test. A *meta*-analysis suggested that the TBST may provide more reliable results in HIV-infected individuals than the TST [26]. According to national and international studies, the new skin tests agree well with IGRAs in the diagnosis of TB. They are not influenced by the host immune status or BCG vaccination [27,28]. These experiments showed that the TBST has the ability to compensate for the lack of specificity of the TST. In 2022, WHO published the WHO operational handbook on TB, which systematically evaluated the TBST technique and recommended that the TBST be used for MTB testing [29]. In the future, new skin tests are expected to replace the TST as a routine screening method in areas with a high HIV burden and limited resources and be widely promoted at the grassroots level.

3.2. IGRAs

IGRAs are an *in vitro* detection technique based on the cellular immune response induced by MTB infection. These assays assess the presence of MTB infection by detecting the number of T lymphocytes that release γ-interferon (interferon-γ, IFN-γ) after MTB-specific antigen stimulation or directly detecting the expression of IFN-γ [30]. IGRAs have been used for the adjunctive diagnosis of active tuberculosis (ATB) in China's TB diagnostic guidelines [31]. IGRAs can be used to diagnose HIV/MTB coinfection in combination with symptomatology screening, imaging tests, etc. Compared with the TST, IGRAs are highly specific [32], can eliminate false-positives from BCG vaccination and are less influenced by immune functions [33,34], so they have a better predictive ability than TB skin tests [35]. Thus, IGRAs are more effective and equitable in the diagnosis of HIV/MTB coinfection. For latent TB infections (LTBIs), the combination of IGRAs and the TST can greatly improve the negative predictive rate, which contributes to the diagnosis and exclusion of LTBIs in areas with a high HIV prevalence [36]. However, both the TST and IGRAs were less effective in predicting the onset of ATB [37]. In recent years, new products based on IGRA technology have entered the market and have been included in the WHO recommendation list [38]. There are two main mature IGRAs: the TB infection T-cell spot test (T-SPOT.TB) and the QuantiFERON-TB Gold In-Tube test (QFT-GIT).

3.2.1. T-SPOT.TB

T-SPOT.TB is an *in vitro* assay based on enzyme-linked immunosorbent assays (ELISA) that assess the presence of MTB infection by detecting the number of IFN-γ-secreting T lymphocytes after stimulation of peripheral blood mononuclear cells (PBMCs) with MTB-specific antigen [39], which is currently used for the diagnosis of LTBI and ATB. It is valuable as a diagnostic tool in detecting ATB in HIV-infected individuals. A *meta*-analysis conducted by Chen et al. [40] showed that the sensitivity and specificity of T-SPOT.TB in the diagnosis of HIV/ATB coinfection was 60.4% and 86.2%, respectively, higher than the sensitivity (35.96%) and specificity (84.88%) of the TST reported by Li et al. [24]. In addition, the positive indication of T-SPOT.TB was not significantly correlated with $CD4^+$ T-cell counts [41]. In the diagnosis of HIV infection combined with LTBI, IGRAs have comparable performance with the TST, and a combination of T-SPOT.TB and the TST may become a potential new diagnostic technique. According to research findings, the sensitivity and specificity of T-SPOT.TB for the diagnosis of HIV combined with LTBI was 51.9% and 99.7%, and those of the TST were 54.2% and 96.8%, respectively [42]. There were no statistically significant differences between the two detection methods mentioned above. However, compared with the TST, T-SPOT.TB has higher positive predicted values and may be

more suitable for screening and diagnosing LTBI in individuals with HIV/AIDS, especially in areas with a lower risk of TB exposure.

Although several studies have demonstrated that the high value in detecting HIV/MTB coinfection, T-SPOT.TB is ineffective in differentiating LTBI from ATB and in predicting the morbidity of ATB [43]. Therefore, several studies have been conducted to improve the diagnostic efficacy of T-SPOT.TB, including enhancing the MTB-specific antigens in IGRAs (adding new antigens Rv3615c and Rv3879c to the original antigens) [44] and using the ratio of TB-specific antigens to the positive antigen immune response as an indicator to differentiate LTBI from ATB [45]. Nevertheless, these studies did not achieve expected results, and the improved IGRAs still need further investigation and validation.

