Effect of CD4 Count and timing of initiation of TB treatment on treatment outcome among TB/HIV Patients

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Abstract

Co infections TB /HIV raised the challenge of the TB control among all TB cases, 8.6% were people living with HIV. Improved ART coverage reported in reducing incidence of TB. WHO has recommended universal access to antiretroviral therapy (ART) for HIV-positive TB patients irrespective of CD4 count. Co-diagnosis of HIV and tuberculosis presents a treatment dilemma. Due to high mortality associated with TB among HIV patients. Treatment outcome of TB in HIV infected patients was poor compared to non- infected. High death rate occurred among HIV infected TB cases. Limited evidence is available on the effect of CD4 count status and timing of initiation of TB treatment on the treatment outcome among HIV infected persons thus this article aimed to review and summarize the available litrature on Scopus, PUBMED and Google Scholar.

Key words: CD4 count, TB/HIV, TB treatment out come,ART,TB

Discussion:

Mortality risk for TB/HIV co-infected patients was least when antiretroviral therapy (ART) was initiated after 14 days of anti-TB (RR = 3.55; 95% CI: 1.44, 8.73 $p < 0.0001$) and highest when ART was initiated 90 days or less prior to anti-TB and within the first 14 days of anti-TB therapy (RR = 10; 95% CI: 3.28, 30.54; $p < 0.0001$(Djimeu, E. W., & Heard, A. C. 2019)

CD4 count of less than 200/ μl at diagnosis [OR2.32, CI (1.06-5.09)], and re treatment cases [OR-2.91, CI (1.22-6.89)] were independent predictors of unfavourable outcome. (SHARMA et al). Similarly study in Myanmar, reported low CD4 cell count at the diagnosis of TB were statistically significant predictors (P value .000) for adverse treatment outcomes of TB. (Brust *et al.*, 2018).Another study in South Africa found CD4 count >350 (AOR: 0.40; CI: 0.36-0.44) were less likely to have an unsuccessful treatment outcome.(Siedner *et al.*, 2015).

Conclusion

In conclusion, CD4 count of less than 200 cells/mm3 is strongly associated with unfavourable treatment outcome which is consistent in all studies. However, there is varying reports on the timing and association on outcome of TB treatment with ART, thus large scale studies are still needed to maintain the WHO policy of two to eight weeks interval to start ART co-treatment plan as soon as TB treatment is tolerated.

1.Introduction

Tuberculosis is a major public health problem claiming lives of millions every year. In spite of more than 50 years of global effort on treatment and prevention of the disease the WHO global TB report of 2018 reported 10 million incident cases and 1.2 million deaths among HIV-negative people an additional 251 000 deaths among HIV-positive and is reported as one of the top 10 causes of death globally.(1,1).Burden of TB is high in certain regions of the world especially in developing country in which the disease affected disproportionately (WHO) regions of South-East Asia (44%), Africa (24%).Incidence of TB is per 100,000 according to WHO 2018 global TB report.

Co infections TB /HIV raised the challenge of the TB control among all TB cases, 8.6% were people living with HIV. Moreover, TB is the most common life-threatening opportunistic infection in patients with HIV/AIDS. In developing countries about 25 to 65 per cent patients with HIV/AIDS TB .TB and HIV co-infection speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infection. WHO report showed people living with HIV have a 26 times higher chance of developing an active TB infection compared to people without HIV infection (WHO 2015b). (Djimeu, E. W., & Heard, A. C. (2019).)

Improved ART coverage reported in reducing incidence of TB.Study in Pune reported similar finding CD4 count < 500 cells/mm3 , virologic failure on ART and receipt of ART without IPT were associated with higher risk of incident TB.A 1-month regimen of rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing tuberculosis in HIV-infected patients.TB/HIV prevention and control strong collaboration with subsequent evidence based interventions could curve incidence of TB and improve treatment outcomes. (Dravid *et al.*, 2019)

Co-diagnosis of HIV and tuberculosis presents a treatment dilemma. Due to high mortality associated with TB among HIV patients, WHO has recommended universal access to antiretroviral therapy (ART) for HIV-positive TB patients irrespective of CD4 count.

WHO recommendation for many TB-HIV patients is to start and complete TB treatment, and then start ART. However, if the patient's clinical status is poor (other signs of HIV clinical stage 3 or 4 or CD4 count less than 350/mm3)to start ART treatment sooner.If CD4 < 200/mm3, start TB treatment.Start ART co-treatment plan as soon as TB treatment is tolerated (between 2 weeks and 2 months).

