Review Article

Indian J Med Res 150, August 2019, pp 131-138
DOI: 10.4103/ijmr.IJMR_660_19

Quick Response Code:

Improving survival with tuberculosis & HIV treatment integration: A mini-review

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Received July 10, 2019

Tuberculosis (TB) is a leading cause of morbidity and mortality among HIV-infected patients while HIV remains a key risk factor for the development of active TB infection. Treatment integration is a key in reducing mortality in patients with HIV-TB co-infection. However, this opportunity to improve outcomes of both infections is often missed or poorly implemented. Challenges in TB-HIV treatment integration range from complexities involving clinical management of co-infected patients to obstacles in health service-organization and prioritization. This is evident in high prevalence settings such as in sub-Saharan Africa where TB-HIV co-infection rates reach up to 80 per cent. This review discusses published literature on clinical trials and cohort studies of strategies for TB-HIV treatment integration aimed at reducing co-infection mortality. Studies published since 2009, when several treatment guidelines recommended treatment integration, were included. A total of 43 articles were identified, of which a total of 23 observational studies and nine clinical trials were informative on TB-HIV treatment integration. The data show that the survival benefit of AIDS therapy in patients infected with TB can be maximized among patients with advanced immunosuppression by starting antiretroviral therapy (ART) soon after TB treatment initiation, *i.e.* in patients with CD4+ cell counts <50 cells/µl. However, patients with greater CD4+ cell counts should defer initiation of ART to no less than eight weeks after initiation of TB treatment to reduce the occurrence and extent of immune reconstitution disease and subsequent hospitalization. Addressing operational challenges in integrating TB-HIV care can significantly improve patient outcomes, generate substantial public health impact by decreasing morbidity and death in settings with a high burden of HIV and TB.

Key words Antiretrovirals - mortality - PLHIV - pulmonary tuberculosis - treatment integration - tuberculosis-HIV co-infection

Introduction

Tuberculosis (TB) remains the leading presenting opportunistic infection among people living with HIV (PLHIV). Globally, in 2018, despite widespread availability of effective treatment and prevention, there were 300,000 deaths from HIV-associated TB, and approximately 464,633 new and relapse cases of TB were diagnosed among PLHIV. Furthermore,

in the same year, approximately 36.9 million people were known to be living with HIV, and 2-3 billion people harboured TB, most with asymptomatic latent infection[1].

In patients with new or latent *Mycobacterium tuberculosis* infection[1], HIV remains the strongest risk factor for TB-associated morbidity and mortality. The risk of clinically evident TB disease is highest soon after HIV seroconversion and doubles within the first year of HIV acquisition[2], becoming more pronounced with advancing immunosuppression[3]. The risk of TB infection in people with HIV infection is 20-37 per cent higher compared to the HIV uninfected, and in some settings in sub-Saharan Africa, co-infection rates of TB-HIV are as high as 80 per cent[4].

In South Africa in 2018, the estimated number of notified TB cases alone was 322,000, occurring mainly among HIV-infected patients, and 1,908,371 in India, mainly in HIV-uninfected patients[1]. Approximately 64 per cent of TB patients in India were aware of their HIV status, and among these patients, three per cent were HIV co-infected – equating to 36,440 individuals[1]. While it is known that India bears the highest TB burden globally, the actual TB burden is being underreported by about 26 per cent per annum, especially among HIV-infected patients[1]. Hence, the magnitude of TB-HIV co-infection problem and its contribution to overall morbidity and mortality in India remain underestimated. TB and HIV case identification and treatment integration remain key strategies in addressing this problem. TB is one of the most common clinical presentations of AIDS in resource-limited settings. Hence, HIV screening in patients attending TB services provides a cost-effective strategy of identifying HIV-positive patients. TB case fatality rates remain higher in HIV co-infected patients, despite effective TB treatment[5].

In settings where the TB and HIV epidemics overlap, significant benefits could accrue to patients, communities and programmes by simultaneously addressing these co-occurring epidemics through an integrated approach. Programmatically, this could reduce costs using existing TB care services to contribute to making antiretroviral therapy (ART) available. Despite having evidence in support of this approach demonstrating an 18-fold increase in HIV testing in TB cases compared to the previous decade, only 55 per cent of TB patients in 2015 received HIV testing globally[1].