3.2.2. QuantiFERON-TB gold in-tube test (QFT-GIT)

QFT-GIT is based on ELISA, which detects plasma IFN-γ level after stimulation with three MTB-specific antigens, ESAT-6, CFP-10, and TB7.7(p4), to determine the presence of MTB infection [39]. QFT-GIT can be used for diagnosing not only LTBI but also ATB. Pettit AA-O et al. founds that the sensitivity and specificity of QFT-GIT for diagnosing ATB in HIV-infected individuals are 66.3% and 86.7%, respectively [42]. There was no significant difference compared to T-SPOT.TB. Studies have showed that the sensitivity of QFT-GIT in diagnosing HIV combined with LTBI is 72.2%, and the specificity is 96.5% [42]. There was no significant difference among QFT-GIT, TST, and T-SPOT.TB. However, the positive predictive value of QFT-GIT (50.7%) is significantly lower than that of T-SPOT.TB. Hence, QFT-GIT may not be suitable for diagnosing HIV/MTB coinfection in areas with a low TB prevalence. Further evaluation is needed to determine the optimal population for this test.

Although QFT-GIT has been widely used, its sensitivity for diagnosing HIV/MTB coinfection is low [33], and the test results may be influenced by the $CD4^+$ T-cell counts [46]. Both internal and external research institutions are seeking updated strategies to improve the diagnostic efficacy of this assay. Quantiferon-TB gold plus (QFT-Plus) is optimized to induce $CD4^+$ and $CD8^+$ T-cell responses for a more accurate assessment of the host immune response to MTB [47]. Studies have shown that HIV infection does not seem to affect the accuracy of QFT-Plus in the diagnosis of MTB [48]. In the diagnosis of ATB and LTBI, the sensitivity of QFT-Plus did not differ significantly between HIV-infected and uninfected individuals. QFT-Plus is highly sensitive in diagnosing MTB infection and is independent of HIV infection, so it is more suitable for the diagnosis of TB in HIV-infected individuals. However, the effectiveness in predicting the onset of active disease remains unproven and needs to be further explored in the future.

3.3. Interferon-gamma inducible protein 10 (IP-10)

IP-10, also known as C-X-C motif chemokine ligand 10 (CXCL10), is a member of the chemokine receptor family and is primarily induced by IFN-γ. In a normal physiological state, the body secretes only tiny amounts of IP-10 by T cells. However, upon infection with MTB, the levels of IP-10 in the serum rapidly increase and bind to chemokine receptor 3 (CXCR3), recruiting lymphocytes, primarily $CD4^+$ T cells, to participate in the immune response against TB (Fig. 1) [49]. Research indicates that under stimulation by TB antigens, the expression of serum IP-10 is significantly higher than that of IFN-γ, and its levels are less influenced by factors such as age, sex, and immune status [50,51]. Furthermore, studies have shown that the expression level of IP-10 transcription (CXCL10 mRNA) can increase approximately 100-fold under the stimulation of TB-specific antigens [52]. It has been demonstrated that IP-10 mRNA release assays perform better in detecting MTB infections in individuals coinfected with HIV compared to traditional IGRAs, with higher sensitivity and lower indeterminate rates [53]. Therefore, IP-10 may replace IFN-γ as a novel detection target

