LUND UNIVERSITY
Faculty of Medicine

Master's Programme in Public Health

Factors associated with adverse treatment outcomes of Tuberculosis among HIV-positive adults in an antiretroviral treatment program in Yangon, Myanmar

June 2016

Student: Tharaphi Lin

Supervisor: Professor Per Björkman

Department of Infectious Diseases, Institution for Translational Medicine

Lund University

Contents

Abstract

Introduction: Tuberculosis (TB) is the most common opportunistic infection (OI) and cause of death in people living with HIV/AIDS (PLHIV), even in settings with access to antiretroviral therapy (ART). This study aims to determine factors associated with adverse outcome of TB treatment in PLHIV.

Materials and Method: The study was retrospective cohort study which includes 958 individuals aged ≥15 years who were registered in a large ART program with comprehensive care for HIV in Yangon. The study period was between January 2012 to December 2014. All individuals who were diagnosed with both HIV and TB were included in the study. Patients' characteristics, TB history, ART status, CD4 cell count and sputum smear microscopy result were extracted from the clinic database and patient's medical journals to determine the association with TB treatment outcomes. Data analysis was done by univariate and multivariate logistic regression.

Result: Median age of patients was 34 years and 61.5% were male patients. Of 958 patients, 654(68.3%) of participants had favorable treatment outcomes, whereas 186(19.4%) died, 88(9.2%) loss to follow up and 30(3.1%) treatment failure during 12 months of study period. The ART coverage was 80% in all TB-HIV co-infected patients. The adverse outcomes were mostly seen in the group of patients who did not receive ART and who did not get tested for CD4 cell counts. Patients who did not receive antiretroviral therapy during the course of anti-tuberculosis treatment and low CD4 cell count at the diagnosis of TB were statistically significant predictors (P value .000) for adverse treatment outcomes of TB. No difference in adverse outcome was seen in patients who had ART in 8 weeks of ATT and after 8 weeks of ATT.

Conclusion: Early diagnosis of both infections and early ART initiation during the course of ATT are important factors in preventing adverse outcome of Tuberculosis.

Key words: HIV, AIDS, TB, ART, ATT, CD4 cell count, adverse treatment outcomes

Acronyms

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ATT	Anti tuberculosis treatment
CD4 cell	T-cell expressing CD4 receptor
GDP	Gross domestic product
HIV	Human Immunodeficiency Virus
IRIS	Immune reconstitution inflammatory syndrome
MAM	Medical Action Myanmar
NGO	Non-government Organization
PLHIV	People living with HIV/AIDS
TB	Tuberculosis

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that infects cells in the human immune system, especially CD4 cells. The HIV weakens the immune system, makes a person vulnerable to various opportunistic infections (OI) and develops into an advanced stage of HIV called acquired immunodeficiency syndrome (AIDS) (WHO 2015a). There were nearly 37 million people living with HIV/AIDS at the end of 2014 and the majority of them were in low and middle income countries. In 2014, an estimated 2 million people were newly infected with HIV and 1.2 million people died from AIDS-related causes(WHO 2015a). The epidemic of HIV/AIDS not only affects individuals but also families, civil societies, health systems and countries' economy.

Although there is no cure for HIV infection, anti-retroviral therapy (ART) leads to suppressed viral replication allowing for immune reconstitution with reduced risk of OIs and dramatically improved survival rates. Globally, nearly 16 million people living with HIV/AIDS (PLHIV) received ART in 2015(WHO 2015a). However, the complexity of ART treatment with poor drug adherence, treatment failure, drug interaction with treatment of several opportunistic infections and side effects of ART can also lead to poor treatment outcomes and poor quality of life. These challenges have been mostly seen in resource-limited settings where incidence of Tuberculosis (TB) infection is high. One of the challenges for medical professionals in giving care to PLHIV is TB/HIV co-infected individuals (Oreagba, Usman et al. 2014).

People living with HIV have a 26 times higher chance of developing an active TB infection compared to people without HIV infection (WHO 2015b). TB is an ancient disease that affected 1.2 million new cases globally among PLHIV in 2014 and it is the most common opportunistic infection (OI) in people living with HIV/AIDS (PLHIV). One third of the world population is infected with latent TB and at risk of developing active TB when the host defense deteriorates. Therefore, in HIV infected individuals the risk is higher than in the general population (Liu, Makubi et al. 2015).

Among HIV infected patients, TB is the leading cause of mortality and 390,000 PLHIV were estimated to have died of TB in 2014(WHO 2015b). TB-related mortality can be reduced by prescribing ART to all PLHIV regardless of their CD4 cell count (Grinsztejn, Hosseinipour et al. 2014, Severe, Juste et al. 2010, Suthar, Lawn et al. 2012). Therefore, all HIV patients with

TB are eligible for early ART initiation regardless of their CD4 counts. According to previous clinical trials, early ART initiation between 2-8 weeks of starting Anti-TB treatment (ATT) reduced mortality rate by about 41.7%, compared to those who deferred ART after 8-12 weeks of ATT (Blanc, Sok et al. 2011, Lancioni, Mahan et al. 2011, Abdool Karim, Naidoo et al. 2011). Although ART can significantly decrease the incidence of tuberculosis, the risk of TB remains increased among PLHIV receiving ART, especially in patients who have pretreatment severe immunodeficiency. (Lawn, Badri et al. 2005).

Furthermore, it is important to detect TB and initiate treatment for TB before initiation of ART. If ART is started before TB is diagnosed, the treatment can unmask and aggravate TB symptoms in severe immunosuppressed patients (Rockwood, Wilkinson 2015). The diagnosis and treatment of TB in PLHIV is complicated for several reasons. Firstly, atypical clinical presentation is seen in HIV-associated TB and many patients present with extra-pulmonary tuberculosis (EPTB) (Lee, Chan et al. 2000). Second, diagnosis with laboratory testing and radiographic imaging are challenging in HIV/TB co-infected patients. There are two widely available routine diagnostic tests for TB in developing countries. The first, sputum AFB microscopy has low sensitivity in PLHIV and the second, chest X-ray sometimes shows atypical pattern in PLHIV. Sputum culture is the gold standard for TB diagnosis, however, it takes time and is not widely available in low income countries.

