Original Research Article

Can Early HAART Reduce Risk of Tuberculosis?

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A B S T R A C T

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At which CD4 count to initiate HAART therapy has continued to be a core controversy within the medical community.For adults with human immunodeficiency virus (HIV) infection who have CD4+ T-cell counts that are greater than 200 cells/μL and less than 350 per cubic millimeter and who live in areas with limited resources, the optimal time to initiate antiretroviral therapy remains uncertain. In the present study 961 HIV infected patients had been screened and total 244(25.39%) pulmonary TB cases were identified either by ZN staining or culture of sputum on LJ Medium. Another 64(06.66%) cases of extra-pulmonary tuberculosis were also noted from the same 961 HIV infected patients. In the present study attempt had been made to co-relate all pathogens with the CD4 count of the patients from which they had been detected. The results of the present study strongly favor early start of HAART at around 350 cells/μL CD4 count rather than standard HAART at around 200 cells/μL CD4 count, as mean CD4 count of the patients with pulmonary tuberculosis in present study was 198.52 $\pm$ 32.25 cells/μL. It means in this part of world HIV patients becomes highly susceptible to pulmonary TB at around 230 to 198 cells/μL CD4 count. Even 72.06 per cent of TB cases in the present study were seen with below 200 cells/μL CD4 count. Thus according to present study's results standard HAART at 200 cells/μL would not give any protection against higher risk of developing TB in the HIV infected   patients. In India we might could not afford to follow recent guideline of WHO recommendations to start HAART at 500 cells/μL CD4 count, due to financial constraint, we should start HAART at least at 350 cells/μL CD4 count to reduce prevalence of TB in our country .The other very big benefit of early HAART to the society would be on control on emergence of MDR-TB and XDR-TB to some extent, as these both forms are seen more frequently with HIV infected patients due to HIV infection may lead to mal-absorption of anti-TB drugs and acquired rifamycin resistance (Wells CD et al, 2007).

Introduction

The optimal time to initiate antiretroviral therapy in adults who are infected with human immunodeficiency virus (HIV) remains uncertain. There have been no randomized trials to determine the optimal time to start antiretroviral therapy in adults

who have CD4+ T-cell counts that are greater than 200 and less than 350 per cubic millimeter. Furthermore, there are few data on the optimal time to start antiretroviral therapy in persons who live in locations with limited resources, like ours where high rates of tuberculosis, malnutrition, and coinfection with tropical diseases may alter the natural history of HIV disease and the optimal time to initiate therapy. Therefore, international guidelines differ on when to start antiretroviral therapy (WHO,2004; Sever et al,2004; WHO, 2006, Hammer SM et al, 2008)

The clinical course of human immunodeficiency virus (HIV) disease and pattern of opportunistic infections varies from patient to patient and from country to country. The clinical profile of HIV disease in India includes a wide range of conditions like tuberculosis, cryptococcal meningitis, popular pruritic eruptions, and cytomegalovirus retinitis, among others. Tuberculosis is the most common opportunistic infection in Indian patients with HIV. Occurrence of various AIDS-associated illnesses determines disease progression. Mean survival time of Indian patients after diagnosis of HIV is 92 months.(Kumarasamy et al, 2005).

Individuals co-infected with HIV and TB are 30 times more likely to progress to active TB disease. Infection with TB enhances replication of HIV and may accelerate the progression of HIV infection to AIDS. Fortunately, TB treatment under the DOTS programs is just as effective in individuals with HIV as it is in peoples who are HIV negative. In addition, clinical trials have shown that there are anti-TB regimens that can prevent or decrease the likelihood of TB infection progressing to active TB disease in an HIV-infected individual, making it an important intervention for increasing the

length and quality of life for those co-infected and their families and communities.

India has the largest number of tuberculosis (TB) cases in the world. India shoulders about 14 million cases of TB and it is estimated that about 1.8 million incident cases of TB occur in India every year of which 0.82 million are highly infectious smear positive cases (Vidyanathan PS, et al,2003).