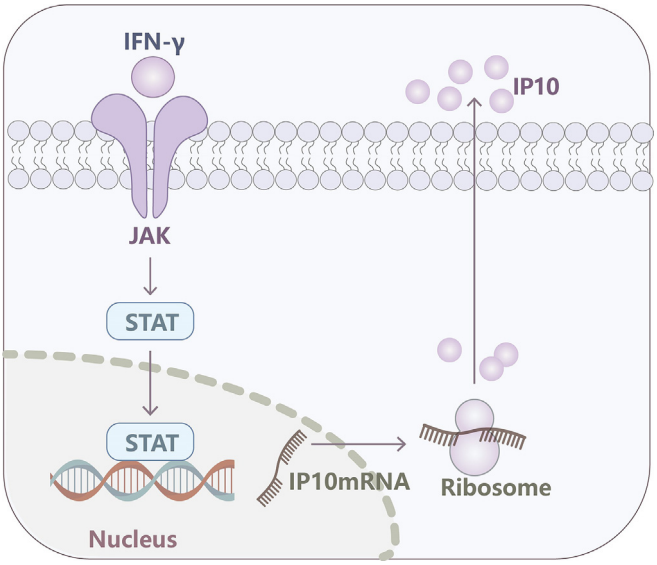

Fig. 1. The possible mechanisms of IP-10 production and the detection principle. IFN-γ can activate intracellular signaling pathways in receptor cells. IP-10 mRNA is stably expressed at a high transcription level within a short time, leading to the synthesis and secretion of IP-10. Comparison of the difference in the expression of IP-10 mRNA or IP-10 protein before and after stimulation can reflect whether the body has a specific T-cell response against MTB. Abbreviations: MTB, *Mycobacterium tuberculosis*; IP-10, interferon-gamma inducible protein 10; JAK, janus kinase; STAT, signal transducers and activators of transcription.

for MTB infection in HIV-infected populations. In addition, traditional IGRAs do not distinguish ATB from LTBI well, whereas IP-10 has a higher sensitivity and specificity for distinguishing ATB from LTBI [54]. A small-scale study showed that in HIV-infected individuals, IP-10 demonstrated 100% sensitivity and specificity in distinguishing ATB from LTBI [55], indicating that IP-10 has certain advantages in the diagnosis and differentiation of MTB infections in HIV-infected individuals. IP-10 may become a biomarker to replace IGRAs, particularly in PLWH.

3.4. C-reactive protein (CRP)

CRP is a nonspecific inflammatory biomarker produced by the body in response to infection or tissue damage. Studies have shown that utilizing CRP combined with symptom screening produces higher sensitivity and specificity for TB screening in ambulatory PLWH [56–58]. Therefore, the latest WHO guidelines [29] recommended CRP and symptom screening as screening tools for TB in the target population. Although current research indicates that the sensitivity and specificity of CRP combined with symptom screening do not meet WHO minimum target standards, it remains a cost-effective approach with considerable potential for widespread application.

3.5. Novel serum biomarkers identified through omics technologies

Serological assays for detecting MTB involve specific antigens, antibodies, or circulating immune complexes and produce early diagnoses. They play a crucial role in auxiliary diagnosis of smear-negative and EPTB. With the advancement of omics technologies, there has been progress in identifying novel biological markers for TB diagnosis. The screening of host immune response markers by omics technology has become the driving force for the development of new immunological detection technologies. In transcriptomics research, Sweeney et al. [59] identified a gene panel consisting of three genes (*GBP5*, *DUSP3*, and *KLF2*). This gene panel can be applied to detect TB and distinguish

between LTBI and ATB. Importantly, this differentiation is not influenced by factors such as HIV infection or BCG vaccination, and it is significantly associated with the severity of ATB. Several studies have also identified specific plasma proteins through proteomic techniques, making it possible to accurately identify MTB and other lung diseases in HIV-infected individuals [60,61]. These studies mentioned above have provided evidence and support for the use of histologic techniques to screen and detect MTB infection in HIV-infected populations. To date, dozens of relevant studies have been conducted and hundreds of new markers have been obtained. Nevertheless, most of these studies remain at the stage of systematic screening, and their shortcomings of low expression and susceptibility to other infections still need to be overcome [62].

4. Instant molecular detection

In recent years, molecular biology has rapidly developed, and TB-related molecular diagnostic techniques such as Xpert MTB/RIF have received widespread attention.