Radiographic imagines, Chest X-ray findings are different in HIV-associated TB from a typical pattern of active TB. The typical pattern of an active TB seen in non-HIV patients is infiltrates in the upper lobe or in apical segment of the lower lobes of the lungs with or without cavities. However, in HIV-infected individuals, the imaging can be varied according to their immunity from consolidation, intrathoracic lymphadenopathy, miliary shadow or normal pattern (Lee, Chan et al. 2000).

Recently introduced Gene X-pert MTB/RIF has become a promising point of care diagnostic tool for TB which can detect pulmonary TB not detected by smear microcopy (O'Grady, Bates et al. 2012). The Gene X-pert MTB/RIF can detect TB as well as rifampicin resistance from sputum or other extra-pulmonary specimens in less than 2 hours, and therefore, it is recommended by WHO as an initial diagnostic tool for TB in PLHIV and suspected drug resistant TB patients or after sputum microscopy (World Health Organization 2015). Although the Gene X-pert technology significantly increases TB detection rates, it requires good

infrastructure with uninterrupted electrical supply and regular maintenance which are sometimes challenging for developing countries (Ardizzoni, Fajardo et al. 2015).

Successful treatment outcomes of TB can be obtained in HIV-infected patients if there is early case detection, effective treatment for tuberculosis, concurrent use of anti-retroviral therapy, high immune status of the patients and prompt management of other opportunistic infections and immune reconstitution inflammatory syndrome (IRIS) (Oshi, Oshi et al. 2014, Sanchez, Bartholomay et al. 2012, Varma, Nateniyom et al. 2009). Regarding treatment of both diseases, several complications can arise such as IRIS, drug interaction, side effects of the drugs and poor adherence. These challenges are mostly seen in the clinics where physicians are not available and these may lead to poor outcomes for treatment and high mortality.

ART coverage in developing countries is still inadequate and Myanmar is one of these countries. In Myanmar ART was first available only in 2001 introduced by Médecins Sans Frontières, Holland (MSFH), a well-known international NGO. The Ministry of Health distributed free ART starting in 2008 with a limited number of patients then several ART programs by other NGOs arose.

Myanmar is a lower-middle income country with a population of 53 million and 1.5% of its GDP was used for health expenditure in 2013 by the government according to World Bank indicators. Myanmar is 1 of the 22 highest tuberculosis burden countries and 41 highest TB/HIV burden countries (Floyd, Falzon et al. 2015). The estimated overall prevalence of HIV infection among adults and adolescents is 0.54% based on data from 2013 HIV sentinel survey in Myanmar (NAP 2015); however, the prevalence is estimated to be much higher in urban areas and in high-risk groups. There are an estimated 210,000 people living with HIV, and 17,000 TB incidence cases among PLHIC which accounts for 33/100,000 of the population. TB-related deaths totaled 4,300 were seen in 2013 among PLHIV in Myanmar (UNAIDS, United Nation AIDS Program 2015).

The Ministry of Health in Myanmar is prioritizing fighting HIV/AIDS and Tuberculosis together with local and international non-government organizations (NGO). The National AIDS Program (NAP) and the National Tuberculosis Program (NTP) have implemented collaborative activities in active TB case finding, HIV testing among TB patients and cross referral for ATT and ART since 2010. In addition, several local and international NGOs are also collaborating with the Ministry of Health for active case finding, diagnosis and treatment of HIV and TB (MOH 2015).

There is scarce research on treatment outcomes on tuberculosis among HIV-infected people in Myanmar. Although ART is now recommended for all patients with concomitant TB, the real outcomes of combined ART and ATT in Myanmar remains poorly understood. Deeper understanding of adverse factors associated with TB treatment outcomes might be helpful in identifying patients with predictors of adverse outcomes as well as a support for the service providers in how to optimize the program priorities in managing TB cases among PLHIV.

Objective of the study

Overall objective

The overall objective is to study aspects of TB treatment in PLHIV receiving care in an ART program in Yangon, Myanmar. The underlying hypothesis is that providing ART during the course of TB treatment leads to reduce adverse TB treatment outcomes in HIV-TB co-infected patients.

Specific objectives

The specific objectives are:

1. To determine TB treatment outcomes in PLHIV with access to ART
2. To determine factors associated with adverse outcomes of TB treatment with regard to patient characteristics and diagnostic methods for TB
3. To compare TB treatment outcomes with regard to ART status at TB diagnosis

Methodology

Study setting and population

The study was conducted at 2 HIV clinics in semi urban area, Hlaing Thar Yar and Shwe Pyi Thar Townships in Yangon, Myanmar. These clinics were run by an international Non-Government Organization named Medical Action Myanmar (MAM) where comprehensive HIV care services were given. MAM was founded by one of the former directors from MSF in 2009 with few MSF's employees to provide basic curative and preventive health care for vulnerable populations.

Yangon is the largest city in Myanmar and former capital with population over five million. It is composed of 33 townships. Hlaing Thar Yar and Shwe Pyi Thar Townships are the most populous semi urban townships with population of 686,827 and 343,270 respectively

according to 2014 population census. These two townships have the poorest population and most of them are manual labourer with low education status.

The study includes all adults and adolescents aged ≥15 years who were diagnosed HIV with 2 HIV rapid tests and TB diagnosis according to sputum smear microscopy or chest X-ray findings or physician's diagnosis who were registered at MAM clinics. Patients who are transfer out to another health facilities during the study period were excluded from the study.

Study design

This study was conducted using a retrospective cohort analysis of subjects registered at the clinics during January 2012 to December 2014. The Tuberculosis treatment outcomes was followed up after one year from initiating of ATT.

Data collection method

The data was collected from cohort of HIV/TB co-infected patients from HIV clinic database at MAM. One dataset was recorded in excel sheets which included all patients diagnosed with Tuberculosis who were under care of MAM with or without HIV co-infection and another dataset was extracted as an excel sheet from database which recorded all HIV infected patients who were on Anti-retroviral therapy (ART). Then those two data were merged based on the patients' code number into one excel sheet and managed by the researcher. In addition, records from patient's journal at the clinics and interviewing the staffs from the clinics were used to fill the missing data and to cross check.

