FUTURITY Medicine

Citation article: Parra-Vera, H. J., Buele-Chica, D., Farfan Cano, G. G., Solorzano-Bravo, M. Comparative Analysis of Diagnostic Methods for Tuberculosis in an HIV-Positive Patient with Acute Respiratory Failure. *Futur Med [Internet].* 2024;3(4): 38-49. Available from: https://doi.org/10.57125/FEM.2024.12.30.04

Comparative Analysis of Diagnostic Methods for Tuberculosis in an HIV-Positive Patient with Acute Respiratory Failure

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Abstract

Aims: To compare the diagnostic utility of TB LAM testing against the gold standard BAL with GeneXpert in a critically ill patient with advanced HIV.

Methodology: A case report of a 28-year-old man with severe respiratory distress, confirmed HIV (CD4 count of 12 cells/cc³), and negative TB LAM test. Initial treatments included caspofungin, ampicillin-sulbactam, and cotrimoxazole forte. Imaging showed alveolar consolidations, and blood cultures were negative.

Results: Notwithstanding the application of empirically validated therapeutic interventions targeting tuberculosis (TB), fungal infections, and Pneumocystis jirovecii, the patient's clinical status progressively deteriorated, culminating in fatality.

Scientific Novelty: This case highlighted the need for combining urine LAM testing with GeneXpert for accurate TB diagnosis in advanced HIV patients.

Conclusion: GeneXpert is essential for confirming TB and rifampicin resistance, while urine LAM should be complemented with additional tests when clinical suspicion remains high. Incorporating these assessments elevates diagnostic precision and improves patient prognoses.

Keywords: Tuberculosis; HIV; acute respiratory failure; TB LAM; GeneXpert.

Received: May 12, 2024

Revised: May 25, 2024

Accepted: September 9, 2024

Published: October 5, 2024

Introduction

The diagnosis of tuberculosis (TB) in individuals with advanced HIV infection can pose challenges due to atypical clinical manifestations and profound immunosuppression. TB is the primary cause of mortality among individuals

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DOI: https://doi.org/10.57125/FEM.2024.12.30.04

infected with HIV, especially in countries with limited resources. Molecular technologies, such as the Xpert MTB/RIF assay, typically require a laboratory infrastructure that is frequently unavailable in peripheral healthcare facilities. Additionally, these technologies often require sputum samples, which can be challenging to provide for severely ill patients [1, 2].

TB is the top killer of people with HIV, causing around 300,000 deaths in 2017 [3]. Individuals afflicted with HIV are at a significantly higher risk of developing active TB due to their weakened immune systems, which can be up to 20 times more likely to occur [3]. The diagnosis of TB in HIV-positive patients is challenging because of atypical presentations and severe immunosuppression, which often result in missed or delayed diagnoses. Conventional diagnostic modalities like sputum microscopy and culture often prove inadequate in detecting tuberculosis (TB) in this demographic, especially within resource-constrained environments [3].

Advanced diagnostic tools such as the GeneXpert MTB/RIF assay and TB LAM tests have demonstrated potential in enhancing TB detection rates among HIV-positive individuals, but their integration into clinical practice faces several barriers, including the need for adequate infrastructure and training [3, 4].

The LAM assay is a rapid urine test for HIV that detects lipoarabinomannan and is valuable for diagnosing TB. It is easy to administer and provides results in 25 min, making it useful for hospitalised HIV patients who are too ill to produce sputum. Although the sensitivity of the test relies on the CD4 count, it has been shown to decrease mortality in hospitalised patients with TB symptoms. However, its use in sub-Saharan African countries remains limited. Therefore, it is crucial to conduct rapid testing. The WHO recommends LAM tests for HIV-positive patients with advanced disease or CD4 counts < 200 cells/μL in inpatient settings, regardless of TB symptoms. The current evaluation suggests that using LAM testing for all HIV patients in medical wards, regardless of TB symptoms and CD4 counts, and assessing mortality six months after admission based on test results, stresses the need for more sensitive and reliable diagnostic tests in resource-limited settings [5, 6].

Case Presentation

Background

This case report described the clinical course and management of a 28-year-old male patient who presented to the emergency department on May 2, 2024, with severe respiratory distress. Despite aggressive medical interventions, the patient's condition deteriorated, and he succumbed to the illness on May 17, 2024 (Table 1).

