

A Retrospective Cross-Sectional Study of the Utility of Cartridge-Based Nucleic Acid Amplification Test in Diagnosis of Pulmonary and Extrapulmonary Tuberculosis in People Living with HIV in Second Highest HIV Prevalent State in India

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Abstract

Introduction Tuberculosis (TB) in people living with human immunodeficiency virus (PLHIV) is difficult to diagnose due to fewer organisms in sputum and extrapulmonary samples. Sputum culture takes 4 to 8 weeks for growth of the mycobacteria. Delayed treatment for TB in PLHIV leads to increased mortality. This study evaluated cartridge-based nucleic acid amplification test (CBNAAT) as a diagnostic tool for diagnosis of pulmonary TB (PTB) and extrapulmonary TB (EPTB) in PLHIV in the second most HIV prevalent state in India and for comparing its efficacy between Ziehl–Neelsen (ZN) staining sputum smear–positive and sputum smear–negative TB.

Methods This cross-sectional study was conducted in RIMS, Imphal, with 167 PLHIV patients, age 15 years or older, having signs and symptoms of TB. Appropriate samples for sputum microscopy and CBNAAT were sent.

Conclusion The overall sensitivity of sputum smear for acid-fast bacillus (AFB) was found to be 30.71% and that of CBNAAT was 38.57%. Sensitivity of CBNAAT for sputum smear–positive and sputum smear–negative TB was 100 and 11.3%, respectively. Sensitivity of ZN smear for AFB of EPTB sample was 48.1% and that of CBNAAT was 59.25%. In both PTB and EPTB, CBNAAT showed an increase in diagnosis of microbiologically confirmed PTB cases by 7.8 and 11.1%, respectively, over and above the cases diagnosed by ZN smear microscopy. Rifampicin resistance was detected in five patients. We conclude that CBNAAT is a rapid test with better sensitivity in diagnosis of PTB and EPTB in PLHIV, compared with ZN smear microscopy. It detects rifampicin resistance for multidrug-resistant TB and helps in early treatment intervention.

Keywords

- ▶ CBNAAT
- ▶ pulmonary tuberculosis
- ▶ rifampicin resistance
- ▶ sputum AFB
- ▶ extrapulmonary tuberculosis
- ▶ HIV

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Introduction

Human immunodeficiency virus (HIV) and tuberculosis (TB) are still considered important causes of mortality and morbidity in developing countries. More than 9 million new active cases of TB and 6 million new cases of HIV infection are reported worldwide.¹ A total of 14 million cases of HIV–TB coinfection worldwide are recorded.² India has one of the world's highest burdens of both HIV infection (2.3 million prevalent cases) and TB (2.1 million cases annually).¹ As per the National AIDS Control Organization, Manipur has the second highest prevalence rate of HIV (1.43%) among the Indian states. The two pathogens, *Mycobacterium tuberculosis* and HIV, synergistically affect the host, causing impairment of immunity.³ HIV coinfection is known to aggravate severity of latent TB and worsens TB infection by 20 times.⁴ TB, on the other hand, is the most common cause of death in AIDS patients (1.8 million death).³

The menace of TB is still a concern due to inaccurate diagnostic tools such as direct smear microscopy, culture, tuberculin skin testing, and chest X-ray.^{5–7} This may be secondary to low counts of *M. tuberculosis* bacilli (MTB) at the site of diseased tissue and difficulty in obtaining clinical samples of deep organs for diagnosis of extrapulmonary TB (EPTB). Globally, EPTB constitutes about 20% of all diagnosed cases of TB.⁸ Moreover, HIV-infected persons with TB are more likely to have negative typical X-ray finding of PTB (cavity, upper lobe infiltrates, and focal infiltrates) and negative sputum smears,⁹ thereby causing delay and missed diagnosis of TB in HIV-infected patients.