Definition of variables

Treatment outcomes of tuberculosis was divided into 2 groups, favourable and adverse outcome. Favourable outcome includes cure and treatment completed, on the other hand, adverse outcome includes failure, loss to follow up and dead. Patients who moved to another health facility were defined as transferred out and they were excluded from the study.

Regarding favourable outcomes, cure was defined as positive sputum AFB cases at the diagnosis had negative sputum AFB at 5 months of smear microscopy. There are 7 cases with stool AFB positive whom were also regarded as smear positive TB. For the AFB smear negative TB cases, completed was used when smear microscopy showed negative AFB at the end of treatment and by clinical judgement of attending physician.

In case of adverse outcomes, the definition of failure in this study was a patient whose sputum smear was still positive 5 months after initiation of ATT and attending physician's clinical judgement for smear negative patients. Died was defined as patients who died of any

reason during the study period and loss to follow up was the patients whose treatment was interrupted and who did not attend the clinic for >2 months during the study period.

Age was divided into 3 groups ranged from 15-29 years, 30-44 years and ≥45 years to see the association in younger, middle and older age group. We divided age into 3 groups because we want to see any significant difference in treatment outcomes in older age group than the younger ones. History of TB treatment which includes new, relapse, failure and loss to follow up; new patients are patients who have never been on ATT before, relapse cases are patients who are bacteriologically confirmed TB cases with the outcome of cured or completed ATT. Failure defined as patients who failed the previous ATT and loss to follow up is the patients who are lost to follow up during the course of ATT.

Type of TB treatment was categorized into new regimen or retreatment regimen, which new regimen is the treatment with daily dose of 2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) and 4 months of Isoniazid and Rifampicin; and retreatment regimen includes 2 months of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S), 1 month of HRZE and 5 months of HRE which were defined according to WHO definition of TB treatment.

CD4 cell count was also divided into 6 categories which includes CD4 not done, CD4 count ≤50, 51-100, 101-200 and >200 cells/mm3. We categorized CD4 cells count into different categories to see whether the level of CD4 count has different association with the treatment outcomes. Analysis of ART status was done by using 4 categories with no ART, ART initiated before TB diagnosis, ART initiated within 8 weeks of TB treatment and ART initiated after 8 weeks of TB treatment to see whether timing of ART have effects on treatment outcomes of TB.

Statistical analysis

Data management was done by Microsoft Excel 2013 and data analysis by IBM SPSS (Statistical Package for Social Sciences) 23. Main outcome variable was 12-month treatment outcomes of tuberculosis whereas baseline variables were age, gender, history of TB treatment, type of TB treatment and CD4 cell count at the time of TB diagnosis and status of ART.

All the continuous variables were described in median and interquartile range (IQR) whereas categorical variables were described in counts and proportions. The analysis was done by using Pearson chi-square test to determine association between baseline variables and treatment outcomes of TB and bivariate logistic regression was done to estimate the significantly associated variables with the outcome variables. Variables for bivariate analysis

were selected from univariate analysis result with p-value of 0.25 and then binary logistic regression analysis was performed by forward stepwise elimination to calculate adjusted odds ratio.

Ethical consideration

The analysis of this report is part of the educational research and the evaluation of the HIV program in Myanmar. As this is not a human subject research and the data were collected as secondary data from a HIV care program, the ethical board in Department of Medical Research in lower Myanmar determined that this research did not require ethical review.

Result

Between 2012 January to 2014 December, a total of 1017 HIV/TB co-infected patients were taking ATT and among them 958 patients were included in the study. 59 of them were excluded from the study whom were 3 cases with missing data on treatment outcomes and 56 patients who were transferred out from the care to other facilities during follow up period. Of 958 patients who were included in the analysis, there were 107 cases with missing data on CD4 and 113 cases on sputum smear result and those were analysed as "Not done" in the analysis.

Characteristics of participants

In the study, total 958 TB/HIV co-infected patients were included in which 38.5% (n=369) were female and 61.5% (n=589) were male with median age of 34 years (range 15-72 years). Various treatment outcomes were shown in Table 1, 654(68.3%) of participants had favorable outcomes which was cured or treatment completed whereas 304(31.7%) of them had adverse outcomes. Adverse treatment outcomes included 186 (19.4%) died, 88(9.2%) loss to follow up and 30(3.1%) treatment failure during 12 months of study period. Median follow up duration was 21 months for all patients.

Previous history of TB and Sputum smear microscopy result

More than 90% were new patients who had never been on ATT before and 7% were relapse patients. Among 876 patients who were taking new regimen, 600(68.6%) had cure or completed outcome and on the other hand, 276(31.4%) patients had poor outcomes during 1 year follow up period. Regards to patients who had previous history of TB, slightly higher adverse outcome was seen compared to new patients, 65.9% had favorable outcome whereas 34.1% had adverse outcomes. Sputum smear microscopy result was negative in nearly 63% HIV/TB co-infected patients and 11% (n=113) had no sputum smear result.

ART and CD4 cells count

Most of the patients had started ART during 8 weeks of starting ATT (n=414, 43.2%) while many of them (n=205, 21.4%) had never received ART during the follow up period. Median follow-up time in the group which had never received ART was 4 months. Even in an ART program, only 79.2% were on ART. Among patients who had never received ART, only 25% had favorable outcome and other 70% were died or loss to follow up (35.1% and 35.6% respectively). More than half of the patients had CD4 cells count <50 cells/mm3 at the time of TB diagnosis with median CD4 cells count was 110 cells/mm3 (range 1-1273 cells/mm3). Number of dead patients reduce with higher CD4 cells count (>100 cells/mm3) was seen in Table 1.

