HIV-TB co-infection with clinical presentation, diagnosis, treatment, outcome and its relation to CD4 count, a cross-sectional study in a tertiary care hospital in coastal Karnataka

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Abstract

Introduction: Tuberculosis (TB) is the leading killer and the commonest opportunistic infection (OI) in human immunodeficiency virus (HIV) infected individuals with 0.3 million deaths in 2017. When HIV and TB co-infection occurs, they form a deadly combination with each accelerating the progression of the other, resulting in increased morbidity and mortality. Aim and Objectives: To study the demographic pattern, clinical presentation, opportunistic infections, radiological and laboratory profile, management, and outcome of HIV-TB coinfected individuals. Materials and Methods: A prospective cross-sectional study was carried out on confirmed HIV cases already diagnosed with TB and those newly detected with TB after admission, where diagnosis was carried out following standard operative procedures. Results: In our study of 58 HIV-TB co-infected individuals, 40–50 years was the most common age group affected. Males were affected more with majority being married. The most common presentation was fever (67%) followed by gastrointestinal symptoms. Majority of TB cases were newly diagnosed (65.5%), with predominance of pulmonary tuberculosis (PTB) (n = 35) followed by those having only extrapulmonary tuberculosis (EPTB) (n = 12) and both (n = 11). TB was diagnosed by microscopy in 32.7%, while radiologically, chest X-ray was most common (36.2%). Also, 50% were infected with other OIs where oral candidiasis was the most common (37.93%). The overall mean CD4 count was 220 cells/µL and those with EPTB had lesser CD4 counts than those with PTB. All were on DOTS regimen and majority showed improvement. Conclusion: In a country like India where both these diseases are rampant, we recommend better information, education, understanding and awareness for prevention, care, early diagnosis, and treatment of these two notorious infectious diseases with prevention of relapse and default of TB cases in HIV-TB co-infected individuals a priority.

Keywords: Extrapulmonary tuberculosis, human immunodeficiency virus, opportunistic infections, pulmonary tuberculosis, tuberculosis
In 2017, globally there were 1.8 million newly infected cases of HIV which claimed an estimated 940,000 lives and till date >35 million lives have been lost.\textsuperscript{[14]} When HIV-TB occurs in combination they accelerate the progression of each other and the risk of death is increased by two times than those infected with HIV alone.\textsuperscript{[57]} In HIV-infected individuals, TB occurs early in the course of infection and the rate of developing active TB is about 20–30 times.\textsuperscript{[37]}

The classic symptoms of TB may be present in HIV patients co-infected with PTB but some may not. Also, co-infection leads to difficulty in both diagnosis and treatment of TB.\textsuperscript{[5,7,8]} Majority of people with HIV have a negative sputum smear resulting in large number of active TB infection cases going undiagnosed and due to lack of proper treatment, death may occur on an average in 45% of sero-negative HIV people with TB and nearly in all coinfected cases of HIV-TB.\textsuperscript{[3]}

Studies in relation to HIV-TB coinfection is lacking from in and around Mangalore. Hence, this study was conducted to study the demographic pattern, clinical presentation, OIs/co-infections, radiological, laboratory profile, management, and outcome in HIV-TB co-infected individuals, so as to have a better understanding of what is really happening in relation to those coinfected with these two infections and guide clinicians and healthcare workers in providing appropriate management and treatment to such cases.

**Materials and Methods**

A prospective cross-sectional study was conducted in a tertiary care teaching hospital in coastal Karnataka, India, for a period of 2 years from August 2013 to July 2015 where Ethical clearance was obtained from the Institutional Ethics Committee. Inform consent was taken from study participants willing to participate in the study.

**Determination of HIV Status**

All persons included in the study were symptomatic confirmed cases of HIV detected according to defined strategies following NACO guidelines where a screening rapid test (HIV Tridot, J. Mitra and Co., India) was used and confirmed by fourth generation ELISA (J. Mitra and Co.).\textsuperscript{[9]}

**WHO Tuberculosis Case Definition**

“A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF).\textsuperscript{[9,10]}

“A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.”\textsuperscript{[9,10]}

**Inclusion criteria**

1. HIV positive cases already diagnosed to have TB on admission and on treatment
2. HIV positive cases detected having TB on investigation after admission.

All those fulfilling the inclusion criteria and willing to participate during the study period were included in the present study and hence no bias.

Tuberculosis was diagnosed by the following investigations:

1. Acid fast bacilli (AFB) staining by Ziehl-Neelsen (ZN) method for given appropriate sample and culture done where ever indicated
2. Fluorescent staining by auramine rhodamine stain done in a DOTS laboratory attached to our institute
3. Radiological diagnosis by chest X-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, and ultrasound with features suggestive of tubercular lesions
4. Cerebrospinal fluid (CSF) analysis showing predominant lymphocyte count with low glucose level.

