Original Article

Outcome of TB in TB-HIV co-infection under RNTCP and Factors affecting Outcome - A Retrospective Analysis

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ABSTRACT

Background : Tuberculosis is commonest opportunistic infection in HIV infected patients. Daily AKT regimens are being introduced by Government of India, but still in resources scarce area alternate day AKT regimen is given. Hence, this study is undertaken to evaluate outcome of TB in HIV patients taking alternate day AKT treatment under RNTCP.

Materials and Method : The study was carried out in Indira Gandhi Government Medical College, Nagpur. It is Observational Retrospective Record Based study. After taking ethical approval data was analyzed for past 2year records from IGGMC TU .

Observation and Results : Favorable outcome was associated with- Extremes of age, Female sex, Sputum negative Pulmonary TB, Cat I treatment, CD 4 more than 200. Unfavorable outcome was associated with-Productive age group, Malesex ,extra-pulmonary TB, Sputumpositive, Cat II i.e. retreatment cases and CD4 <200.

Conclusion : Though Daily regimen is recommended and is ideal for treating tuberculosis with HIV; DOTS with alternate day treatment is quite effective with favorable outcome in more than 70% cases as shown in this study. Hence where resources do not permit, alternate day regimen can still be given and may yield good or satisfactory outcome in more than 80% of new cases till daily regimen becomes accessible to all.

Introduction :

Tuberculosis is commonest opportunistic infection in HIV infected patients[1,2]. Testing and Counseling for HIV in TB patients is mandatory under RNTCP. Testing for active tuberculosis (TB) either pulmonary or extra pulmonary (EPTB) in human immunodeficiency virus (HIV) positive patients is also mandatory, in fact intensive case finding for TB is advised in all HIV positive patients. Government of India has introduced Daily drug regimens for TB patients, but still in resources scarce area alternate day AKT regimen is given. Hence, this study is undertaken to evaluate outcome of TB in HIV patients taking alternate day AKT treatment under RNTCP.

There is a paucity of data from India on response to treatment of tuberculosis (TB) in patients with HIV-TB co-infection. This study was done to assess the frequency and pattern of TB, outcome of anti-tuberculosis treatment, and the factors related to poor outcome of TB treatment in adult patients with HIV infection. The dual epidemics of tuberculosis (TB) and human immunodeficiency virus (HIV) infection is a major public health problem, particularly in resource limited settings such as India. Patients with HIV-TB co-infection frequently have advanced HIV disease and are at an increased risk of death and new opportunistic infections[3]. The HIV-TB co-infection has been aptly described as the "cursed duet"[4].

The World Health Organization (WHO) estimated 8.8 million incident cases of TB globally in 2010; with 12-14 per cent of cases among people with HIV[5]. India accounted for maximum number of incident cases of TB (2-2.5 million) worldwide, with an estimated 5 per cent (3.3-7.1%) having HIV co-infection[5]. Despite the high burden of disease, there is a paucity of data from India on response to anti-tuberculosis treatment (ATT) in patients with HIV-TB co-infection[6-8]. Information on the pattern of TB, the outcome of ATT and the associated factors will

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help in planning interventions to improve outcomes in these patients. The present study was carried out to assess the frequency and pattern of TB, outcome of ATT, and the factors related to poor outcome of TB treatment in HIV-infected patients with TB, attending a tertiary care health facility in NAGPUR.

Methods :

The case records of HIV/AIDS patients attending the IGGMC Tuberculosis Unit (TU) in a tertiary care center in NAGPUR, India, over a period of 2 years between May 2013 and April 2015 were retrospectively reviewed. Patients with HIV/AIDS attending various departments / facilities in the hospital were referred to the IGGMC TU for further evaluation and treatment. The study included HIV infected adult patients registered at the IGGMC TU between May 2013 and April 2015 who were diagnosed with active TB. Patients referred from other hospitals with incomplete baseline data or transferred out before complete baseline evaluation were excluded from the study.