4.1. Xpert MTB/RIF detection

Xpert MTB/RIF is a fully automated integrated semiquantitative nested real-time polymerase chain reaction (PCR) system based on the GeneXpert platform that is capable of detecting MTB complexes and rifampicin resistance in less than two hours by detecting the 81 bp rifampicin resistance-determining region of MTB rpoB 507–533 [63]. According to research, Xpert MTB/RIF has been shown to have a sensitivity of 84.7% and specificity of 98.4% as an initial diagnostic method for TB, replacing sputum smear microscopy. It also has a sensitivity of 95.3% and a specificity of 98.8% for detecting rifampicin resistance [64]. Currently, WHO recommends Xpert MTB/RIF as the initial diagnostic method for symptomatic TB patients and initial testing of rifampicin resistance [29].

However, the sensitivity of Xpert MTB/RIF is suboptimal, especially in sputum smear-negative patients and PLWH [29]. To overcome this limitation, a new test kit-Xpert MTB/RIF Ultra was introduced. Compared to Xpert MTB/RIF, the new kit adds two additional targets (IS6110 and IS1081) to the original amplification sequence, significantly reducing the detection limit for MTB from 112.6 CFU/mL to 15.6 CFU/mL [65,66]. It has been shown that Xpert MTB/RIF Ultra is slightly more sensitive than Xpert MTB/RIF in TB detection in sputum smear-negative and HIV-infected individuals [67]. Compared to Xpert MTB/RIF, Xpert MTB/RIF Ultra may be more useful in achieving early diagnosis of TB or drug-resistant TB in high-risk populations.

4.2. Line probe assays (LPAs)

LPAs are a detection method based on deoxyribonucleic acid (DNA) strip reverse hybridization technology. First, DNA is extracted from patient samples and amplified by PCR. The amplification products are hybridized with probes immobilized on nylon membranes (including multiple targets such as MTB genomic key sequences and resistance-associated mutations common to first- and second-line anti-TB drugs), and the results are finally evaluated by enzyme-linked immunochromatography [68]. Although LPAs are technically more complex than Xpert MTB/RIF, their ability to detect resistance to multiple anti-TB drugs, including isoniazid (INH) resistance, and their time-consuming operation make them most suitable for countries with a high TB burden [29]. A *meta*-analysis showed a high diagnostic efficacy of LPAs for rifampicin and INH resistance [69]. The overall sensitivity and specificity of LPAs for detecting rifampicin resistance were 96.7% and 98.8%, respectively, and 90.2% and 99.2%, respectively, for detecting INH resistance compared with phenotypic tests for drug sensitivity, which may be an excellent alternative to phenotypic tests for drug sensitivity, but further large-scale studies are needed in the future. In addition, a study has shown that LPAs have a sensitivity of 94.4% for detecting MTB in sputum smear-positive samples. In contrast, they performed poorly in sputum smear-negative samples, with a sensitivity of 44% only [69]. Therefore, WHO currently recommends LPAs as initial tests for INH/rifampicin resistance in sputum smear/MTB culture-positive patients [29]. The obvious disadvantage of LPAs is the complexity and contamination of the amplification products when subjected to hybridization, which limits their popularization and application. Previous study reported that the sensitivity and specificity of LPAs for MTB detection in HIV-infected individuals were 88.4% and 94.6%, respectively, and their sensitivity in sputum smear-negative samples was 72.5% [70], confirming the applicability of LPAs in HIV-infected populations. However, data from related studies are still limited, and more studies are needed in the future to provide data to support the update of the LPA application policy.