The lifetime risk of tuberculosis in immunocompetent persons is 5% to 10%, but in HIV positive individuals, there is a 5% to 15% annual risk of developing active TB disease (Swaminathan *et al* 2000). WHO estimated 9.2 million new cases of TB globally in 2006 (139 per 100,000); of whom 7,09,000 (7.7%) were HIV positive (World Health Organization 2008). India, China, Indonesia, South Africa and Nigeria rank first to fifth in terms of incident TB cases. In India, there were 2.5 million people living with HIV and AIDS (PLWHA) at the end of 2007 while the incidence of TB was approximately 1.8 million cases per year (WHO Release 2007, RNTCP 2008). In a survey carried out among new tuberculosis patients by the Revised National TB control Program (RNTCP) in 2007, HIV sero-prevalence

There exists a synergistic relationship between TB and HIV. The interface between TB and HIV is increased in countries like India where both TB and HIV infection are maximally prevalent in people of 15-49 years of age (Jain SK, et al,2000). The association between HIV and tuberculosis present an immediate and grave public health and socioeconomic threat in developing countries(Stylblo K. 1990).

Persons infected by *Tubercle bacilli* have about a 10% chance of developing tuberculosis during the remainder of their lives: Thus, they have a less than 0.5%

chance of developing overt disease annually, (Grange JM.,1998) while 10% of persons infected by both TB and HIV develop tuberculosis disease annually. (Enarson DA et al, 2000). The implication of HIV infection is that it activates dormant tuberculosis to rapid disease progression of tuberculosis and death(Escott S et al,2001). In fact, tuberculosis is now the most common opportunistic infection in patients from developing countries who die from AIDS(DeCock KM et al,1992). Reports show that active tuberculosis increases the morbidity and fatality of HIV-infected person and about one-third die of tuberculosis.(Enarson DA et al, 2000). The largest increase in tuberculosis has occurred in locations and demographic groups with the highest HIV prevalence, which suggests that the epidemic of HIV is at least partially responsible for the increase of tuberculosis. (Shafer RW. et al,1994) There is evidence that immune responses in tuberculosis and in other infection induce cytokines that enhance the replication of HIV and this drives the patient into full picture of AIDS(Festenstein F, Grange JM.1991).

Materials and Methods

The present study got approval from the ethical committee of Government Medical College, Surat and even got permission of GSACS, Ahmedabad.

A predesigned and pretested questionnaire was used to collect data on socio-demographic profile. Blood samples of these subjects were tested for HIV. The HIV-infected patients were all diagnosed as HIV reactive as per the NACO guidelines(2010). In the patients found HIV sero-positive even, CD4 count was calculated on FACScount, by flowcytrometry method (Becton Dickinson) method from their blood samples.

Three consecutive early morning sputum samples were collected and even samples were concentrated before reporting negative for AFB from 961 HIV infected patients who had complaint of cough and fever for more than one week. Sputa samples were collected in a sterile wide mouthed container. The quality of the expectorated sputum was assessed both by macroscopic and microscopic examination. Any sample that was thin, watery and with no purulent matter was considered unsuitable for further processing. Bartlett's scoring method was used for microscopic evaluation of the expectorated sputum(Koneman EW et al.,1997). A sputum was considered unsuitable if it had a final score of 0 or less. All unsuitable specimens were discarded and a repeat specimen was collected.

Case Defination for T:

Cases were defined as patients with both HIV sero-positive as well as having complaints of cough and fever for more than one week or in other words suffering from respiratory tract infections (RTI) at the time of sputum and data collection. One patient was included only once.

Sputum smear microscopy: The most frequent method of TB detection involved microscopic examination of sputum for acid-fast bacilli (AFB) (Hopewell P,et al,2006) . Microscopy had the advantage of being inexpensive, relatively rapid to perform, and specific in most settings. However, to be considered smear positive a specimen needs to contain approximately 10^5 mycobacteria per milliliter. The sensitivity of sputum microscopy in HIV infection ranges from 43 to 51 per cent(Cattamanchi A et al.2009), and in many resource-limited settings with high rates of co-infection, the sensitivity may be much lower(Elliot AM, et al, 1993). Methods that

improved speed or sensitivity include fluorescence microscopy (Steingart KR, et al,2006) and alternative specimen processing methods, such as concentration, bleach sedimentation and same-day sputum collection (so called front loading) strategies(Cattamanchi A, et al,2010; Steingart KR, et al, 2006). Any procedure for digestion or liquefaction followed by centrifugation, prolonged gravity sedimentation, or filtration increased sensitivity by 13 to 33 per cent over direct microscopy, when culture was used as the reference standard (Steingart KR, et al ,2006) .