Investigations for the diagnosis of other OIs when suspected were also carried out. CD4 counts were obtained from ICTC center and Wenlock District hospital, Mangalore. A detailed clinical history on presentation with complete examination findings and outcome were also recorded.

**Statistical analysis**

The data were collected and then analysed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY) where representation of discrete categorical data was in the form of either a number or a percentage (%) and group (pulmonary tuberculosis [PTB] present/absent), (extrapulmonary tuberculosis [EPTB] present/absent), (extrapulmonary) comparisons by Chi-square test or Fisher’s exact test. Continuous data were represented as mean ± SD, range or median and interquartile range, as appropriate. Measures of Kolmogorov Smirnov tests of normality were done to check the normality of quantitative data. P < 0.05 was considered statistically significant.

**Results**

During the study period, 137 HIV-infected individuals diagnosed with different OIs who were willing to participate in the study were enrolled out of which 58 were found to be co-infected with TB, where the most common age group affected were of the 40–50 years age group (n = 23; 40%) followed by >50 years (n = 14; 24%), 30–40 years (n = 13; 22%), and <30 years (n = 8; 14%). Males were affected more than females in a ratio of 3.461 (45:13) with majority being married (n = 46; 73%) followed by single (n = 10; 17%) and widowed (n = 2; 4%), while known cases of HIV was 48.27% (n = 28) and those on ART treatment was 43% (n = 25). The most common presentation was fever (n = 39; 67%) followed by gastrointestinal symptoms.
such as loss of appetite, vomiting, diarrhea, nausea, dysphagia, and pain abdomen present in 56.8% \((n = 33)\). Respiratory symptoms such as breathlessness and cough were present in 51.7% \((n = 30)\) followed by generalized weakness present in 37.9% \((n = 22)\), whereas central nervous system symptoms such as headache, convulsions, and altered sensorium were present in 36.2% \((n = 21)\) and others like weight loss \((n = 19)\) and lymphadenopathy \((n = 11)\) were also seen. Also, patients were seen to have pleural effusion \((n = 8)\) and ascites \((n = 8)\).

In our study, we also observed that majority of TB cases were newly diagnosed \((n = 38; 65.5\%)\), while known cases of TB on treatment was 24% \((n = 14)\) and relapse of TB occurred in 10.34% \((n = 6)\). We also found that majority were diagnosed as PTB \((n = 35; 60\%)\) followed by those having only EPTB \((n = 12; 21\%)\), whereas the rest had both PTB and EPTB \((n = 11; 19\%)\).

The diagnosis of TB was done by microscopy in 32.7% \((n = 19)\). ZN staining samples included sputum, pus, biopsy, and urine \((n = 11)\) while fluorescent microscopy in DOTS center were of sputum samples only \((n = 8)\). Radiologically for diagnosis, chest X-ray was the most commonly used out of which 36.2% \((n = 21)\) had chest X-ray changes suggestive of TB while TB changes by CT scan \((n = 9)\), MRI \((n = 5)\) and ultrasonography \((n = 4)\) were also seen. Gene Xpert was positive only in two patients were in one MTB detection was low and the other medium, whereas no rifampicin resistance was detected in both.

Laboratory investigations of CSF of eight \((n = 8)\) suspected TB meningitis patients showed mean values of CSF glucose is 50.8 mg/dL \((40–70 \text{ mg/dL})\), CSF protein 371.2 mg/dL \((15–45 \text{ mg/dL})\), CSF chloride 96.5 mEq/L \((120–130 \text{ mEq/L})\), CSF Adenosine deaminase 31.8 IU/L \((\text{up to } 10 \text{ IU/L})\) and predominance of lymphocytes mean value at 84% compared with neutrophils at 16%.

In our study, 50% \((n = 29)\) were infected with HIV and TB only, whereas another half \((n = 29; 50\%)\) were coinfected with other OIs. For which the most common was oral candidiasis found in 37.93% \((n = 22)\) followed by hepatitis B virus \([\text{HBV in } (n = 3)]\), toxoplasmosis \((n = 3)\), cryptococcus \((n = 2)\), and cytomegalovirus \((n = 2)\). A combination of HIV/TB with one or more OI was seen in 46.5% \((n = 27)\) and with two OIs in 3.4% \((n = 2)\).