4.3. Lipoarabinomannan (LAM) assay

Lipoarabinomannan (LAM) is an important component of the cell wall of MTB and possesses strong immunogenicity. LAM detection is one of the most widely used methods for specific antigen detection in MTB research. Various tests for LAM in urine and serum have been developed based on its characteristics. However, the sensitivity of detecting LAM antigen in blood is relatively low, particularly in patients coinfected with HIV and TB. Research has primarily focused on urine testing. Lateral flow urine lipoarabinomannan (LF-LAM) testing allows the immediate detection of LAM in urine and can be used for rapid screening and auxiliary diagnosis of ATB [71]. Studies have shown that LF-LAM has suboptimal sensitivity in immunocompetent individuals but performs better in diagnosing MTB infections in HIV-infected individuals, especially in those with lower $CD4^+$ T-cell counts [72]. A *meta*-analysis revealed that the sensitivity and specificity of the LF-LAM assay in HIV-infected individuals were 45% and 92%, respectively, and increased to 56% in patients with $CD4^+$ T cell counts below 100 cells/μL [73]. Despite its lower sensitivity, LF-LAM can be a valuable tool for diagnosing HIV and MTB coinfections in settings with limited diagnostic resources and in patients with immune suppression [71]. As a result, WHO recommends LF-LAM as an auxiliary diagnostic tool for HIV and ATB coinfection in patients with TB symptoms/signs, advanced disease, and $CD4^+$ T-cell counts below 200 cells/μL [74]. According to the recommendations above, the LF-LAM Alere Determine TB LAM Ag (USA) test, referred to as AlereLAM, is the only commercially available urine LAM test that has the potential to assist in the diagnosis of TB in HIV-infected individuals with signs and symptoms of TB and severely immunosuppressed patients admitted to hospitals with advanced HIV disease or with $CD4^+$ T-cell counts of 100 cells/μL, irrespective of their symptoms [75]. Despite these efforts, national programming for the adoption of AlereLAM has been slow, and it has been approved for marketing in only a few countries and regions [76]. Fujifilm SILVAMP TB LAM (Fuji LAM test) is a recently developed more sensitive and specific rapid LAM-based test that can detect lower LAM concentrations than AlereLAM. This technology reduces the detection limit of the LAM concentration in urine by approximately 1/30 compared to AlereLAM by using high-affinity monoclonal antibodies directed toward largely MTB-specific LAM epitopes and adding a silver amplification step, improving the efficiency of TB diagnosis at the point of care [77]. Fuji LAM shows improved sensitivity for diagnosing HIV-infected individuals with ATB compared to previous methods [78,79]. Consequently, Fuji LAM has the potential to be a more efficient diagnostic method for HIV and MTB coinfections, although its widespread adoption and application require further validation.

4.4. Loop-mediated isothermal amplification (LAMP)

LAMP is a nucleic acid amplification detection technique in which the amplification reaction requires specific primers to bind complementarily to six regions on the target genes (*gyrB* and *IS6110*), thereby initiating DNA synthesis and strand replacement reactions in an efficient and specific amplification reaction at a constant temperature of 65 °C. Compared to traditional pathogenic tests, this assay is easy to perform and time-consuming, and the results can be observed visually under UV light. They could be an alternative to sputum smear microscopy in resource-limited areas [29,80]. Domestic and international data show that LAMP has a sensitivity for 78% to 99% and a specificity range from 82% to 96% for the diagnosis of TB and can be used as an alternative to sputum smear microscopy for the diagnosis of adult TB in the presence of symptoms and signs [81,82]. A regional study in Uganda showed that the sensitivity and specificity of LAMP compared to sputum MTB culture in HIV/AIDS patients were 52.3% and 97.1%, respectively [83], indicating a limited role of LAMP in the diagnosis of TB in HIV/AIDS patients. Further research is needed to clarify the applicability of LAMP in HIV/AIDS patients in resource-limited areas and to develop new assays with higher sensitivity.