***Growth based detection*:** Culture of *Mycobacterium tuberculosis* is much more sensitive than smear microscopy and has been recommended to assist in the diagnosis of TB in HIV-infected individuals (WHO,2007). But in the present study it had been used in the limited number of the patients, which were clinically suggestive of pulmonary TB but negative by ZN staining even after concentration of sputa samples. Culture also allows subsequent strain characterization and drug susceptibility tests. The traditional method of inoculating solid medium such as the Lowenstein-Jenson (L-J) medium or Middlebrook medium is sensitive but slow, as growth may not be visible until after 6-8 wk of incubation. This results in delay in initiation of therapy, with detrimental effects on outcome of HIV TB co-infected patients. Automated liquid culture systems detected growth of mycobacteria within 1-2 wk by bacterial carbon dioxide production or oxygen consumption with radiometric sensors (BACTEC 460 TB; Becton Dickinson Diagnostic Instruments Systems, USA), fluorescent sensors [BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960; Becton Dickinson Diagnostic Instruments Systems], colorimetric sensors

(MB/ BacT system; Organon Teknika), pressure sensors (ESP culture system II; Difco Laboratories, USA), or redox reagents, such as Alamar blue(Williams-Bouyer N, et al, 2000: Gil-Setas A et al.2004; and Farnia P et al,2004).

Results and Discussion

In the present study 209 pure pulmonary tuberculosis cases were noted, other 35 PTB cases were co-infected with either fungus or bacterium. So, total 244 cases of pulmonary tuberculosis were detected. Mean CD4 count of all these only pulmonary TB cases were when calculated, it was found to be 198.25 +32.52 cells/µL, which is almost near 200 cells/µL and if upper limit of standard deviation when considered, it is exactly 230 cells/µL . It means the HIV patients in our study region started becoming susceptible more to pulmonary tuberculosis at 230 cells/µL. So when standard HAART which is started at 200 cells/µL CD4 count, the patients might had already acquired active pulmonary tuberculosis. In the present study mean CD4 cell count observed in TB patients was 198.52 + 32.25 cells/µl in the HIV-sero-positive T group patients, which almost matches with the study of E.J.Peters et al.(2007), as they found mean CD4 cell count 173.85+5.4cells/µl in their study. So, if we calculate their higher risk of susceptibility to TB, even it comes around 178 which might be due to their method of diagnosis of TB, which was by culture on LJ medium, which is more sensitive method than ZN staining, where they detected TB cases in the early stage of TB, while in the present study due to less sensitive method used, TB cases might be detected late.

The other probable reasons, if we calculate mean CD4 cell count of only 209 monomicrobial TB patients in the present study, it was found around 187 cells/µL,

which is very close to the mean CD4 cell count observed by other workers. In addition, it is likely that demographic and regional differences and exposure to various predisposing factors like bio-mass fuel, malnutrition, unhygienic habitat and smoking will also affect the spectrum of illness seen in our environment. In the present study 811(84.39%) HIV patients belonged to age group 15-54, out of which 281(91.23) patients belonged to age group 15-54, this was even supported well by findings of Jain S.K. et al(2000).

In the present study 261(84.74%) patients out of total 308 TB patients, belonged to lower socio-economic group, which were naturally staying in unhygienic habitat, malnourished and even badly exposed to predisposing factors like bio-mass fuel, smoking which might had increased their susceptibility at slightly higher CD4 count, i.e. at the 230 cells/µL CD4 count, these patients were having higher risk of developing pulmonary tuberculosis. So, treating with standard HAART, naturally increases more pulmonary TB cases.

But anyway, it is evident from the result of mean CD4 count of TB patients in the present study which was 198.25+32.25 cells/µL, and it was fact due to what so ever might be the reasons for this much high CD4 count which might be a matter of controversy itself but when other studies of Sever et al, (2010) who also from their direct study on TB, recommended the same, which means starting of early HAART at 350, instead of standard HAART, in which HAART is started at 200 CD4 count, one should not try to find reasons for higher mean CD4 count rather than support early HAART, which is helpful to HIV patients themselves, their relatives and close society surrounding them and ultimately to whole society and nation.

