TUBERCULOSIS TREATMENT OUTCOMES AND THE PREDICTORS FOR SURVIVAL OF TB/HIV CO-INFECTED PATIENTS IN THE KLANG VALLEY, MALAYSIA

ISMAWATI BINTI ISMAIL

THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PUBLIC HEALTH

FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR

2014

UNIVERSITI MALAYA

ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: Ismawati Binti Ismail (781127-11-5142)

Registration/Matric No: MHC090003

Name of Degree: Doctor of Public Health (DrPH)

Title of Project Paper/Research Report/Dissertation/Thesis ("this Work"):

Tuberculosis Treatment Outcomes and the Predictors for Survival of TB/HIV Co-Infected Patients in the Klang Valley, Malaysia.

Field of Study: Public Health (Epidemiology and Biostatistics)

I do solemnly and sincerely declare that:

(1) I am the sole author/writer of this Work;
(2) This Work is original;
(3) Any use of any work in which copyright exists was done by way of fair dealing and for permitted purposes and any excerpt or extract from, or reference to or reproduction of any copyright work has been disclosed expressly and sufficiently and the title of the Work and its authorship have been acknowledged in this Work;
(4) I do not have any actual knowledge nor do I ought reasonably to know that the making of this work constitutes an infringement of any copyright work;
(5) I hereby assign all and every rights in the copyright to this Work to the University of Malaya ("UM"), who henceforth shall be owner of the copyright in this Work and that any reproduction or use in any form or by any means whatsoever is prohibited without the written consent of UM having been first had and obtained;
(6) I am fully aware that if in the course of making this Work I have infringed any copyright whether intentionally or otherwise, I may be subject to legal action or any other action as may be determined by UM.

Candidate's Signature Date

Subscribed and solemnly declared before,

Witness's Signature Date

Name:

Designation:

ABSTRACT

Background: Tuberculosis and human immunodeficiency virus (TB/HIV) co-infection are important global public health problems. Tuberculosis (TB) is the most common opportunistic infection and the leading cause of death in HIV-infected patients. Co-infection with TB and HIV is a situation that is becoming rampant worldwide and Malaysia is no exception. However, there are no substantial data concerning the co-infection of both diseases in this country.

Objectives: To determine the risk factors for defaulters of TB treatment and predictors of death among TB/HIV co-infected patients in Malaysia.

Methods: Medical records at the time of TB diagnosis and subsequent follow-up of all newly registered TB patients with HIV co-infection seen at TB clinics in the Institute of Respiratory Medicine and three public hospitals in the Klang Valley between January 2010 and September 2010 were reviewed. These medical records were reviewed again twelve months after their initial diagnosis to determine TB treatment outcomes and survival. Kaplan Meier and Cox proportional hazard regression analysis were performed using SPSS.

Results: Of 227 patients analysed, the majority of patients were males (88.1%) and single/divorced (67.0%). A total of 48.5% were Malays. The mean age of the patients was 39.1 (standard deviation 8.6). The most common mode of HIV transmission was through injecting drug use (55.9%). Among 227 patients, successful outcomes were achieved in 117 patients (53.4%) with 18.7% of patients 'cured' and another 34.7% 'completed treatment'. The unsuccessful outcomes were those who 'defaulted treatment' (25.6%, n=56), 'died'

(21.0%, n=46); and another 8 (3.4%) who were still on treatment. There were no cases of treatment failure. After adjusting for other predictors in multiple Cox regression analysis, the significant predictors of default from TB treatment in HIV-infected patients were: (i) not on antiretroviral therapy (AHR 3.75; 95%CI 2.19-6.42), (ii) low serum albumin level (AHR 2.89; 95%CI 1.22-6.84), (iii) presence of lymphadenopathy (AHR 2.03; 95%CI 1.18-3.49) and (iv) alcohol intake (AHR 1.93; 95%CI 1.10-3.38). At the end of the study, seven (7) patients who were originally classified as defaulters were later reclassified as having died, making the total number of deaths during TB treatment 53 (23.3%), with 40% of deaths occurring within two months of TB diagnosis. Survival at 2, 6 and 12 months after initiating TB treatment were 90.7%, 82.8% and 78.8% respectively. After adjusting for other factors, death in TB/HIV co-infected patients were associated with being Malay (AHR 4.48; 95%CI 1.73-11.64), CD4 T-lymphocytes count < 200 cells/µl (AHR 3.89; 95% CI 1.20-12.63), three or more opportunistic infections (AHR 3.61; 95% CI 1.04-12.55), not receiving antiretroviral therapy (AHR 3.21; 95% CI 1.76-5.85) and increase per 10^3 total white blood cell count per microliter (AHR 1.12; 95% CI 1.05-1.20).

Conclusion: TB/HIV co-infected patients had a high case fatality rate during TB treatment. Initiation of antiretroviral therapy in these patients can improve survival by restoring immune function and preventing opportunistic infections.

ABSTRAK

Latar belakang: Koinfeksi jangkitan Tuberkulosis dan virus HIV (TB/HIV) adalah masalah kesihatan awam global yang penting. Tuberkulosis (TB) adalah jangkitan oportunis yang paling kerap dan merupakan penyebab utama kematian di kalangan pesakit yang dijangkiti HIV. Koinfeksi TB dan HIV semakin berleluasa di seluruh dunia dan tidak terkecuali di Malaysia. Walau bagaimanapun, tiada data yang jelas berkaitan dengan koinfeksi kedua-dua penyakit ini di negara ini.

Objektif: Untuk menentukan faktor-faktor risiko pesakit yang engkar rawatan TB dan meramalkan faktor kematian di kalangan pesakit koinfeksi TB / HIV di Malaysia.

Metodologi: Rekod perubatan pesakit-pesakit koinfeksi TB/HIV yang baru didaftarkan di antara bulan Januari 2010 sehingga September 2010 di Institut Perubatan Respiratori dan tiga buah hospital kerajaan di Lembah Klang telah disemak. Rekod-rekod perubatan ini diperiksa semula dua belas bulan selepas tarikh diagnosis awal bagi menentukan hasil rawatan TB dan status kemandirian. Anggaran Kaplan Meire dan analisis regresi berbilang Cox telah dijalankan menggunakan perisian SPSS.