Association between predictors and outcome variables

In univariate analysis shown in Table 2, all variables were tested for association by using Pearson chi square test. Gender, age, TB regimen, TB history and sputum smear result were not significantly associated with the treatment outcomes of tuberculosis. However, sputum smear result showing p value of 0.09 was tested for bivariate analysis according to previous literature. ART status and CD4 cell counts were statistically significant with p value of .000, therefore, binary logistic regression was done on sputum smear result, ART status and CD4 cell count with adverse outcome of tuberculosis.

Correlation between significant predictors and adverse outcome

The multivariate analysis between potential significant variables from univariate analysis and adverse TB treatment outcomes is shown in Table 3. Patients who had positive sputum smear result, who did not receive ART and who had low CD4 cell count were significant predictors of adverse outcomes for Tuberculosis treatment in bivariate analysis.

Negative sputum smear result showed protective effect (AOR=0.71, 95%CI=0.52-0.98) of developing adverse treatment outcomes compared to positive smear result. Patients who had never started ART had much higher odds of getting adverse outcomes of TB than patients who started on ART (AOR=15.65, 95%CI=9.96-24.59).

Patients who were on ART before TB treatment had about twice likely to develop adverse outcomes (OR= 2, 95%CI=1.07-3.71) than patients who started ART after 8 weeks of ATT, however, odds ratio became insignificant (AOR=1.85, 95%CI= 0.97-3.53) after adjusting for age, sex and treatment history. There was no significant difference of getting adverse

outcomes while comparing patients who were initiated ART in 8 weeks and after 8 weeks of initiating ATT.

Regarding CD4 cells count, patients who had not done CD4 testing and who had CD4 cells count of ≤50 cells/mm3 had higher risk to get adverse outcomes compared to patients whose CD4 cells count were above 200 cells/mm3 (AOR-11.46, 95%CI=6.67-19.69 and AOR=1.82, 95%CI=1.20-2.76 respectively).

Discussion

In this retrospective study, participants mostly represented productive middle age population between 15 to 45 years of age. This study showed similar results on predictors of adverse treatment outcomes of TB as in many TB/HIV studies done in developing countries. A TB treatment success rate of 68.3% was seen which is similar to many previous studies from the Asia region which range from 53.4% to 74.5% (Ismail, Bulgiba 2013a, Tabarsi, Chitsaz et al. 2012, Ambadekar, Zodpey et al. 2015, Shastri, Naik et al. 2013, Sanchez, Bartholomay et al. 2012).

Mortality was high (19.4%) as the majority had very severe immunosuppression; the proportion is similar to studies in Malaysia (21%), Thailand (17%) and Nigeria (19%) (Ismail, Bulgiba 2013b, Varma, Nateniyom et al. 2009, Oshi, Oshi et al. 2014). Early diagnosis of HIV and early case detection of TB can prevent mortality and in this case, high mortality is explained by the fact that patients were not diagnosed early for either HIV or TB. Mortality may be as high as 20-60% among patients who were lost to follow up from the program, although, there was no published evidence of this rationale from Myanmar (Brinkhof, Pujades-Rodriguez et al. 2009).

Apart from high mortality, high rate of loss to follow up 9%, which was more than the WHO recommended <5% loss to follow up rate. This finding is higher than the study from Vietnam with 7% loss to follow up rate (Huyen, Nhung et al. 2016) but, lower than in other settings (Ismail, Bulgiba 2013a, Sume, Hoshen et al. 2009). The cause of lower defaulted patients may due to one-stop service nature of this ART program with access to free ART, ATT, treatment of opportunistic infections, nutritional support and defaulter tracing system. Loss to follow up patients were important for control of TB because they are one of the sources for transmission of TB inside the community. Therefore, additional program strategies to reduce

loss to follow up rates and to retrieve loss to follow up patients from the program are needed to improve the treatment outcomes.

Treatment failure is higher than other studies from resource-limited settings (Chunpongthong, Ko et al. 2011, Ismail, Bulgiba 2013a), which might be due to over diagnosis of treatment failure. Physicians diagnosed treatment failure according to patients' clinical symptoms due to limited access of diagnostic tools and limited availability of drug sensitivity test (DST). Therefore, more resources are needed for infrastructure and diagnostic tools in this setting. In addition, treatment failure may contribute to multidrug resistant TB (MDRTB) cases; but we cannot detect in our study because we could not collect sputum culture for drug sensitivity test. According to a study conducted from National program in Yangon in 2002, MDR TB was detected in 4.2% of new cases and 18.4% of relapse cases in a cohort of 567 patients (Phyu, Lwin et al. 2005). MDR TB can lead to adverse treatment outcomes with high mortality. In this study retreatment cases had no association with the treatment outcomes of TB which is similar to some recent studies (Tabarsi, Chitsaz et al. 2012, Oshi, Oshi et al. 2014)

Sputum smear microscopy was not done in 11% of patients and the exact reason for not doing sputum smear was not known, though, this might be due to problems with sputum collection and sending to the health care centre by the patients or might be extra-pulmonary TB patients who did not have cough and sputum expectoration. Patients with positive sputum smear result tends to have more adverse outcomes and the result is different from the study in Ethiopia which and Vietnam (Amante, Ahemed 2015, Thuy, Shah et al. 2007). These two studies showed different results between sputum smear microscopy result and adverse treatment outcomes. Therefore, more studies are needed.

Providing ART for TB patients during the course of ATT improves the prognosis of both diseases and reduces the mortality (Ismail, Bulgiba 2013a, Tabarsi, Chitsaz et al. 2012, Shastri, Naik et al. 2013, Blanc, Sok et al. 2011). In our study, patients who were on ART before diagnosis of TB had higher odds to have adverse outcomes compared to those taking ART after diagnosis of TB although it is not statistically significant when potential confounders were adjusted. This might be due to non-adherence to ART in those patients who had taken ART before diagnosis of TB. Nearly half of the participants had started ART during 8 weeks of starting ATT, although we could not find any significant difference in outcomes while comparing the group of ART during 8 weeks of ATT and after 8 weeks of ATT.