Moreover, some other studies also have been discussed to decrease the risk of developing TB in HIV patients by starting early HAART at 350 cells/µL CD4 count instead of starting standard HAART at 200 cells/µL CD4 count, and maintaining high CD4 count above the threshold of mean CD4 count of TB, in most studies it is in between 170-200 cells/µL , in present study it was found to be 198.25 + 32.52 cells/µL for longer duration which in turn reduces the risk of developing TB in HIV infected patients,(Severe et al, 2010). Even other serious threats due to increased prevalence is emergence of more cases of MDR and XDR TB, in HIV infected patients which are discussed in this article.

In short, antiretroviral therapy is a potentially safe, well-tolerated, and HIV-transmission-interrupting intervention (Cohen MS, et al,2011) necessary to increase life expectancy in people with HIV (Kitahata MM, et al,2009). There has been considerable debate on the optimal timing to start antiretroviral therapy in asymptomatic adults with HIV. Published results from ongoing randomized trials are expected in 2016 and are eagerly awaited (French National Agency for Research on AIDS and Viral Hepatitis 2007). The review of Amitabh Suthar et al(2012) found that antiretroviral therapy is strongly associated with a reduction in tuberculosis incidence in adults with HIV across all CD4 cell counts.

Their key finding was that antiretroviral therapy had a significant impact on preventing tuberculosis in adults with CD4 counts above 350 cells/µl was consistent with studies from developed countries (Podlekareva D, et al,2006) and will need to be considered by healthcare providers, researchers, policymakers, and people living with HIV when weighing the

benefits and risks of initiating antiretroviral therapy above 350 cells/µl. The mean CD4 count of all the patients in the present study also support this finding of starting HAART above CD4 count 350 to reduce prevalence of TB, as even mean CD4 count of M. tuberculosis was 198.52+ 32.25, means the patients studied in the present study were at the risk of acquiring TB at around 230 CD4 count, which mean standard HAART starting at 200 CD4 count will give not any protection against TB.

Changes in HIV therapy initiation guidelines affect clinicians, patients, and policymakers who continue to search for the most efficient and effective treatment strategies. Prior to 2013, initiation was recommended at 350☐cells/µL (WHO,2010) and developing countries—where governments and international agencies play a greater role in HIV management due to low per capita income on the part of patients—are still adjusting to these changes. The WHO and USDHHS in 2013 recommended starting therapy at >500☐cells/µL based on the scientific body of science for HIV clinical research. Some support for this change in recommendation may be provided through the meta-analysis of studies that compares the former recommendation (initiation at <350☐cells/µL) to the new recommendation (>500☐cells/µL) but only when <200☐cells/µL are used as a referent group (Babatunde Olubajo et al.2014).

Early antiretroviral therapy means maintaining CD4 count higher also decreased the incidence of tuberculosis by 50% in the study of Severe et al,(2010) . This finding is consistent with observational studies from Africa showing a decrease in the incidence of tuberculosis after antiretroviral therapy was started early (Lawn SD et al,2005; Lawn SD et al,2009 & Badri M et al 2002). Tuberculosis is a

leading cause of death among HIV-1– infected patients in developing countries, and the effect of early antiretroviral therapy on the incidence of tuberculosis explains in part the decreased rate of death seen in the trial study of Severe et al.(2010). Furthermore, the HIV epidemic has dramatically increased the incidence of active tuberculosis in countries with limited resources and is overwhelming tuberculosis-control programs (Nunn P, et al, 2007). Provision of early antiretroviral therapy on a large scale in areas with limited resources has the potential to decrease the incidence of active tuberculosis in the general population.

The WHO has promoted a public health approach in its guidelines to antiretroviral therapy, emphasizing feasibility, cost-effectiveness, and large-scale implementation. (Gilks CF et al, 2006). Earlier initiation of antiretroviral therapy — when the CD4+ T-cell count is less than 350 per cubic millimeter — is likely to be consistent with this approach. Early antiretroviral therapy also decreased the incidence of tuberculosis by 50% in the study of Severe et al,(2010). This finding is consistent with observational studies from Africa showing a decrease in the incidence of tuberculosis after antiretroviral therapy is started(Lawn SD et al, 2009 ; Lawn SD et al, 2005 & Badri M et al. 2002). Tuberculosis is a leading cause of death among HIV-1–infected patients in developing countries, and the effect of early antiretroviral therapy on the incidence of tuberculosis explains in part the decreased rate of death seen in the trial of Severe et al.(2010).