Keputusan: Daripada 227 pesakit dianalisis, majoriti pesakit adalah lelaki (88.1%) dan tidak berkahwin/bercerai (67.0%). Sebanyak 48.5% adalah berketurunan Melayu. Min umur di kalangan pesakit adalah 39.1 (sisihan piawai 8.6). Punca jangkitan HIV yang paling biasa adalah melalui penggunaan dadah suntikan (55.9%). Daripada 227 pesakit, rawatan TB berjaya ditamatkan oleh 117 pesakit (53.4 %) dengan 18.7% daripada pesakit tersebut ‘sembuh’; manakala 34.7% yang lain ‘sempurna rawatan’. Pesakit yang tidak berjaya menamatkan rawatan adalah mereka yang ‘gagal rawatan’ (25.6%, n=56), ‘mati’ (21.0%, n=46) dan 8 yang lain (3.4%) masih di dalam rawatan. Tiada kes

kegagalan rawatan direkodkan. Selepas pelarasan bagi peramal lain dilakukan dalam analisis regresi berbilang Cox, peramal kepada engkar rawatan TB di kalangan pesakit yang dijangkiti HIV adalah: (i) tidak menerima rawatan antiretroviral (AHR 3.75 ; 95% CI 2,19-6,42), (ii) tahap serum albumin yang rendah (AHR 2.89 ; 95% CI 1,22-6,84), (iii) mempunyai limfadenopati (AHR 2.03 ; 95% CI 1,18-3,49) dan (iv) pengambilan alkohol (AHR 1.93 ; 95% CI 1,10-3,38). Pada akhir kajian ini, tujuh (7) pesakit yang asalnya dikategorikan sebagai engkar rawatan kemudiannya dikategorikan semula sebagai telah meninggal dunia, memberikan jumlah kematian sepanjang rawatan TB menjadi 53 orang (23.3%), dengan 40% daripada kematian tersebut berlaku dalam tempoh dua bulan selepas didiagnosa penyakit TB. Kebarangkalian jangka hayat pada 2, 6 dan 12 bulan selepas memulakan rawatan TB, masing-masing adalah 90.7%, 82.8% dan 78.8%. Selepas pelarasan bagi faktor-faktor lain, kematian bagi koinfeksi TB/HIV dikaitkan dengan berketurunan Melayu (AHR 4.48; 95% CI 1,73-11,64), kiraan CD4 T-limfosit <200 sel/μl (AHR 3.89; 95% CI 1.20 -12,63), mempunyai tiga atau lebih jangkitan oportunis (AHR 3.61; 95% CI 1,04-12,55), tidak menerima rawatan antiretroviral (AHR 3.21; 95% CI 1,76-5,85) dan peningkatan jumlah sel darah putih per 10^3 setiap mikroliter (AHR 1.12 ; 95% CI 1,05-1,20).

Kesimpulan: Koinfeksi TB/HIV mempunyai kadar kematian yang tinggi semasa rawatan TB. Permulaan rawatan antiretroviral kepada pesakit-pesakit ini boleh meningkatkan jangka hayat dengan memulihkan fungsi imun dan mencegah jangkitan oportunis.

Acknowledgements

First and foremost, my grateful thanks to God Almighty, the most gracious and the most merciful for providing His guidance throughout the completion of this thesis.

My deepest gratitude goes to my supervisor Professor Dr. Awang Bulgiba. I am indebted to him for the ideas, guidance and encouragement that he had shown to me and the long hours that he has spent in reading and correcting my manuscripts. I have learned a lot under his supervision.

Special acknowledgements to the University of Malaya for the grant that has enabled me to carry out this work (University of Malaya student research grant: PS230/2010A). Also, thank you to the head and staff of Julius Centre University of Malaya (JCUM) who assisted in my work directly or indirectly, especially for the funding of my first journal published under the University of Malaya/Ministry of Higher Education (UM/MOHE) High Impact Research Grant (Grant number E000010-20001).

Special thanks go to Associate Professor Dr Maznah Dahlui the Head of Department Social and Preventive Medicine. Associate Professor Noran N Hairi the Head of Julius Centre University of Malaya. Associate Professor Choo Wan Yuen the Head of Epidemiology and Biostatistics Unit. Dr Farizah M. Hairi the Head of Postgraduate student and Dr. Azlan Darus the Coordinator of DrPH student, Department of Social and Preventive Medicine.

I would also like to thank the Public Service Department for giving me the scholarship to further my studies. I also extend my thanks to my colleagues in the Disease Control Division, Ministry of Health Malaysia for all the encouragement and help that was continuously offered to me.

My deepest appreciation to my father, Ismail bin Abdul Rahman and my mother, Meriam Taib who have always encouraged me to work hard and stay focused on what I am doing, and my four adorable children Aliff, Aiman, Aqil and Amira for being so

understanding about the time that their mum did not give to them because she was concentrating on this thesis. The person I loved most, my beloved husband, Mohd Noorul Ikhsan, thank you for the support, time, understanding and love that you have shown throughout these years, which have made this dream possible.

Table of Contents

List of Figures

List of Tables

Publications

The following papers have been published or submitted from this thesis:

Publications:

i) Ismail I, Bulgiba A (2013) Determinants of unsuccessful tuberculosis treatment outcome in HIV-infected Malaysian patients. Prev Med. 2013;57 Suppl:S27-30. doi: 10.1016/j.ypmed.2012.12.023. Epub 2013 Jan 5.

ii) Ismail I, Bulgiba A (2013) Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS ONE 8(8): e73250. doi:10.1371/journal.pone.0073250

Conferences:

i) Poster presentation title "Systematic Review: Predictors of mortality in HIV-associated tuberculosis", in the International Health Conference IIUM 2011, 7-8 December 2011, Kuantan.

ii) **Poster** presentation title "Characteristics of TB associated with HIV in Klang Valley", in the International Health Conference IIUM 2011, 7-8 December 2011, Kuantan.

iii) **Oral** presentation title "Determinants of unsuccessful tuberculosis treatment outcome in Malaysian HIV-infected patients", in the 1st Asia Pasific Clinical Epidemiology and Evidence Based Medicine Conference, 6-8 July 2012, Kuala Lumpur.

iv) **Oral** presentation title "Predictors of survival in TB/HIV co-infected patients in Klang Valley". In the 2nd International Public Health Conference, 3-4 October 2012, Kuala Lumpur.

List of Symbols and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ART	Antiretroviral therapy
AZT	Zidovudine
BCG	Bacillus Calmette–Guérin
BMI	Body Mass Index
CDC	Centres for Disease Control and Prevention
cells/µl	Cells per microlitre
CI	Confidence Interval
CPG	Clinical Practice Guidelines
CPT	Cotrimoxazole Prophylactic Therapy
CTX	Cotrimoxazole
CXR	Chest radiography
d4T	Stavudine
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment, Short Course
EFV	Efavirenz
EHIS	Electronic Hospital Information System
EHRZ	Ethambutol, Isoniazid, Rifampicin and Pyrazynamide
ELISA	Enzyme Linked Immunosorbent Assay
FTC	Emtricitabine
H_0	Null Hypothesis
H_1	Alternative Hypothesis
HAART	Highly Active Anti Retroviral Therapy
Hb	Hemoglobin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRZ	Isoniazid, Rifampicin and Pyrazynamide
HTAR	Hospital Tuanku Ampuan Rahimah
HZ	Isoniazid and Pyrazinamide
IDU	Intravenous Drug User

IGRA	Interferon-Gamma Release Assays
IPR	Institute of Respiratory Medicine
IQR	Inter Quartile Range
IRIS	Immune Reconstitution Inflammatory Syndrome
KM	Kaplan Meier
kg	Kilograms
LFT	Liver Function Test
LML	Log Minus Log
MARPS	Most At Risk Populations
MDG	Millenium Development Goals
MDRTB	Multidrug Resistant Tuberculosis
mmol/l	Milimoles per litre
MOH	Ministry of Health
NGO	Non-governmental Organization
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NPV	Nevirapine
NRIC	National Registered Identification Card
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NSEP	Needle and Syringe Exchange Programmes
NTBC	National TB Centre
NTCP	National TB Control Program
OI	Opportunistic Infection
OR	Odds Ratio
PCP	Pneumocystis Carinii Pneumonia
PI	Protease Inhibitors
PLWH	People Living with HIV
PPD	Purified Protein Derivate
PPP	Postgraduate Research Grant
PS	Power and Sample Size
PTB	Pulmonary Tuberculosis
RCT	Randomized Controlled Trial
RPR	Rapid Plasma Reagen
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences

TB	Tuberculosis
TBIS	National TB Information System
TDF	Tenofovir Disoproxil Fumarate
TST	Tuberculin Skin Testing
UNAIDS	United Nation Joint Programs on AIDS
VIF	Variation Inflation Factor
VL	Viral Load
WBC	White Blood Cell
WHO	World Health Organization

List of Appendices

CHAPTER 1: INTRODUCTION

About this chapter

This chapter provides the background for this thesis, which describes the tuberculosis (TB), Human Immunodeficiency Virus (HIV) and TB/HIV situation locally and globally. Section 1.1 begins with a presentation of the epidemiology of TB and HIV/acquired immune deficiency syndrome (AIDS) in Malaysia and globally. Important socio-demographic and health indicators of Malaysia, the organisation of the health system and the national TB and HIV/AIDS control programmes and the local strategies adopted to control TB and HIV infections are presented.

The problem statement, rationale of the research, objectives and research hypothesis are discussed in Section 1.2 to Section1.5.

Finally, the structure of this thesis is discussed in Section 1.6.

1.1 Epidemiology of TB, HIV and TB/HIV co-infection

1.1.1 Global Situation of TB

The World Health Organization declared tuberculosis (TB) as a global health emergency in 1993. Despite the downward trend in the absolute number of TB cases since 2006 and the fall in the incidence rates since 2001, the burden of TB disease remains a global health challenge (WHO). TB is among the top three diseases worldwide, along with HIV and Malaria. Globally, there were an estimated 8.7 million incident cases of TB in 2011 of which 13% were co-infected with HIV. About 82% of global TB infections are concentrated in 22 high burden countries. The highest ranking five are India, China, South Africa, Indonesia, and Pakistan.

The African region had the highest proportion of TB cases coinfected with HIV. In this region, about 39% of TB cases were estimated to be coinfected with HIV which accounted for 79% of TB/HIV cases worldwide, followed by South East Asia with 13%. Deaths among TB patients who were HIV-negative were almost one million and an additional 0.43 million deaths were reported among TB patients who were HIV-positive.

TB is more common among men than women, and affects mostly adults in the economically productive age groups. Approximately two-thirds of cases were estimated to occur among people aged 15–59 years (WHO, 2011a). As part of WHO's global TB control strategy, in 1994 the organization launched the 'Directly Observed Therapy, Short Course' or better known as DOTS. This strategy includes five key components including a government commitment to support TB treatment, passive detection of active tuberculosis cases by the use of sputum microscopy, direct observation of short course therapy for TB treatment, ensuring a regular supply of medicines, and a monitoring system for program supervision and evaluation (WHO, 2006).

1.1.2 TB Situation in the Western Pacific Region

The World Health Organization (WHO) reported in 2011 that there were 22 High TB Burden Countries in the world which account for 81 percent of the TB burden. Four countries from the Western Pacific Region, namely Cambodia, China, the Philippines and Vietnam were included in this group. WHO also stated that based on the 2004 data, there were an estimated four million prevalent cases of TB or 236 per 100,000 population in the Western Pacific Region out of the total population of 174 million. Nearly two million were new cases. It was estimated that more than 300,000 deaths from tuberculosis occurred in the region in 2004.

WHO acknowledged in its report that there were three main reasons which contributed to the rise in TB cases all over the world in recent years, namely HIV; insufficient application of disease control measures; and economic decline. The threat posed by TB-HIV co-infection and Multidrug Resistant Tuberculosis (MDR-TB) is an area of concern that may reverse the gains in TB control. In the Western Pacific region, TB associated with HIV infection is a growing threat, particularly in certain areas of China, among specific high risk groups in Malaysia and in Papua New Guinea and Vietnam (WHO, 2011b).

1.1.3 TB Situation in Malaysia

Malaysia is located in the South-East Asian region, which comprises the peninsular area known as West Malaysia and part of Borneo Island known as East Malaysia. There are thirteen states and three Federal Territories in Malaysia with an area of about 329,758 km square. Malaysia has a population of 29.2 million, with about 65.5% aged between 15-64 years, and approximately 72% living in urban areas (“Malaysia Demographic Profiles,” 2013). Although demographic changes with rapid industrial and socioeconomic development are likely to shift disease patterns towards an increasing

importance of non-communicable disorders, nevertheless communicable diseases are still of tremendous importance.

In the early 1940s and 1950s, TB was the number one cause of death in Malaysia. Anti-tuberculosis drugs became available in Malaysia only in the late 1950s. During that era, TB had been already a major cause of morbidity and mortality. Realizing the seriousness of this public health problem, the Malaysian government launched its National TB Control Program (NTCP) in 1961 with the main aim to control and reduce the prevalence of TB. From 1961 until 1994, the National TB control programme was coordinated technically and administratively by the National TB Centre (NTBC) located in Kuala Lumpur.

In 1995, the National TB Control was integrated into the general communicable disease control programme and placed under the Disease Control Division, Ministry of Health. Each state and Federal Territory has its own State TB Control Program which is headed by the Health Director and the Chest Physician as the technical advisor. The state TB team consists of a TB epidemiologist, TB treatment manager and laboratory manager. The NTBC was re-designated as the country's tertiary National Chest Institute. Malaysia had implemented directly observed treatment, short course (DOTS) strategy in the national TB control program in the late 90s. DOTS is the most effective treatment strategy recommended by the WHO for controlling TB and has been one of the most rapidly expanding and successful health interventions since the 1990s. DOTS was developed based on collective best practices, findings of clinical trials and program operations of TB control over the past two decades. The success of the strategy has been proven in both rich and poor countries.

Malaysia is categorized by the World Health Organization (WHO) as an intermediate TB burden country (WHO, 2011a). As in other developed and industrialized countries, the TB problem in Malaysia declined significantly between 1970 and 1980. Factors that have contributed to the reduction in TB incidence include improvements in socioeconomic status, better ventilation of homes and work sites and an improved health system. However, from early 1995, the incidence of tuberculosis has slowly increased from an incidence rate of 58 per 100,000 in 1995 to 72 per 100,000 in 2011. Data from the National TB Control Programme showed that the rate of TB deaths in Malaysia in 2011 was 8.0% of the total notified TB cases in that year; making it the highest mortality rate among infectious diseases in Malaysia. Several factors were responsible for the increasing TB incidence in Malaysia. These included the HIV/AIDS infection, influx of immigrants from endemic neighbouring countries, increased rural-urban migration and drug abuse. Thus the emergence of the HIV epidemic reinforced the need to focus on the identification and cure of infectious TB patients (MOH, 2011).