According to World Bank data 2015, there was only 36% coverage of ART for the whole country in Myanmar and even in the ART program about 80% of TB patients received ART. This may be due to advanced immunosuppression of the patients and late presentation to the ART program. Therefore, many of them died before getting ART or during early treatment TB. Early diagnosis of HIV and early ART initiation can reduce patients with advanced immunosuppression, development of TB and complicated concurrent treatments.

Another significant association seen in this study was CD4 cells count. There were 107 cases which had no recorded CD4 cells count which might be due to patients died or were not follow up before getting CD4 tested or operational weakness from limited resources. Low CD4 cell count is a well-known risk factors for adverse treatment outcomes from previous knowledge and studies (Ackah, Digbeu et al. 1995, Tabarsi, Chitsaz et al. 2012). The more severe the immunosuppression is, the higher the risk of mortality in TB/HIV coinfection (Grinsztejn, Hosseinipour et al. 2014).

The above findings affirm comprehensive care for early diagnosis of both infections and providing early ART during the course of ATT. In Myanmar, diagnosis of tuberculosis mainly depends on sputum AFB microscopy, chest X-ray and clinical presentation of patients. There was limited access to Gene X-pert and drug sensitivity testing as these tests were only available in 3 TB hospitals in the whole country. Therefore, installing better diagnostic tools that are made more widely available might be a necessary action to improve the patient's survival.

Methodological discussion

A strength of this study was that it was conducted in a large cohort setting of ART program in Myanmar. This is one of the first studies on HIV/TB coinfection performed in a high risk area of Myanmar which could represent other high risk urban setting. There were some limitations in our study. We excluded transfer out patients which could lead to underestimating adverse treatment outcomes. Moreover, TB diagnosis was only based on sputum smear microscopy and physician's judgement, therefore, we could not exclude other opportunistic infections rather than TB. We also could not detect the adverse effects from drug to drug interaction and IRIS which could be the causes of poor outcomes of TB. In addition, cause of death and the outcome of loss to follow up patients could not be determined.

Although there was evidence that smear-negative pulmonary and extra-pulmonary TB especially TB meningitis had high mortality rate in HIV patients, we did not collect data on site of TB infection (Kingkaew, Sangtong et al. 2009). It is difficult to differentiate between

pulmonary and extra-pulmonary TB due to lack of diagnostic tools in this setting, and, this might increase the confounding of the study. Some variables which could have affected outcomes of TB treatment, such as employment, drug or alcohol abuse, haemoglobin level and BMI were not available.

The data were not retrieved from national data so participants were not necessarily representative of the entire Myanmar population. In addition, the majority of the participants were daily labourers and in urban settings; this may restrict the generalizability of the results gained. As data were collected retrospectively, some important information could not be retrieved. In addition, electronic data for patients who were not on active follow up were in poor data accuracy if those could not be cross-checked with patients' journals. Due to some missing baseline data (CD4 cell count), the magnitude of confounding could not be estimated.

Conclusion

In conclusion, our research points out that early diagnosis of both infections and ART initiation during the course of ATT can prevent adverse outcome of tuberculosis. Moreover, the findings support early initiation of ART can reduce adverse treatment outcomes of TB despite the challenges in concurrent treatment of both diseases. There are still gaps in the diagnosis of TB, early detection of HIV, ART coverage and retrieving loss to follow up patients in this setting.

Implication of the study

This study has some programmatic implications. First of all, the data recording system should be improved and updated with every patient registered at the clinics. Second, it is necessary to upgrade the infrastructure with TB diagnostic tools and finally, to improve the tracing system of patients who did not come to the clinics on follow up dates to control TB transmission in the community. These changes cannot be done alone without collaboration with MOH and intervening by the government at the national level.

References

ABDOOL KARIM, S.S., NAIDOO, K., GROBLER, A., PADAYATCHI, N., BAXTER, C., GRAY, A.L., GENGIAH, T., GENGIAH, S., NAIDOO, A., JITHOO, N., NAIR, G., EL-SADR, W.M., FRIEDLAND, G. and ABDOOL KARIM, Q., 2011. Integration of antiretroviral therapy with tuberculosis treatment. *The New England journal of medicine,* **365**(16), pp. 1492-1501.

ACKAH, A.N., DIGBEU, H., DAILLO, K., GREENBERG, A.E., COULIBALY, D., COULIBALY, I., VETTER, K.M. and DE COCK, K.M., 1995. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire. *The Lancet,* **345**(8950), pp. 607-610.

AMANTE, T.D. and AHEMED, T.A., 2015. Risk factors for unsuccessful tuberculosis treatment outcome (failure, default and death) in public health institutions, Eastern Ethiopia. *The Pan African medical journal,* **20**, pp. 247.

AMBADEKAR, N.N., ZODPEY, S.P., SONI, R.N. and LANJEWAR, S.P., 2015. Treatment outcome and its attributes in TB-HIV co-infected patients registered under Revised National TB Control Program: a retrospective cohort analysis. *Public health,* **129**(6), pp. 783-789.

ARDIZZONI, E., FAJARDO, E., SARANCHUK, P., CASENGHI, M., PAGE, A.L., VARAINE, F., KOSACK, C.S. and HEPPLE, P., 2015. Implementing the Xpert(R) MTB/RIF Diagnostic Test for Tuberculosis and Rifampicin Resistance: Outcomes and Lessons Learned in 18 Countries. *PloS one,* **10**(12), pp. e0144656.

BLANC, F.X., SOK, T., LAUREILLARD, D., BORAND, L., REKACEWICZ, C., NERRIENET, E., MADEC, Y., MARCY, O., CHAN, S., PRAK, N., KIM, C., LAK, K.K., HAK, C., DIM, B., SIN, C.I., SUN, S., GUILLARD, B., SAR, B., VONG, S., FERNANDEZ, M., FOX, L., DELFRAISSY, J.F., GOLDFELD, A.E. and CAMELIA (ANRS 1295-CIPRA KH001) STUDY TEAM, 2011. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *The New England journal of medicine,* **365**(16), pp. 1471-1481.

BRINKHOF, M.W., PUJADES-RODRIGUEZ, M. and EGGER, M., 2009. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PloS one,* **4**(6), pp. e5790.