HIV infection was documented by commercially available third generation enzyme-linked immunosorbent assay (ELISA) kits to detect antibodies to HIV-1 and HIV-2, as per the WHO strategy[9]. A diagnosis of TB was made as per the Revised National Tuberculosis Control Programme (RNTCP) and WHO criteria for smear-positive pulmonary TB, smear-negative pulmonary TB (PTB), or extra pulmonary TB (EPTB)[10,11].

Briefly, a sputum smear-positive pulmonary TB case was a patient with two or more initial sputum smear examinations positive for acid-fast bacilli (AFB), or one sputum smear examination positive for AFB plus radiographic abnormalities consistent with active pulmonary TB. A patient having symptoms suggestive of TB with at least three sputum examinations negative for AFB, and radiographic abnormalities consistent with active pulmonary TB was classified as smear negative TB; and EPTB referred to TB of organs other than the lungs which was substantiated by one culture positive specimen from an extra pulmonary site, or histological or radiological findings.

Sputum smear examination was done at the designated microscopy center following the RNTCP guidelines[10]. Detailed clinical examination was done at enrolment and repeated at every follow up. The timing of highly active antiretroviral therapy (HAART) initiation was decided as per the NACO guidelines, and the regimen comprised two nucleoside reverse transcriptase inhibitors (zidovudine or stavudine plus lamivudine) and one no nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine)[12].

Patients with TB were offered treatment free of cost from Directly Observed Treatment Short-Course (DOTS) Centre in accordance with the RNTCP of Ministry of Health and Family Welfare, Government of India[10].

New cases received Category I treatment (thrice-weekly intermittent treatment with rifampicin, isoniazid, pyrazinamide and ethambutol in the intensive phase followed by the administration of rifampicin and isoniazid in the continuation phase); whereas, retreatment cases received Category II treatment (thrice-weekly intermittent treatment with rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin for 2 months followed by rifampicin, isoniazid, pyrazinamide and ethambutol for 1 month followed by rifampicin, isoniazid and ethambutol). The intensified TB-HIV package was implemented and patients were given co-trimoxazole prophylaxis therapy in the clinic from 2013 onwards. The ethics committee of the institute approved the study protocol.

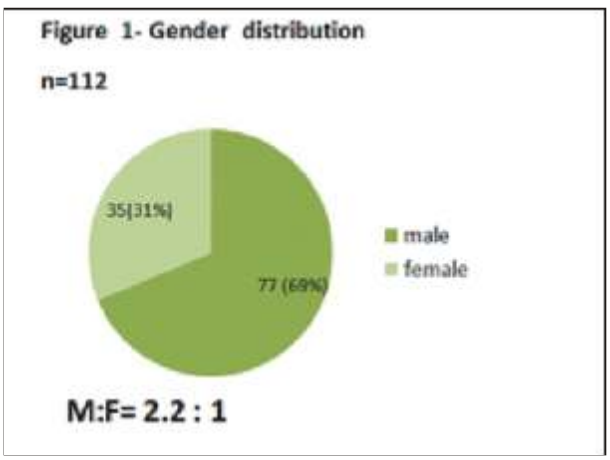
The operational definitions used for sputum positive, cure, treatment completed, failure, defaulter were according to the RNTCP guidelines[10]. Briefly, a patient registered as pulmonary smear-positive, who completed treatment and had negative smear results on two occasions, one of which was at end of treatment was classified as cured; a patient with pulmonary smear-positive TB with no smear results at the end of treatment, and smear-negative or extra pulmonary TB patients completing treatment were classified as completed treatment. Patients registered as pulmonary smear-positive CAT I, who was smear-positive at five months or registered as

