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A Study to Evaluate Pattern of Rifampicin Resistance in Seropositive HIV Patients in Tertiary Care Center in Western Uttar Pradesh

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Abstract:

INTRODUCTION: Tuberculosis in the PLHIV population is a major cause of morbidity and mortality and presents a substantial hazard of nosocomial disease transmission to other patients and health care workers. These risks are heightened when patients have multidrug-resistant TB. To address these challenges, there is a critical need in such a setting for rapid, effective screening for TB and the detection of drug resistance and early initiation of treatment. Delayed treatment is associated with higher morbidity and mortality.

METHOD: This was a cross-sectional survey among HIV infected adult patients attending A.R.T Nodal centers, Medicine Opd and ward and chest, and T.B OPD and wards. All the patients with presumptive pulmonary TB were assessed for sputum for microscopy AFB and underwent Drug susceptibility test (CBAAT) for Rifampicin resistance. The primary aim of the Study is "TO EVALUATE PATTERN OF RIFAMPICIN RESISTANCE IN SEROPOSITIVE HIV PATIENTS IN TERTIARY CARE CENTER IN WESTERN UTTAR PRADESH"

RESULT: The present study concluded that the prevalence of sputum positive pulmonary tuberculosis is very high of 39% among presumptive pulmonary tuberculosis patients. BY using CBNAAT we found that 27% of rifampicin resistance was prevalent among 78 patients. In the study population maximum sputum, positive pulmonary tuberculosis was in-between age group 31 to 50 years. Majority 81% of the patients were male.

CONCLUSION: Sputum microscopy has very low sensitivity (35.9%) in our study for diagnosing tuberculosis in PLHIV. whereas CBNAAT has a sensitivity of 95 %,it detected double numbers of patients than AFB microscopy.

Keywords MDR TUBERCULOSIS/RRTB, RIFAMPICIN-RESISTANCE, CBNAAT, PLHIV

1. INTRODUCTION

According to WHO, nearly 50% of the world's burden of MDR-TB cases is in India and China. The situation of TB is further threatened by the devastating effect of human immunodeficiency virus (HIV) on tuberculosis susceptibility and the rapid expansion of MDR-TB threaten to undermine the advances made by tuberculosis management programs. Tuberculosis is one of the earliest opportunistic diseases to develop amongst persons infected with HIV, and HIV infection is the most powerful risk factor of progression of TB from infection to disease with 21-34 times more chances to develop the disease as compared to those who are HIV-negative. Globally, just over one in ten of the almost 9 million people who develop TB each year are HIV-Positive, equivalent to 1.1 million new TB cases people living with HIV

India is a high burden country for tuberculosis (TB) and multidrug-resistant TB (MDR-TB). The World Health Organization has estimated that India accounted for 27% of the total number of TB cases worldwide in 2017, with 4.1% and 19% of the new and retreatment cases respectively being caused by multidrug-resistant strains (1). The estimated number of MDR/rifampicin-resistant (RR)-TB in India is 147 000, accounting for one fourth of the global burned of MDR/RR-TB(1).

Further, India is home to approximately 2.4 million people living with HIV(2) and considered to have a high burden on account of the large absolute numbers of people living with HIV in the country.

The dual burden of HIV and TB/MDR-TB in India is significantly high with a combined rate of 5.2%, ranging from 0.4% to 28.8% in various studies, with increasing treads noted in states having a higher burden of HIV infection (2-6-11). A crude estimate from studies suggests that 2500-3000 HIV- infected persons develop MDR-TB annually in India.

2. AIMS AND OBJECTIVES OF THIS STUDY

"A STUDY TO EVALUATE PATTERN OF RIFAMPICIN RESISTANCE IN SEROPOSITIVE HIV PATIENTS IN TERTIARY CARE CENTER IN WESTERN UTTAR PRADESH "

- The primary aim of the Study is "TO EVALUATE PATTERN OF RIFAMPICIN RESISTANCE IN SEROPOSITIVE HIV PATIENTS IN TERTIARY CARE CENTER IN WESTERN UTTAR PRADESH"
- The primary goal is to assess the burden of rifampicin-resistant tuberculosis among HIV-infected patients attending antiretroviral treatment (ART) centers in a tertiary care center of western Uttar Pradesh.

