

# Sero-Prevalence of TB-HIV & HIV-TB Co-Infection among Visakhapatnam Urban Population in Andhra Pradesh - A Retrospective Observational Study

Kodandarao Kuna<sup>1</sup>, Vasundhara N<sup>2</sup>, Padmanabham Y<sup>3</sup>, Chandrareddy<sup>4</sup>, Rameshbabu B<sup>5</sup>

<sup>1,3</sup>Faculty GIMSR (Gitam Institute of Medical Sciences & Research), Visakhapatnam, AP.

<sup>2</sup>Disrict Tuberculous Officer, Pedawaltair, Visakhapatnam, AP.

<sup>4</sup>Senior Medical Officer, ART Center, DTC, Visakhapatnam, AP.

<sup>5</sup>Faculty, Konaseema Institute of Medical Sciences, Amalapuram (EG), AP.

Email address: <sup>5</sup>kkraomsgs@gmail.com

## Abstract—

**Background &Objectives:** Globally patients living with HIV (PLHIV) are more prone to develop active TB disease than those living without HIV due to immunosuppression and reactivation. Also the fact that MDR-TB & XDR-TB are more common among HIV-TB co-infection cases. WHO suggests the use of Gene-Xpert to diagnose HIV-TB and the RIF resistance. PTB is reported in 75% of cases of HIV-TB. The objective is to study the burden of seroprevalence of HIV-TB co-infection among the population of Visakhapatnam in Andhra Pradesh. Material & Methods: The case finding data is collected from the ART center of District Tuberculous Center of Visakhapatnam, AP with permission and clearance. A total of 22,504 cases of tuberculosis and 1577 cases of HIV out of it for the period 2015 to 2018 is tabulated and analysed on excel sheet with SPSS software to study the HIV rate among TB cases. The present study deals with 361 cases of confirmed TB (Table-5) out of presumptive TB cases of tested 4704 of the total screened 69,566 cases of HIV-TB. It is retrospective, study conducted at the research center, GIMSR (Gitam Institute of Medical Sciences & Research) Visakhapatnam, AP. Results: The prevalence is 0.52% which is just higher than the National average prevalence of 0.26%. And average prevalence rate of HIV-TB per one lakh population is 3.89 (Table-6) of total population of Visakhapatnam Urban in AP State. Conclusions: The confirmed HIV-TB cases range from 6.64% to 7.87% out of the presumptive TB cases among the screened cases at ART-OP. Raising the immune status of the patient by improving nutrition, correcting anaemia with blood transfusion. HIV-TB Co-Infection has to be regarded as a special area of public health problem by linking RNTCP with NACP.

Keywords— Co-Infection, HIV-TB, Prevalence, Retrospective, study.

# I. INTRODUCTION

*Definition of HIV-TB Co-infection:* The presence of both TB & HIV infection in an individual patient is defined as HIV-Co-Infection.

Patient died of HIV-TB is considered as death due to HIV. TB in HIV-AIDS background requires modern state of art DNA based molecular diagnostics like CBNAAT as it is difficult to diagnose with smear or FNAC. Bronchoscopy and

Table: 1							
GLOBAL - INDIA TB BURDEN: 2017							
	Glo	bal	India				
Indices	Cases	Rate Per Lakh	Cases	Rate Per Lakh			
Incidence	1,04,00,000	140	27,90,000	211			
Deaths	16,74,000	22	4,35,000	33			
HIV-TB Cases	10,30,000	14	87,000	6.6			
HIV-TB Deaths	3,74,000	5	12,000	0.9			
MDR/RR Cases	6,01,000	8.1	1,47,000	11			

Indian Average TB Burden - 217 Per One Lakh Per Annum, END-TB Target -10 Cases Per One Lakh Per Annum, 33MDR TB - 2.84 % In New Cases - 11.60% In Previously Treated Cases.