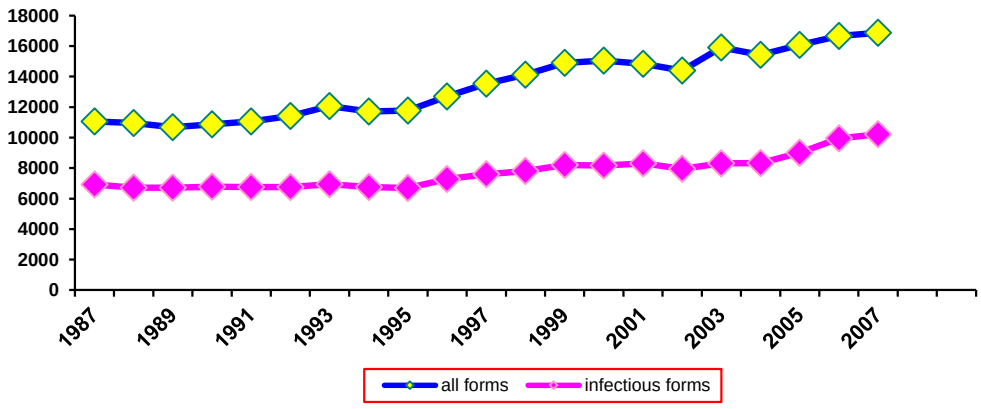


Figure 1.1: Notified TB Cases in Malaysia, 1987-2007

Source: Ministry of Health.

Although the TB situation in Malaysia is still under control, Malaysia has a high risk of experiencing a re-emergence of TB because it is surrounded by neighbouring countries with a high TB burden. Neighbouring South East Asian countries with high prevalence of TB infections are Cambodia, Myanmar, Vietnamsample size

and Indonesia. These countries 'export' the biggest group of migrants to Malaysia (Table 1.1). According to Malaysian Ministry of Health regulations, all legally registered migrant workers have to be screened for TB as part of their pre-employment requirements. If they are found to be infected with TB, they have to be deported. However, migrants that enter Malaysia illegally do not appear on the radar of the screening program and therefore become a potential source of TB. In 2011, immigrants made up 10 per cent of the 20,666 TB cases in the country.

Table 1.1: Case notification in South East Asian countries, 2010

Country	Number of cases	Incidence Rate (per 100,000)
Brunei Darussalam	232	57.7
Cambodia	39 994	285.7
Singapore	1 478	29.6
Malaysia	18 018	64.4
Laos	3 836	63.9
Myanmar	127 134	264.9
Thailand	64 512	93.5
Philippines	163 248	175.5
Indonesia	296 272	123.4
Vietnam	88 033	180.0

Source: Global Tuberculosis Control 2011

In Malaysia, TB treatment is initiated at Treatment Centre 1 (Pusat Rawatan 1/ PR1) by doctors in Hospitals and Health Clinics. Patients are referred to the nearest health care facility (Treatment Center 2 / PR2) which oversees Directly Observed Therapy (DOT). Follow up treatment are continued at PR2 which consist of Health Clinics and

Community Clinics (Klinik Desa) manned by Medical Assistants or trained nurses. Currently they are 229 Treatment Center 1 and 2,410 Treatment Center 2 in Malaysia (MOH, 2010).

First line drugs for the treatment of TB are Isoniazid (H), rifampicin (R), pyrazinamide (Z), Streptomycin (S) and Ethambutol (E). TB treatment comprises two phases, namely, the initial or intensive phase (two months) and the continuation or maintenance phase (four months). For cases with extrapulmonary TB, the duration of treatment may be extended depending on the patient's clinical and radiological response (MOH, 2002).

The National Tuberculosis Control Program's policy states that HIV screening is compulsory for all patients who present with signs or symptoms suggestive of tuberculosis as recommended by the WHO. TB is often the first clinical indication that a person may have an underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention, care and treatment. In addition, the HIV status of TB patients makes a difference in their TB treatment (WHO, 2010a). Detecting HIV infection in a TB patient is also critical for the TB patient's household members because HIV-positive TB patients may have household members who are also living with HIV. Household contacts of an infectious TB case are given high priority for TB screening and treatment, especially if they are living with HIV. Those who are found to have active TB disease need prompt treatment. Among household contacts, people living with HIV and children who do not have active TB are candidates for isoniazide treatment as a prophylaxis to prevent the development of active TB.

1.1.4 Global Situation of HIV/AIDS

The HIV/AIDS epidemic has created a huge challenge in many parts of the world and become one of the greatest threats to human health and development since the 1980s. Despite enhanced global efforts to curb the HIV/AIDS epidemic, HIV remains a leading

cause of death worldwide and the number one cause of death in Africa. Since its recognition, approximately 40 million people are currently living with HIV infection, and an estimated 25 million have died due to acquired immunodeficiency syndrome (AIDS).

According to the United Nations Joint Program on AIDS (UNAIDS), the number of people living with HIV had increased from 29.4 million in 2001 to 34.0 million by the end of 2011, resulting from continuing new infections, better survival of people living with HIV and general population growth. However, the number of new infections is lower by 20% than in 2001; which is 2.5 (95%CI: 2.2-2.8) million. The number of AIDS-related deaths worldwide have also declined by 24% from a peak of 2.3 million in 2004 (95%CI: 2.1 million-2.6 million) to about 1.7 (95%CI: 1.5-1.9) million in 2011 (UNAIDS, 2012).

Globally, the HIV epidemic varies considerably across geographical areas. HIV epidemic can be categorized as low, centralized or generalized. The region that is most severely affected by HIV is the Sub-Saharan Africa. About 23.5 million (69%) of people living with HIV (PLWH) and 94% of children with HIV live in this region. Sub-Saharan Africa is categorized as experiencing a generalized epidemic. In a generalized epidemic, HIV is firmly established and transmission occurs in the general population with their national HIV prevalence rate that is greater than 1 percent. In addition, according to the UNAIDS report, women and youth aged 15-24 are disproportionately affected, leading to large numbers of AIDS orphans, households headed by children and subsequent medical, social, economic and development challenges in the worst affected countries. An estimated 1.8 million of people in this region became newly infected with HIV in 2011. The vast majority of new infections result from unprotected heterosexual intercourse, including paid sex and sexual union in long-term and concurrent relationships, or as a result of mother-to-child transmission.

The Caribbean, Eastern Europe and Central Asian regions ranked second as being heavily affected by the HIV epidemic. The Caribbean is the region outside sub-Saharan Africa with the highest HIV prevalence. However, the rate of new HIV infection in this region has declined by 42 per cent since 2001 and the number of AIDS-related deaths have declined by 48 per cent. In Eastern Europe and Central Asia the new HIV infection started to increase in the late 2000s with an accompanying 21 percent increase in mortality from AIDS (UNAIDS, 2012).

In Asia, the impact of AIDS is even greater than in Africa because this region is home to about fifty percent of the world's population. Therefore, even a small increase in the infection rates can mean large differences in the absolute number of infected people. It was estimated that the total number of PLWH in Asia was five million people with around half of people (2.4 million) living in India. In East Asia, an estimated 14,000 new infections were reported in 2011; but in the South and South-East Asia, the annual number of new HIV infections declined during that year (UNAIDS, 2012).