3. MATERIAL AND METHODOLOGY

Patient's Source: The work was conducted in the DEPARTMENT OF MEDICINE, L.L.R.M MEDICAL COLLEGE, MEERUT. Patients from medicine OPD/IPD, ward, A.R.T nodal center, and CHEST and T.B OPD and ward were selected. Total no patients selected were 200 those who are HIV serology positive, having presumptive pulmonary TB i.e cough with sputum > weeks, chest pain, breathlessness, fever > weeks, significant weight loss, haemoptysis. Demographic, clinical, and laboratory data, antiretroviral treatment(yes/no), duration on A.R.T. Data on previously T.B treatment, last visit CD4 count whether <200 or >200 data were collected.

Eligibility Criteria

Inclusion criteria:

- Age>18 years.
- both sex
- HIV 1 OR 2 seropositive with presumptive pulmonary tuberculosis
- Patients registered under A.R.T center
- Subjects who are cooperative/give written informed consent
- Approval to be taken from the institutional ethical committee of L.L.R.M Medical College Meerut

Exclusion criteria:

- Age <18
- Transgenders
- Patients not registered under A.R.T center
- Patients who are altered
- Uncooperative/unable to provide informed written consent

4. METHODS

This was a cross-sectional survey among HIV infected adult patients attending A.R.T Nodal centers, Medicine Opd and ward and chest, and T.B OPD and wards. All the patients with presumptive pulmonary TB were assessed for sputum for microscopy AFB and underwent Drug susceptibility test (CBAAT) for Rifampicin resistance sample size – The population covered as estimated by taking the prevalence's of rifampicin resistance in HIV positive patient i.e. 16.2% (Alarming levels of Drug-resistant tuberculosis in HIV infected Patients in Metropolitan Mumbai, India) with 5% absolute precision and confident interval being 95% the following formula is used.

5. OBSERVATIONS AND RESULTS

This was a cross-sectional survey among 200 patients of PLHIV attending A.R.T Nodal centers, Medicine OPD and ward and chest, and T.B OPD and wards. All the patients with presumptive pulmonary TB were to be assessed for sputum for AFB,CBNAAT, last visited CD4 counts, ESR, CBC, LFT, KFT,chest X-ray P.A view.

Age distribution

In this study group, it was seen that 36%(72) of the study population belonged to 31 to 40 years. 22 % (44) were young adults from 18 to 30 years. 25 % (50) belonged to the age group 41 to 50 years. And 17 % (34) of the population were above 50 years. Most patients 61 % were in the age group 31 to 50 years. The age distribution of the population has been summarized in table 1. and figure 1.

Table 1

Age	Frequency	Percentage (%)
18-30	44	22
31-40	72	36
41-50	50	25
51+	34	17
total	200	100

Gender distribution

In the study population, 143 (71%) were men. There were 57 (29%) females. The Gender distribution has been summarized in table no. 2 and figures no. 2

Table no. 2

Sex	Frequency	Percentage
male	143	71
female	57	29
Total	**200**	**100**

Distribution of CD4 Count

In our study population range of CD4 count was from 03 to 1174 cells/µL.

Nine patients had CD4 count less than 50 and 16 had cd4 count in between 50 to 100. 24 patients had CD4 count in between 101 to 150 and 34 patients had CD4 counts between 151 to 200, thus 41.5% of patients had CD4 counts less than 200 cells/µL. And 58.5% of patients had CD4 counts greater than 200 cells/µL. Maximum patients 70 (35%) had CD4 counts more than 351.The distribution of CD4 count is summarized in table no. 3 and figure no .3

Table no. 3

CD4 Count	Frequency	Percentage
<50	**9**	**4.5**
50-100	**16**	**8**
101-150	**24**	**12**
151-200	**34**	**17**
201-250	**24**	**12**
251-300	**11**	**5.5**
301-350	**12**	**6**
351+	**70**	**35**

Total no. of pulmonary tuberculosis

In our study, the total number of pulmonary tuberculosis including Sputum negative (13) and sputum positive(78) was 91 (45.5%). 109 (54.5%) were non-tubercular.

Table no. 4

Pulmonary tuberculosis	(n)	Percentage
present	91	45.50%
absent	109	54.50%
Total	**200**	**100**

Comparison of sputum AFB Microscopy and CNAAT for MTB

In comparison with sputum AFB microscopy which detected 28 sputum positive, CBNAAT detected 50 more patients having Tuberculosis. Thus detection rated doubled with the use of CBNAAT as compared to sputum AFB microscopy. Based onthe table no. 5 total number of patients with sputum positive was 78 (39%).