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Antiretroviral therapy's effect on the population incidence of tuberculosis depends on HIV prevalence and the extent to which antiretroviral therapy (1) reduces HIV transmission, (2) increases patient life expectancy, (3) reduces the annual risk of tuberculosis, and (4) reduces subsequent tuberculosis transmission. Dynamic models have suggested that antiretroviral therapy reduces new HIV infections and that increasing antiretroviral therapy coverage in people living with HIV will lower the population tuberculosis incidence (Williams BG et al ,2010). Indeed, programmatic data

thus far indicate that antiretroviral therapy scale-up is associated with reductions in tuberculosis incidence of 33% and 24% in high-burden Malawian and South African communities (Middelkoop K, et al,2011). Earlier antiretroviral therapy initiation could lead to a more substantial reduction in population tuberculosis incidence (Williams BG et al ,2010). Expansion of antiretroviral therapy may also reduce HIV incidence at the city ,(Cowan SA,et al,2012) district (Tanser F et al,2012) and national levels(Granich RM, et al,2009) while decreasing tuberculosis mortality (Havlir DV et al, 2011) and HIV-related mortality(Kitahata et al, 2009).

WHO's Policy on HIV/TB Collaborative Activities currently recommends the Three I's for HIV/TB: intensified tuberculosis case-finding (World Health Organization (2011), isoniazid preventive therapy (World Health Organization (2011), and infection control (. World Health Organization ,2009) to prevent tuberculosis in people with HIV. WHO infection control guidelines recommend administrative, managerial, engineering, and personal respiratory methods to avoid nosocomial tuberculosis transmission, such as logistical changes to avoid patient congestion, and early identification and diagnosis of tuberculosis patients in healthcare facilities, congregate settings, and households .(World Health Organization ,2009). Intensified tuberculosis case-finding involves screening people with HIV for current cough, night sweats, fever, and weight loss at every clinical encounter (World Health Organization ,2011). Those without any of these symptoms have a very low probability of having tuberculosis (98% negative predictive value in settings with a tuberculosis prevalence of 5% . Getahun H, et al, 2011) and should be initiated on isoniazid preventive therapy (World Health Organization (2011).

Isoniazid stops *Mycobacterium tuberculosis* replication during latent infection and reduces tuberculosis incidence by 33% (Akolo C, et al, 2010). WHO has recommended isoniazid preventive therapy for prevention of tuberculosis in adults with HIV since 1993. (World Health Organization (2011), (World Health Organization, Joint United Nations Programme on HIV/AIDS,1998) however, only a small fraction of the millions eligible received isoniazid preventive therapy in 2010 (World Health Organization, 2011).

Antiretroviral therapy causes viral suppression and immune recovery, which reduces tuberculosis incidence by 65% across all CD4 counts. Initiating antiretroviral therapy as early as possible strengthens the WHO Three I's for HIV/TB strategy by building upon antiretroviral therapy's synergy with isoniazid preventive therapy. Indeed, observational studies from South Africa (Charalambous S, et al,2010), Brazil , and 16 other countries (Fenner L, et al,2011) indicate that combined isoniazid preventive therapy and antiretroviral therapy was superior to antiretroviral therapy or isoniazid preventive therapy alone in reducing tuberculosis incidence among adults with HIV. This finding was recently confirmed through a cluster-randomized trial in Brazil, where isoniazid preventive therapy reduced tuberculosis incidence among Brazilians who remained in care and received antiretroviral therapy (Durovni B et al,2011).

These data suggest that antiretroviral therapy and isoniazid preventive therapy work by complementary mechanisms and that simultaneous use substantially decreases tuberculosis incidence in adults with HIV. Results from other ongoing trials assessing the synergy between antiretroviral therapy and isoniazid preventive therapy are eagerly awaited (French National Agency for Research on AIDS and Viral Hepatitis 2007), and ecological, operational, and clinical research on the impact of scaling up antiretroviral therapy and the Three I's for HIV/TB on community and/or national tuberculosis incidence rates is needed(Granich R et al,2011).

Anti Tuberculous Treatment:- The standard recommendation for the treatment of tuberculosis is a 6-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol, irrespective of HIV status. However, the Centers for Disease Control and Prevention/Infectious Diseases Society of America guidelines recommend extending treatment beyond 6 months in HIV-infected patients, especially when there is delayed sputum conversion or evidence of dissemination and low CD4 cell count (American Thoracic Society ,CDC,2003).