Table 1. Timeline of diagnostic steps and treatment

Date	Event
May 1, 2024	CT of the chest showed significant pulmonary involvement with ground-glass opacities and areas of consolidation.
May 2, 2024	Admission to the emergency department with severe respiratory distress. Initial treatment included caspofungin, ampicillin-sulbactam, and cotrimoxazole forte. Two fourth-generation HIV tests confirmed HIV, and the patient had a CD4 count of 12 cells/cc^3. Initial lab results showed reactive HIV 1+2, leukocytes 4.0, hemoglobin 10.0, hematocrit 30.0, urea 19.39 mg/dL, creatinine 0.7 mg/dL, AST 51.41 U/L, and ALT 32.38 U/L.
May 3, 2024	Admission to the Intensive Care Unit (ICU).
May 5, 2024	First intubation and placement of a central venous catheter (CVC).
May 6, 2024	Negative SARS-CoV-2 antigen test, negative Ziehl-Neelsen stain in sputum, recommendation for BAL and PCR testing. The blood cultures were negative for both aerobes and anaerobes.
May 7, 2024	Unplanned extubation at 05:30 AM.
May 8, 2024	Start of caspofungin treatment. Prothrombin time 13.6 seconds, INR 1.06, and TTP 29.7 seconds.
May 10, 2024	Reintubation.
May 12, 2024	Negative urine culture for TB-DNA PCR.
May 13, 2024	Change of CVC and nasogastric tube. Negative urine culture.
May 14, 2024	Start of colistin treatment.

May 16, 2024	Tracheal secretion culture identified *Acinetobacter baumannii* resistant to multiple antibiotics. TB LAM and GeneXpert tests were both negative. Tracheal secretion culture showed *Acinetobacter baumannii* resistant to multiple antibiotics, with no fungal structures observed.
May 17, 2024	Despite exhaustive medical intervention, the patient succumbed to his illness, and the time of death was declared at 16:25.

Source: clinical history of the patients; TB-DNA PCR: Detection of Mycobacterium tuberculosis AND by PCR-RT; TTP Thromboplastin Time; INR international normalised ratio;

Clinical Presentation and Initial Management

The patient presented with severe respiratory distress on May 2, 2024. The initial treatment included caspofungin, ampicillin-sulbactam, and cotrimoxazole forte. Diagnostic tests confirmed HIV with a COI greater than 1.0 and a critically low CD4 count of 12 cells/cc³. A chest CT scan performed on May 1, 2024, revealed significant pulmonary involvement with ground-glass opacities and areas of consolidation (Figure 1a-d).

