Clinical Outcomes of New Algorithm for Diagnosis and Treatment of Tuberculosis Sepsis in HIV Patients

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Abstract

Background: Despite effort to diagnose tuberculosis (TB) in the Human Immunodeficiency Virus (HIV) infected population, 45% of adults with HIV that had a previously unknown reason for death, demonstrated TB was the cause by autopsy examination. We aimed to assess the clinical outcomes of implementation a new algorithm for diagnosis and treatment of tuberculosis (TB) related sepsis among PLHIV presenting with life-threatening illness. Methods: This study is a prospective cohort conducted in three-referral hospitals in Kilimanjaro, recruited 97 PLHIV from February through June 2018. Patients provided urine and sputum samples for testing lateral flow – lipoarabinomannan (LF-LAM) and Xpert Mycobacterium tuberculosis (MTB)/rifampicin (RIF) assays, respectively. Anti-TB was prescribed to patients with positive LF-LAM or Xpert MTB/RIF or received broad-spectrum antibiotics but deteriorated. Results: Of 97 patients, 84 (87%) provided urine and sputum, and 13 (13%) provided only urine. The mean age (95% confidence interval) was 40 (38–43) years and 52 (54%) were female. In 84 patients, LF-LAM increased TB detection from 26 (31%) by Xpert MTB/RIF to 41 (55%) by both tests. Of 97 patients, 69 (71%) prescribed anti-TB, 16 (16.5%) patients died, of which one died before treatment, 73% (11/15) died within 7 days of admission. The 30-day survival was similar in both treatment groups (log rank = 0.1574). Mortality was 67% (46/69) and 33% (23/69) had definitive and probable TB respectively. Sixteen (16.5%) patients died, of which one died before treatment, LF-LAM increased TB detection from 26 (31%) by Xpert MTB/RIF to 41 (55%) by both tests. Of 97 patients, 69 (71%) prescribed anti-TB, 16 (16.5%) patients died, of which one died before treatment, 73% (11/15) died within 7 days of admission. The 30-day survival was similar in both treatment groups (log rank = 0.1574). Mortality was 67% (46/69) and 33% (23/69) had definitive and probable TB respectively. Sixteen (16.5%) patients died, of which one died before treatment.

Keywords: Lateral flow, lipoarabinomannan, PLHIV- danger signs, tuberculosis

Introduction

Tuberculosis (TB) is the leading cause of death among People living with human immunodeficiency virus (PLHIV), and use it consistently. Unlike patients with pulmonary TB (PTB) without HIV, those with TB/HIV coinfection have atypical clinical presentations which make definitive diagnosis challenging.[1,2] In advanced HIV disease, many patients present with disseminated TB, including bloodstream infection and extrapulmonary locations such as lymph nodes, meninges, and the pleural space.[3,4] TB in these forms may also predispose to the clinical presentation of TB-related sepsis; the life-threatening systemic immune dysregulation manifest by organ dysfunction. Furthermore, these conditions often present with paucibacillary disease in the lungs and sputum, and/or the person is unable to expectorate quality sputa due to clinical deterioration, and thus, sputum testing by smear microscopy for acid-fast bacilli, culture systems, or rapid molecular tests such as the Xpert Mycobacterium tuberculosis (MTB)/rifampicin (RIF) assay are all of diminished sensitivity compared to classical cases of PTB without HIV.[5-7]

Conclusion: Implementation of new algorithm increased TB case detection in patients that could have been missed by Xpert MTB/RIF assay. Survival of PLHIV with confirmed or probable TB was significantly higher among hospitalized patients compared to outpatients (P ≤ 0.027).