4.5. Next-generation sequencing technology

Next-generation sequencing (NGS) technology uses the principle of birdshot sequencing to collect all the DNA and ribonucleic acid (RNA) information already present in a specimen, allowing up to millions of DNA fragments to be sequenced simultaneously or independently and thus analyzed for information on the causative microorganism [84]. NGS can be applied to various clinical samples, offering features such as broad-spectrum capability, lack of bias, high sensitivity, and low detection limits. The common technology is metagenomics next generation sequencing (mNGS). A study showed that mNGS was more sensitive than smear, Xpert, and culture methods in the diagnosis of TB [85]. Currently, domestic and international studies have affirmed the diagnostic value of mNGS in central nervous system infections, including tuberculous meningitis [86,87]. Cerebrospinal fluid mNGS testing may be a useful tool for diagnosing central nervous system infections in PLWH [88]. It has also been shown that mNGS technology is more advantageous in sputum-negative extrapulmonary TB patients [89]. Additionally, targeted next generation sequencing technology (tNGS) combined high-throughput sequencing technology with ultra multiplex PCR amplification technology, offering particular advantages in detecting low concentrations of pathogenic bacteria and their resistance genes. Compared with mNGS, tNGS has a well-defined pathogen spectrum, high detection accuracy, and low sequencing cost. The TB detection efficiency in bronchoalveolar lavage fluid (BALF) samples is equivalent to that of Xpert MTB/RIF, more importantly, it can effectively detect INH and other first-line anti-TB drug resistance gene information. However, both mNGS and tNGS have difficulties in clinical application, such as high cost, and difficulty of detecting trace pathogens. Further research in diagnosis of patients with HIV/TB coinfection is still needed.

4.6. Multiplex-polymerase chain reaction (multiplex-PCR) technology

Multiplex PCR technology enables the amplification of multiple target gene sequences in a single PCR experiment, such as *IS6110*, *MPB64*, and *16SrRNA*. It not only enhances the sensitivity for MTB detection [90], but also detect NTM and distinguish the lineage of *Mycobacterium tuberculosis* complex (MTBC) [91–93]. A study showed that multiplex PCR technology also has great advantages in diagnosing cases of EPTB [94]. In diagnosis of HIV coinfected with tuberculous lymphadenitis, the sensitivity of multiplex PCR technology was the highest (91.67%) compared with LAMP and GeneXpert, and had no false positive [95]. In recent years, a considerable number of studies based on multiplex PCR technology have emerged [92,96]. However, the application in HIV-infected individuals is still relatively limited and needs further evaluation since the identification of mycobacterial species and identification ability are quite different.

4.7. Simultaneous use of different methods

To achieve new perspectives on MTB bloodstream infection, different methods for serial measurement of bacillary load in blood were compared. GeneXpert MTB/RIF-Ultra (Xpert-ultra) and Myco/F lytic culture were used after processing the blood through lysis-wash steps to remove LPA inhibitors and anti-microbial drug carry-over. Blood samples of HIV-positive patients predicted to have MTB bloodstream infection were taken 0, 4, 24, 48, and 72 h after anti-TB treatment initiation. Bacillary loads were quantified using microscopy, Xpert-ultra cycle threshold, and culture time-to-positivity. Those were used to characterize the response to anti-TB therapy and its relationship with 12-week mortality [97].

4.8. Molecular correlates of HIV/MTB coinfection

Though HIV-infected individuals may acquire both drug-sensitive and drug-resistant TB, the latter has statistically higher prevalence in the HIV-infected population [98]. Recent studies have shown that this may be due to the spread of such genetic variants of MTB in communities with high prevalence of HIV-infected individuals. MTB Beijing 14717–15 cluster was recently discovered as both multidrug-resistant, hypervirulent, and highly lethal strain circulating in the Far Eastern region of Russia [99]. If markers of an epidemic are found, the chances to encounter drug-sensitive TB diminish remarkably. This results in a treatment paradigm shift and administration of highly effective anti-TB drugs, such as bedaquiline, linezolid, clofazimine, delamanid, pretomanid, and investigational new molecules [100].