Many studies have shown lower cure rates and higher mortality and recurrence rates after standard ATT in coinfected patients (Korenromp EL et al.2003). Recurrences can result from endogenous reactivation or exogenous reinfection, with the relative proportions depending on the background incidence of tuberculosis, the level of immune suppression, the length of rifampicin-containing ATT, and adherence to treatment(Korenromp EL, et al, 2003, Nahid P et al,2007).

Baseline isoniazid resistance has been identified as a risk factor for failure and the development of acquired rifampicin resistance, a phenomenon observed among HIV-infected patients treated with intermittent (once-, twice-, or thrice-weekly) regimens (Menzies D, et al,2009; Swaminathan S et al,2010 and Burman W et al,2006).

Table 1 : Prevalence of Pulmonary TB

| Microorganisms	HIV +VE RTI +VE (T)	
	(n)	%
M. tuberculosis	209	21.75
M. tuberculosis + Candida (NCAC)	17	1.77
M. tuberculosis + Candida albicans	6	0.62
M. tuberculosis + S. pneumonia	12	1.25
Total Mixed Pulmonary TB	**35**	**2.39**
Total PTB(Pure +Mixed)	**(209+35) 244**	**25.39**

Table 2: Comparison of Mean CD4 of patients of various groups**.**

Organisms	**Mean CD4 cells/µL**	**Standard Deviation**	**Cases**	**%**
Pulmonary tuberculosis	198.52	+32.25	244	25.39
Extra-pulmonary TB	104.89	+47.09	64	06.66
All TB cases	151.71	+27.62	308	32.05
Patients excluding only pulmonary TB	408.40	+202.23	653	67.95
Other organisms excluding MTB(Pulm)	269.80	+114.47	444	46.20
Total Patients	**339.10**	**+108.96**	**961**	**100**

Table 3 : Distribution of Demographic characters: Age Group & Socio-economic distribution in T Group and TB Patients.

Age Groups	No. of Total Patients	% of Total Patients	No. of TB Patients	% of All TB Patients
<15 years	85	8.84	8	2.60
15-54 years	811	84.39	281	91.23
>55 years	65	06.76	19	6.17
Socio-economic Distribution				
	No. of Total Patients	% of Total Patients	No. of TB Patients	% of All TB Patients
Very Low	433	45.06	162	52.60
Low	324	33.82	99	32.14
Middle Class	204	21.23	47	15.26
Total	**961**	**100**	**308**	**100**

CIPRA HT 001 *(Severe et al. NEJM 2010)*
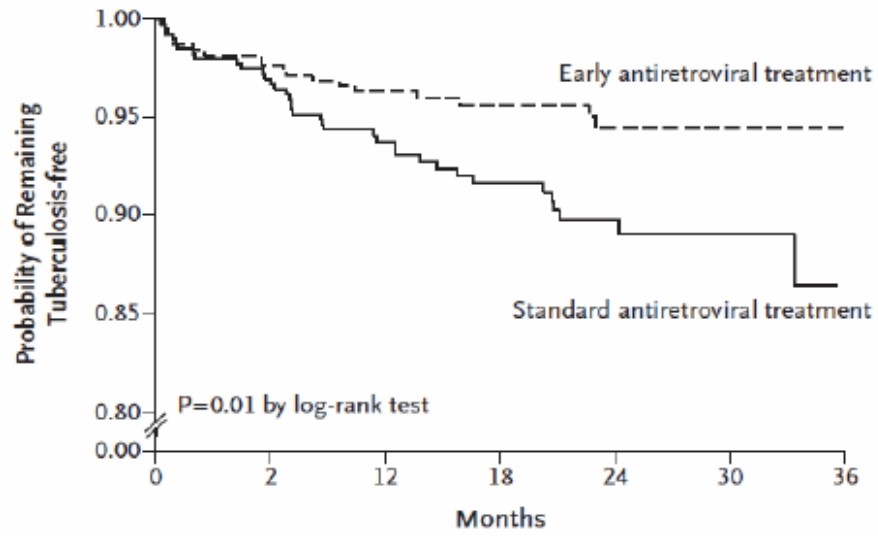
No. at Risk