II. 5,10,16,28,30 EPIDEMIOLOGY AND INDIAN SCENARIO

The risk of developing tuberculosis (TB) is estimated to be between 16-27 times greater in people living with HIV (PL-HIV) than among those without HIV infection. In 2015, there were an estimated 10.4 million cases of tuberculosis disease globally, including 1.2 million (11%) among PL-HIV and biopsy specimens from HIV-seropositive should be subjected to mycobacterial smear and <sup>26</sup>culture examinations. *As per WHO 'END-TB'*<sup>17,18</sup>*strategy, the TB incidence and* 

As per WHO 'END-TB' <sup>17,18</sup>strategy, the TB incidence and death rate have to be reduced by 90% & 95% respectively for the year 2035 but for India by 2025 (Table-2). As per global-India TB burden report 2017 the HIV-TB cases & deaths are 14, 5 per one lakh population globally, and for India 6.6, 0.9 per one lakh population respectively (Table-1).

Table: 2							
W.H.O. GUIDELINES							
Indicies	Miles	Milestones		End TB			
indicies	2020	2025	2030	2035			
Reduction in No. Of TB Deaths	35%	75%	90%	95%			
Reduction in TB Incidence	20%	50%	80%	90%			
TB Famili's Catastrophic Costs	0%	0%	0%	0%			
SDG - Sustainable development goals.							

DO - Sustainable development goals.

almost 60% (57%) of tuberculosis cases among PL-HIV were not diagnosed or treated, resulting in 3,90,000 tuberculosisrelated deaths among PL-HIV, globally about 11% new TB cases were registered.

Currently the national prevalence is 0.26 percent as compared to global 0.2 percent. However, the prevalence rate



in high risk group like female sex workers is 7 percent. HIV epidemics in India are characterized by low prevalence in general population and high prevalence in high risk groups.

The <sup>11</sup>WHO-<sup>8</sup>UNAIDS revised update of global estimate of PLHIV has been calculated to be 33.2 million, a reduction of 16% compared with the estimate of 39.5 million in 2006. About 2.5 million or 0.4% of adult population in India are HIV sero positive which is less than the earlier reported figure of 5.7 million.

Total 4,00,000 patients who has suffered from both HIV & TB have died in the year 2015, in comparison to those 1.4 million cases who died of tuberculosis alone. HIV +VE patients co-infected with tuberculosis are having 20 to 40 times more chances to get an active TB disease than those not infected with HIV residing in the same geographical area. Tuberculosis is a leading cause of death in HIV +VE patients leading to more than a quarter of 2 million AIDS deaths in year 2008; globally it is the commonest HIV associated opportunistic infection; as it facilitates infectivity, HIV disease progression and decreases efficacy of anti-retroviral therapy.

In India, there were 2.5 million patients living with HIV and AIDS in 2007, while the incidence of new TB cases was about 1.8 million cases per year. The level of immune suppression in patients determines clinical profile of the disease. Pulmonary infection is common and involved in about 75% of all co-infected patients. HIV-TB co-infection finally results in more rapid <sup>25</sup> progression to severe forms of <sup>14,22,33</sup>MDR and XDR tuberculosis.

Globally and in India, TB is one of the most common opportunities infections affecting people with HIV. This assumes importance in a country like India which has 2.7 million HIV infections and 23% of the world's incident TB cases. HIV infection is often cited as an important reason for failure to control TB, and for causing resurgence in TB worldwide. While this is true, our results suggest that implementation of program guidelines in a coordinated manner can result in good treatment outcomes among those co-infected with HIV.

## III. METHODS

*Study Design:* <sup>2</sup>Retrospective observational study.

*Study settings:* Municipal corporation, city area, Visakhapatnam.

*Study population:* Total of 1577 HIV-TB co-infected patients are selected out of 22,504 TB (Table-3) patients to understand the burden of HIV among presumptive TB patients at first to take it as a baseline to further study the prevalence of TB among HIV cases, reported at the District Tuberculous Center, Visakhapatnam, AP.