Table no.5

Smear status	AFB microscopy	CBNAAT for MTB
smear-positive	28	28
smear-negative	172	50
Total	**200**	**78**

Distribution of CD4 count in MTB detected by CBNAAT patients

Among the MTB positive in CBNAAT patients 50 (64%) were having CD4 count less than 200 cells/µL and 28 (36%) were having more than 200 cells/µL

Table no. 6

CD4 Count	No. of patients	Percentage
CD4 Count<200	50	64%
CD4 Count>200	28	36%

Correlation of CD4 count in CBNAAT MTB detected patients

We used a chi-square test, P-value was 0.000 which is < 0.05. so there is a significant difference in the number of patients with CD4 count less than 200 and CD count more than 200 in MTB detected patients by CBNAAT test.

CD4 Count	MTB detected	MTB not detected	significance
CD4count <200	50	33	p value=0.000
CD4count>200	28	89	p value < 0.05
Total	**78**	**122**	

Correlation of Gender with CD4 count in MTB detected patients by CBNAAT

There was no correlation between CD4 counts and Gender in MTB detected patients by CBNAAT as P-Value was 0.1532 which was > 0.05.

Table no.07

CD4 Count	Male	Female	Significance
CD4 <200	38	12	P value=0.1532
CD >2OO	25	3	P value > 0.05
Total	**63**	**15**	

Rifampicin resistant detected by CBNAAT

78 patients were detected MTB positive by CBNAAT of which 21 (27%) were found to be rifampicin-resistant and 57 (73%) were Rifampicin sensitive.

Table no. 8

Drug sensitive	No of patients	Percentage
Rifampicin resistant	21	27
Rifampicin sensitive	57	73

Distribution of CD4 count with Rifampicin resistant patients

In rifampicin-resistant patients, 15 (71%) had CD4 count less than 200 and 6 (29%) had CD4 count more than 200.

Table no. 9

CD4 count	Frequencies	Percentage
CD4<200	15	71
CD4>200	6	29
Total	**21**	**100**

Correlation of CD4 count with Rifampicin Resistant

There is no significant difference between the number of patients with CD4 count less than 200 and CD4 count more than 200 in rifampicin-resistant. P-value is 0.4129 which is >0.05.

Table no. 10

CD4 count	Rifampicin resistant	Rifampicin sensitive	Significance
CD4 <200	15	35	P Value = 0.4129
CD4 >200	3	22	P Value >0.05
Total	**21**	**57**	

Correlation of Gender with CD4 counts in Rifampicin resistant patients

Table no. 11

CD4 count	Male	Female	Significance
CD4 < 200	12	3	P Value = 0.8605
CD4 > 200	5	1	P Value > 0.05

6. OBSERVATIONS AND RESULTS

This study was conducted to evaluate the burden of Rifampicin resistance in PLHIV patients in a tertiary care center in the western Uttar Pradesh region. The study was conducted in the department of medicine, L.L.R.M medical college Meerut. Patients were selected from medicine OPD/IPD, ward, A.R.T nodal center, and CHEST and T.B OPD and ward.

Tuberculosis in the PLHIV population is a major cause of morbidity and mortality and presents a substantial hazard of nosocomial disease transmission to other patients and health care workers (12). These risks are heightened when patients have multidrug-resistant TB. To address these challenges, there is a critical need in such a setting for rapid, effective screening for TB and the detection of drug resistance and early initiation of treatment. Delayed treatment is associated with higher morbidity and mortality.

In PLHIV, diagnosis of pulmonary tuberculosis may be challenging as there is scanty sputum production, lack of caseous necrosis leading to a decreasing number of bacilli sputum. These factors decrease the sensitivity of sputum microscopy which currently is the most frequent method used in diagnosing pulmonary tuberculosis. To overcome these shortcomings sputum culture for mycobacteria can be used but it is not easily available and is very time-consuming. This delays initiation of therapy and increases the risk of the spread of extrapulmonary forms of TB. Radiological tests like chest X-ray may appear normal in HIV patients having pulmonary tuberculosis (13).

Recently launched new technique, cartridge-based nucleic acid amplification test (CBNAAT) has been claimed to have the advantage of giving faster results and also detect Rifampicin resistance (14). The WHO in December 2010, endorsed the rollout of a novel rapid test, CBNAAT, for the investigation of patients suspected of having TB, especially in setting with a high prevalence of HIV associated disease and MDR-TB (15.

The HIV epidemic in India continues to affect the young between the age group of 16 – 49 years with women constituting 39% of the PLHIV population as reported by NACO annual report 2012-2013. In our study, the maximum number of patients was found in the age group of 31 to 50 years (61%). Young patients remain at the center of the HIV/AIDS epidemic. Out of 200 patients, 57 (29%) were female and 143 (71%) were males.