1.1.5 HIV/AIDS Situation in Malaysia

HIV/AIDS was first reported in Malaysia in December 1986. By the end of 2011, Malaysia had a cumulative figure of 94,841 HIV, 17,686 AIDS and 14,986 deaths, thus giving reported PLHIV of 79, 855. The epidemic in this country is still concentrated within most-at-risk populations (MARPS) especially among IDU, sex workers and transgender population. The number of people newly infected that was reported by the Ministry of Health has shown a consistent downward trend from a peak of 6,978 in 2002. In 2011, there were 3,479 new cases reported to the Ministry of Health, approximately half of what was reported in 2002 with an average of nine new cases each day. The notification rate of HIV also continues to experience a decrease from 28.4

in 2002 to 23.4 in 2005 and to 12.2 cases per 100,000 populations in 2011. The number of HIV/AIDS-related deaths were 805 (26.1%) (MOH, 2012a).

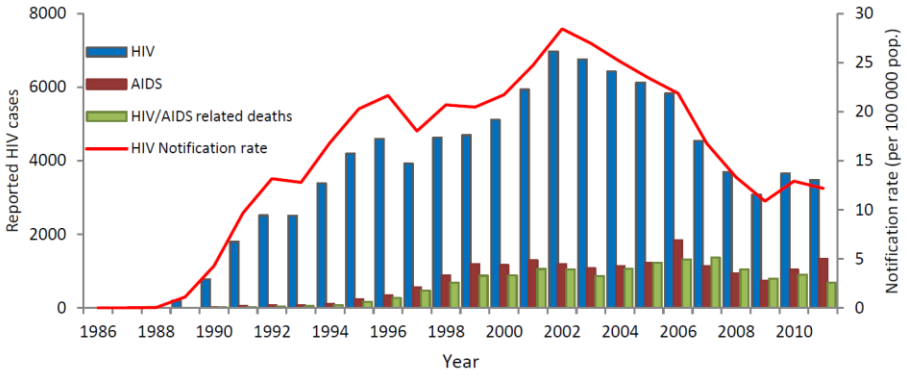


Figure 1.2: HIV and AIDS-related deaths reported in Malaysia 1986 – 2011.
Source: Ministry of Health.

HIV in Malaysia is predominantly among males as they constitute 90% of cumulative HIV cases, of whom the majority are intravenous drug users (IDU). However, the number of new cases among women had increased from around 5 percent of new infections during the late 1990s, to around 21 percent in 2011. In the earlier phase of HIV pandemic in Malaysia, new infections were largely driven by IDU. This trend has eventually changed over time from only one sexual transmission for every nine IDU in 1990 to two sexual transmissions for every eight IDU in 2000 and five sexual transmission for every five IDU in 2010. Since 2005 the Malaysian MOH has launched an intensive harm reduction program which includes needle and syringe exchange programmes (NSEP) and drug substitution therapy for drug users. This program had successfully reduced the number of HIV infections transmitted via needle sharing. In 2011, sexual transmission had replaced IDU as the main driving factor in the HIV epidemic with a ratio of six sexual transmissions for every four IDU reported. A training module was also developed by the Ministry of Health to teach religious leaders

about HIV. This is an important step in a country where the majority of people are Muslim.

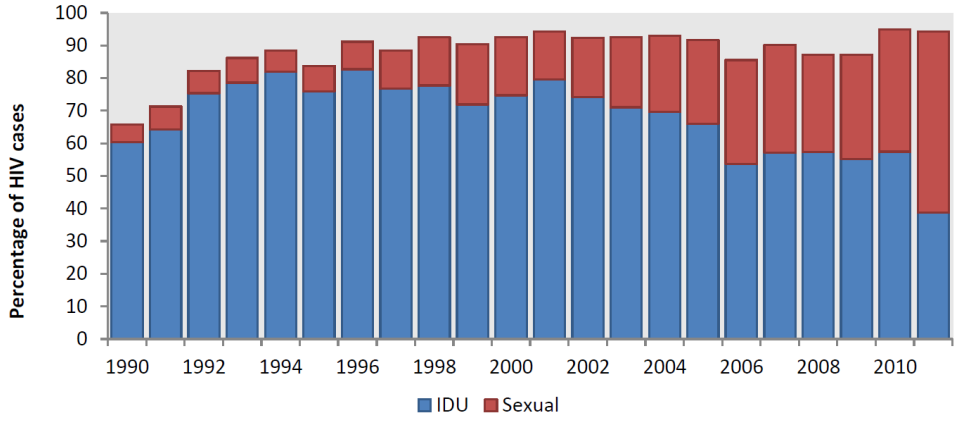


Figure 1.3: Reported HIV cases attributed to IDU and sexual transmission, Malaysia 1986 – 2011.

Source: Ministry of Health.

About 26% of reported infections are amongst young people aged between 13 to 29 years old. From 1980 to December 2011, children aged below 13 years consistently contributed approximately one percent of the cumulative total of HIV infections.

Malaysia is classified by the WHO as having a concentrated HIV epidemic where the HIV prevalence continues to be less than 1% in the general population but concentrated among most-at-risk groups. The most at risk populations are injecting drug users and sex workers with HIV prevalence ranging from 3 percent to 20 percent.

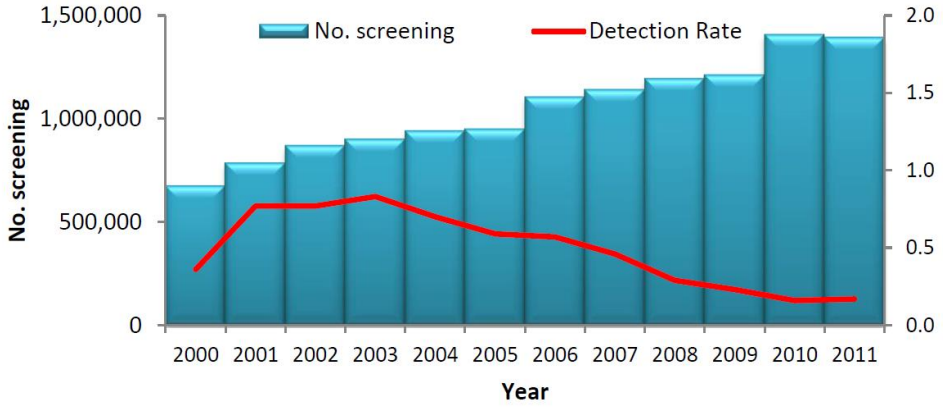


Figure 1.4: No. of Screening Test and Case Detection Rate of HIV Infection, Malaysia, 2000-2009.

Source: Ministry of Health.

The Ministry of Health (MOH) had targeted to achieve a reduction of new HIV cases to 11 per 100,000 populations by 2015. However, this target was achieved much earlier, that is, in 2009. With the current achievement, the MOH has reviewed its programs, to further reduce the new HIV cases to 9 per 100,000 populations by 2015.

HIV screening was started in Malaysia since 1985. Currently, all government health facilities (2,836 health clinics inclusive of community clinics and 143 hospitals inclusive of non-MOH hospitals) are providing free HIV screening facilities. Malaysia has implemented various HIV screening programs. Among the screening programs that have been implemented are mandatory HIV screening of all donated blood, blood products and organs; antenatal screening and routine screening of inmates in drug rehabilitation centres and prisons, TB and STI cases, clients of harm reduction programs, contacts of cases; and voluntary screening for premarital couples. Over the past five years, a total of 1.3 million HIV screenings was conducted. Despite maintaining surveillance program and intensified screening activities, the detection rate of HIV is decreasing. This figure is compatible with the declining HIV reported cases through the surveillance system.