Keywords: Lateral flow, lipoarabinomannan, PLHIV- danger signs, tuberculosis

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Prevalence and incidence of tuberculosis (TB) among patients with human immunodeficiency virus (HIV) infection varies by geographical location. Previously, the World Health Organization (WHO) recommended screening of TB in PLHIV with a four-symptom screening tool that included cough, weight loss, fever, and night sweats.\(^{[8]}\) Yet, evaluation of the sensitivity and specificity of the four-symptom screening tool from multiple research studies found it neither sensitive nor specific.\(^{[9]}\) Furthermore, Gupta et al. conducted a systematic review and meta-analysis of autopsy studies and reported that 45% of deaths in HIV-infected adults were secondary to undiagnosed TB disease, and the proportion of TB attributable deaths was greatest in settings with the highest regional prevalence of TB.\(^{[10]}\) Given these trends, in 2016, the WHO released guideline recommendations for a new algorithm to optimize TB diagnosis and treatment among PLWH in TB-endemic settings.\(^{[11]}\) The algorithm recommends presuming TB in PLWH presenting with serious illness defined as having one or more of the following danger signs: respiratory rate >30/min; temperature >39°C; heart rate >120/min; or unable to walk unaided and/or CD4 count <100 cells/µL. The guideline recommends all PLWH presenting with one or more of these danger signs should provide a urine sample for TB testing by the lateral flow lipoarabinomannan (LF-LAM) assay.\(^{[12]}\) Furthermore, patients who are able to produce sputa should be additionally tested using the Xpert MTB/RIF assay or culture (if available).\(^{[12]}\) If a TB diagnosis is confirmed by either of these tests, anti-TB medication should be provided; otherwise, a broad-spectrum antibiotic should be prescribed. Patients prescribed broad-spectrum antibiotics are then assessed at approximately day 5, and if their condition has worsened and another alternative diagnosis is not established, then empirical anti-TB treatment is recommended.

To date, there has not been widespread uptake of the algorithm in HIV/TB coendemic settings, and before this study, we were not aware of its systematic use in Tanzania. This study aimed to determine the clinical impact, including time to TB treatment initiation, and the treatment outcomes of implementing the new algorithm for diagnosis and treatment of TB-related sepsis among PLWH presenting to care with danger signs in three healthcare settings in northern Tanzania. Given the high mortality with undiagnosed TB in this clinical presentation, we hypothesized that introduction of the algorithm would result in similar survival between PLWH treated for TB and those treated with broad-spectrum antibiotics alone.

**Methods**

**Study setting**

Kibong’oto Infectious Diseases Hospital (KIDH), a national referral hospital for TB, Kilimanjaro Christian Medical Center (KCMC), a zonal referral hospital for the Northern Tanzania, and Mawenzi Regional Referral Hospital (MRRH), all located in the Kilimanjaro region of Tanzania, piloted the algorithm. At all three sites, PLWH seek care through outpatient departments (OPD) and emergency departments/inpatient care units.

**Study design and population**

Within a prospective cohort design, PLWH were successfully screened for eligibility by an attending clinician either on arriving at the OPD or in the admitting ward. They were enrolled if they met the following inclusion criteria: (i) willingness to sign the informed consent, (ii) >18 years of age, and (iii) either presence of one or more of the 4 stated danger signs regardless of CD4 count or exclusively CD4 count <100 cells/µL. Participants were excluded if they were taking anti-TB treatment. Eligible participants were followed for a maximum of 30 days to determine sepsis survival rates.

**Sample collection for Xpert Mycobacterium tuberculosis/rifampicin and lateral flow lipoarabinomannan test**

Each eligible patient provided midstream urine and sputum samples in fresh standardized sterile containers for testing by LF-LAM and Xpert MTB/RIF, respectively. If a patient could not spontaneously void, then urine was collected via catheter. All samples were collected on the same day. During sputum sample collection, the patient was instructed to take a deep breath, hold for a moment, and cough into the sputum container. In case a participant could not expectorate sputum, only urine was collected. Blood for CD4 + T-cell count testing was collected at baseline, unless the patient had CD4 + T-cell count testing results performed within the last 6 months.