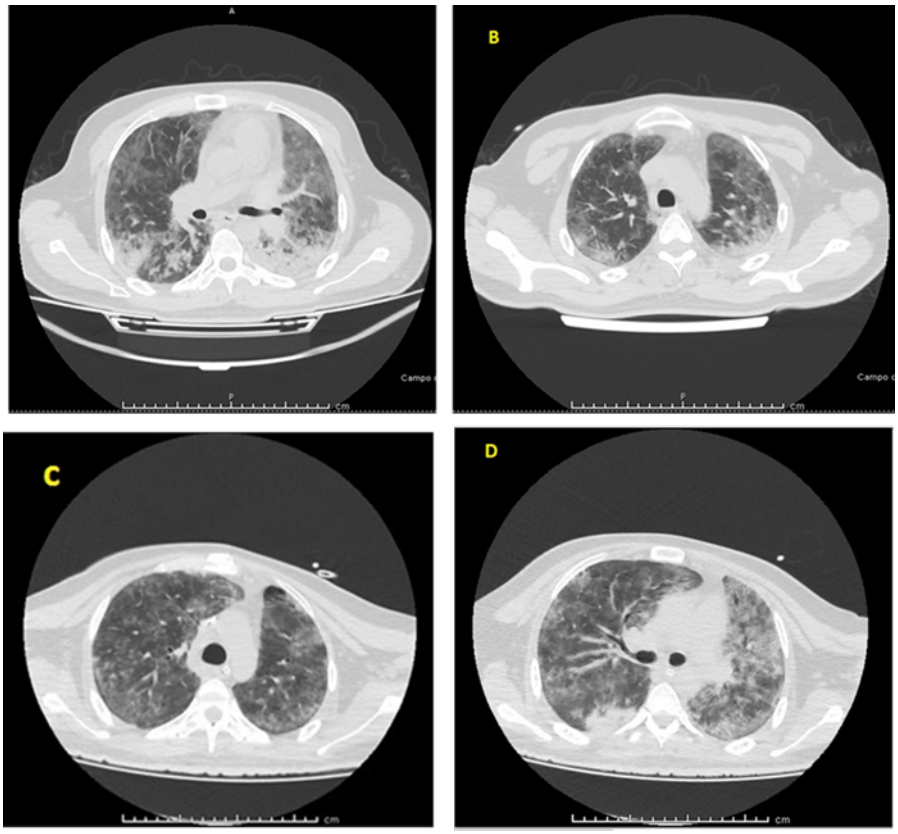

Figure 1. Computed Tomography of the Chest

Source: Synapse Imaging System, Hospital Los Ceibos

The CT images demonstrated lesions in both lung parenchymas, characterized by ground-glass opacity and peripheral alveolar interstitial patterns with areas of air bronchograms, consistent with pneumonia.

The patients' history of antimicrobial treatment is summarised in Table 2. He was treated with various antimicrobials to treat his infections. Imipenem was administered at a dosage of 1 g every 8 h, starting on May 5, 2024. Linezolid was introduced on May 6, 2024, at a dose of 600 mg intravenously every 12 h. TMP/SMX was administered at 1600 mg+320 mg every 8 h on May 2, 2024. Caspofungin (50 mg daily) was added on May 8, 2024, and colistin was introduced on May 14, 2024, with an initial IV dose of 300 mg, followed by 100 mg every 8 h.

Table 2. History of antimicrobial treatment

Medication	Dosage and Frequency	Start Date
Imipenem	1g every 8 hours	May 5, 2024
Linezolid	600 mg IV every 12 hours	May 6, 2024
TMP/SMX	1600mg+320mg every 8 hours	May 2, 2024
Caspofungin	50 mg daily	May 8, 2024
Colistin	300 mg IV stat, then 100 mg every 8 hours	May 14, 2024

Source: Clinical history of the patients

Laboratory and Diagnostic Findings

Additional diagnostic and laboratory findings are presented in Table 3. On May 1, 2024, a computed tomography (CT) scan revealed significant pulmonary involvement. Initial laboratory results on May 2, 2024, confirmed reactive HIV 1+2 with leukocytes at 4.0 x10^9/L, hemoglobin at 10.0 g/dL, hematocrit at 30.0%, urea at 19.39 mg/dL, creatinine at 0.7 mg/dL, AST at 51.41 U/L, and ALT at 32.38 U/L. Tests on May 6, 2024, showed negative results for SARS-CoV-2 antigen and Ziehl-Neelsen stain in sputum, with recommendations for BAL and PCR testing. On May 8, 2024, coagulation parameters were assessed, revealing a prothrombin time of 13.6 seconds, INR of 1.06, and TTP of 29.7 seconds. The urine culture results on May 13, 2024, were negative. A tracheal secretion culture on May 16, 2024, identified Acinetobacter baumannii resistant to multiple antibiotics, with no fungal structures observed.

Table 3. Additional Diagnostic and Laboratory Findings

Date	Finding
May 1, 2024	CT of the chest showed significant pulmonary involvement with ground-glass opacities and areas of consolidation.
May 2, 2024	Initial lab results: reactive HIV 1+2, leukocytes 4.0, hemoglobin 10.0, hematocrit 30.0, urea 19.39 mg/dL, creatinine 0.7 mg/dL, AST 51.41 U/L, and ALT 32.38 U/L.
May 6, 2024	Negative SARS-CoV-2 antigen, negative Ziehl-Neelsen stain in sputum, and recommendation for BAL and PCR testing.
May 8, 2024	Prothrombin time 13.6 seconds, INR 1.06, and TTP 29.7 seconds.
May 13, 2024	Negative urine culture.
May 16, 2024	Tracheal secretion culture showed *Acinetobacter baumannii* resistant to multiple antibiotics, with no fungal structures observed.

Source : Clinical histories of the patients

Despite the implementation of aggressive antimicrobial therapy, including coverage for multidrug-resistant *Acinetobacter baumannii*, the patient's clinical status continued to decline. On May 7, 2024, the patient experienced unplanned extubation and required multiple reintubations due to respiratory failure.

Considering the patient's precarious state and recent HIV diagnosis, the administration of anti-TB medications was halted subsequent to negative TB LAM and GeneXpert test outcomes. The patient was administered an extended antimicrobial regimen, including imipenem, TMP/SMX, colistin, and amphotericin B. Despite these interventions, the patient remained hemodynamically unstable and required vasopressor support.