In the study population maximum patients, 70 (35%) had CD4 count more than 351 cells/ μL.

In our study of 200 patients, 91 (45.5%) had pulmonary tuberculosis which included 13 number of patients were sputum Negative for MTB and 78 were sputum positive for MTB.

Sputum microscopy for AFB is a simple, economical, and easy to do the test for diagnosing pulmonary tuberculosis. However,as it needs at least 10,000 bacilli per ml to give a positive result and is a highly subjective test, its sensitivity has been shown to range from 20-60 % under different conditions(16). This sensitivity is further decreased in PLHIV due to lower rates of caseous necrosis and sputum production. In our study, 28 patients were positive for sputum AFB by microscopy, by CBNAAT along with these 28 patients 50 more patients had MTB positive in sputum, altogether 78 (39%) patients were sputum positive pulmonary tuberculosis. The sensitivity of AFB microscopy was 35.9% in our study and specificity 100 %. Similar study SHILPA et al. had a sensitivity of 45% and 100% specificity(17).

Thus CBNAAT detected double patients than sputum AFB microscopy. A study in Peru showed the sensitivity of CBNAAT was 73.3% and specificity 99.2% and 28% of sensitivity for AFB microscopy and 100 % specificity.(18)

50 (64%) patients had CD4 count less than 200 and 28 (36%) patients had CD4 count more than 200. P-value was 0.000 which is <0.05.There was a significant difference in these two groups that is if the CD4 count is less than 200 there are more chances of having sputum positive tuberculosis. There was no significant correlation seen between CD4 count and gender among sputum positive pulmonary tuberculosis in the PLHIV population.

Besides, CBNAAT also detects Rifampicin resistance in the same report. Past studies alone and 90% of rifampicin-resistant patients turn out to be MDR-TB. Hence CBNAAT can be a useful test for screening for MDR-TB.(19)

In our study out of 78 sputum positive patients by CBNAAT 21 (27%) patients demonstrated Rifampicin resistance. A similar study by Richa Dewan et al.2015(20) had 25 % cases of rifampicin resistance. Another study by Pragati Rao et al. 2016 (21) had 14 % of cases detected rifampicin resistance. A study done by Sethi et al at PGIMER, Chandigarh suggested a high prevalence of 27.3% in HIV positive cases.(22). Another study Praveen B Gautam et al. 2018 (23). has a prevalence of 20% among HIV-positive patients.

7. CONCLUSIONS

From the above observation, we conclude that

- The present study concluded that the prevalence of sputum positive pulmonary tuberculosis is very high of 39% among presumptive pulmonary tuberculosis patients. Such patients have a greater risk of spread of tuberculosis and hence early diagnosis and treatment are very important.

- In the study population maximum sputum, positive pulmonary tuberculosis was in-between age group 31 to 50 years. This age group needs to make them more aware and educated related to their condition and preventive measures. majority 81% of the patients were male. These may be due to their working away from home and their aggressive behaviours.
- Sputum microscopy has very low sensitivity (35.9%) in our study for diagnosing tuberculosis in PLHIV. whereas CBNAAT has a sensitivity of 95 %,it detected double numbers of patients than AFB microscopy. Hence using sputum microscopy alone is not sufficient as a screening test to diagnose such patients.
- BY using CBNAAT we found that 27% of rifampicin resistance was prevalent among 78 patients. Resistance was common especially in those patients who had a history of ATT (71.5%). There is a need for proper counselling and strict supervision regarding the ATT course. All patients need to get proper and right drug doses. Nutrition plays a very crucial role in the recovery of the disease. There is a high prevalence e of rifampicin resistance in western Uttar Pradesh because of the high-density population with the hub of HIV and low socioeconomic status.