*Sampling Technique:* A retrospective study of available secondary data of diagnosed HIV-TB co-infection cases registered at the DTC, <sup>29</sup>Visakhapatnam for the period 2015 – Aug 2018 is performed.

*Method of data collection:* We had contacted the senior medical officer of ART center at the DTC, Visakhapatnam informing the DTO with due permission and only the data relating to HIV-TB co-infection is noted with possible information.

*Exclusion Criteria:* Other co-morbid conditions like COPD, CKD, Hepatitis, Alcoholism, smoking, special groups like <sup>6</sup>antenatal, children and occupational diseases are not considered part of the present study as the present study aims to know the burden and the prevalence of tuberculosis among PL-HIV affected, the co-infection of HIV-TB.

*Visakhapatnam urban* has a population of 22 to 28 lakh over the period from 2015 to Sept 2018. It is a wide expanding cosmopolitan city with massive migrant influx, yet little slum ridden.

			Table: 3			
	<sup>7,13</sup> TB HIV	- QUARTE	ER / YEAR WISE S	CREENED /	+VE D	ATA
Year	Visakhapatnam Urban Population at Risk	Quarter	Total Registered	HIV +VE	%	TB-HIV prevalence per 1,00,000 population
		1	1452	128	8.82	
2015	2769383	2	1531	124	8.10	
2015	2703383	3	1537	108	7.03	16.97
		4	1540	110	7.14	
	TOTAL :		6060	470	7.77	
		1	1615	127	7.86	
2016	2178359	2	1559	106	6.80	
2010	2178559	3	1439	88	6.12	19.74
		4	1470	109	7.41	
	TOTAL :		6083	430	7.05	
		1	1471	105	7.14	
2017	2193299	2	1369	111	8.11	
2017	2193299	3	1360	98	7.21	18.10
		4	1412	83	5.88	
	Total :		5612	397	7.08	
		1	1618	136	8.41	
2018	2193299	2	1521	49	3.22	
2010	2193299	3	1610	95	5.90	12.76
		4	NA	NA	-	
Total :			4749	280	5.84	
	Grand Total :		22504	1577	6.94	16.89

41

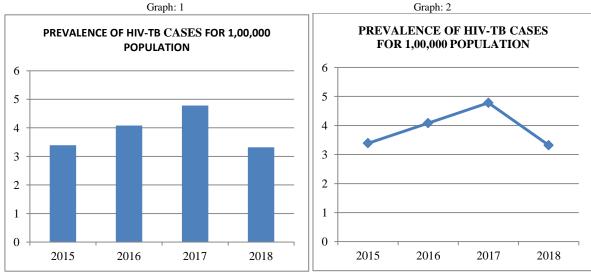


	Table: 4								
	PL HIV - TB <sup>1</sup> CASE PROFILE								
Year	Art - OP	Screened	Presumptive & Tested FOR TB	Diagnosed As TB	On Treatment				
2015	17772	16313	1197	94	92				
2016	17297	16201	1340	89	84				
2017	27995	21401	1240	105	98				
Sep-18	16504	15651	927	73	63				
Total :	79568	69566	4704 (6.76%)	361 (0.52%)	337				

	Table: 5							
	HIV - TB CASE PROFILE FOR 2015 - Sept 2018							
V	DTD	DTD EDTD	MDD TD	TOTAL	<sup>34</sup> Deaths			
Year	PTB	EPTB	MDR - TB		PRE-ART	<sup>4</sup> ON-ART		
2015	61	33	2	94	2	2		
2016	53	36	2	89	3	10		
2017	68	37	3	105	4	17		
Sep-18	45	28	3	73	1	7		
Total :	227 (62.88%)	134(37.12%)	10(2.77%)	361	10 (2.77%)	36 (9.97%)		
					12.7	4%		

More no. of deaths on ART treatment than in Pre-ART cases is due to immune reconstitution inflammatory 9.20.24.2 syndrome (IRIS).