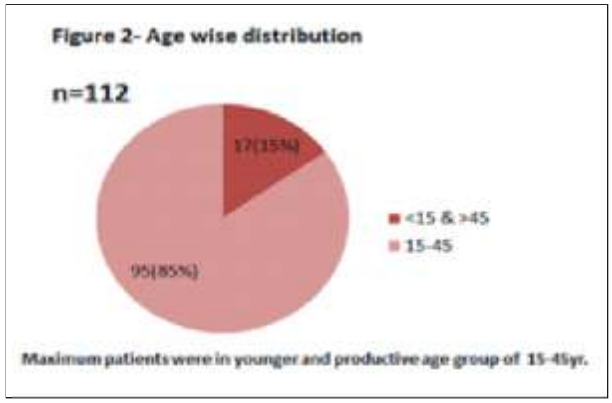
pulmonary smear-positive CAT II (retreatment), and were smear-positive at five months or later of CAT II treatment, or registered as pulmonary smear-negative or EPTB, but were smear positive any time during treatment were classified as treatment failure. Patients not taking drugs for more than two months consecutively any time after starting treatment were classified as defaulters.

The TB treatment outcomes were assessed as 'favorable' (cure and treatment completed) and 'unfavorable' (default, failure and dead). Retreatment cases were those having history of previous TB treatment of more than one month. CD4+ cell counts were performed by flow cytometry at baseline and every six months thereafter in accordance with the NACO guidelines[12]. Plasma HIV viral load estimation was not done in the National Programme. Drug susceptibility testing (DST) for tuberculosis was not performed routinely due to resource constraints.

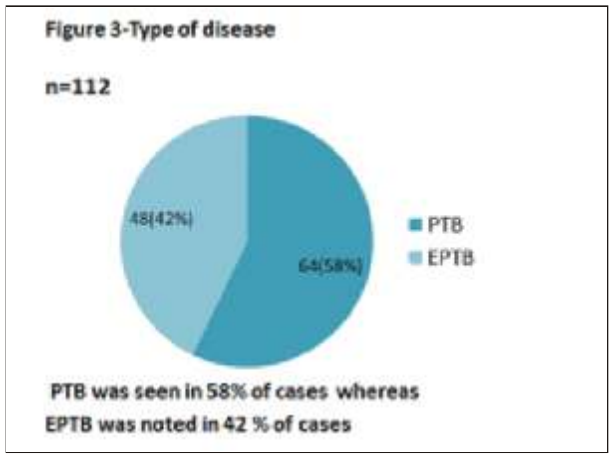
Medical social workers ensured regular visits of the patients to the DOTS clinics. During each visit the patients were evaluated for clinical improvement, drug toxicity and development of new opportunistic infections. Adherence to AKT (95% of drugs taken) was assessed during each visit by pill count, and through counseling, patients were motivated to adhere to the therapy. Patients were contacted telephonically or their houses were visited in case they failed to turn up for their scheduled visits.

Observation and Results :





There was male preponderance with M:F ratio of 2.2:1. Majority of 85% patients were in the age group of 15 to 45 years.



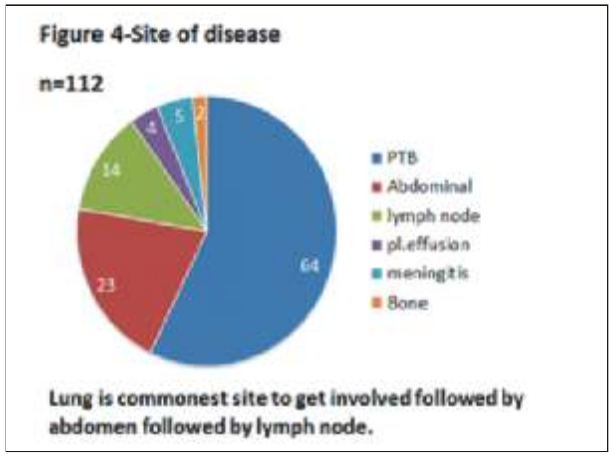
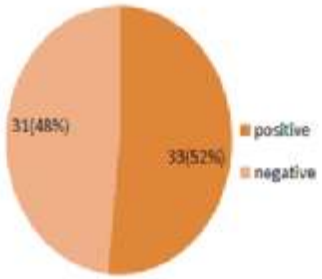