In relation to CD4 count which was available only for 27 patients, the overall mean value was 210 cells/µL and majority had values of <250 cells/µL \((n = 19)\) and the rest >250 cells/µL \((n = 8)\). The mean value for patients with PTB \((n = 18)\) was 230 cells/µL, whereas those who had EPTB \((n = 7)\) was 166.8 cells/µL and those who were diagnosed having both \((n = 2)\) had a mean value of 220 cells/µL where one had a CD4 count value of 104 cells/µL and the other 336.1 cells/µL.

Hemoglobin levels which were available for only 56 patients showed that majority had anemia \((69\%, n = 40)\), whereas 27.5% \((n = 16)\) had normal levels. Severe anemia \((<7 \text{ g/dL})\) was seen in 6.9% \((n = 4)\), moderate anemia \((7–<10 \text{ g/dL})\) in 37.9% \((n = 22)\) and mild anemia \((10–11.5 \text{ g/dL})\) in 24.1% \((n = 14)\). All patients were undergoing/started treatment by DOTS (directly observed treatment, short course) regimen for which majority \((82.75\%, n = 48)\) were on Category I and 17.2% \((n = 10)\) on Category II where the overall hospital stay of patients was 8.6 days. It was also observed that majority showed improvement \((n = 47.81\%)\), whereas 16% \((n = 9)\) left against medical advice and only 3% \((n = 2)\) expired. A flowchart of the findings have been summarised in Figure 1.

**Discussion**

In this present study where 58 HIV-TB co-infected individuals were included, we found that 40–50 years age group were most affected which is of a higher age group when compared to other studies who had reported 30–40 years age group to be the most common.\([11–13]\) We believe that with the availability of antiretroviral therapy, it has resulted in decreased mortality and morbidity in these HIV infected individuals, which, in turn, has led to prolonged life where it has also been observed that PLHIV was 8.74 million in 1990 which has increased to 36.82 million in 2017.\([14,15]\)

Also, males were found to be more commonly affected than females in a ratio which is also similar to other studies\([12,13,16–20]\) where in a study conducted by Kumar P et al., they had even reported a very high male to female ratio of 9:1.\([21]\) Majority of our participants were married which is also similar to other studies\([11,12,22]\)

The most common presentation was fever followed by gastrointestinal and respiratory symptoms, but Kumar et al. had reported respiratory symptoms like cough and expectoration to be more common followed by fever and gastrointestinal features.\([21]\) The rate of CNS symptoms which were encountered in our study was very high when compared with Kumar et al. who had reported only in 7.2%.\([21]\)

In our study, we also observed that majority were newly diagnosed HIV-TB co-infection while relapse of TB occurred in 10% which is similar to findings of Shastri et al. who found in their study for the state of Karnataka as a whole with available data from all the ART centers of the state that majority were new TB cases and relapse occurred at a rate (9.6%), which is very similar to our finding.\([18]\) One should keep in mind that these relapse cases might also be due to re-infection with TB or a true relapse fitting the WHO definition.\([10]\) Narayanan et al. also reported that the recurrence of TB in co-infected individuals was caused by a new strain of TB in 88%, whereas TB recurrence in HIV uninfected individuals was caused by the same strain in 91%.\([23]\) Crampin et al. also concluded that the high recurrence rate of TB in HIV-infected individuals is due to re-infection and not relapse.\([24]\)

We also found that majority were diagnosed with PTB where similar findings were reported by Kamath et al.\([22]\) who had
reported PTB (59%) to be the most common presentation followed by EPTB (38%) and those having both (3%) and even Shastri et al. had reported that in Karnataka state PTB was found in nearly three-fourths of co-infected individuals.[12] But other studies have reported that EPTB to be more common than PTB,[13,16,19,21] whereas some studies had reported nearly equal percentages for both PTB and EPTB.[17,20] The number of individuals in our study having both PTB and EPTB was nearly 20% which is similar to the finding by Maniar et al.,[17] but Kumar et al. had reported at a rate of 35.6% which is very high.[21]

Microscopy positivity which included both ZN and fluorescent microscopy for diagnosis was 32.7%, which was similar to findings of Maniar et al.,[17] who reported 36.5%, whereas Kamath et al.[22] reported very high positivity of 43% but Ghiya et al. reported only 2.4% positivity.[12] Radiologically, chest X-ray was the most common modality which was used for diagnosis which is similar to other studies.[12,17,21] USG sensitivity in our study was less when compared with other studies.[12,17] GeneXpert which was introduced in our Institute at nearly the end of our study could detect two cases which were both sensitive to Rifampicin. Laboratory investigations of CSF showed high mean values for protein and ADA with predominance of lymphocytes which are diagnostic of TB meningitis in 13.7% (n = 8) of all patients while Ghiya et al. reported in 5%.[12]