5. Discussion

The Global TB Report 2022 stated that TB is the 13th leading cause of death worldwide and the leading cause of death from a single infectious source. It was estimated that there would be 10.6 million new cases of TB worldwide and 1.6 million new deaths in 2021, posing a grave threat to public health. After infection with MTB, only 5%-10% of these infected individuals may develop ATB, while the rest of the infected individuals show latent infection [101]. HIV/AIDS patients are at high risk of MTB infection and are 20 times more likely to develop ATB after infection than HIV-negative individuals [2], so early screening and intervention are crucial for HIV infected populations [102]. Currently, there is no gold standard test method for LTBI, and recognized assays are based on immunological approaches, in which TST and TGRAs are commonly used. However, impaired immunity of HIV-infected individuals reduced the ability to produce IFN-γ, thus causing uncertain test results. Although IGRA technology and skin experimental technology are constantly updated and iterated, and new detection technologies such as IP-10 and omics detection have also been developed, its application accuracy in HIV-infected individuals still needs further exploration.

The dual infection of HIV and MTB can mutually exacerbate disease progression, ultimately leading to dramatic disease progression and even death. To reduce the morbidity and mortality of HIV/MTB coinfection and reduce the transmission of TB, rapid screening and early diagnosis of HIV/MTB coinfections are essential. The clinical symptoms and chest imaging of HIV/MTB co-infected individuals are often atypical, so laboratory tests are usually needed to assist diagnosis (Fig. 2). Pathogen detection is still an important method for laboratory detection of TB. In resource-limited areas, acid-fast staining microscopy and MTB culture are relatively inexpensive, and commonly used to diagnose TB. However, the application of pathogen testing in the