Treatment outcome of TB in HIV infected patients was poor compared to non- infected. High death rate occurred among HIV infected TB cases. Limited evidence is available on the effect of CD4 count status and timing of initiation of TB treatment on the treatment outcome among HIV infected persons thus this article aimed to review and summarize the available litrature on Scopus, PUBMED and Google Scholar.

Patients with HIV and TB may develop a paradoxical response (immune reconstitution inflammatory syndrome [IRIS]) when starting antiretroviral therapy. This response has been attributed to a stronger immune response to Mycobacterium tuberculosis. The term "**immune reconstitution inflammatory syndrome**" (IRIS) describes a collection of **inflammatory** disorders associated with paradoxical worsening of preexisting infectious processes following the initiation of antiretroviral therapy (ART) in HIV-infected individuals. This response has been attributed to a stronger immune response to *M tuberculosis*. Clinical findings include fever, worsening pulmonary infiltrates, and lymphadenopathy.

Drug drug interactions in the treatment of TB and ART

Tb treatment protocol recommends the administration of intermittent treatment with rifampicin, isoniazid, pyrazinamde and ethambutol in the intensive phase followed by the administration of rifampicin and isoniazid in the continuation phase. Retreatment,cases with rifampicin, isoniazid, pyrazinamde, ethambutol and streptomycin for 2 months followed by rifampicin, isoniazid, pyrazinamde and ethambutol for 1 month followed by rifampicin, isoniazid and ethambutol).Studies reported drug drug reaction between Tb drugs and antiretroviral therapy and effect on treatment outcome and toxicity are of concern when initiating treatment. Nevirapine is indicated in combination with other antiretrovirals for treatment of HIV infection in adults and pediatric patients 15 days of age and older.

Decline in CD4 cell count among HIV positive adults (aged ≥15 years) not receiving ART was a strong risk factor for incident TB, with the IRR for TB increasing exponentially as CD4 cell count declines and cause of poor virological outcome(Dravid *et al.*, 2019).

HIV-infected individuals with TB receive combined treatment for both diseases, irrespective of CD4+ cell count.CD4 count during initiation of anti TB was reported as the major determinant of treatment outcome. Effective virological suppression among people living with human immunodeficiency virus (PLHIV) receiving antiretroviral therapy (ART) is achieved with initiating ART at CD4 count > 500cells/μL. Prospective study in south Africa reported participants initiating ART with CD4 counts ≥500 cells/μL had very good virological outcomes, being better than those with CD4 counts 200–499 cells/μL.Similarly study among MDR /HIV infected Patients in South Africa found CD4 count ≤100 cells/mm3 (adjusted hazards ratio, 15.6; 95% confidence interval, 4.4–55.6) was strong risk factor for mortality (Dravid *et al.*, 2019)

Study conducted New Delhi, India CD4 count of less than 200/ μl at diagnosis [OR2.32, CI (1.06-5.09)], and re treatment cases [OR-2.91, CI (1.22-6.89)] were independent predictors of unfavourable outcome. (SHARMA et al). Similarly study in Myanmar, reported low CD4 cell count at the diagnosis of TB were statistically significant predictors (P value .000) for adverse treatment outcomes of TB. (Brust *et al.*, 2018).Another study in South Africa found CD4 count >350 (AOR: 0.40; CI: 0.36-0.44) were less likely to have an unsuccessful treatment outcome.(Siedner *et al.*, 2015)

Timing of ART initiation among TB/HIV infected patients on anti TB is also reported as vital in maintaining favourable treatment outcome. However; due to the risk of immune reconstitution inflammatory syndrome (IRIS) the timing of initiation is debatable.

Study conducted in Tanzania reported compared to HIV un-infected TB patients, mortality risk for TB/HIV co-infected patients was least when antiretroviral therapy (ART) was initiated after 14 days of anti-TB (RR = 3.55; 95% CI: 1.44, 8.73 $p < 0.0001$) and highest when ART was initiated 90 days or less prior to anti-TB and within the first 14 days of anti-TB therapy (RR = 10; 95% CI: 3.28, 30.54; $p < 0.0001$). In contrast no changes in effect by timing of HIV treatment initiation or different thresholds of CD4 count for the primary outcome was reported by Djimeu, E. W., & Heard, A. C. (2019).