**Determine tuberculosis lipoarabinomannan assay**

The determine TB LAM assay (Alere Inc., Waltham, MA), here abbreviated as LF-LAM, detects lipoarabinomannan, a structural component of the outer cell wall of mycobacteria, that is metabolized and excreted by the kidney, and can be recovered from urine. In this study, testing was performed either at the bedside or OPD in accordance with the manufacturer’s instructions.\(^{[12]}\) Briefly, 60 µL of urine was applied to the white sample pad of the test strip. Results were read after 25 min but not beyond 30 min. A patient’s results and that of the control bar were interpreted against the reference scale card provided by the manufacturer. Results were positive if two bar lines for both the patient and control were formed. A single line was regarded as a negative test. All results were recorded in the patient’s chart for the admitting clinician to make a treatment decision.

**Xpert Mycobacterium tuberculosis/rifampicin assay**

Sputum specimens were tested by Xpert MTB/RIF assay (Cepheid, USA) as previously described.\(^{[13,14]}\) Briefly, 1 mL of sputum was mixed with 2 mLs of sample reagent, shaken to homogenize, followed by 15 min incubation at room temperature. Thereafter, 2 mLs of homogenized sputum was transferred into the cartridge before it was loaded into the Xpert MTB/ RIF machine to proceed with automatic DNA extraction, amplification and detection of *M. tuberculosis* complex (MTBC). Based on this assay, MTBC is susceptible to rifampicin when there is no mutation(s) on rifampicin resistant determining region of the rpoB gene.

**Follow-up during treatment**

Patients with positive LF-LAM test results started four-drug
anti-TB regimens with weight-based oral RIF, isoniazid, pyrazinamide and ethambutol. Those with negative LF-LAM results were prescribed broad-spectrum antibiotics such as third-generation cephalosporins (ceftriaxone) or amoxicillin/clavulanic acid (co-amoxiclav), respectively, as per Tanzania standard guideline [Figure 1]. For patients with negative LF-LAM results but later found to have a positive Xpert MTB/RIF assay, broad-spectrum antibiotics were stopped at that time and the anti-TB regimen was started. Other standards of care such as chest radiograph, urinalysis, and other microbiological testing were left to the decision of the attending clinician. All patients were evaluated for either worsening or improvement of danger signs at day 5–7 posttreatment. If danger signs persisted or worsened among patients receiving broad-spectrum antibiotics at any of these days of assessment, they were switched to anti-TB medications. Assessment for the final outcome of survival was performed at 30 days of treatment. Patients who recovered and were discharged from the hospital were contacted by telephone either directly or through their next of kin or district TB and HIV coordinators.

**Data management and statistical analysis**
Mean with standard deviation and/or median with 25th and 75th interquartile range were used to summarize parametric and nonparametric continuous variables respectively. Comparisons of categorical variables such as frequencies and proportions of PLWH screened, diagnosed, and prescribed anti-TB medicine and broad-spectrum antibiotics were performed using the Pearson Chi-square test. Independent t-test and Mann–Whitney U-tests were respectively used to summarize parametric and nonparametric continuous variables such as age, CD4+ T-cells, and vital signs. Overall mortality was compared between patients that received anti-TB medications and those that received broad-spectrum antibiotics only, and were stratified between patients with definitive TB (positive LF-LAM or Xpert MTB/RIF), probable TB (both tests are negative but treated empirically for TB) and unlikely TB (treated with broad-spectrum antibiotic only). 95% confidence interval (CI) that did not include 1.0 and \( P \leq 0.05 \) were considered statistically significant. All analyses were performed using Statistical Package for Social Sciences version 24.0. (IBM SPSS, Armonk, NY, USA).

**Ethical approval**
Approval to conduct the study was obtained from the Kilimanjaro Christian Medical University College Ethical Committee on October 4, 2017, with reference number 2033. Permission to conduct the study was granted from KIDH, KCMC, and MRRH authorities. All eligible participants signed informed consent before enrollment into the study.