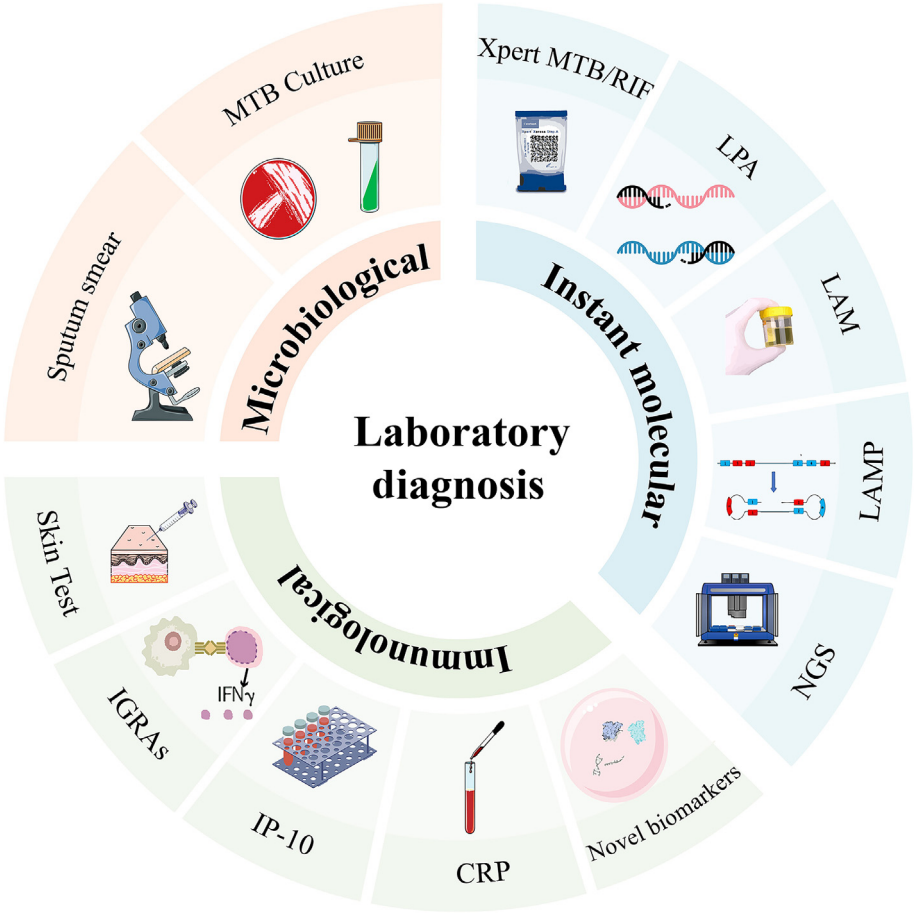

Fig. 2. Current assays for tuberculosis diagnosis in HIV-infected individuals. The inner circle represents the classification of the main TB testing methods used in clinics, including microbiological assays, immunological diagnostic technologies and instant molecular detection. The outermost circle displays the specific testing methods for each category of TB diagnosis. Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus; MTB, *Mycobacterium tuberculosis*; LPA, line probe assay; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; NGS, next-generation sequencing; CRP, C-reactive protein; IP-10, interferon-gamma inducible protein 10; IGRAs, Interferon-gamma release assays. The Figure was partly generated using Servier Medical Art and DBCLS, licensed under the Creative Common Attribution 3.0 Generic License (https://creativecommons.org/licenses/by/3.0/) and the Creative Common Attribution 4.0 Generic License (https://creativecommons.org/licenses/by/4.0/).

population of HIV-positive patients is limited due to its low bacilli excretion and tendency to manifest as extrapulmonary TB. At the same time, the long incubation time and cumbersome operation also greatly affect timely anti-TB treatment. The increasing number of immunological assays offers additional advantages for diagnosis of LTBI, but it cannot distinguish LTBI with ATB. Although the new IGRA and IP-10 assay kits offer greater sensitivity and specificity for HIV/MTB co-infected individuals, they still need to be verified in a multicenter, large sample cohort. In such a context, instant molecular biology techniques including Xpert MTB/RIF, LAMP, LPA, and NGS have been employed to diagnose and characterize TB. They enable rapid, specific, and highly sensitive detection of active pulmonary TB. However, instant molecular biology techniques require expensive instrumentation and reagents as well as professional laboratory facilities and experienced laboratory operators, which limit their application in resource limited areas. For example, the latest recommended Xpert MTB/RIF by WHO is cost-effective in diagnosis of MTB in HIV infected individuals, but its application should consider local implementation conditions and environment [29]. Therefore, cost reduction may be the primary issue for future large-scale applications.

Of note, over the past decades, nontuberculous mycobacteria (NTM) infection is very common in immunocompromised individuals, especially in HIV/AIDS patients, so it is necessary to rule out NTM infection in the diagnosis of MTB infection [103]. Traditional phenotyping is a very cumbersome and time-consuming operation and is unable to identify some of the NTM bacilli to species, which can lead to delays in the initiation of anti-NTB mycobacteria therapy. And, as NTM grows slowly, molecular biology diagnostics have a time advantage here. Based on the above, WHO recommends rapid molecular diagnostics as the initial diagnostic method for NTM [29]. Currently, DNA sequencing is the most common method for identifying and characterizing different NTM species and subspecies [104]. Among them, NGS is widely used because of its high resolution and the ability to track the spread of NTM [105]. However, due to its high cost and dependence on specialized technicians, DNA sequencing cannot be promoted as a routine testing technology in resource-limited countries.

In summary, the detection of HIV coinfection with MTB includes traditional methods such as smear, culture, and immunology as well as a range of molecular detection methods. However, the shortcomings and limitations of various methods are very obvious, and no single detection technique can solve all the problems. The accurate diagnosis of MTB still depends on the clinical manifestations, imaging features and other information of patients. Currently, we still need more promising methods to optimize the diagnostic strategy of TB and to complement the advantages of traditional detection methods with emerging molecular diagnostics.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Jin Sun: Data curation, Writing – original draft. **Xiaoxu Han:** Data curation, Writing – original draft. **Hongxia Yan:** Conceptualization, Writing – original draft. **Xin Zhang:** Writing – review & editing. **Taiyi Jiang:** Writing – review & editing. **Tong Zhang:** Writing – review & editing. **Hao Wu:** Writing – review & editing. **Grigory Kaminskiy:** Writing – review & editing. **Yingmin Ma:** Supervision, Resources. **Eduard Karamov:** Resources, Writing – review & editing. **Bin Su:** Supervision, Resources, Writing – review & editing.

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