The timing of ART in TB-HIV co-infected patients can present challenges of competing clinical risks and benefits. On the one hand, deferred ART after TB treatment commencement has been linked to increase mortality and AIDS disease progression, on the other hand, early initiation of ART during TB therapy raises concerns over increased risk of complexities of co-treatment such as high pill burden, immune reconstitution inflammatory syndrome (IRIS) and potentiated toxicity arising from co-administration of three antiretroviral drugs and standard four-drug anti-TB therapy[6]. Over the last decade, substantial data have become available to address this challenge and provide an evidence-based approach that guides the timing of ART initiation in HIV-TB co-infected patients as well as on effective operational strategies for co-treatment.

Searching the data sources

Three bibliographic databases were searched from January 2009 to December 2018, including PubMed, ScienceDirect and BioMed Central for full-text articles using the initial search terms TB, HIV, mortality, antiretrovirals and timing. The search strategy was initially established in PubMed and, following modification, applied to other databases. Published literature evaluating ART timing on survival outcomes in adult patients who were co-infected with TB and HIV were selected for inclusion. Peer-reviewed full-text journal articles, published in English, were included, and fatally flawed studies, such as those with no endpoint data were excluded[7]. Articles describing survival outcomes among drug-susceptible pulmonary TB patients also co-infected with HIV who initiated ART either before, concurrently or after TB therapy, were selected.

Eligible searched materials were evaluated for inclusion. Screening of studies followed a two-step process: study titles and abstracts were screened first and those deemed eligible for inclusion were further screened in Step 2 using the full-text article. The data were abstracted from selected articles into a standardized template. The extraction template for data collection included the names of authors, journal and year of publication, study setting, study design, study objective and key findings pertaining to the impact of ART on mortality. Studies were included if those were cohort, cross-sectional or clinical studies in which survival outcomes in TB-HIV co-infection were the primary aim or a defined outcome.

Data synthesis and analysis

Our review findings were based on study design of selected articles: data from randomized control trials from 2010 to 2018 and data from cohort and observational studies from 2009 to 2018 evaluating ART impact on mortality in co-infected patients. Search strategy for bibliographic databases was based on findings from hand-searched reference lists. Experts were consulted to verify the completeness of these electronic searches and inclusion of additional studies.

A total of 1124 citations were identified. Following removal of duplicates, a total of 1099 citations were screened. Of these, 1056 were excluded and 43 full-text articles were assessed for eligibility. A total of 11 articles were excluded for the following reasons: ART timing was not investigated (6/11), endpoint did not include death (3/11), studied extrapulmonary TB (EPTB) only (1/11) and patients not co-infected (1/11). A final selection of 32 articles, comprising 23 observational and nine randomized clinical trials, met our exclusion and inclusion criteria and were included in the review (Tables I and II).

Impact of ART on survival outcomes in TB-HIV co-infection: Cohort and observational studies

Notwithstanding available published findings from several thousand TB-HIV co-infected patients in numerous cohort and observational studies conducted before 2010[17-19], conflicting evidence on the impact of concurrent ART on mortality still prevailed. While the majority of studies found reduced mortality in patients receiving co-treatment for HIV and TB[17-31] some studies found increased mortality in patients receiving co-treatment[32-34] and others found no impact of ART on mortality[35-37]. Initiating ART during TB therapy was associated with improved survival, improved ART uptake and continuation[17,18,20-22] and improved retention in care, particularly among those with severe immunosuppression[19,20].

Variation in mortality rates relative to ART timing and duration in TB treatment was also observed. While a few earlier cohort studies did not report significant differences in survival among patients initiating ART within 60 or 90 days compared to later during TB treatment[27,35], findings from a study demonstrated a 89 per cent reduction in risk of death in initiating early ART during TB therapy compared to delayed

Table I. Data from randomized controlled trials evaluating the impact of antiretroviral therapy (ART) on mortality in HIV-infected tuberculosis (TB) patients: 2010-2018