Figure 5-Sputum status at the time of diagnosis in PTB

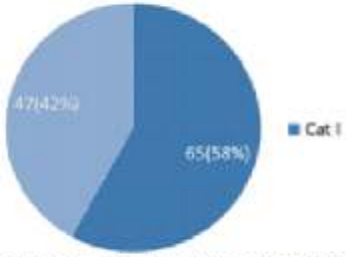
n=64



There is not much difference as far as sputum status of patients of PTB at the time of diagnosis

Figure 6-Category wise distribution

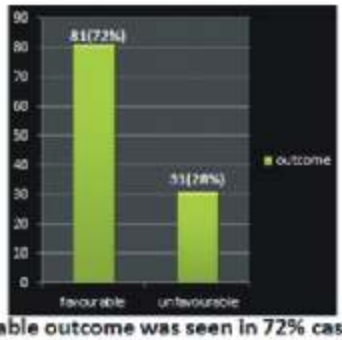
n=112



58% cases were newly diagnosed tuberculosis (PTB AND EPTB) and were on CAT I treatment of AKT
42% cases were of retreatment and were put on CAT II AKT

Figure 7-Overall outcome

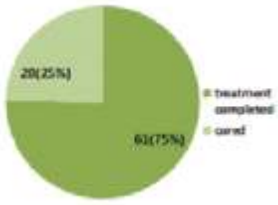
n=112

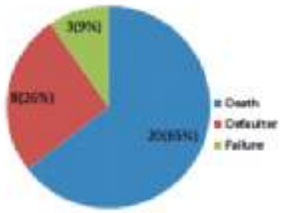


Favourable outcome was seen in 72% cases whereas Unfavourable outcome was seen in 28% case

Figure 8-Defining favourable and unfavourable outcome

n=112



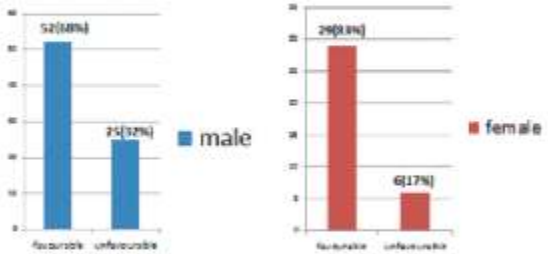


Favourable outcomes include treatment completed and cured

Unfavourable outcome include death ,default and failure

Figure 9-Correlation of outcome with gender

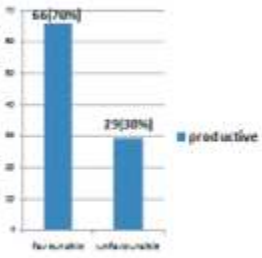
n=112

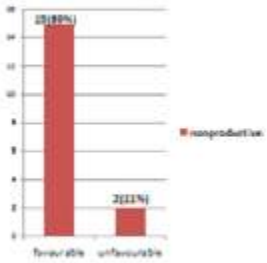


Females were associated with more favourable outcome as compared to males.(p=0.14)

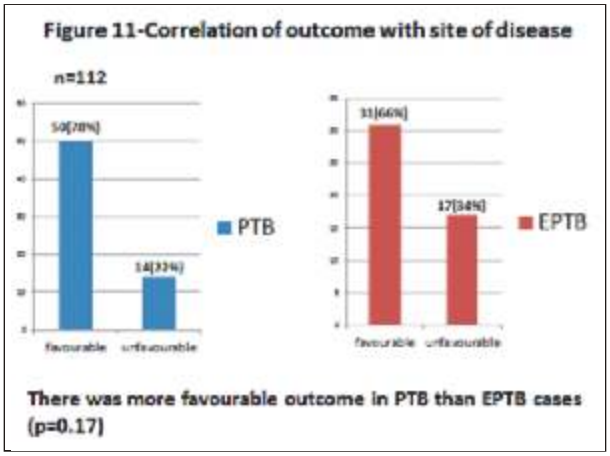
Figure 10-Correlation of outcome with Age