![Figure 1](image-url)
RESULTS

Baseline characteristics of study participants
From February through June 2018, a total of 116 PLHW were screened for eligibility criteria. Of these, 97 (84%) were enrolled [Figure 2]. Of 97 participants, 52 (54%) were female. The median age and CD4 + T-cell count was 40 (95% CI: 38–43) years and 114 (36–234) cells/mm³, respectively [Table 1]. Seventy-seven (79%) of participants had at least one danger sign on admission. Inability to walk unaided was the most common sign and present in 72 (74%) participants [Table 1] while 38 (39%) had a Karnofsky scores <50.

Diagnosis of tuberculosis by urine lateral flow–lipoarabinomannan and sputum Xpert Mycobacterium tuberculosis/rifampicin assays
All 97 participants provided urine, for which 13 (13%) urine specimens were collected through a catheter, and all specimens had the LF-LAM test performed on the day of admission. Thirty-four (35%) of those tested were positive for TB by LF-LAM. Of the 97 participants, only 84 (87%) provided sputa specimens adequate for testing by Xpert MTB/RIF [Figure 2]. Twenty-six (31%) had positive results by Xpert MTB/RIF test, and no specimens had rpoB mutation detected. Of 13 patients who were unable to expectorate sputa, 6 (46%) had a positive LF-LAM test on the same day of admission. Of 84 patients who provided both sputa and urine for testing, LF-LAM increased TB cases from 26 (31%) detected by Xpert® MTB/RIF alone to 41 (55%), [Figure 2]. In total, 46 (48.5%) of all 97 patients recruited had a definitive TB diagnosis by Xpert MTB/RIF and/or LF-LAM.

Treatment and clinical outcomes
Of the 97 patients, 69 (71%) and 27 (28%) received anti-TB medications and broad-spectrum antibiotics, respectively. Of these 69 TB patients, anti-TB therapy was received by 33 (48%) on the same day and 13 (19%) on the second day after positive LF-LAM and Xpert MTB/RIF test results, respectively. The remaining 23 (33%) were empirically switched to anti-TB medications due to worsening of their clinical conditions at either of day 5–7 or 14 of treatment with broad-spectrum antibiotics.

In total, 16 (16.5%) patients died in this cohort, of which 1 patient died instantly on the same day before either anti-TB or antibiotic medications. However, no autopsy was performed. Of the 15 remaining deaths, 10 (67%) were in the anti-TB treatment group [Figure 3]. Eleven (73%) deaths occurred within 7 days, including 7 (64%) from the anti-TB treatment group [Figure 3]. There was no statistically significant difference in mortality between patients with definitive TB (15%, 7/46), probable TB (9%, 2/23) and unlikely TB (19%, 5/27), (P = 0.735). The 30-day survival between patients who received anti-TB treatment at any time and those who received broad-spectrum antibiotics alone was similar (log rank = 0.1574). Expectedly, mortality was significantly higher among patients hospitalized than those treated as outpatients (P = 0.027), [Table 1]. In addition, those unable to walk unaided during initial assessment were more commonly found among patients who died as compared to those who survived (P = 0.05), [Table 1].

DISCUSSION
The main findings of implementing the new algorithm in typical HIV care settings in northern Tanzania were a remarkable

![Figure 2: Study procedures including urine tuberculosis - Lipoarabinomannan and Xpert Mycobacterium tuberculosis/rifampicin testing results](image-url)
Table 1: Study participant’s clinical characteristics according to outcomes at day 30