On May 17, 2024, despite extensive medical efforts, the patient ultimately succumbed to his illness and death was declared at 16:25.

Research Problem

The patient had no known history of TB, although Ecuador is a TB endemic country, and there was no significant family history of respiratory or infectious diseases. He presented with acute respiratory failure, initially suspected to

be pneumonia, and had no prior symptoms typical of TB such as weight loss, night sweats, or persistent cough. He was diagnosed with HIV upon emergency admission and had not yet started antiretroviral therapy.

Objectives

- To evaluate the diagnostic utility of TB LAM in urine and BAL with GeneXpert for TB in critically ill patients with HIV.

Research Results

The diagnostic pathway for this patient involved several critical decision points owing to the complexities of managing dual infections in severely immunosuppressed individuals. The initiation of broad-spectrum antimicrobial therapy was guided by the patient's severe respiratory distress and suspected opportunistic infections due to their HIV-positive status. The CT scan results on May 1, 2024, indicated significant pulmonary involvement, leading to the need for further diagnostic testing (Figure 1a and 1b).

Upon the confirmation of HIV infection, the patient's critically low CD4 count necessitated the use of advanced diagnostic tools to identify potential co-infections. The negative results for SARS-CoV-2 and initial sputum testing directed the medical team to consider other opportunistic infections, including TB. Given the patient's severe immunosuppression, the possibility of paucibacillary TB, for which traditional sputum-based diagnostics might be insufficient, was considered.

TB LAM and GeneXpert tests were used to rapidly and accurately diagnose the patient without requiring sputum samples. TB LAM, with its quick point-of-care test and suitability for patients with low CD4 counts, was used despite its low sensitivity. GeneXpert, with its high sensitivity and specificity for M. TB and rifampicin resistance, was also used.

Diagnostic Pathway

The diagnostic pathway for this patient is shown in Figure 2. The initial step involved the administration of broad-spectrum antimicrobials due to severe respiratory distress and suspected opportunistic infections. A CT scan performed on May 1, 2024, revealed significant pulmonary involvement characterized by ground-glass opacities and areas of consolidation (Figure 1a and 1b). Following confirmation of HIV infection and a critically low CD4 count, advanced diagnostic tools are required. Negative results from SARS-CoV-2 and sputum testing have shifted the diagnostic focus towards TB and other opportunistic infections. Owing to severe immunosuppression, paucibacillary TB should be considered, as traditional sputum diagnostics might be insufficient. The TB LAM test provides a rapid point-of-care diagnostic tool for patients with low CD4 counts. Finally, the GeneXpert test was used because of its high sensitivity and specificity in detecting *Mycobacterium tuberculosis* and rifampicin resistance.

The figure provides a visual summary of the diagnostic steps and rationale for each decision, emphasising the integration of various diagnostic tools to enhance the accuracy in critically ill patients.

Figure 2. Diagnostic Pathway

Source: Author's own development

The following table provides a comprehensive comparison of diagnostic tests for TB, particularly in HIV-positive patients. Table 4 highlights the sensitivity, specificity, and time to the results of the various diagnostic methods used to detect TB. This comprises the TB LAM test, exhibiting a sensitivity range of 21-54% and delivering results within 25 minutes, rendering it appropriate for critically ill patients unable to produce sputum.

Table 4. Comparative Summary of Diagnostic Tests

Diagnostic Test	*Sensitivity*	*Specificity*	*Time to Results*	*Notes*
TB LAM	21-54% (improves with CD4 <100)	95%	25 minutes	Suitable for severely ill patients unable to produce sputum, dependent on immunosuppression level.
GeneXpert MTB/RIF	72.5-99.0% (varies by sample type)	98.0-99.4%	2 hours	High specificity for TB and rifampicin resistance; requires laboratory infrastructure.
Sputum Ziehl-Neelsen Stain	Low in HIV-positive, paucibacillary patients	High	Several hours to days	Often fails to detect TB in severely immunocompromised patients.
PCR for Tuberculosis	Variable, generally high	High	Several hours to days	Requires respiratory samples, may not be effective in paucibacillary cases.
Blood Cultures	Varies	Varies	Several days	Negative for aerobes and anaerobes in this case.