CHUNPONGTHONG, P., KO, Z.Z., YEEKIAN, C., LUVIRA, V. and PITISUTTITHUM, P., 2011. Outcomes of antituberculosis treatments at 18 months follow-up in TB-HIV co-infected patients on ART: a retrospective review of 166 cases. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet,* **94**(6), pp. 664-670.

FLOYD, K., FALZON, D., GETAHUN, H., KANCHAR, A., MIRZAYEV, F., RAVIGLIONE, M., TIMIMI, H., WEYER, K. and ZIGNOL, M., 2015. *Use of high burden country lists for TB by WHO in the post-2015 era.* Geneva: World Health Organization.

GRINSZTEJN, B., HOSSEINIPOUR, M.C., RIBAUDO, H.J., SWINDELLS, S., ERON, J., CHEN, Y.Q., WANG, L., OU, S.S., ANDERSON, M., MCCAULEY, M., GAMBLE, T., KUMARASAMY, N., HAKIM, J.G., KUMWENDA, J., PILOTTO, J.H., GODBOLE, S.V., CHARIYALERTSAK, S., DE MELO, M.G., MAYER, K.H., ESHLEMAN, S.H., PIWOWAR-MANNING, E., MAKHEMA, J., MILLS, L.A., PANCHIA, R., SANNE, I., GALLANT, J., HOFFMAN, I., TAHA, T.E., NIELSEN-SAINES, K., CELENTANO, D., ESSEX, M., HAVLIR, D., COHEN, M.S. and HPTN 052-ACTG STUDY TEAM, 2014. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *The Lancet.Infectious diseases,* **14**(4), pp. 281-290.

HUYEN, T.T., NHUNG, N.V., SHEWADE, H.D., HOA, N.B. and HARRIES, A.D., 2016. Collaborative activities and treatment outcomes in patients with HIV-associated tuberculosis in Viet Nam. *Public health action,* **6**(1), pp. 8-14.

ISMAIL, I. and BULGIBA, A., 2013a. Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients. *Preventive medicine,* **57 Suppl**, pp. S27-30.

ISMAIL, I. and BULGIBA, A., 2013b. Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. *PloS one,* **8**(8), pp. e73250.

KINGKAEW, N., SANGTONG, B., AMNUAIPHON, W., JONGPAIBULPATANA, J., MANKATITTHAM, W., AKKSILP, S., SIRINAK, C., NATENIYOM, S., BURAPAT, C., KITTIKRAISAK, W., MONKONGDEE, P. and VARMA, J.K., 2009. HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death. *International Journal of Infectious Diseases,* **13**(6), pp. 722-729.

LANCIONI, C.L., MAHAN, C.S., JOHNSON, D.F., WALUSIMBI, M., CHERVENAK, K.A., NALUKWAGO, S., CHARLEBOIS, E., HAVLIR, D., MAYANJA-KIZZA, H., WHALEN, C.C. and BOOM, W.H., 2011. Effects of antiretroviral therapy on immune function of HIV-infected adults with pulmonary tuberculosis and CD4+ >350 cells/mm3. *The Journal of infectious diseases,* **203**(7), pp. 992-1001.

LAWN, S.D., BADRI, M. and WOOD, R., 2005. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS (London, England),* **19**(18), pp. 2109-2116.

LEE, M.P., CHAN, J.W., NG, K.K. and LI, P.C., 2000. Clinical manifestations of tuberculosis in HIV-infected patients. *Respirology (Carlton, Vic.),* **5**(4), pp. 423-426.

LIU, E., MAKUBI, A., DRAIN, P., SPIEGELMAN, D., SANDO, D., LI, N., CHALAMILLA, G., SUDFELD, C.R., HERTZMARK, E. and FAWZI, W.W., 2015. Tuberculosis incidence rate and risk factors among HIV-infected adults with access to antiretroviral therapy. *AIDS (London, England),* **29**(11), pp. 1391-1399.

MOH, M., 12/17/2015, 2015-last update, Health in Myanmar 2014: Diseases of National Concern [Homepage of Ministry of Health Myanmar], [Online]. Available: http://www.moh.gov.mm/file/Diseases%20of%20National%20Concern.pdf [12/30, 2015].

NAP, 2015. *Global AIDS response Progress Report Myanmar.* Nay Pyi Taw: National AIDS Program Myanmar.

O'GRADY, J., BATES, M., CHILUKUTU, L., MZYECE, J., CHEELO, B., CHILUFYA, M., MUKONDA, L., MUMBA, M., TEMBO, J., CHOMBA, M., KAPATA, N., MAEURER, M., RACHOW, A., CLOWES, P., HOELSCHER, M., MWABA, P. and ZUMLA, A., 2012. Evaluation of the Xpert MTB/RIF assay at a tertiary care referral hospital in a setting where tuberculosis and HIV infection are highly endemic. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America,* **55**(9), pp. 1171-1178.

OREAGBA, I.A., USMAN, S.O., OLAYEMI, S.O., OSHIKOYA, K.A., OPANUGA, O., ADEYEMO, T.A., LESI, O.A., DODOO, A.N. and AKANMU, A.S., 2014. Pharmacoepidemiology of antiretroviral drugs in a teaching hospital in Lagos, Nigeria. *Ghana medical journal,* **48**(4), pp. 194-203.

OSHI, D.C., OSHI, S.N., ALOBU, I. and UKWAJA, K.N., 2014. Profile, Outcomes, and Determinants of Unsuccessful Tuberculosis Treatment Outcomes among HIV-Infected Tuberculosis Patients in a Nigerian State. *Tuberculosis research and treatment,* **2014**, pp. 202983.

PHYU, S., LWIN, T., TI, T., MAUNG, W., MAR, W.W., SHEIN, S.S. and GREWAL, H.M., 2005. Drug-resistant tuberculosis in Yangon, Myanmar. *Scandinavian Journal of Infectious Diseases,* **37**(11-12), pp. 846-851.

ROCKWOOD, N. and WILKINSON, R.J., 2015. Understanding and intervening in HIV-associated tuberculosis. *Clinical Medicine,* **15**, pp. s43-s49.