Main author	Country	Sample size	Impact of ART on mortality
Abdool Karim *et al*[8]	South Africa	642	Mortality reduction of 56% with ART initiation during TB treatment
Török *et al*[9]	Vietnam	253	Mortality high and unchanged in HIV-infected TBM treated with immediate and deferred ART
Abdool Karim *et al*[10]	South Africa	642	Similar rates of AIDS and death with ART irrespective of when during TB therapy, ART was started
Blanc *et al*[11]	Cambodia	661	Significant survival gains with ART initiation 2 wk after initiation of TB treatment
Havlir *et al*[12]	Brazil	809	No decrease in AIDS-defining illness and mortality regardless of whether patients received immediate or early ART
Manosuthi *et al*[13]	Thailand	156	No change in survival with either immediate of early ART in TB therapy Low baseline CD4+ cell counts and low albumin at TB diagnosis were predictors of poor survival
Sinha *et al*[14]	India	150	Similar mortality rates were observed in those who started ART 2-4 wk after initiation of TB treatment and in those starting ART 8-12 wk after starting TB treatment
Mfinanga *et al*[15]	Multi-country	13,588	No significant benefit from early ART initiation in those with less-advanced immunodeficiency, highlighting need to prioritize people with low CD4+ cell count for early initiation of ART
Amogne *et al*[16]	Addis Ababa, Ethiopia	478	ART one week after TB did not improve survival. Two-thirds of all mortalities occurred within the first two weeks

TBM, tuberculous meningitis

Table II. Data from cohort and observational studies evaluating the impact of antiretroviral therapy (ART) on mortality in HIV-infected tuberculosis patients: 2009-2018

Main author	Country	Sample size	Impact of ART on mortality
Gadkowski *et al*[19]	North Carolina	5332	5% patients died before initiating TB treatment. Among those who survived, 13.6% died before to completing TB treatment.
Velasco *et al*[17]	Spain	6934	Treatment was associated with better survival.
Varma *et al*[18]	Phuket	5851	Mortality during TB treatment occurred in 17%. Factors associated with reduced risk of mortality were ART use, fluconazole use and co-trimoxazole use.
van Lettow *et al*[21]	Malawi	2155	Early initiation of ART in co-infected patients on TB treatment improved ART guideline uptake.
Franke *et al*[20]	Rwanda	308	Early ART decreased mortality rates in patients with low CD4+ cell counts and enhanced retention in care, regardless of CD4+ cell count.
Worodria *et al*[22]	Uganda	302	68% of the 53 patients died within the first six months of TB infection.
Ansa *et al*[38]	Ghana	1330	Mortality rates were 18% in all cases and 25% in HIV-related cases after treatment integration.
Gupta *et al*[23]	South Africa	1544	Mortality rates during the first year of ART were 8.84 deaths/100 person-years decreasing to 1.14 deaths/100 person-years after five years. Mortality risk was greater in the initial six months of ART for those with prevalent TB at baseline (IRR: 2.33) and within six months after diagnoses of incident TB (IRR: 3.8).
Sileshi *et al*[24]	Northwest Ethiopia	422	29.3% TB-HIV co-infected patients died in the non-ART cohort compared to 18% who died that were on ART.
Shastri *et al*[25]	India	6480	Treatment success in co-infected patients not on ART was 54% versus 80% success rates for those on ART. Mortality rates in co-infected patients were two-fold higher than TB only patients.
Stockdale *et al*[36]	Kenya	404	CD4+ cell counts ≤50 cells/µl had a significant reduction in death in the early group versus the late group. No difference in mortality in CD4 count >50 cells/µl between both.
Saraceni *et al*[26]	Rio de Janeiro	947	ART started early following treatment in co-infected patients showed 89% decreased risk of death versus delayed ART initiation.
Yang *et al*[27]	Taiwan	229	Initiating ART in TB treatment showed improved one-year survival. Early start of ART within two months of TB treatment showed no significant difference in survival versus late initiation.
Han *et al*[35]	Asia-Pacific Region	768	Treatment outcomes and mortality of TB-HIV patients starting ART within three months of TB treatment did not differ significantly from those starting late. Mortality overall was greater among those diagnosed with TB while initiating ART.
Kirenga *et al*[28]	Kampala, Uganda	96	34% of HIV-infected patients had a successful outcome after initiating treatment.
Nglazi *et al*[34]	South Africa	797	Higher mortality in TB-HIV-infected patients not on ART versus HIV-uninfected patients. Increasing age was associated with higher mortality.
Bigna *et al*[32]	Cameroon	99	Higher death rates in the intensive phase of TB treatment among TB-HIV co-infected patients.
Podlekareva *et al*[37]	LA, WE, EE	1406	19% of participants died within 12 months, 188 (71%) of these deaths were TB related, 18% received ART at TB. The proportion of patients who initiated ART prior to TB diagnosis was similar among those who died and stayed alive.