Unfortunately, in rural areas there is no rapid test, and culture diagnostics and molecular line probe assays are costly, with inadequate biosafety measures and insufficient trained staff making detection of early TB difficult.^{10,11} The Löwenstein–Jensen method, being a culture-based “gold standard test,” takes several weeks to produce result, with simultaneous progression of the disease in the meantime. Thus, many active TB patients remain undiagnosed and continue to spread the disease in the community. Cartridge-based nucleic acid amplification test (CBNAAT) assay¹² is a simplified type of automated molecular polymerase chain reaction (PCR) that can detect TB and does screening for multidrug resistance. It takes 2 to 3 hours to detect MTB and rifampicin resistance from one sputum sample.¹³ WHO recommends the use of CBNAAT assay as initial diagnostic test for suspected multidrug-resistant TB (MDR-TB) or TB–HIV coinfection.^{14,15} There has been a scarcity of data regarding diagnostic role of CBNAAT, specially in diagnosis of sputum smear–negative PTB cases, from the population of Manipur, a northeastern state of India (having the second highest HIV rate). In this background, the present study was undertaken to evaluate the diagnostic role of CBNAAT assay in PTB and EPTB in people living with HIV (PLHIV) and to compare the sensitivity of CBNAAT with Ziehl–Neelsen (ZN) staining microscopy in diagnosing PTB in HIV-infected patients.

Materials and Methods

We have conducted this cross-sectional study in the Department of Medicine and Centre of Excellence (COE), ART Centre, RIMS,

within a period of 2 years from September 2016 to August 2018. HIV-positive patients suspected of TB infection were included in our study based on the following criteria.

Inclusion Criteria

- Age above 15 years.
- Features suggestive of RTB and EPTB according to Revised National TB Control Programme (RNTCP) guidelines:
 - Persistent fever and/or cough for 2 weeks or more.
 - Loss of weight (loss of >10% of highest weight recorded in the past 3 months).
 - Loss of appetite.
 - History of contact with infectious TB cases.

Exclusion Criteria

- Those receiving treatment for TB.
- Unwilling patients.

Sample Size

The sample size was estimated using the formula:

$$TP + FN = z^2 [SN(1 - SN)]w^2,$$

$$NSN = (TP + FN)p,$$

where TP is the true positive and FN is the false negative.

The values of sensitivity (SN)¹⁶ of CBNAAT and prevalence (p)¹⁷ of HIV–TB coinfection were taken to be 82.3 and 55%, respectively, from a previous study with accuracy (w) of 2% and allowable error (z) of 5%:

$$TP + FN = 5^2 \times [82.3(100 - 82.3)]2^2 = 9104.43.$$

Now, sample size = $(TP + FN)/p = 9104.43/0.55 = 1655$.

Thus, the calculated sample size is equal to 166.

Study Variable

The study included demographic data such as age, sex, symptoms, CBNAAT, ZN staining for AFB, and blood tests (hemoglobin, serum albumin, random blood sugar, fasting lipid profile, serum creatinine, total leucocyte count, CD4 count, and viral load).

Working Definitions

- HIV infection: HIV infection is diagnosed as per the NACO guideline. HIV infection is screened by Comb Aids-RS (kit 1) by the principle of ELISA (enzyme-linked immunosorbent assay) and confirmed by AIDSCAN Trispot Test Kit (kit 3) and Meriline (kit 2) by the principle of immunofiltration and immunoconcentration, respectively.
- Clinically diagnosed TB case¹⁸:
 - A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture, or CBNAAT.
 - clinically diagnosed TB case is defined as one who fulfills clinical symptoms with diagnosis on X-ray/histology and is given full course of TB medications. This group does not have bacteriological confirmation
 - Presumptive PTB defines a person with any of the symptoms and signs suggestive of PTB such as more than 2 weeks of fever, cough, or significant weight loss, hemoptysis, or abnormal chest X-ray.

- Presumptive EPTB is suspected in patients having any constitutional symptoms, such as fever for more than 2 weeks, night sweats, and weight loss, or any symptoms specific to organs, such as node swelling.