Early treatment	380	302	140	20
Standard treatment	393	288	122	16
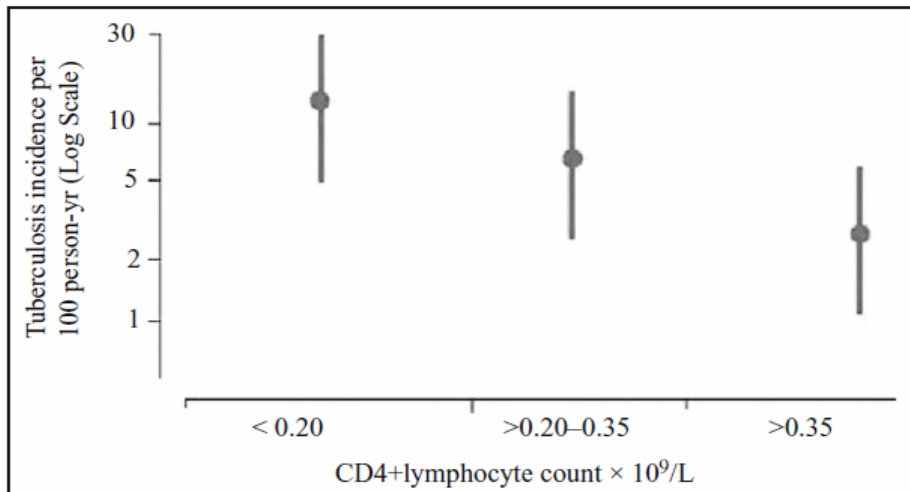
Risk of tuberculosis among HIV infected persons by CD4 + lymphocyte count (Antonucci *et al* 1995).

In light of the clinical trials conducted, it is clear that rifampicin plays a key role in the treatment of HIV-associated tuberculosis: recurrence rates were 2–3 times higher when rifampicin was not included in the continuation phase (Jindani A, et al,2004 & O'Donnel MM, et al,2002). The addition of quinolones in the induction phase did not increase the cure rate any further (El Sadr WM, et al, 1998).

Among antiretroviral therapy (ART)–naive patients, extending treatment to 9 months reduced recurrences but did not change mortality or the acquisition of rifampicin resistance, compared with a 6-month thrice-weekly regimen (Swaminathan S et al,2010). Acquired rifamycin resistance is a unique feature of HIV-associated tuberculosis, being rarely seen in HIV-uninfected patients. In a cohort of 1435 seronegative patients with drug-susceptible tuberculosis enrolled in 2 trials at the Tuberculosis Research Centre, Chennai, India, only 4 developed rifampicin resistance (Tuberculosis Research Centre (ICMR), Chennai ,2001). Suboptimal drug concentrations due to malabsorption coupled with increased tissue bacillary load and defective clearance apparently lead to the selection of genomic mutants resistant to rifampicin (Gurumurthy P et al,2004; Perlman DC, et al,2005). Although no trials have directly compared daily and thrice-weekly treatment among coinfected patients, the current recommendation is to use daily treatment at least in the intensive phase for patients with CD4 cell counts <100 cells/µL(American Thoracic Society, CDC,2003 & Li J, Munsiff SS, et al, 2005).

All the TB patients in the present study were started on DOTS (direct observation therapy) treatment and most of them had responded well with smear negative for PMTB after treatment for about 6 months. Few of the patients even died but many more did not return for follow-up within the tenure of this study, so here the discussion about mortality becomes useless.

Another alarming threat in TB due to HIV is the emergence of more MDR and XDR-TB cases. Delayed diagnosis, inadequate initial treatment, and prolonged infectiousness led to extraordinary attack rates and case-fatality rates among HIV-infected persons. Whether this sequence occurs in communities is less clear. MDR-TB appears not to cause infection or disease more readily than drug-susceptible TB in HIV-infected persons.

HIV infection may lead to malabsorption of anti-TB drugs and acquired rifamycin resistance (Wells CD et al,2007). HIV-infected patients with MDR-TB have unacceptably high mortality; both antiretroviral and antimycobacterial treatment are necessary. Simultaneous treatment requires 6-10 different drugs. In HIV-prevalent countries, TB programs struggle with increased caseloads, which increase the risk of acquired MDR-TB. Surveillance data suggest that HIV infection and MDR-TB may converge in several countries.

Even more emergence of XDR-TB has been observed with HIV patients .Institutional outbreaks, overwhelmed public health programs, and complex clinical management issues may contribute to the convergence of the MDR-TB and HIV infection epidemics. To forestall disastrous consequences, infection control, rapid case detection, effective treatment, and expanded program capacity are needed urgently.

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