Contd...

Main author	Country	Sample size	Impact of ART on mortality
Mutembo *et al*[29]	Zambia	4452	Of the 257 co-infected patients on ART, 9% died and 8% were lost to follow up. Of the 80 patients not on ART, 25% died and 24% were lost to follow up. Patients on ART had better survival outcomes versus those not treated.
Nagu *et al*[30]	Tanzania	1696	Mortality risk for TB-HIV patients was reduced when initiating ART after 14 days of TB therapy. Initiation of ART reduced mortality among TB-HIV patients.
da Silva Escada *et al*[31]	Brazil	310	Mortality rate following the first 30 days of TB treatment start was 44/100 person-years. Death probability in one year from TB treatment start was ~13%.
Adamu *et al*[39]	Nigeria	1424	6.6% died after initiating TB treatment with a death rate of 3.68/100 person-years. Most deaths occurred soon after treatment initiation with a death rate of 37.6/100 person-years in the first week of treatment.
Kaplan *et al*[33]	South Africa	60,482	Patients on ART at the beginning of TB therapy demonstrated greater risk of TB death with increased age.

LA, Latin America; WE, Western Europe; EE, Eastern Europe; IRR, incidence rate ratio

ART initiation[26], and in a retrospective cross-sectional analysis, treatment success among TB-HIV co-infected patients on ART was much higher (80%) in comparison to those who were ART naïve (54%)[25]. A 20 yr cohort study conducted between 1987 and 2004 in Spain showed better survival with simultaneous ART use and TB treatment[17]. Death rates of 8.84 deaths/100 person-years among patients commencing ART in the first year of TB treatment were observed in a Cape Town cohort. Here, mortality peaked in the initial six months post-ART initiation, decreasing after five years to 1.14 deaths/100 person-years[23]. Studies have also demonstrated a case fatality rate of 3.8/100 person-years within six months of incident TB diagnosis among ART patients who developed incident TB[23,32]. In Europe and Latin America, among 1406 TB patients studied, 19 per cent died within one year of TB treatment initiation, with 71 per cent of these deaths attributable to TB. In addition, there was no difference in rates of ART initiation among those who died and survived[37].

Impact of ART on survival outcomes in TB-HIV co-infection: Randomized controlled clinical trials

A South African randomized study demonstrated a 56 per cent increase in survival with integrated ART and TB treatment[8,10]. This study further described unexpectedly high mortality rates after cessation of TB therapy in co-infected patients not initiated on ART. Findings from this study were rapidly incorporated into local and global policy guidelines, recommending integration of TB and HIV treatment[11]. Further analysis of study data demonstrated similar incidence rates of AIDS or death irrespective of whether ART was started within one month of the intensive phase of TB treatment or within a month of the continuation phase of TB treatment[10].

Since findings from these three landmark trials became available, several other research groups that investigated the optimal time to initiate ART in patients infected with TB have published findings from systematic reviews and meta-analyses[10,11,12], modelling studies[20], clinical trials[13,14] and cohort and modelling studies which uniformly concluded that early ART in TB therapy was associated with reduced mortality compared with delayed ART; however, the survival benefit with initiating ART early was most pronounced in those with CD4+ cell counts of <50 cells/µl.

Risk factors related to mortality among patients receiving integrated treatment for TB and HIV

Studies have identified multiple factors associated with higher risk mortality among co-infected patients initiating ART. Most of the studies consistently reported that baseline CD4+ cell counts <200 cells/µl were associated with increased mortality with mortality rates substantially greater among patients with CD4+ cell count ≤50 cells/µl [hazard ratio (HR): 3.10][33,36]. Additional risk factors for mortality include (*i*) not having initiated ART during TB treatment[36], (*ii*) initiating ART among admitted patients, (*iii*) initiating ART in those with extrapulmonary and/or disseminated TB (HR: 3.70)[31], (*iv*) presence of non-AIDS comorbidities[37], (*v*) initiating ART in patients undergoing mechanical ventilation (HR: 2.81)[32], (*vi*) low albumin <3 g/dl (HR: 2.3)[10,16], (*vii*) patients not receiving co-trimoxazole prophylaxis

(adjusted HR 3.03)[10], and (*viii*) those interrupting TB treatment[16,18,34].