Recent guideline by the WHO recommends that ART should be started for all people living with HIV with active TB disease irrespective of their CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first eight weeks of starting TB treatment. If the CD4 cell count is less than 50 cells/mm^3, ART should be started within first two weeks of TB treatment as a matter of emergency (WHO, 2011c).

In patients with TB-HIV co-infection, WHO recommends that the first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, WHO recommends either efavirenz (EFV) or nevirapine (NVP). The recommended first-line ART regimens for TB patients are those that contain efavirenz (EFV), since interactions with anti-TB drugs are minimal.

1.1.6 TB/HIV Situation in Malaysia

TB infection among HIV patients do not show a declining trend despite reduction in new HIV cases notification (Figure 1.5). The number of TB-HIV co-infection reported nationwide has increased from 64 to 1,819 cases from 1990 to 2008.

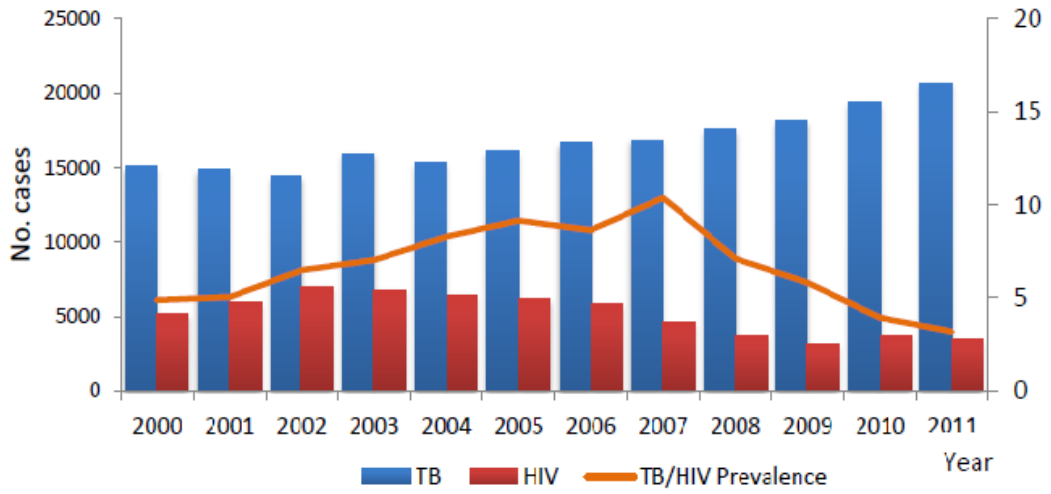


Figure 1.5: TB, HIV and TB/HIV Prevalence in Malaysia, 2000-2011

Source: Ministry of Health.

The government has conducted routine TB-HIV screening for all new inmates in incarcerated closed settings such as prisons and drug rehabilitation centres since 2001 as part of its prevention and control measures. As with other opportunistic infections, the risk of dying is higher if TB/HIV co-infected patients are not treated. Isoniazid prophylaxis therapy (IPT) was started in 2011 as an effort to reduce morbidity and mortality of TB/HIV co-infection (MOH, 2012b).

In Malaysia, TB and HIV programs collaboration was strengthened at the national level by placing all TB and HIV programs under the Disease Control Division, Ministry of Health. Such joint efforts included the formation of a National Committee for TB/HIV, implementation of a joint TB-HIV strategic plan and the development of the National AIDS Registry with a TB data management component. The provision of TB and HIV screening and treatment services are provided by primary health care services and hospitals with specialist expertise. TB/HIV patients were provided with universal access to ARTs at no cost by government health care facilities.

The current structure of Disease Control Division gives an advantage in the management of TB/HIV in which both sectors are located under the same umbrella namely the Communicable Disease Section which is led by a Deputy Director of Disease Control. Therefore the TB and HIV program's collaboration can be strengthened at the national level. Both sectors will be better coordinated and will have the same goals and directions.

1.2 Problem Statement

TB is still a public health problem in Malaysia despite socioeconomic progress and advancement in health services. TB has physical, social and economic impacts on those infected, their families and the populations where they live. Although TB is preventable and treatable, patients can die due to delayed diagnosis and inadequate treatment.

Despite the long and continuous efforts to battle it, TB continues to be around in this country. The absolute number of TB cases in Malaysia is still increasing every year. In 2011, there were 19,337 cases of all forms of TB reported with an incidence rate of 68.4 per 100,000 people (WHO, 2011c). If these trends are sustained, the MDG target that TB incidence should be falling by 2015 will not be achieved.

The HIV epidemic is believed to contribute to this inability to reduce TB incidence in Malaysia. In 2008 HIV prevalence among TB patients in Malaysia was 10.4% based on routine screening done, which put Malaysia into Category I based on the Interim Policy on Collaborative TB/HIV Activities by the WHO, even though the HIV prevalence rate among the adult population is $\leq 1\%$ (WHO, 2004).

It is also of public health importance in Malaysia that the death rates for HIV-infected TB patients are particularly high, ranging from 30% to 35% every year with an average of 450 deaths per year. In 2007, 30.3% of deaths were attributed to TB-HIV co-infection.

Routine HIV screening among TB patients was introduced in Malaysia since 1990. HIV testing is not only a collaborative activity, but it links TB-HIV co-infected patients to availability of HIV treatment and care, thus reducing the death rate. Expert opinion and operational research provide evidence that HIV testing and counselling offer a direct entry point for care and support of tuberculosis patients with HIV. The cost-effectiveness of voluntary HIV counselling and testing improves significantly when the testing is targeted at populations with high HIV prevalence.

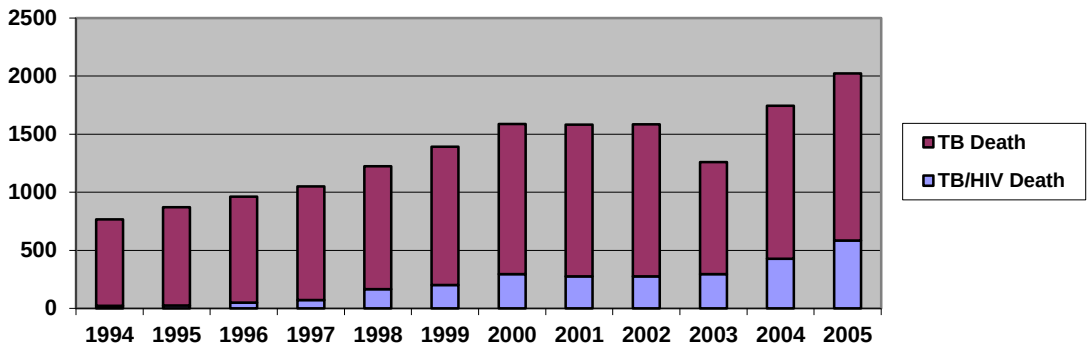


Figure 1.6: TB Death and TB/HIV Death in Malaysia, 1994-2005

Source: Ministry of Health.

The World Health Organization (WHO) strongly recommended that a TB/HIV Collaborative Committee be formed in this country to formulate policies and guidelines for the TB/HIV collaboration. HIV/AIDS programs and TB programs need to have closer collaboration to improve diagnosis, care and prevention services for people living with HIV and TB. The aim of collaborative TB/HIV activities is to decrease the burden of diseases in the populations where HIV is fuelling the TB epidemic by expanding the scope of TB and HIV programs and improving the quality of service provision.