| Participant’s characteristics                      | Overall, (n=97) | Survived (n=76) | Died (n=15) | P    |
|---------------------------------------------------|-----------------|-----------------|------------|------|
| Age, mean (95% CI)                                | 40 (38-43)      | 41 (39-44)      | 37 (32-43) | 0.182|
| Gender, n (%)                                      |                 |                 |            |      |
| Male                                               | 45 (46)         | 35 (46)         | 8 (53)     | 0.703|
| Female                                             | 52 (54)         | 41 (54)         | 7 (47)     |      |
| Temperature (°C), mean (SD)                        | 37.8 (1.07)     | 37 (1.07)       | 36 (1.07)  |      |
| <39, n (%)                                         | 74 (76)         | 57 (75)         | 13 (87)    | 0.662|
| ≥39, n (%)                                         | 23 (24)         | 19 (25)         | 2 (13)     |      |
| Respiratory rate, mean (SD)                        | 32 (6.6)        | 33 (6.6)        | 22 (4.1)   |      |
| <30, n (%)                                         | 40 (41)         | 32 (42)         | 8 (42)     | 0.974|
| ≥30, n (%)                                         | 57 (59)         | 44 (58)         | 3 (32)     |      |
| Pulse rate, median (IQR)                           |                 |                 |            |      |
| <120, n (%)                                        | 29 (30)         | 24 (32)         | 3 (20)     | 0.667|
| ≥120, n (%)                                        | 68 (70)         | 52 (68)         | 12 (80)    |      |
| Absolute CD4 counts, median (IQR)                  |                 |                 |            |      |
| <100, n (%)                                        | 33 (43)         | 29 (40)         | 8 (62)     | 0.335|
| 100-199, n (%)                                     | 18 (24)         | 19 (26)         | 3 (23)     |      |
| ≥200, n (%)                                        | 25 (33)         | 25 (34)         | 2 (15)     |      |
| Was the patient on ART?, n (%)                     |                 |                 |            |      |
| Yes                                                | 63 (65)         | 48 (63)         | 2 (13)     | 0.335|
| No                                                 | 34 (35)         | 28 (37)         | 3 (20)     |      |
| Karnofsky scores, n (%)                            |                 |                 |            |      |
| <50                                                | 38 (39)         | 28 (37)         | 9 (60)     | 0.179|
| 50-70                                              | 51 (53)         | 40 (53)         | 6 (40)     |      |
| ≥80                                                | 8 (8)           | 8 (10)          | 0          |      |
| Ability to walk unaided, n (%)                     |                 |                 |            |      |
| Able                                               | 25 (26)         | 21 (28)         | 0 (o)      | 0.05 |
| Unable                                             | 72 (74)         | 55 (72)         | 15 (100)   |      |
| Was the patient admitted?, n (%)                   |                 |                 |            |      |
| Hospitalized care                                  | 77 (79)         | 59 (78)         | 15 (100)   | 0.027|
| Outpatient care                                    | 20 (210)        | 17 (22)         | 0          |      |
| Hemoglobin, median (IQR)                           | 9.3 (7.4-11.5)  | 9.7 (8.4-11.5)  | 0 (0)      | 0.227|
| <11, n (%)                                         | 68 (70)         | 52 (68)         | 13 (87)    | 0.196|
| ≥11, n (%)                                         | 29 (30)         | 24 (32)         | 2 (13)     |      |
| LF-LAM results, n (%)                              |                 |                 |            |      |
| Positive                                           | 34 (35)         | 26 (34)         | 6 (40)     | 0.908|
| Negative                                           | 63 (65)         | 50 (66)         | 9 (60)     |      |
| Xpert® MTB/rifampicin results (n=84), n (%)        |                 |                 |            |      |
| MTB detected                                       | 26 (31)         | 24 (35)         | 1 (10)     | 0.211|
| MTB not detected                                   | 58 (69)         | 44 (65)         | 9 (90)     |      |

CI: Confidence interval, ART: Antiretroviral therapy, IQR: Interquartile range, SD: Standard deviation, LF-LAM: Lateral flow-liparabinomannan, MTB: Mycobacterium tuberculosis