8. REFERENCES

[1] Global Tuberculosis Report 2016. Geneva: World Health Organization; 2016 (www.who.int/tb/publications/global_report, accessed 19 December 2017).
[2] Department of AIDS Control (2013), National AIDS Control Organization, Annual Report 2012–2013, Ministry of Health & Family Welfare, Government of India.
[3] Paramasivan CN, Venkataraman P (2004) Drug resistance in tuberculosis in India. Indian J Med Res120: 377–386. [PubMed]
[4] Deivanayagam CN, Rajasekaran S, Venkatesan R, Mahilmaran A, Ahmed PR, et al. (2002) Prevalence of acquired MDR TB and HIV co-infection. Indian J Chest Dis Allied Sci 44: 237–242. [PubMed]
[5] Williams BG, Granich R, Chauhan LS, Dharmshaktu NS, Dye C (2005) The impact of HIV/AIDS on the control of tuberculosis in India. Proc Natl Acad Sci U S A 102: 9619–9624. [PMC free article] [PubMed]
[6] Swaminathan S, Paramasivan CN, Ponnuraja C, Iliayas S, Rajasekeran S (2005) Anti-tuberculosis drug resistance in patients with HIV and tuberculosis in South India. Int J Tuberc Lung Dis 9: 896–900.[PubMed]
[7] Maniar JK, Kanuth RR, Mandalia S, Shah K, Maniar A (2006) HIV and tuberculosis: partners in crime. Indian J Dermatol Venereol Leprol 72: 276–82. [PubMed]
[8] Pereira M, Tripathy S, Inamdar V, Ramesh K, Bhavsar M, et al. (2005) Drug resistance pattern of Mycobacterium tuberculosis in seropositive and seronegative HIV-TB patients in Pune, India. Indian J Med Res 121: 235–239. [PubMed]
[9] Sethi S, Mewara A, Dhatwalia SK, Singh H, Yadav R, et al. . (2013) Prevalence of multidrug resistance in Mycobacterium tuberculosis isolates from HIV seropositive and seronegative patients with pulmonary tuberculosis in north India. BMC Infect Dis 1471–2334/13/137. [PMC free article] [PubMed]
[10] Menon S, Dharmshale S, Chande C, Gohil A, Lilani S, et al. (2012) Drug resistance profiles of Mycobacterium tuberculosis isolates to first-line anti-tuberculous drugs: a five years study. Lung India 29: 227–231. [PMC free article] [PubMed]
[11] Kumar P, Balooni V, Sharma BK, Kapil V, Sachdeva KS, et al. (2014) High degree of multi-drug resistance and hetero-resistance in pulmonary TB patients from Punjab state of India. Tuberculosis (Edinb)94(1): 73–80. [PubMed]

[12] Bock NN, Jensen PA, Miller B,Nardel E. Tuberculosis infection control in a resource-limited setting in the era of expanding HIV care and treatment. J Infect Dis 2007 Aug 15;196 suppl 1: S108 -13
[13] Perlman Dc, el-Sard WM, Nelson ET, Matts JP, Telzak EE, Saloman N, et al.variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunocompression.clin infect Dis 1997;25:242-6.
[14] Boehme CC, Nabeta P, Hilleman D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampicin resistance. N Eng J.Med 2010; 363: 1005-15
[15] World health organization and STOP TB department. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR- TB (cited 2013 Mae 02). Available from http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf
[16] Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. International standards for tuberculosis care. Lancet Infect Dis 2006 nov; 6(11):710-25.
[17] Shilpa, Shobha D, Nadagir, Jnaneshwara K.B, Asha B. Patil, Aaftab G. Pendari, Uma Chikkaraddi: detection of rifampicin resistance in HIV seropositive individuals with suspected pulmonary tuberculosis by using CBNAAT October 2016.
[18] Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A et al. Screening for HIV associated Antiretroviral therapy using the XpertMTB/RIF Assay: A prospective study. PLoS Med 8(7):e1001067.doi:1371/journal.pmed.1001067
[19] Boehme CC, NicolMP, Nabeta P,Michael JS, Gotuzzo E et al. Feasibility, diagnostic accuracy, and effectiveness of decentralized use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multidrug resistance:a multicentre implementation study.Lancet 2011;377:1495-1505.
[20] RDewan, S Anuradha, A Khanna, S Garg, S Singla, P Ish, S Agarwal, A Narayana H, M Hanif, H Singh, S Uppal, et al: role of cartridge-based nucleic acid amplification test (CBNAAT) for early diagnosis of pulmonary tuberculosis
[21] Pragati Rao, K Lakhmi Sowjanya et al. Role of CBNAAT in rapid detection of Mycobacterium tuberculosis in PLHIV in highly prevalent state.
[22] Sethi S, Mewara A Dhatwalia S K et al. prevelance of multidrug resistance in mycobacterium tuberculosis isolated from HIV seropostitive and seronegative patients with pulmonary tuberculosis in north India, 2013.
[23] Praveen B Gautam, Ashwini Mishra, Santosh kumar et al. prevelamce of rifampicin resistance Mycobacterium tuberculosis and associated factors among presumptive tuberculosis patients in eastern Utter Pradesh.