Source: Author's own development

Additionally, the GeneXpert MTB/RIF test, with a sensitivity ranging from 72.5-99% and a specificity of 98.0-99.4%, delivers results within 2 h but requires proper laboratory infrastructure. Although highly specific, the sputum Ziehl-

Neelsen stain has low sensitivity in HIV-positive, paucibacillary patients and can take several hours to days to obtain results. PCR DNA-TB is generally sensitive and specific but requires respiratory samples and can be ineffective in paucibacillary cases, taking several hours to days to obtain results. Blood cultures, which vary in sensitivity and specificity and take several days to obtain results, were negative for both aerobes and anaerobes.

This case emphasised the necessity of using various diagnostic tools in order to detect TB and other opportunistic infections in severely immunocompromised patients. The adoption of these tactics can improve patient outcomes and inform clinical practice, particularly in regions with limited resources. Policymakers should consider providing support for the widespread implementation of these diagnostic tools by increasing funding, developing infrastructure, and offering training programs.

Such policy changes could lead to substantial improvements in TB control among HIV-positive populations as well as contribute to the achievement of the broader objectives of reducing TB-related deaths and enhancing global public health outcomes. To further improve (Figure 3) TB diagnosis in HIV-infected patients, further research is imperative to develop novel diagnostic instruments that can supplement the current methodologies, thereby facilitating a more comprehensive approach. Certain specific domains necessitate additional exploration.

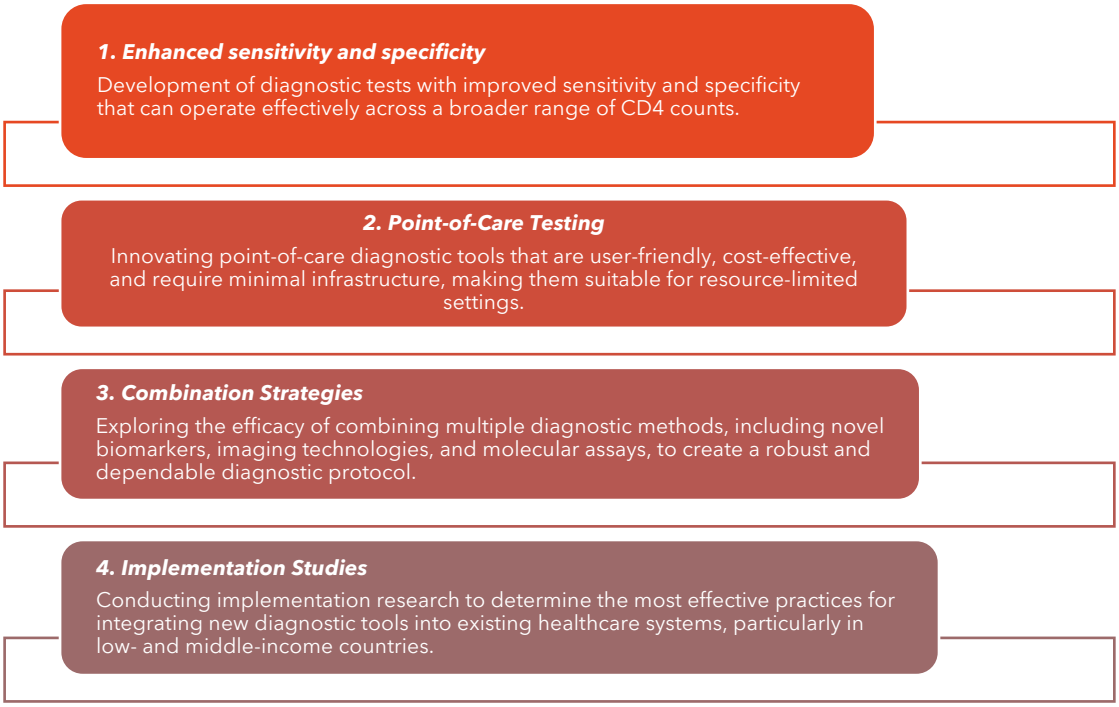

Figure 3. Directions for Enhancing TB Diagnosis in HIV Patients in Resource-limited Settings.

Source: Author's own development

The medical community has the potential to achieve substantial advancements in the realm of tuberculosis (TB) diagnosis by focusing its efforts on these pivotal domains, which will ultimately result in improved health outcomes for HIV-positive patients globally.