SANCHEZ, M., BARTHOLOMAY, P., ARAKAKI-SANCHEZ, D., ENARSON, D., BISSELL, K., BARREIRA, D., HARRIES, A. and KRITSKI, A., 2012. Outcomes of TB Treatment by HIV Status in National Recording Systems in Brazil, 2003-2008. *PLoS ONE,* **7**(3), pp. 1-6.

SEVERE, P., JUSTE, M.A., AMBROISE, A., ELIACIN, L., MARCHAND, C., APOLLON, S., EDWARDS, A., BANG, H., NICOTERA, J., GODFREY, C., GULICK, R.M., JOHNSON, W.D.,Jr, PAPE, J.W. and FITZGERALD, D.W., 2010. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *The New England journal of medicine,* **363**(3), pp. 257-265.

SHASTRI, S., NAIK, B., SHET, A., REWARI, B. and DE COSTA, A., 2013. 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,* **13**, pp. 838-2458-13-838.

SUME, G.E., HOSHEN, M., BITA, G., KABORE, S. and NZIMA, V.N., 2009. Treatment outcome of TB/HIV positive and negative smear positive pulmonary tuberculosis patients treated using daily self-administered therapy in a Cameroonian district hospital. *East African medical journal,* **86**(10), pp. 469-475.

SUTHAR, A.B., LAWN, S.D., DEL AMO, J., GETAHUN, H., DYE, C., SCULIER, D., STERLING, T.R., CHAISSON, R.E., WILLIAMS, B.G., HARRIES, A.D. and GRANICH, R.M., 2012. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS medicine,* **9**(7), pp. e1001270.

TABARSI, P., CHITSAZ, E., MORADI, A., BAGHAEI, P., MARJANI, M. and MANSOURI, D., 2012. Treatment outcome and mortality: Their predictors among HIV/TB co-infected patients from Iran. *International journal of mycobacteriology,* **1**(2), pp. 82-86.

THUY, T.T., SHAH, N.S., ANH, M.H., NGHIA DO, T., THOM, D., LINH, T., SY, D.N., DUONG, B.D., CHAU, L.T., MAI, P.T., WELLS, C.D., LASERSON, K.F. and VARMA, J.K., 2007. HIV-associated TB in An Giang Province, Vietnam, 2001-2004: epidemiology and TB treatment outcomes. *PloS one,* **2**(6), pp. e507.

UNAIDS, UNITED NATION AIDS PROGRAM, 2015-last update, AIDS info: indicators [Homepage of UNAIDS], [Online]. Available: http://aidsinfo.unaids.org/ [12/15, 2015].

VARMA, J.K., NATENIYOM, S., AKKSILP, S., MANKATITTHAM, W., SIRINAK, C., SATTAYAWUTHIPONG, W., BURAPAT, C., KITTIKRAISAK, W., MONKONGDEE, P., CAIN, K.P., WELLS, C.D. and TAPPERO, J.W., 2009. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. *BMC infectious diseases,* **9**, pp. 42-2334-9-42.

WHO, Nov 2015, 2015a-last update, HIV/AIDS: Fact Sheet [Homepage of WHO], [Online]. Available: http://www.who.int/mediacentre/factsheets/fs360/en/ [12/01, 2016].

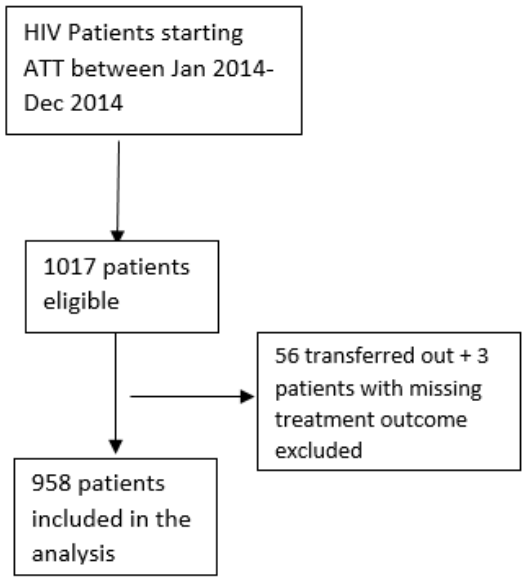
WHO, 2015b-last update, TB/HIV facts [Homepage of World Health Organization], [Online]. Available: http://www.who.int/hiv/topics/tb/tbhiv_facts_2015/en/ [12/30, 2015].

WORLD HEALTH ORGANIZATION, 2015. *Implemeting Tuberculosis Diagnostics: Policy Framework.* Geneva: World Health Organization.

Figure and Tables

Figure

Figure 1. Number of eligible patients in the study



Tables 1-3

Table 1. Demographic and clinical characteristics of study population with regard to TB treatment outcomes