TB among all OIs is the commonest in HIV infected individuals but other OIs frequently infect such patients.[1,2] In our study, we found that half of the total number of HIV-TB co-infected individuals were also co-infected with other OIs of which oral candidiasis was the most common followed by HBV and toxoplasma which is similar to findings of Maniar et al. who reported predominance of oral candidiasis among the OIs and cases of cerebral toxoplasmosis (4.9%) and HBV (8.2%) were also reported.[17] Vohra et al. also observed that oral candidiasis was the most common oral manifestation in HIV patients.[25]
In relation to the CD4 count which was available for half of the patients, it was found that it is similar to other studies\textsuperscript{[16,18]} who also reported decreased CD4 values but we found that those having EPTB had a lower mean CD4 value than those who were diagnosed with PTB alone but Sharma \textit{et al.} observed that in HIV patients co-infected with PTB or EPTB, the median CD4 showed no significant difference.\textsuperscript{[16]} Also, Kamath \textit{et al.} found that the mean CD4 count at initial presentation was 174.47 cells/µL which after treatment of 6 months increased to 300 cells/µL and they had concluded that when compared to those infected with HIV alone the CD4 counts of co-infection was very much low.\textsuperscript{[22]} Majority in our study had CD4 counts <250 cells/µL, which is similar to findings of other studies.\textsuperscript{[11,20]}

Anemia was present in nearly three fourths of our patients, findings similar to Patil \textit{et al.}\textsuperscript{[11]} who reported anemia to be present in 94% of HIV patients, whereas Sobhani \textit{et al.} concluded that Hb levels <7 g/dL were associated with increased mortality in HIV infected individuals.\textsuperscript{[29]}

All patients were either undergoing or started on DOTS treatment which showed the effectiveness of the program which was possible since we have a DOTS center attached to our institute which is similar to a study by Kamath \textit{et al.} who conducted in an ART center in South India, where they found 97.2% of those infected with HIV-TB were under DOTS therapy but without a doubt the worrying part is that nearly one-fifth of the cases were on category II treatment.\textsuperscript{[22]}

Majority of our patients showed improvement on discharged, while only 3% expired during hospital stay which is much better than Shastri \textit{et al.}\textsuperscript{[18]} who reported as high as 15% and Sharma \textit{et al.} as high as 13.2% mortality.\textsuperscript{[24]} Our findings might have been affected by the fact that 16% left against medical advice and their outcome is unknown, which would be a limitation of the study.

Role of primary care physician

Primary care physicians are the first to see patients who will be presenting with a wide variety of presentation ranging from mild to severe diseases and the ones likely to diagnose or suspect patients with either HIV or TB or both. Hence, they can guide them to obtain diagnosis, treatment from nearest ART centers, and also in giving prophylaxis for the prevention of OIs.

Also, the rate of depression in a study conducted in China, among HIV-infected individuals was as high as 50.6% compared with 7.6% for general population. So, with an increase in PLHIV in 2017 compared with 1990, primary care physicians will not only have to deal with the known effects of these two diseases but also with others related to it like depression, anxiety disorders, long-term treatment, and life-long infection and ensure that PLHIV can lead a healthy life beyond viral suppression.\textsuperscript{[14,27]}

Conclusion

In our study, we observed that most commonly affected are those of 40- to 50-year age group, married, and males. They generally present with fever. Majority being newly diagnosed cases of TB, where PTB was more common than EPTB and oral candidiasis being the most common OI seen. The overall mean CD4 count was 220 cells/µL and counts for those diagnosed with EPTB was lesser than those of PTB. Even though all were already on or started with DOTS regimen, the worrying part is that 17.2% were on category II treatment and many left against medical advice. In conclusion, in a country like India where both these diseases are rampant, we recommend better information, education, understanding, awareness, and early diagnosis of these two notorious infectious diseases with prevention of relapse and default of TB cases in HIV-infected individuals a priority.

Research Quality and Ethics Statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is FMMC/FMIEC/1447/2013. Finally, the authors also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Conflicts of interest

There are no conflicts of interest.

References

1. Patil VC, Patil HV. Clinical manifestations and outcome of patients with human immunodeficiency virus infection at tertiary care teaching hospital. Indian J Sex Transm Dis 2016;37:38-45.

2. Ramesh K, Gandhi S, Rao V. Clinical profile of human immunodeficiency virus patients with opportunistic
3. World Health Organization (WHO). Tuberculosis. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis. [Last accessed on 2019 Jul 19].

4. World Health Organization (WHO). HIV/AIDS factsheet. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids. [Last accessed on 2019 Jul 19].