Discussion

The patient's clinical course was complicated by the presence of multidrug-resistant *Acinetobacter baumannii* and a critically low CD4 count, indicative of advanced HIV. Despite the administration of an extensive antimicrobial regimen, including imipenem, TMP/SMX, colistin, and amphotericin B, the patient remained hemodynamically unstable and required vasopressor support. The insufficient availability of advanced molecular diagnostics has exacerbated the complexity of opportunistic infection management. The diagnosis of tuberculosis in HIV-positive patients poses considerable challenges, primarily due to the prevalence of advanced immunosuppression, which often results in a paucibacillary disease [1,2,7,8]. Traditional diagnostic techniques, including sputum microscopy and culture, frequently fail to detect TB in this population. Nevertheless, incorporating innovative diagnostic technologies, such as the Alere Determine™ TB LAM Ag (AlereLAM), can help improving the detection rates [9] the

use of the Xpert MTB/RIF assay in combination with the standard tuberculosis (TB) test has demonstrated the potential to increase the detection rates of TB among HIV-positive individuals [10].

Urine LAM Testing

The AlereLAM test detects the lipoarabinomannan (LAM) antigen in urine samples, offering a noninvasive, rapid, and easy-to-perform diagnostic technique. It is particularly useful for patients with advanced HIV and CD4 counts ≤ 200 cells/mm³. Despite its benefits, the sensitivity of the AlereLAM test ranges from 21% to 54%, improving in patients with CD4 counts < 100. While the specificity remains robust at 95%, the persistence of false negatives remains a concern attributable to diminished levels of LAM or fluctuations in LAM production. The WHO recommends the use of urine LAM testing in HIV patients with CD4 counts ≤ 200 cells/mm³ [7,11–14].

A comprehensive review of the literature indicates that LF-LAM has low sensitivity for TB diagnosis and screening in HIV-positive adults [12,15,16]. The combination of LF-LAM with sputum microscopy can increase sensitivity but often at the expense of specificity [17,18]. This test is particularly beneficial for diagnosing TB in HIV-positive individuals with low CD4 counts, who are seriously ill [11–13,15–19].

GeneXpert MTB/RIF Assay

The GeneXpert MTB/RIF assay is critical for rapid detection of Mycobacterium tuberculosis (MTB) and rifampicin resistance (RIF) [10,11,20–23]. It exhibits high specificity and possesses the capability to analyze a wide array of respiratory and non-respiratory samples. The sensitivity of respiratory samples was 100%, with a specificity of 99.4%. However, it does not distinguish between live and dead bacilli, which limits its use in treatment monitoring. In Uruguay, GeneXpert has proven valuable for rapid TB diagnosis in pediatric patients, although positive RIF resistance results should be confirmed with culture tests owing to its low resistance prevalence [20].

The latest version, Xpert Ultra, improves rifampicin resistance detection through melting temperature (Tm) analysis, enhancing its accuracy compared to its predecessor. However, systematic errors, including false RR and RS results, have been reported [24,25].

Integration and Performance in Clinical Practice

In a study of 320 HIV-infected adults, the mean age was 33 years (51% male). Among the participants, 17% had culture-confirmed TB and 4% were clinically suspected of having TB. The diagnostic sensitivity and specificity of the urine LAM test varied with the band intensity used as the threshold for positivity. A single LAM test identified an additional 26% of participants with culture-confirmed TB compared to sputum AFB testing alone [26].

The study conducted by Gupta-Wright et al. (2016) identified 161 citations, out of which 49 studies underwent comprehensive full-text review. Subsequently, 10 studies were deemed suitable for inclusion in the systematic review and meta-analysis. The range of urinary LAM-positive TB cases ranged from 22% to 65%, with hospital inpatients exhibiting a higher proportion than outpatients. Across all studies, there was a two-fold increased mortality risk in the urinary LAM-positive TB cases compared to LAM-negative cases, with a pooled summary estimate of RR 2.3 (95% CI 1.6–3.1) [27].

The integration of the GeneXpert and LAM tests into clinical practice algorithms for HIV-infected patients is crucial. In a study of hospitalised HIV-infected patients, combining the Xpert and LAM tests provided better diagnostic performance than either test alone. Sequential and concurrent testing strategies increase sensitivity, particularly in patients with CD4 counts ≤ 50 cells/mm³ [11, 28, 29].