CBNAAT/GeneXpert

It is a nucleic acid amplification test (NAAT) which uses PCR. It is used in identification and amplification of genomic DNA sequences of MTB and rifampicin resistance. It also detects the mutation (leading to rifampicin resistance) in RNA polymerase β (rpoB). GeneXpert model GX IV (GXIV-4-D) is manufactured by Cepheid Inc (United States). It has 89% sensitivity and 99% specificity when used as an initial test to replace smear microscopy. And it has a sensitivity of 67% and a specificity of 99% when used as an adjunct for smear-negative microscopy. Sensitivity and specificity were slightly higher when 3 samples were tested.⁸

Procedure

A cartridge-containing mixture (sputum + reagent, provided with the assay) is placed in the GeneXpert machine. All further processing is fully automated. Samples (except urine and blood) were sent to Intermediate Reference Laboratory, Imphal. sA composite diagnostic index (comprising radiology and/or clinical judgment) was considered as the reference standard for diagnosis of TB in this study and compared with the result of CBNAAT.

Viral Load

Viral load was quantified with real-time PCR technique (COBAS TagMan 48 Analyser (Roche Molecular Systems Inc., United States)).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 21. For validity test of CBNAAT of sputum in diagnosis TB, the sA composite diagnostic index was considered as the reference standard and result of CBNAAT was compared with that composite diagnostic index. All *p*-values < 0.05 were considered significant.

Approval of Research Ethics Board

Ethical approval was obtained from the Research Ethics Board, Regional Institute of Medical Sciences, Imphal (Refno.A/206/REBComm(SP)/RIMS/2015/149/17/2016).

Informed written consent was obtained from the respondents.

Results

A total of 167 patients were enrolled for the study. Out of these, 140 were PTB cases and 27 were EPTB cases. Majority of them had moderate anemia with hemoglobin level of 8 to 10.9 mg/dL (males, 51%; females, 61.2%). More than half of the patients (58.2%) had serum albumin of less than 2.8 g/dL. Majority of the patients had random blood sugar level of 79 to 140 mg/dL (60.4%) and hypertriglyceridemia. Also, 73.7% had serum cholesterol level of less than 200 mg/dL, and 71.1% had serum triglycerides level of less than 150 mg/dL. In addition, 58.6% of the total patients had total leucocyte count of less than 4,000/L. At the time of presentation, 61.1% had CD4 count of less than 100 cells/mm³ and 93.4% had viral load of more than 1,000 copies/mL.

Among the presenting symptoms of the patients, the commonest was fever (98.8%), followed by loss of appetite (93.4%) (► **Table 1**). Sputum smear for AFB was positive in 30.71% (43 out of 140 cases) and sputum for CBNAAT detected TB in 54 patients. CBNAAT was found to be positive in all 43 (100%) cases of sputum smear-positive PTB, but in 11 out of 97 (11.3%) cases of sputum smear-negative PTB (*p* < 0.001). Thus, sputum for CBNAAT testing resulted in a relative increase in detection rate of microbiologically confirmed TB cases by 7.8% compared with sputum smear microscopy (► **Table 2**).

Overall, in this study population, sensitivity of sputum smear for AFB was only 30.71%, with specificity of 100%, while the overall sensitivity of sputum CBNAAT was 38.57%, with specificity of 100% (► **Table 3**). Sensitivity of CBNAAT

Table 1 Presenting symptoms of the patients

Symptoms	Frequency (n = 167)	Percentage (%)
Fever (≥ 2 wk)	165	98.8
Loss of appetite	156	93.4
Cough (≥ 2 wk)	136	81.4
Weight loss (>10% of highest weight recorded in the past 3 mo)	117	70
Lymphadenopathy	14	8.3
Headache	9	5.3
Shortness of breath	6	3.5
Hemoptysis	3	1.7
Abdomen pain	2	1.1
Abdomen distension	1	0.5

Table 2 Diagnostic yield of CBNAAT versus sputum smear microscopy

	Sputum AFB smear-positive	Sputum AFB smear-negative	Total	<i>p</i> -Value
CBNAAT sputum-positive	43 (30.7%)	11 (7.8%)	54	<0.001
CBNAAT sputum-negative	0	86 (61.4%)	86	
Total	43	97	140	

Abbreviations: AFB, acid-fast bacillus; CBNAAT, cartridge-based nucleic acid amplification test.