Typically, patients with TB-related sepsis suffer a delay in diagnosis and treatment initiation as compared to those with PTB.[18,19] Following this algorithm, of the 69 patients ultimately started on TB treatment, 46 (66%) were started within 48 h of presentation. Early diagnosis and treatment should translate to favorable treatment outcomes when such an algorithm is brought to scale. We hypothesized that mortality would be similar across treatment groups given that the broad-spectrum antibiotic alone group was by definition clinically improving at 5–7 days, and that TB-related sepsis when typically diagnosed prealgorithm has been associated with a high mortality, whereby equivalence in mortality postalgorithm would be considered a marker of success. Importantly, irrespective of proportion of PLHIV diagnosed and rapidly initiated on anti-TB treatment, and an improved yield of urine LF-LAM and sputum Xpert MTB/RIF in combination compared to sputum Xpert MTB/RIF alone.[15] These findings are in keeping with a report from South Africa that implementation of LF-LAM along with Xpert MTB/RIF not only increased TB diagnostic yield but also reduced the cost of care among seriously ill HIV coinfected adults.[16] However, our findings differ from a cohort of 972 PLHIV in Mozambique where XpertMTB/RIF detected more TB from sputa compared to urine LF-LAM.[17] The differences in detection could partly be because in the present study, patients presented with signs of sepsis and advanced HIV disease, and a notable proportion were unable to expectorate sputum.
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early TB treatment, overall mortality remained high (16.5%) and was consistent with previous systematic review and meta‑analysis findings in sub‑Saharan Africa.\[20‑22\]

This high mortality may partially be attributed to late stage presentation, advanced immunosuppression, weight loss and malnutrition, altered anti‑TB drug pharmacokinetics in the sepsis state that rendered anti‑TB medications’ subtherapeutic, or coexistent of other comorbidities and bloodstream pathogens in addition to the detection of TB.\[23‑25\]

In a similar cohort with from Uganda where a multipathogen polymerase chain reaction test was performed from the blood of people presenting with sepsis, MTBC detection was common and independently associated with mortality, but other pathogens such as Plasmodium species and Streptococcus pneumoniae were also frequent etiologies.\[7\]

As such, our findings raise questions as to whether it may be beneficial to continue with broad‑spectrum antibiotics and anti‑TB medicines considering the coexistence of TB and other bloodstream pathogens.\[7,26,27\]

Our findings also highlight the urgent need to develop effective strategies to improve outcomes for adults with sepsis particularly in resource‑constrained countries. For instance, the remaining mortality in our current study suggests the potential benefit of studying an approach of an immediately administered empirical anti‑TB regimen along with broad‑spectrum antibiotics in PLWH presenting with life‑threatening illness. Furthermore, broad‑spectrum antibiotics such as fluoroquinolones or carbapenems have activity against TB infections and are active against a broad range of Gram‑positive and Gram‑negative bacterial pathogens, while linezolid, now currently recommended for rifampin‑resistant TB, has activity against Gram‑positive bacteria including Enterococcus species, and methicillin‑resistant Staphylococcus aureus.\[24\]

Such alterations in the empiric antibacterial regimen would need to be balanced against potential toxicities and concerns of antimicrobial stewardship.

This study implemented the new algorithm in the routine clinical settings. However, the study was limited by neither routine bacterial nor mycobacterial blood culture was performed to influence clinical decision. Alternative microbiological diagnoses were thus unable to be factored into our analyses of mortality.

Figure 3: Clinical decisions and treatment outcomes of tuberculosis sepsis among people living with human immunodeficiency virus *One patient died instantaneously before antituberculosis medications
Conclusion

This small-scale implementation of a new algorithm for the diagnosis and treatment of TB-related sepsis in PLWH markedly improved TB case detection and the rapidity of anti-TB treatment initiation. As such, the mortality was found to be similar among patient with definitive, probable and those with unlikely TB cases. We recommend development and scale-up of this model in Tanzania and comparable regions, and new trials to determine the impact of immediate empiric anti-TB treatment in all PLHIV and the optimal content of antimicrobial regimens for sepsis in similar settings.

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Conflicts of interest

There are no conflicts of interest.

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