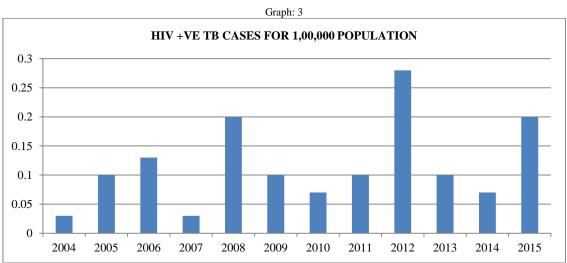
	Table: 6								
	<sup>15,21</sup> HIV-TB PREVALENCE RATE PER 1,00,000 POPULATION OF VISAKHAPATNAM URBAN, AP								
Year	Urban Population of Visakhapatnam	Presumptive TB Tested Out of Screened at A R T Center	TB Confirmed Cases Out of Presumptive	Percentage of Confirmed TB Out of Presumptive	Prevalence of HIV-TB Cases Per 1,00,000 Population				
2015	27,69,383	1197	94	7.85	3.39				
2016	21,78,359	1340	89	6.64	4.08				
2017	21,93,299	1240	105	8.46	4.78				
Sep-18	21,93,299	927	73	7.87	3.32				
	AVERAGE :	4704	361	7.67	3.89				



Graph: 1

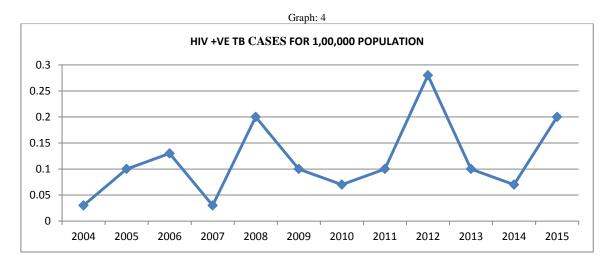
Study of 361 cases of HIV-TB by Dr. Kodandarao Kuna et al from Visakhapatnam AP, India for 2015 to 2018.



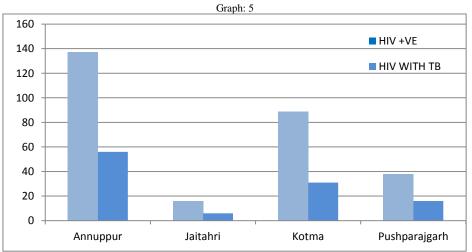


The Distribution of HIV +VE TB CASES/1,00,000 Populations, By Years 2004 – 2015.

Study of 77 cases of HIV-TB by <sup>3</sup>Matilda Gjergji from Albania in 2017 for the period 2004 to 2015.



Study of 77 cases of HIV-TB by Matilda Gjergji from Albania in 2017 for the period 2004 to 2015.



Quantitative depiction of HIV + and HIV +TB status in different subdivisions/blocks of district Anuppur, Madhya Pradesh.

280 cases of HIV-TB for the period Apr 2013 to Mar 2017 - study by Kachhi R, Saket V, Sharma P & Singh P. from Annuppur dist, MP.



The population is taken as population at risk to calculate the prevalence rate of HIV, TB and TB-HIV & HIV-TB. For the period 2015 – Sept, 2018 the total out patient data at the ART OP of Dist. Tuberculous Center (DTC), Visakhapatnam is 79,568 and 69,566 (Table-4) are screened out of it. 4,704 cases are considered as presumptive TB and tested for TB positivity, out of which 361(0.52%) cases are confirmed as TB among the total HIV cases. For the same period the HIV +Ve rate is 6.94% which is just less than the National average (Table-3).