The present study reports on the survival of a cohort of HIV-positive tuberculosis patients registered in 2010 in the central region of Malaysia. In Malaysia, there is still a gap in knowledge in the understanding of TB/HIV co-infection, particularly those aspects pertaining to survival and predictors of death in TB-HIV co-infected patients. Most of the studies on TB/HIV survival were conducted in African countries. Some studies have been published recently in neighbouring countries such as Thailand and Vietnam (Manosuthi et al., 2006; Sanguanwongse et al., 2008; Sungkanuparph et al., 2007; Thuy et al., 2007). There are only a few articles regarding characteristics of TB/HIV co-infected patients in selected states in Malaysia (Mohammad & Naing, 2004; Nissapatorn et al., 2005), but none has reported on the factors associated with differences in treatment outcomes and survival. Adding data from a country with a moderate TB burden and concentrated HIV epidemic is a useful step forward.

1.3 Rationale of the study

Based on the research problem statement, there is a strong need to do a study focusing on the outcomes of tuberculosis treatment and the determining factors associated with survival in TB-HIV co-infected patients. This study expands current knowledge of predictors of survival to an Asian sample.

This issue is important because, monitoring the outcomes of treatment is one of the five elements of TB control emphasized in the DOTS strategy, and remains one of the core elements of the Stop TB Strategy. It is important to know the treatment outcomes and the survival of TB/HIV co-infected patients in Malaysia because such information will provide for a better understanding of the epidemiology of TB/HIV co-infection, the survival rate and the predictors of survival. Information about the risk factors associated with death in TB/HIV co-infected patients is crucial in developing strategies to be targeted at this high risk group and would allow for improvements in the clinical care of

these patients. Hence, appropriate activities and preventive measures can be planned to improve the treatment outcomes and survival.

1.4 Study Objectives

1.4.1 General Objective

The overall objective of this study is to study the characteristics of TB patients who are HIV positive, treatment outcomes and their survival probabilities in Institute of Respiratory Medicine, Kuala Lumpur and at three public hospitals in Selangor.

1.4.2 Specific Objectives

The specific research objectives are as follows:

1. To determine the characteristics of TB patients with HIV co-infection.
2. To determine the treatment outcomes of TB-HIV co-infected patients.
3. To assess the risk factors for defaulting TB treatment in HIV-infected patients.
4. To determine the predictors of survival in HIV-infected TB patients during TB treatment.

1.5 Research Hypothesis

1) There is an association between the socio-demographic characteristics, clinical characteristics, laboratory profile, radiological and treatment factors and defaulted TB treatment in TB/HIV co-infected patients.

2) There is an association between the prognostic factors (socio-demographic characteristics, clinical characteristics, laboratory profile, radiological and treatment factors) and the survival of TB/HIV co-infected patients.

1.6 Structure of the thesis

This thesis is divided into 6 chapters. Chapter 1 is the introduction which provides the background of the research and outlines the chapters in the thesis. Chapter 2 presents the literature review of tuberculosis treatment outcomes and survival of TB-HIV co-infected patients. It provides a background to the thesis by reviewing the evidence from published literatures.

Chapter 3 details the work done in extracting data from the study sites which took place between 1st of January 2010 to 30th of September 2011. For the purpose of this study, four hospitals were selected. The study was carried out at their TB Clinics.

Chapter 4 documents the comprehensive statistical analysis and results of factors associated with unsuccessful tuberculosis treatment outcomes and predictors of survival in TB/HIV co-infected patients. Data collected from the four participating sites were analysed. This chapter provides basic data on patients' characteristics. Both univariate and multivariate statistical techniques using logistic regression and Cox proportional hazard are used.

Chapter 5 discusses on the findings of this research in comparison with other studies from developed and developing countries. Relevant discussions regarding the implications of the findings are highlighted.

Chapter 6 is the concluding chapter and rounds up the thesis. Finally, recommendations for policy-makers and programme managers involved in the implementation and scale-up of TB/HIV collaborative activities are discussed, together with suggestions for further research.

The overview of the thesis is presented graphically in **Figure 1.7.**

1.7 Summary

In this chapter, the prevalence of TB, HIV and TB/HIV co-infection is reviewed. The structure of the thesis is explained and contributions to this field are detailed. This thesis represents the first known attempt by a Malaysian researcher in determining the TB/HIV prognosis in Malaysia.