Clinical stages of HIV AIDS progression was reported as indipendent determinant of treatment outcome. Study in Ethiopia indicated initial World Health Organization (WHO) clinical stage III (COR: 2.60; 95%CI: 1.17–5.76) and stage IV (COR: 4.00; 95%CI: 1.29–12.40) were associated with unfavorable outcome. Both WHO stages (III, IV) at the time of HIV diagnosis were independent predictors of poor treatment outcome (AOR: 3.08; 95%CI: 1.14–8.38; AOR: 5.80; 95%CI: 1.36–24.71 respectively).(**Teshome, et. al,2017.**)

The SAPiT trial, Salim Abdool Karim and colleagues compared outcomes between 214 coinfected patients who started ART within 4 weeks after initiating TB treatment and 215 who started ART within 4 weeks after completing the intensive phase of TB treatment.Overall, no significant difference was seen in the rate of AIDS or death between the two treatment groups. However, for patients with baseline CD4 counts <50 cells/mm^3 the rate of AIDS or death was significantly lower in the earlier-therapy group than in the later-therapy group (8.5 vs. 26.3 cases per 100 person-years). For all patients, regardless of CD4-cell count, earlier therapy was associated with a higher incidence of IRIS and of adverse events that required a switch in ART drugs. Two deaths were attributed to IRIS. (Carlos del Rio, MD,2010)

Multidrug resistant TB among HIV infected patients is also a major concern with high probablity of unfavorable treatment. However significant favorable tresatmet outcome was reported in Tehran, cure of MDR TB among HIV infected. Out of 269 TB-HIV patients, 34 patients were recruited. Isoniazid (INH) resistant, rifampin (RIF) resistant and multidrug resistant (MDR) was diagnosed in 11 (32.4%), 7 (20.6%) and 16 (47.1%), respectively. Mean CD4 count was 91.61 ± 23.55. In the INH-resistant cases was cured in 5 (45.5%), failure in 2 (18.2%) and death in 4 (36.4%). In the RIF-resistant group, cured 5 (71.4%) and failure in 2 (28.6%). In the MDR-TB patients' group, cured, failure and death were 12 (75%), 2 (12.5%) and 2 (12.5%), respectively.(Tabarsi *et al.*, 2015)

Discussion

International guidelines went the last step further and recommended treating all HIV-infected adults regardless of their CD4 count. Moreover, since 2011 WHO recommended beginning ART within eight weeks of initiation of TB treatment in co-infected patients with a CD4 count between 200/mm3-350/mm3 and within two weeks for those with a CD4 count lower than 200/mm3.This policy is reported as less efficient and faced challenges.

The CD4 cell count has been an essential component of HIV treatment and care programmes. The CD4 cell count has guided key clinical decisions ranging from when to start antiretroviral therapy for long period of tme (ART) .How ever current evidences suggest rather than marely concidering CD4 count timing of initiation for ART and TB treatments is vital.(Eholié *et al.*, 2016) CD4 testing has also provided valuable insight into programme performance over time and predicted patient prognoses.(Siedner *et al.*, 2015).Lower CD4 count less than 100 cells/mm3 was strongly associated with death of PLHIV. Early initiation of ART has great impact immune suppression on treatment outcome which outweighs the dis advantage related to immune reconstitution syndrome.(Article, 2018)

Timing of initiation of TB treatment need to be considered where withholding ART until the third week of antituberculosis reported to reduce TB mortality. In Tanzania. mortality risk for TB/HIV co-infected patients was least when antiretroviral therapy (ART) was initiated after 14 days of anti-TB (RR = 3.55; 95% CI: 1.44, 8.73 $p < 0.0001$) and highest when ART was initiated 90 days or less prior to anti-TB and within the first 14 days of anti-TB therapy (RR = 10; 95% CI: 3.28, 30.54; $p < 0.0001$).(Djimeu, E. W., & Heard, A. C. (2019.Due to very few no of studies in the area I was not possible to conduct metaanalysis and give stronger conclusions. Large scale study and framing of policy is inevitable in this area to gain maximum output.

Conclusion

In conclusion, CD4 count of less than 200 cells/mm3 is strongly associated with unfavourable treatment outcome which is consistent in all studies. However, there is varying reports on the timing and association on outcome of TB treatment with ART, thus large scale studies are still needed to maintain the WHO policy of two to eight weeks interval to start ART co-treatment plan as soon as TB treatment is tolerated.

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Competing Interests The authors declare there are no competing interests

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