# IV. RESULTS

The present study deals with 361 cases of confirmed TB (Table-5) out of presumptive TB cases of tested 4704 of the total screened 69,566 cases of HIV-TB that comes to 0.52% which is just higher than the National average prevalence of 0.26%. And average prevalence rate of HIV-TB per one lakh population is 3.89 (Table-6) of total population of Visakhapatnam Urban in AP State. The confirmed HIV-TB cases range from 6.64% to 7.87% out of the presumptive TB cases among the screened cases at ART-OP. Pulmonary TB constitutes about 63%, EP-TB 37% and MDR-TB 3% among the total identified HIV-TB load. In other studies PTB ranges from 75% to 85% (Table-6). Death rate is about 3% and 10% in pre-ART and on-ART. Average death rate is 12.74% which is 46 cases of deaths out of 361 HIV-TB by percentage. As per graph-1&2, the peak effect of prevalence is shown in 2017 with gradual increase from 2015 which indicates increasing burden of HIV-TB or increasing case diagnosis of it. However similar conclusions cannot be drawn from the downward trend of the graph received in 2018 cannot be regarded as decrease in prevalence rate as it covers only three quarters of the year upto Sept 2018. Even then it can be assumed as the starting of decreasing prevalence due to the more effective control measures. Graph-1 is the bar diagrammatic presentation of the same.

<sup>9</sup> comparision with One Indian and One Foreign Study – In the study of Anuppur dist. MP by Kachhi R & Singh P for the period 2013 to 2017, the HIV & HIV-TB prevalence rate showed variable trend as per Graph-5. From an European <sup>12,23,31,32</sup>Albania study by Matilda Gjergji for 2004 to 2015 the HIV-TB prevalence rate per one lakh population showed fluctuating trend with peaks & troughs unlike in the present study which shows uniform gradual decrease in prevalence, indicating no confusion in the policy of HIV, TB or HIV-TB control programme implementation in India. Even Albania study as per Graph – 3 & 4, the prevalence rate averages from 1.5 to 3.0 % per one lakh population, which is a resource rich nation with limited population, Indian average is 0.26% and the present study is 0.52%.

### V. CONCLUSIONS

There is a need to decriminalize and destigmatize the disease to improve patient acceptance and increase case findings there by reducing the reservoir of infection and its spread. Overall prevalence rate of HIV received downward trend by 20% from 2000 - 2016, from 183 per one lakh

population to 140 per one lakh population. But there is no corresponding decrease in HIV-TB rate over decades due to no special emphasis on the detection of EP-TB which is more often effected in HIV-TB individuals, esp. in cases of pleural effusion and TB meningitis. The confirmed HIV-TB cases range from 6.64% to 7.87% out of the presumptive TB cases among the screened cases at ART-OP. Raising the immune status of the patient by improving nutrition, correcting anaemia with blood transfusion. HIV-TB Co-Infection has to be regarded as a special area of public health problem by linking RNTCP with NACP.

*Financial Support:* No funding resources. Study performed out of academic interest.

### ACKNOWLEDGEMENT

Our deep regards and gratitude to Senior Medical Officer, ART Center, DTC, Visakhapatnam and the Dist. Tuberculous Officer for issuing the necessary data and encouraging us for the conduct of research. The Data Entry Operator Mr. Kiran of ART center and Mr. Srinivasa Rao Nammi, Junior Assistant/Data Entry Operator of GIMSR for their constant commitment in the making of the research article.