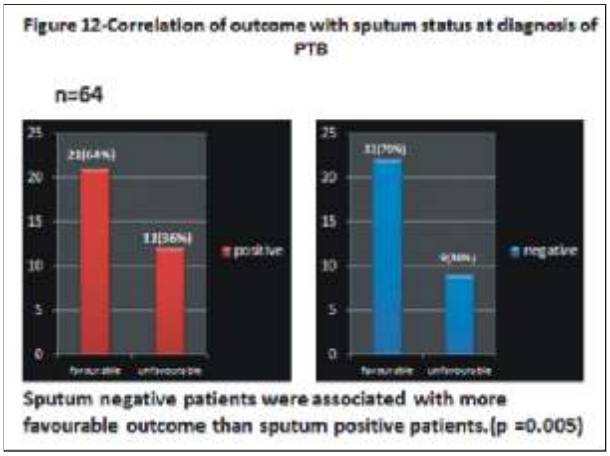
n=112

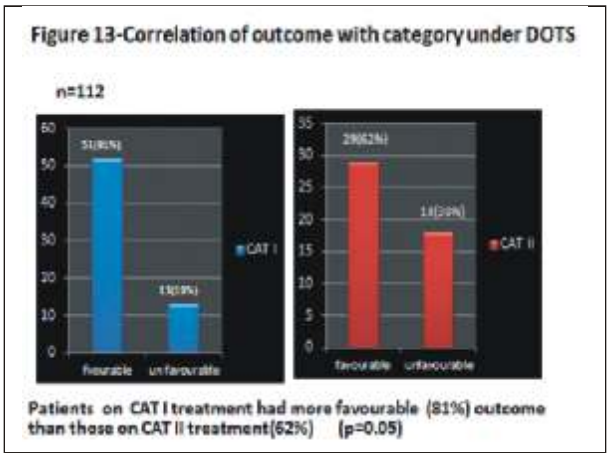


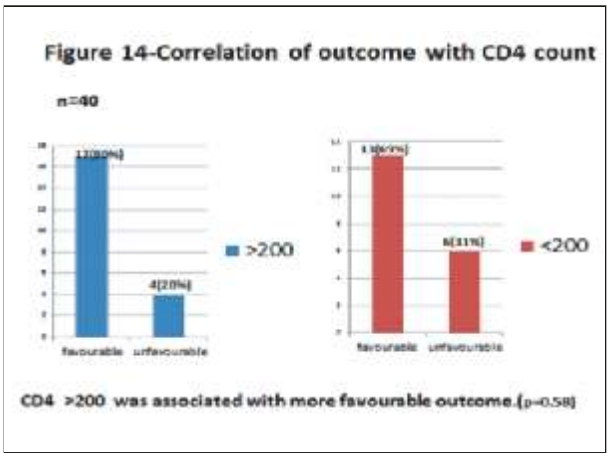


Non productive age group had more favourable outcome than the productive age group (p =0.14)









Statistical Analysis

112 patients were studied retrospectively over 2 year periods out of which 77 (69%) were male and 35 (31%) were female; (85%) patients were in productive age (15-45 yrs.) group ***(figure 1 & 2).***

EPTB was diagnosed in 48 (42%) patients whereas pulmonary TB was diagnosed in 64 (58%) patients ***(figure 3).*** Lung was commonest site to get involved followed by abdomen and lymph nodes ***(figure4).*** Amongst the PTB cases; there were almost equal number of sputum smear positive and smear negative cases of PTB at the time of diagnosis. (48% Vs 52%) ***(figure 5).*** 58% cases had been given CAT I AKT for newly diagnosed PTB and 42 % cases had been given CAT II AKT for retreatment (default / failure / relapse) ***(figure 6).***

"Favorableoutcome" was observed in 81 (72%) patients; 50 (62%) having PTB and 31 (38%) having EPTB ***(figure 7 & 8).*** Among PTB patients, sputum positives had lower success rate compared to sputum negative group (70% vs 64%); mainly attributed to higher rates of default among patients with sputum positive PTB. ***(figure 12)***

The variables of patients with 'favorable' and 'unfavorable' treatment outcomes were compared initially through univariate analysis and subsequently with logistic regression analysis to identify the independent predictors of treatment outcome. Variables with P<0.01 in univariate analysis were included for logistic regression model. All tests were two-sided, and P<0.05 was considered significant. All analyses were done using SPSS (version 17) (SPSS Inc., USA).