Sensitivity and Specificity in Different Settings

For TB screening, LF-LAM's sensitivity and specificity of the LF-LAM significantly vary, with sensitivity estimates ranging from 0% to 58% and specificity estimates ranging from 90% to 97% [12]. Combining LF-LAM with other diagnostic tests, such as sputum microscopy or GeneXpert MTB/RIF, can improve sensitivity but often reduces specificity [16,18,28,30]. Therefore, LF-LAM should be considered as part of a broader diagnostic strategy rather than a standalone test [12,15,31].

Overall, among adults with CD4 counts <100 cells/mm³, the urine LAM sensitivity was notably higher than that among adults with CD4 counts ≥100 cells/mm³ [12, 14, 19, 26, 32–34]. This underscores the importance of considering CD4 count thresholds when interpreting the LAM test results in clinical practice.

Summary of Recent Studies

In the DETECT-TB study, 532 participants underwent classification of their tuberculosis (TB) status and retrospective FujiLAM testing, while 389 participants contributed paired samples. Out of the 43 participants diagnosed with TB, 29 were detected through FujiLAM testing, resulting in a sensitivity of 67.4%. Thirty participants were identified by testing a morning urine sample, with a sensitivity of 69.8%. A two-sample strategy increased the sensitivity to 74.4%, but the specificity decreased slightly from 90.2% to 87.3 %. [19]. The FujiLAM testing strategy's

performance remained consistent across different subgroups, except for women's morning urine samples, where the specificity decreased significantly compared to spot urine samples.

Practical Recommendations and Implementation in Resource-Limited Settings

To effectively implement the urine LAM and GeneXpert tests in resource-limited settings, it is essential to address several barriers including the cost, infrastructure, and training. The healthcare providers should prioritise the following strategies, as illustrated in Figure 4.

Figure 4. Strategies for Implementing Urine LAM and GeneXpert Testing in Resource-limited Settings. Source: Author's own development

Source: Author's own development

By integrating these diagnostic tools into clinical protocols and addressing barriers to their implementation, the healthcare providers can significantly improve the detection and management of TB in HIV-positive patients, ultimately reducing mortality and improving patient outcomes.

Conclusions and Implications

This case highlighted the challenges in managing severe respiratory distress in HIV-positive patients with multidrug-resistant infections in a resource-limited setting. Despite aggressive and comprehensive treatment, the patient's condition continued to deteriorate, ultimately resulting in death. This underscored the importance of timely diagnosis, availability of advanced diagnostic tools, and early initiation of ART for managing HIV-positive patients with critical infections.

Suggestions for Future Research

Future research should focus on refining diagnostic protocols for TB in critically ill patients with severe immunosuppression. Investigating the efficacy of TB LAM and GeneXpert in diverse clinical settings and among different patient populations will be crucial. Studies could explore the integration of these tests with novel biomarkers and imaging techniques to improve diagnostic accuracy and speed. Additionally, research should evaluate the impact of early and accurate TB detection on patient outcomes, particularly in those with concurrent opportunistic infections. Comparative studies assessing the cost-effectiveness and practical implementation of various diagnostic strategies will provide valuable insights for optimizing care in similar clinical scenarios.

Declarations

Author Contributions

Conceptualisation, Parra-Vera Henry and Farfán Cano Galo; methodology, Farfán Cano Galo; software, not applicable; validation, Parra-Vera Henry, Buele-Chica Daicy, Farfán Cano Galo, and Solorzano-Bravo María; formal analysis, Parra-Vera Henry and Buele-Chica Daicy; investigation, Farfán Cano Galo and Solorzano Bravo María; resources, Farfán Cano Galo; data curation, Farfán Cano Galo; writing—original draft preparation, Parra-Vera Henry, Buele-Chica Daicy, Cano Galo and Solorzano Bravo María; writing—review and editing, Farfán Cano Galo; visualization, Parra-Vera Henry; supervision, Farfán Cano Galo; project administration, Farfán Cano Galo; funding acquisition, not applicable. All the authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data sharing was not applicable; no new data were created or analysed in this study. Data sharing was not applicable in this study.

Funding

No funding was received for this study.

Acknowledgements

We thank the medical and nursing staff of the ICU at the Hospital General del Norte de Guayaquil Los Ceibos for their support and dedication in managing this case.

Institutional Review Board Statement

Not Applicable. The investigation was conducted in an observational and retrospective manner, and ethical review and approval were exempted.

Informed Consent Statement

Consent was procured from the family of the patient after providing them with comprehensive information regarding the procedures and potential outcomes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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