#### REFERENCES

- Diwakar Tumkur Narasimhamurthy and David Mathew Thomas, "Clinical profile and outcome of HIV-TB Co-Infection at a centre of excellence for HIV care," *Asian J. of Med. Sci.*, vol. 9, issue 2, Mar-Apr 2018.
- [2] Prashant D. Warkari and Mahavir P. Nakel, "Study of treatment outcome of tuberculosis among HIV co-infected patients: a cross section study in Aurangabad city, Maharashtra," *Int. J. Of Comm. Med. & Pub. Health*, vol. 4, issue 12, Dec 2017.
- [3] Matilda Gjergji and Jul Bushati, "Tuberculosis in HIV/AIDS patients," *Adv. Tech. In clinical Microbiology*, vol. 1, no. 3: 16, 2017.
- [4] Ramachandran Vignesh and Chinnambedu R Swathirajan, "Risk factors and frequency of tuberculosis-associated immune reconstitution inflammatory syndrome among HIV/Tuberculosis co-infected patients in southern india," *Ind. J. of Med. Microbilogy*, vol. 35, issue 2, pp. 279-281, 2017.
- [5] R. Kachhi and V. Saker, "Epidemiological study of TB as major HIV-AIDS co-infection," *J. of Mathematical & Stat. Anal.*, vol. 1, issue 1, pp. 1–14, Aug 2018.
- [6] Dorian Fernandez and Imoleayo Salami, "HIV-TB coinfection among 57 million pregnant women, obstetric complication, alcohol use, drug abuse, and depression," J. of Pregnancy, Articl ID 5896901, 2018.
- [7] V. Vasudeviah, "HIV infection among tuberculosis patients," *Indian J Tuberc*, vol. 44, pp. 97-98, 2007.
- [8] UNAIDS. The Gao Report 2014.
- [9] S. K. Sharma, P. K. Saha, Y. Dixit, N. H. Siddaramaiah, P. Seth, and J. N. Pande, "HIV seropositivity among adult tuberculosis patients in Delhi," *Indian J Chest Dis Allied Sci*, vol. 42, issue 3, pp. 157-160, 2000.
- [10] S. K. Sharma, A. Mohan, and T. Kadhiravan "HIV-TB co-infection: epidemiology, diagnosis and management," *Indian J med Res*, vol. 121, issue 4, pp. 550-67, 2005.
- [11] World Health Organization, A guid to monitoring and evaluation for collaborative TB/HIV activities, Geneva, 2005.
- [12] J. H. Parriens, M. E. St Louis, Y. B. Mukadi, C. Brown, J. Prignot, et al., "Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months," *N Engl J Med*, vol. 332, issue 12, pp. 779-784, 1995.
- [13] C. P. Theuer, P. C. Hopewell, D. Elias, G. F. Schecter, G. W. Rutherford, and R. E. Chaisson, "Human Immunodeficiency virus infection in tuberculosis patients," *J Infect Dis*, vol. 162, issue 1, pp. 8-12, 1990.



- [14] S. Assoc, L. Knowles, A. Rai, B. E. Jones, J. Pogoda, and P. F. Barnes, "Relationship of isoniazid resistance to human immunodeficiency virus infection in patients with tuberculosis," *Am J Respir Crit Care Med*, vol. 153, issue 5, pp. 1708-1710, 1996.
- [15] D. V. Halvir and P. F. Barmes "Tuberculosis in patients with human immunodeficiency virus infection," *N Engl J Med*, vol. 340, issue 5, pp. 367-373, 1999.
- [16] J. P. Narain and Y. R. Lo, "Epidemiology of HIV-TB in Asia," *Indian J Med Res*, vol. 120, issue 4, pp. 277-289, 2004.
- [17] Regional strategic plan on HIV/TB (2003) World Health Organization Regional Office for South-East Asis 2003, SEA/TB/261, SEA/AIDS/140. New Delhi: World Health Organization Regional Office for South-East Asia.
- [18] World Health Organization Regional Office for Sout-East Asia, HIV/AIDS. SEARO Publications on HIV/AID, Tuberculosis and HIV-Some Questions and answers, 2008.
- [19] G. Meintjes, S. D. Lawn, F. Scano, M. A. French, W. Worodria, et al., Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings," *Lancet Infect Dis*, vol. 8, issue 8, pp. 516-523, 2008.
- [20] H. Mcilleron, G. Meintjes, W. J. Burman, and G. Maartens, "Complications of antiretroviral therapy in patients with tuberculosis: Drug interactions, toxicity, and immune reconstitution inflammatory syndrome," *J Infect Dis*, vol. 196, S63-75, 2007.
- [21] H. Getahun, C. Gunneberg, R. Granich, and P. Nunn, "HIV infectionassociated tuberculosis: The epidemiology and the response," *Clin infect Dis*, vol. 50, pp. 5201-5207, 2010.
- [22] S. Suchindran, "Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review," *PLoS ONE*, vol. 4, issue 5, e5561, 2009.
- [23] The Global Fund, To figh AIDS, tuberculosis and malaria, TB and HIV, concept note, Investing for impact against tuberculosis and HIV, Single TB and HIV concept Note Albania, 2015.
- [24] N. Kumarasamy, K. K. Venkatesh, R. Vignesh, B. Devaleenal, S. Poongulali, T. Yepthomi, T. P. Flanigan, C. Benson, and K. H. Mayer, "Clinical outcomes among HIV/tuberculosis-coinfected patients developing immune reconstitution inflammatory syndrome after HAART initiation in South India," *JInt Assoc Provid AIDS Care*, vol. 12, issue 1, pp. 28-31, 2013.