Table 3 Diagnostic sensitivity and specificity of CBNAAT in PTB

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Negative likelihood ratio
Overall PTB	38.57%	100%	100%	20.35%	0.37

Abbreviation: PTB, pulmonary tuberculosis.

was found to be 100% for microbiologically confirmed PTB, but sensitivity came down to 11.3% for sputum smear-negative PTB (► **Table 4**).

The overall sensitivity of ZN smear for AFB of EPTB sample was only 48.1%, while that of CBNAAT was 59.25% (► **Table 5**). Of the 27 EPTB cases, maximum (14; 8.3%) were cases of lymph node TB (LNTB), followed by TB pleural effusion (5; 2.9%), cerebrospinal fluid (CSF) (5; 2.9%), Koch's abdomen 2 (1.1%), and pericardial TB 1 (0.5%). Sensitivity of CBNAAT for lymph node specimens was observed to be 78.57%, that for pleural fluid and CSF was 20%, and that for ascitic and pericardial fluid was 100%. CBNAAT was found to be positive in all 13 cases (100%) of ZN smear-positive EPTB. CBNAAT was also found to be positive in 3 cases (2 ascitic and 1 pericardial fluid) out of 14 (21.4%) cases of ZN smear-negative EPTB (► **Table 6**). Only five patients (3.5%) of PTB were detected to have rifampicin resistance (► **Table 7**).

Discussion

India accounts for around one-fourth of the global TB cases.¹⁹ In sputum smear, detection of AFB is simple, rapid, inexpensive, and specific for diagnosis for PTB; however, it has low sensitivity.^{6,7} Culture for MTB is more sensitive and specific, but it is expensive and takes on average 2 to 8 weeks' time for the result.^{20,21} Moreover, diagnosis of TB in HIV

patients is even more difficult, as, in HIV-TB coinfection, typical X-ray findings of TB are uncommon. Thus, there is a need for a newer rapid diagnostic test for TB with improved sensitivity and specificity. WHO has recommended CBNAAT as a rapid diagnostic test for TB diagnosis in special cases such as drug-resistant TB, TB in children, TB-HIV coinfection, EPTB, and sputum smear-negative PTB.¹⁴

In our study, most of the patients (56.2%) had low CD4 counts of less than 100 cells/mm³ and had high viral load (93.4% patients) of more than 1,000 copies/mL. Devi et al²² found that PTB and EPTB were significantly more common in HIV-seropositive patients ($p < 0.02$) in whom the CD4 cell count was low (less than 100 cells/mm³). High viral load and low CD4 count are the markers of advanced HIV disease, which precedes the onset of TB.²³

The clinical symptoms of the patients at the time of presentation were mainly fever (98.8%), followed by loss of appetite (93.4%) and cough (33.8%), similar to the study conducted by Devi et al²² and Kumar et al.²³

At least 10,000 bacilli per milliliter is a prerequisite for positive sputum microscopy result and is an operator-dependent test. Sensitivity may be low due to lower rates of caseous necrosis and sputum production.⁴ In the present study, only 43 patients were found to be sputum-positive for AFB by direct microscopy and 86 cases were found to be smear-negative, with an overall sensitivity of 30.71%. In cases in which sputum microscopy is done, it can lead to delayed or missed cases, which contributes to increased morbidity and mortality rates and continuing spread of TB in community. Cattamanchi et al²⁴ have reported 43 to 51% sensitivity of sputum microscopy in HIV, whereas Mecky et al have reported a sensitivity of only 55%.²⁵ Smear-negative cases are treated with broad-spectrum antibiotics course for 7 to 14 days, and if symptoms persisted, TB were suspected. However, by this time, there is delay in starting the specific anti-TB medication and thus it can result in higher mortality.²

On the other hand, CBNAAT showed an advantage of significant increase ($p < 0.001$) of 7.8% in diagnosis of microbiologically confirmed PTB cases over and above the cases diagnosed by sputum smear for AFB, which is consistent with the studies by Alvarez-Uria et al,²⁶ Dewan et al,²⁷ and Geleta et al²⁸ (increase of 10.8, 29, and 31%, respectively).