These studies collectively demonstrated the optimal timing of ART initiation in co-infected patients, which was dependant on the degree of immunosuppression. An important limitation to note is that these findings are largely restricted to patients with pulmonary TB (PTB) susceptible to treatment, with questionable generalizability to TB presenting in other sites notably disseminated and extrapulmonary TB. While rates of PTB are approximately six times higher than EPTB globally[1], patients infected with HIV present with all forms of TB including disseminated or extrapulmonary TB. Tuberculous meningitis (TBM), a life-threatening form of TB disease, is associated with case fatality rates of approximately 30 per cent and severe disability among survivors, despite effective TB chemotherapy[40]. Antiretroviral treatment commencement in HIV-infected patients who have TBM may be complicated by IRIS manifesting in the central nervous system (CNS). This results in decline in neurological functioning or even death. A randomized, double-blind, placebo-controlled trial that enrolled 253 Vietnamese participants with TBM in whom ART was started within one week or deferred until eight weeks showed similarly high mortality irrespective of whether ART was offered immediately or deferred[9]. These findings support the recommendation of delayed ART initiation in those with HIV-associated TBM.

These studies provide clarification on optimal ART timing in patients with concurrent HIV and pulmonary TB, and indicate that patients with advanced immunosuppression (CD4+ cell count <50 cells/µl) gain the most from starting ART in the first two weeks of TB treatment[28,41]. Patients who are stable and ambulant with higher CD4+ cell counts regardless of initiating ART earlier or later during TB therapy had comparable incidence rates of AIDS and/or death. Hence, careful consideration of other clinical factors may be warranted when weighing the benefits and risks of initiating ART in TB-HIV co-infected patients who are immunologically stable.

These studies have collectively recommended[8-13,16-25,27-33,38,39,42] on the optimal timing of ART in TB patients. The majority of these strategy trials concur that ART co-administered with TB therapy improves survival irrespective of CD4+ cell count. These studies also concur that in patients with advanced immunosuppression (CD4+ cell counts <50 cells/µl), mortality was reduced when ART was started within the first two weeks of TB treatment. For patients with CD4+ cell counts >50 cells/µl, these studies advocate that ART should be deferred until after the intensive phase of TB treatment completion. This strategy does not adversely impact survival while offering a benefit of reduced morbidity from TB-IRIS and drug toxicity. An econometric analysis evaluating antiretroviral treatment scale-up and TB mortality in 41 high TB-HIV burden settings suggests that a one per cent increase in ART coverage will result in 27 per cent fewer TB deaths in one year that would not have occurred without ART[40].

The current WHO guidelines[1] cite these findings and have recommended that co-infected patients commence TB treatment first and then start ART in the next eight weeks or sooner, irrespective of CD4+ cell count. Patients with CD4+ cell counts <50 cells/µl should commence ART within two weeks of initiation of TB therapy. Patients diagnosed with HIV-associated TBM remain an exception to these recommendations, supported by findings of high death rates of up to 60 per cent, and overall poor prognosis attributable to CNS TB-IRIS.

Conclusion

High-quality evidence from several randomized studies, supported by findings from observational studies, demonstrates a substantial survival benefit of ART commencement while patients receive TB therapy among TB-HIV co-infected patients. These gains are more profound in patients with a CD4+ cell counts <50 cells/µl. High mortality irrespective of ART in patients with TBM makes this category an important exception to co-treatment. While concerns about IRIS and treatment-limiting toxicity persist, low rates of mortality associated with these conditions indicate that programmatic implementation of TB-HIV service integration can be done without the threat of worsened clinical outcomes or of increasing resources needed for the management of these complexities. Findings from multiple clinical trials have translated into local and international policy and guideline change. It is important to note that this study was focussed on published evidence on clinical integration of TB and HIV treatment. Furthermore, it is essential to recognize the controlled circumstances under which most of the studies are undertaken. Numerous operational challenges would need to be overcome for effective translation of evidence from these clinical trials into

public health benefit. Despite considerable progress in generating evidence for clinical integration, there is a need for high-quality evidence guiding operational implementation that informs the successful and sustained implementation of TB and HIV service integration in various settings.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

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