The variables compared between the groups with "favorable" and "unfavorable" outcomes were gender, age, AKT regimen, sputum smear status in PTB patients, disease classification (PTB / EPTB) and CD4 counts.

Favorable outcome was seen predominantly in females, patients in extremes of their age, patients on CAT I AKT, sputum negative patients, patients of PTB and patients with CD4 count more than 200 ***(figure 9 to 14).*** Unfavorable outcome was seen in males, patients of productive age group, patients on CAT II AKT, sputum positive patients, extra pulmonary TB patients, & patients whose CD4 count is less than 200 ***(figure 9 to 14).***

CD4 count of less than 200/ µl at diagnosis was independent predictors of unfavorable outcome.

Discussion :

The estimated annual risk of reactivation among those co-infected with HIV and TB is about 5 to 8 per cent, with a cumulative lifetime risk of 30 per cent or more; compared to a cumulative lifetime risk of 5-10 per cent in HIV-negative adults[4]. TB is the most common life-threatening opportunistic infection in patients with HIV/AIDS in developing countries with about 25 to 65 per cent patients with HIV/AIDS having the disease[1,4,13-16.] Extra pulmonary TB was more common than pulmonary TB, consistent with the findings in other studies[17-19]. In a study from south India, higher proportion of patients had pulmonary TB in a district[6]; however, the discrepancy was attributed to underreporting of extrapulmonary TB cases by peripheral health centers due to the limited diagnostic facilities. Advanced immunosuppression at presentation and high burden of extra pulmonary TB pose significant diagnostic challenges for resource-limited settings in India and newer diagnostic tests are urgently required that are not only sensitive and specific but easy to use in programme settings. The overall rate of favourable outcome to antituberculosis treatment was 72 per cent. Studies from resource-constrained settings have shown a success rate of 66-75 per cent[6,8,20]. The mortality rate while on treatment with ATT was high (17%), consistent .High rate of default is a major problem in the management of these patients in the programme[21]. Adverse drug reactions, initial symptomatic improvement, social stigma and lack of awareness of the disease could have been the contributory factors. Patients with advanced immunosuppression at presentation were at increased risk for poor outcome, consistent with the literature[22]. Retreatment cases were also associated with poor outcome. Though drug susceptibility test (DST) was not done routinely in the Programme setting, prior suboptimal therapy may lead to multidrug resistant (MDR) TB, a known risk factor for poor outcome[23]. Further, various factors including increased susceptibility to tuberculosis, increased opportunity to acquire TB due to overcrowding, exposure to patients with MDR-TB during hospital visits, and suboptimal therapeutic levels of anti tuberculosis drugs due to malabsorption may potentially increase the chances of MDR-TB in these patients[24]. The limitations of the study were non-availability of DST routinely under the programme, a high rate of attrition and lack of effective measures of retrieval of these patients, and inherent weakness associated with any retrospective study.

In conclusion, our results indicate towards an urgent need to strengthen the information, education, and communication activities and expand the AKT services to meet the requirements of early testing and initiation of AKT. The findings also highlight the importance for performing DST for patients starting retreatment regimen to improve outcome. Prospective studies are required to assess the efficacy of short course chemotherapy regimens on outcome of patients with HIV-TB co- infection including relapse rates on a long term follow up.

Though Daily regimen is recommended and ideal; DOTS with alternate day treatment is quite effective with favorable outcome in more than 70% cases as shown in this study. Hence where resources do not permit; alternate day regimen can still be given and may yield good or satisfactory outcome in more than 80% of new cases till daily regimen becomes accessible to all.

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