Overall, CBNAAT was positive in 38.57% of PTB cases in this study, but its result varied significantly between 100% in sputum smear-positive PTB and 11.3% in sputum smear-negative PTB. Similar results of very high sensitivity of CBNAAT in smear-positive cases but low sensitivity in smear-negative cases were observed in several studies. Dewan et al,²⁷ Theron et al,²⁹ Geleta et al,²⁸ and Agrawal et al³⁰ found CBNAAT sensitivity of 100, 94.7, 95.2, and 100 in smear-positive PTB

Table 4 Diagnostic sensitivity of CBNAAT in sputum smear-positive PTB and sputum smear-negative PTB

Sputum PTB	Sensitivity of CBNAAT
Smear-positive	100%
Smear-negative	11.3%

Abbreviations: CBNAAT, cartridge-based nucleic acid amplification test; PTB, pulmonary tuberculosis

Table 5 Sensitivity of CBNAAT in EPTB diagnosis

	ZN smear-positive EPTB sample	ZN smear-negative EPTB sample	Total	p-Value
CBNAAT-positive EPTB sample	13	3	16	<0.001
CBNAAT-negative EPTB sample	0	11	11	
Total	13	14	27	

Abbreviations: CBNAAT, cartridge-based nucleic acid amplification test; EPTB, extrapulmonary tuberculosis; ZN, Ziehl-Neelsen.

Table 6 Sensitivity of CBNAAT in EPTB site

EPTB specimen	No. of cases (total 27)	TB detected by CBNAAT	TB not detected by CBNAAT	TB detected by ZN staining	TB not detected by ZN staining	Percentage of TB detected by CBNAAT (%)
Lymph node	14	11	3	11	3	78.57
Pleural fluid	5	1	4	1	4	20
CSF fluid	5	1	4	1	4	20
Ascitic fluid	2	2	0	0	2	100
Pericardial fluid	1	1	0	0	1	100

Abbreviations: CBNAAT, cartridge-based nucleic acid amplification test; CSF, cerebrospinal fluid; EPTB, extrapulmonary tuberculosis; TB, tuberculosis; ZN, Ziehl-Neelsen.

Table 7 Rifampicin resistance detected by CBNAAT

Rifampicin resistance	PTB	EPTB
Detected	5	0
Not detected	135	27
Total	140	27

Abbreviations: EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis.

and 32.58, 46.8, 48.6, and 79.1% in smear-negative PTB, respectively (► **Table 8**).

HIV-TB coinfection can decrease the sensitivity of sputum microscopy (to 47%)^{2,32}; however, it does not significantly affect CBNAAT. Hopewell et al⁶ suggested that in patients infected with HIV with a CD4 count of less than 200 cells/mL, there has been better sensitivity of combined smear microscopy and CBNAAT than smear microscopy alone (69.6 vs. 39.1%; $p = 0.05$).

Rifampicin resistance was detected in five (3.5%) cases of PTB; however, no rifampicin resistance was found in EPTB sample. In fact, there were very few EPTB cases. MDR-TB in these five rifampicin-resistant PTB cases were not confirmed as mycobacterial culture (gold standard) was not done in this study. However, according to the study done by Theron et al,²⁹ rifampicin resistance is rarely detected alone and MDR-TB was detected in 90% of rifampicin-resistant patients by CBNAAT.

In our study, maximum cases of EPTB were of LNTB (14 out of 27), followed by pleural fluid TB (5 out of 27). Similar findings were reported by Devi et al,²² where the commonest extrapulmonary lesion in the HIV-seropositive patients was found in the lymph nodes ($n = 15$), followed by pleural effusion ($n = 11$). The overall sensitivity of CBNAAT in EPTB