		Favourable outcomes (N=725)	Adverse outcomes (N=233)			Total (N=958)
		cure/ completed N (%)	Failure N (%)	Dead N (%)	Loss to follow up N (%)	
sex	Female	252(38.5)	14(46.7)	73(39.2)	30(34.1)	369(38.5)
	Male	402(61.5)	16(53.3)	113(60.8)	58(65.9)	589(61.5)
Age	15-29	162(24.8)	8(26.7)	45(24.2)	26(29.5)	241(25.2)
	30-44	385(58.9)	15(50.0)	108(58.1)	48(54.5)	556(58.0)
	≥45	107(16.4)	7(23.3)	33(17.7)	14(15.9)	161(16.8)
Treatment Regimen	New regimen	600(91.7)	29(96.7)	163(87.6)	84(95.5)	876(91.4)
	Retreatment regimen	54(8.3)	1(3.3)	23(12.4)	4(4.5)	82(8.6)
Treatment History	New	600(91.7)	29(96.7)	162(87.1)	84(9.6)	875(91.3)
	Relapse	43(6.6)	1(3.3)	18(9.7)	4(4.5)	66(6.9)
	Failure	6(0.9)	0(0.0)	3(1.6)	0(0.0)	9(0.9)
	Loss to follow up	5(0.8)	0(0.0)	3(1.6)	0	8(0.8)
Sputum Smear result	Not done	74(11.3)	1(3.3)	28(15.1)	10(11.4)	113(11.8)
	Negative	424(64.8)	14(46.7)	110(59.1)	51(58.0)	599(62.5)
	Positive	156(23.9)	15(50.0)	48(25.8)	27(30.7)	246(25.7)
ART status	No ART	50(7.6)	10(33.3)	72(38.7)	73(83.0)	205(21.4)
	ART before ATT	47(7.2)	1(3.3)	17(9.1)	1(1.1)	72(7.5)
	ART between 8 weeks of ATT	330(50.5)	6(20.0)	71(38.2)	7(8.0)	414(43.2)
	ART after 8 weeks of ATT	227(34.7)	13(43.3)	26(9.5)	7(8.0)	273(28.5)
CD4 cell count (cells/mm3)	No CD4	26(4.0)	7(23.3)	64(34.4)	10(11.4)	107(11.2)
	CD4≤50	149(22.8)	8(26.7)	55(29.6)	12(13.6)	224(23.4)
	CD4 51-100	143(21.9)	2(6.7)	32(17.2)	11(12.5)	188(19.6)
	CD4101-200	151(23.1)	6(20.0)	18(9.7)	28(31.8)	203(21.2)
	CD4 >200	185(28.3)	7(23.3)	17(9.1)	27(30.7)	236(24.6)

Table 2 Univariate analysis on Treatment outcomes of Tuberculosis

		12-month treatment outcomes		Total	χ^2
		Favourable N (%)	Adverse N (%)	N=958	P value
Gender					1
	Female	252 (68.3)	117 (31.7)	369	
	Male	402 (68.3)	187 (31.7)	589	
Age(Years)					.737
	15-29	162 (67.2)	79 (32.8)	241	
	30-44	385 (69.2)	171 (30.8)	556	
	≥45	107 (66.5)	54 (33.5)	161	
TB Treatment regimen					.353
	New regimen	600 (68.5)	276 (31.5)	876	
	Retreatment regimen	54 (65.9)	28 (34.1)	82	
TB Treatment History					.926
	New	600 (68.6)	275 (31.4)	875	
	Relapse	43 (65.2)	23 (34.8)	66	
	Failure	6 (66.7)	3 (33.3)	9	
	Loss to follow up	5 (62.5)	3 (37.5)	8	
Sputum Smear result					.089
	Not done	74 (65.5)	39 (34.5)	113	
	Negative	424 (70.8)	175 (29.2)	599	
	Positive	156 (63.4)	90 (36.6)	246	
ART status					.000**
	No ART	50 (24.4)	155 (75.6)	205	
	ART before ATT	47 (71.2)	19 (28.8)	66	
	ART within 8 weeks of ATT	330 (79.7)	84 (20.3)	414	
	ART after 8 weeks of ATT	227 (83.2)	46 (16.8)	273	
CD4 cell count (cells/mm3)					.000**
	No CD4	26 (24.3)	81 (75.7)	107	
	CD4 ≤50	149 (66.5)	75 (33.5)	224	
	CD4 51-100	143 (76.1)	45 (23.9)	188	
	CD4 101-200	151 (74.4)	52 (25.6)	203	
	CD4 >200	185 (78.4)	51 (21.6)	236	

ART: Antiretroviral therapy, ATT: Anti TB treatment

** Statistically significant

χ^2= Pearson Chi square test

Table 3. Multivariate analysis on predictors of adverse TB treatment outcomes in HIV/TB co-infected patients showing crude odds ratio and adjusted odds ratio by age, sex, treatment history

	Crude OR	95% CI		AOR**	95% CI	
		Lower	Upper		Lower	Upper
Sputum Smear Result						
Smear not done	.91	.57	1.46	.90	.56	1.44
Smear negative	.72	.52	.98	.71	.52	.97*
Smear positive	Ref					
ART status						
No ART	15.30	9.76	23.98	15.61	9.94	24.53*
ART before ATT	2.00	1.07	3.71	1.85	.974	3.53
ART in 8 weeks of ATT	1.26	.84	1.87	1.26	.85	1.88
ART after 8 weeks of ATT	Ref					
CD4 cell count						
No CD4	11.30	6.59	19.39	11.46	6.67	19.69*
CD4 ≤50	1.83	1.20	2.77	1.82	1.20	2.76*
CD4 51-100	1.14	.72	1.80	1.15	.73	1.82
CD4 101-200	1.25	.80	1.94	1.25	.80	1.96
CD4 >200	Ref					

Ref: Referent
**AOR: Adjusted odds ratio by age, sex and treatment history
*P-value <0.05

Popular Science Summary

Human Immunodeficiency virus (HIV) and Tuberculosis (TB) are most common co-infected infections in people living with HIV and TB is the most common cause of death in HIV patients. Therefore, it is important to know the risk factors associated with adverse treatment outcomes of Tuberculosis to improve quality of life in people who are infected with both TB and HIV.

A study conducted in Myanmar among 958 HIV patients aged 15 years and above found that adverse TB treatment outcomes were seen in patients who were not receiving ART during the course of TB treatment and severely weakened immune system. The data was collected from the database and from the medical journals of the patients who were treated in an ART program of a non-government organization called Medical Action Myanmar (MAM) during January 2012 to December 2014.

Majority of participants were middle aged men aged between 30-44 years. Although all patients with both TB and HIV infections should receive early treatment for both HIV and TB, only 80% of patients were provided with HIV treatment so called antiretroviral therapy (ART) in this program. About 30% of patients had adverse outcomes, either died or loss to follow up from the program or treatment failure of TB. Adverse outcomes were mostly seen in a group of patients who did not get their immunity tested and who never received ART. This is because they come to clinic in their late stage of HIV, developed several complications and most of them died shortly after the diagnosis.

The study showed that comprehensive HIV care program, with early HIV diagnosis, providing early ART to all HIV-TB infected patients, early diagnosis of TB and effective treatment of TB, is needed in Myanmar to reduce adverse treatment outcomes of Tuberculosis in HIV patients.