- [25] E. M. Shankar, R. Vignesh, R. Ellegard, M. Barahan, Y. K. Chong, M. K. Bador, et al., "HIV-Mycobacterium tuberculosis co-infection: A 'danger-couple model' of disease pathogenesis," *Pathog Dis*, vol. 70, issue 2, pp. 110-118, 2014.
- [26] S. Solomon, P. Balakrishnan, R. Vignesh, G. Waldrop, S. S. Solomon, K. G. Murugavel, et al., "A rapid and low cost microscopic observation drug susceptibility assay for detecting TB and MDR\_TB among individuals infected by HIV in South India," *Indian J Med Microbiol*, vol. 31, issue 2, pp. 130-137, 2013.
- [27] R. P. Lai, J. K. Nakiwala, G. Meintjes, and R. J. Wilkinson, "The immunopathogenesis of the HIV tuberculosis immune reconstitution inflammatory syndrome," *Eur J immunol*, vol. 43, issue 8, pp. 1995-2002, 2013.
- [28] S.K. Sharma, A. Mohan and T. Kadhiravan, "HIV-TB co-infection: epidemiology, diagnosis & management," *Indian J Med Res*, vol. 121, issue 4, pp. 550-567, 2005.
- [29] S. Shastri, B. Naik, A. Shet, B. Rewari, and A. De Costa "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*, vol. 13, issue 1, 838, 2013.
- [30] H. Getahun, C. Gunneberg, R. Granich, and P. Nunn, "HIV infectionassociated tuberculosis: The epidemiology and the response," *Clinical Infectious Diseases*, vol. 50, Supplement 3, pp. S201-s207, 2010.
- [31] C.J. Murray, K. Styblo, and A. Rouillon, "Tuberculosis in developing countries: burden, intervention and cost," *Bulletin of the International Union against Tuberculosis and Lung Disease*, vol. 65, no. 1, pp. 6-24, 1990.
- [32] A. D. Harries, R. B. Chimzizi, T. E. Nyirenda, J. Van Gorkom, and F. M. Salaniponi, "Preventing recurrent tuberculosis in high HIV-prevalent areas in sub-Saharan Africa: What are the options for tuberculosis control programmes?," *The International Journal of Tuberculosis and Lung Disease*, vol. 7, no. 7, pp. 616-622, 2003.
- [33] E. L. Korenromp, F. Scano, B. G. Williams, C. Dye, and P. Nunn, "Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: An analytical review," *Clinical Infectious Diseases*, vol. 37, no. 1, pp. 101-112, 2003.
- [34] D. Zenner, I. Abubakar, S. Conti et al., "Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland," *Thorax*, vol. 70, no. 6, pp. 566-573, 2015.