was found to be 59.25% in our study, which is similar to the study done by Scott et al³³ (59%), Shah and Bhabhor³⁴ (59%), Moure et al³⁵ (58.3%), Armand et al³⁶ (53.1%), and Pandie et al³⁷ (63.8%). CBNAAT sensitivity was found to be more than ZN smear AFB microscopy, i.e., 59.25 and 48.1%, respectively. Mittal and Kumar³⁸ compared the diagnostic yield of CBNAAT and ZN staining in serosal fluids from HIV and non-HIV patients with EPTB. Out of 81 EPTB samples (21 from HIV and 60 from non-HIV patients), 28 (34.5%) were both CBNAAT- and ZN stain-positive, while only 11 (13.58%) were ZN stain-positive. Out of 21 HIV patients, 4 (19.05%) were ZN stain-positive and 9 (42.85%) were CBNAAT-positive. Among 60 non-HIV patients, 7 (11.66%) were ZN stain-positive and 19 (31.66%) were CBNAAT-positive, showing that CBNAAT is more sensitive than ZN staining in EPTB in both HIV and non-HIV patients. In our study, CBNAAT testing resulted in a relative increase in detection rate of TB cases by 11% compared with ZN smear microscopy ($p < 0.001$).

In our study, sensitivity of CBNAAT for diagnosing LNTB was found to be 78.57%, as compared with 72 to 87% found in Vadwai et al,³⁹ Zeka et al,⁴⁰ Ligthelm et al,⁴¹ and Denking et al.⁴² However, a negative CBNAAT test does not rule out LNTB. CBNAAT is recommended as an additional test to smear microscopy, culture, and cytology in FNAC (fine needle aspiration cytology) specimens for detection of EPTB in new guideline.⁴³

Regarding the diagnosis of TB meningitis, Denking et al⁴² and Tortoli et al⁴⁴ assessed CBNAAT in CSF samples and found a variable sensitivity of 20 to 86%. CBNAAT detected only one MTB out of the five samples in this study (sensitivity, 20%), suggesting that a negative CBNAAT result does not rule out TB meningitis. CBNAAT is recommended as an adjunctive test for TB meningitis as per guidelines on EPTB for India.⁴³

Table 8 Comparison of the diagnostic yield of sputum microscopy and CBNAAT in PTB in PLHIV

Study	Sample size	TB-positive	Sputum microscopy AFB-positive	CBNAAT-positive
Present study	167	140	43 (30.7%)	54 (38%)
Dewan et al ²⁷	100	40 (40%)	11 (11%)	40 (40%)
Bansal et al ³¹	604	91 (15.06%)		6 (0.99%)
Rao and Sowjanya ¹⁶	231	59	14 (6.06%)	59 (25.54%)
Gupta et al ¹⁷	30	25(83.3%)	8 (26.67%)	17 (56.7%)

Abbreviations: AFB, acid-fast bacillus; CBNAAT, cartridge-based nucleic acid amplification test; TB, tuberculosis.

Studies by Rufai et al,⁴⁵ Shah and Bhabhor,³⁴ Meldau et al,⁴⁶ and Porcel et al⁴⁷ have reported much lower sensitivities of CBNAAT in diagnosing pleural fluid TB, i.e., between 15 and 48%. In our study also, the sensitivity of CBNAAT pleural fluid specimens was found to be low, i.e., 20%, with more than half of all pleural TB patients being missed by this test. CBNAAT should not be used exclusively to diagnose pleural TB.⁴³ In our study, sensitivity of CBNAAT in diagnosing both ascitic and pericardial fluid were found to be 100%, which is in contrast to studies done by Sharma et al,⁴⁸ Lawn et al,⁴⁹ and Fuladi and Gupta et al,⁵⁰ which showed sensitivity range of 8 to 50%.

Limitation

We did not compare CBNAAT with mycobacterial culture, the current gold standard for diagnosis of TB. Further studies with large EPTB sample size, comparing the results of CBNAAT with mycobacterial cultures, are needed.

Conclusion

CBNAAT detects TB in HIV patients in Manipur with greater efficacy than ZN smear microscopy, both in PTB and EPTB. It gives early diagnosis in less than 2 hours. Thus, it decreases delayed or misdiagnosed cases, contributing to early start of treatment and thus decreasing the morbidity and mortality rates. It also detects rifampicin resistance and can be used for screening for MDR-TB.

Conflict of Interest

None declared.

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