5. MacLean E, Saravu K, Pai M. Diagnosing active tuberculosis in people living with HIV: An ongoing challenge. Curr Opin HIV AIDS 2019;14:46-54.

6. TB FACTS.ORG. TB in India – Elimination, Private care, TB burden, NSPs. Available from: https://www.tbfacts.org/tb-india/. [Last accessed on 2019 Jul 19].

7. TB FACTS.ORG. TB & HIV-Co-infection, statistics, diagnosis, treatment. Available from: https://www.tbfacts.org/tb-hiv/. [Last accessed on 2019 Jul 19].

8. Padmapriyadarsini C, Narendra G, Swaminathan S. Diagnosis & treatment of tuberculosis in HIV coinfected patients. Indian J Med Res 2011;134:850-65.

9. National AIDS Control Organization. Ministry of Health and Family Welfare, Government of India: Guidelines for HIV testing, March, 2007.

10. World Health Organization (WHO). Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014). Available from: https://www.who.int/tb/publications/definitions/en/. [Last accessed on 2019 Jul 19].

11. Giri PA, Deshpande JD, Phalke DB. Prevalence of pulmonary tuberculosis among HIV positive patients attending antiretroviral therapy clinic. N Am J Med Sci 2013;5:367-70.

12. Ghiya R, Naik E, Casanas B, Izurieta R, Marfatia Y. Clinicoepidemiological profile of HIV/TB coinfected patients in Vadodara, Gujarat. Indian J Sex Transm Dis 2009;30:10-5.

13. Jindal S, Damor PH, Patel R. A study of tuberculosis and HIV coinfection and its correlation with CD4 count. Natl J Community Med 2018;9:110-3.

14. Pandey A, Galvani AP. The global burden of HIV and prospects for control. Lancet HIV 2019;6:e809-11.

15. Bhattacharya J. HIV prevention & treatment strategies - Current challenges & future prospects. Indian J Med Res 2018;148:671-4.

16. Sharma SK, Soneja M, Prasad KT, Ranjan S. Clinical profile & predictors of poor outcome of adult HIV-tuberculosis patients in a tertiary care centre in north India. Indian J Med Res 2014;139:154-60.

17. Maniar JK, Kamath RR, Mandalia S, Shah K, Maniar A. HIV and tuberculosis: Partners in crime. Indian J Dermatol Venereol Leprol 2006;72:276-82.

18. Shastri S, Naik R, Shet A, Rewari B, De Costa A. TB treatment outcomes among TB-HIV co-infections in Karnataka, India: How do these compare with non-HIV tuberculosis outcomes in the province?. BMC Public Health 2013;13:838.

19. Chennaveerappa PK, Nagaral J, Nareshkumar MN, Praveen G, Halesha BR, Vinaykumar MV. TB-DOTS outcome in relation to HIV status: Experience in a medical college. J Clin Diagn Res 2014;8:74-6.

20. Kapadiya DJ, Dave PV, Vadera B, Patel PG, Chawla S, Saxena D. Assessment of tuberculosis prevalence in newly diagnosed human immunodeficiency virus-infected adults attending and treatment center in Gujarat, India. Indian J Community Med 2018;43:185-9.

21. Kumar P, Sharma N, Sharma NC, Patnaik S. Clinical profile of tuberculosis in patients with HIV infection/AIDS. Indian J Chest Dis Allied Sci 2002;44:159-63.

22. Kamath R, Sharma V, Pattanshetty S, Hegde MB, Chandrasekar V. HIV-TB coinfection: Clinicoepidemiological determinants at an antiretroviral therapy center in Southern India. Lung India 2013;30:302-6.

23. Narayanan S, Swaminathan S, Supply P, Shammugam S, Narendra G, Hari L, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. J Infect Dis 2010;201:691-703.

24. Crampin AC, Mwaungulu JN, Mwaungulu FD, Mwafulirwa DT, Munthali K, Floyd S, et al. Recurrent TB: Relapse or reinfection? The effect of HIV in a general population cohort in Malawi. AIDS 2010;24:417-26.

25. Vohra P, Jamatia K, Subbada B, Tiwari RV, Althaf MS, Jain C. Correlation of CD4 counts with oral and systemic manifestations in HIV patients. J Family Med Prim Care 2019;8:3247-52.

26. Sobhani R, Basavaraj A, Gupta A, Bhave AS, Kadam DB, Sangale SA, et al. Mortality & clinical characteristics of hospitalized adult patients with HIV in Pune, India. Indian J Med Res 2007;126:116-21.

27. The Lancet HIV (Editorial). Living well with HIV. The Lancet HIV 2019;6:e807.