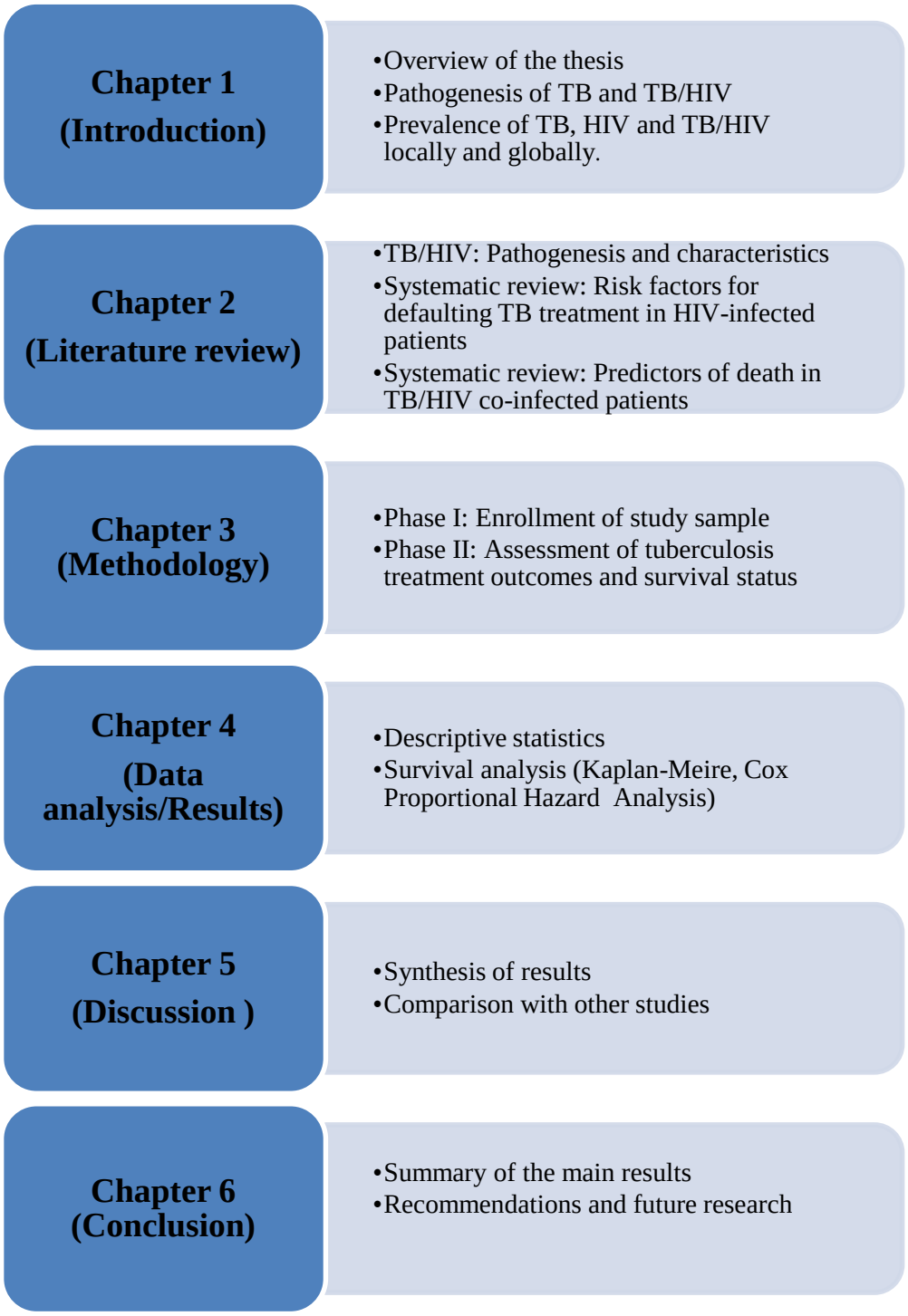


Figure 1.7: Structure of the thesis

CHAPTER 2: LITERATURE REVIEW

About this chapter

This chapter provides a detailed review of studies of tuberculosis with HIV co-infection. All inclusive searches for references were conducted over a span of 2.5 years. Few methods were utilized including querying databases, cross-referencing of bibliographies, journal supplements and review material, index searches of scientific proceedings, backtracking references from articles, consultations with experts in this area and contacting authors.

This chapter starts with describing the background of the disease. Sections 2.1 to 2.3 give an overview of TB, HIV and the pathogenesis of Tuberculosis and Human Immunodeficiency Virus (TB/HIV) co-infection. Section 2.4 to Section 2.7 describes the diagnosis of TB in HIV co-infected patients, TB treatment and management of HIV-infected patients, TB prevention and TB/HIV policies. Section 2.8 covers the characteristics of TB/HIV co-infected patients, including the socio-demographic factors, lifestyle factors, TB-related characteristics, HIV-related characteristics and laboratory profiles. Section 2.9 is a systematic review of tuberculosis treatment outcomes in HIV-infected patients from published literature. The risk factors for TB treatment default from previous studies were discussed in Section 2.10. Section 2.11 describes the survival time of TB/HIV co-infected patients and finally Section 2.12 is a discussion on the predictors of TB/HIV survival reported from the literatures. Section 2.13 is the summary of the whole chapter.

2.1 Tuberculosis

Tuberculosis bacilli was discovered by Robert Koch in 1895 and his finding on the etiology of tuberculosis was presented in a famous paper of the Physiological Society of Berlin. His description on the method of staining specimen slides, the method of culturing and inoculating of the bacilli into animals was a major advance in understanding TB bacteriology. The discovery boosted further development in finding a cure for TB (Sakula, 1982).

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) which is transmitted via the airborne route. While TB is completely curable, it has persisted for over two centuries since its discovery in 1882. The most common site for TB infection is the lungs (pulmonary TB) but it can also affect other parts of the human body due to lymphohaematogenous dissemination during primary tuberculosis infection (extra-pulmonary TB). It is spread via air contaminated with nuclei droplets when a person with active TB expel bacteria for example by speaking, coughing, laughing, sneezing or singing. If a healthy person inhales air containing the bacilli, it will be lodged in the pulmonary bronchiole or alveolar. The bacilli multiply and produce the primary lesions there. Some of the bacilli spread to the hilar lymph node and caused enlargement of hilar lymph node. The bacilli from the alveolar lesion and from the enlarged hilar lymph nodes will be more disseminated through the lymphatic system or the bloodstream, causing extrapulmonary TB such as meningitis, or joint and bone tuberculosis. The host will respond via cell-mediated immunity involving macrophage and T-lymphocytes cells. The lymphocytes will identify TB antigens and will release cytokines such as interferon gamma which in turn will activate the macrophage at the site of the lesion (Dunlap, Bass, & Fujiwara, 2000).

However, not everyone who is exposed to TB bacilli will develop TB disease. A person who has a good immune system will be able to fight the infection. In general, only 10%

of healthy people who are infected with MTB have a probability of developing active TB disease in their lifetime, which has devastating consequences if left untreated. For some patients, they are able to control the infection, but unable to completely remove it from their bodies. These cases are known as Latent TB Infection (LTBI), whereby the infection remains in an inactive or "latent" state. Normally, they do not realize that they have LTBI because people with LTBI do not show any signs or symptoms of infection. However, this latent infection can convert to active disease and spread it to other individuals. The probability of developing TB is much higher when the immune system of a person becomes weak; for example in people who are infected with the human immunodeficiency virus (HIV) or as a result of a tissue or organ transplant or other medical treatment designed to suppress the immune system (Hauck, Neese, Panchal, & El-Amin, 2009).

2.2 Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a lentivirus which contains double strands of ribonucleic acid (RNA) as its genetic material. It is associated with immune suppression diseases where patients observe symptoms of diseases much later, after infection due to long viral incubation. HIV causes Acquired Immune Deficiency Syndrome (AIDS) (Barré-Sinoussi et al., 1983).

HIV is a sexually transmitted infection, but can also be spread through blood and blood products. Generally HIV appears in high concentration in the blood, genital secretions and breast milk. These are significant HIV transmission routes to other individuals. The low concentration of HIV in urine, sweat, saliva and tears has lower chances of spreading HIV to other individuals (Lifson, 1988). Unprotected sexual intercourse is the main transmission source of HIV. Sexual transmission occurs when HIV secretion of infected individual gets in contact with genital mucous, rectal mucous or oral contact with another individual (Boily et al.,2009).

Primarily, HIV was a sexually transmitted disease that affected a certain risk group in the population. It is different from the other infectious diseases where the whole population is at risk. The spread of HIV can develop from a man who has sex with woman, man who has sex with man (MSM) and a woman who has sex with man. HIV infections can be transmitted through sexual relationships with multiple sexual partners, with men with sexually transmitted diseases (STD's), with men who are not circumcised and without protection.

HIV transmission can also occur when the blood of HIV infected individual gets contact with another person's wound. Different modes of infection transmission are by intravenous drug users, blood transfusion, hemophiliacs and blood product recipients. Although the chances of accident occurrence are rare, health care workers such as nurses, laboratory workers and doctors are also exposed to the risk of being infected with HIV. Healthcare workers should take necessary precautions have to be taken to protect themselves from getting contact with HIV infected individual's blood (Lifson, 1988).

The virus affects the lymphocytes, which mediate immune responses and therefore an infected person progressively loses the capacity to protect the body from pathogens. AIDS occurs when the infection progresses to a stage where physical symptoms manifest. HIV infection damages the lymphocytes and alveolar macrophages responsible for mediating immunity against TB by progressively depleting them or making them dysfunctional (Iseman, 2000).

2.3 Pathogenesis of Tuberculosis and Human Immunodeficiency Virus (TB/HIV) co-infection.

Human immunodeficiency virus (HIV) and tuberculosis (TB) have a complex relationship which fuels both epidemics resulting in the worsening of the morbidity and

mortality from both diseases. Tuberculosis (TB) is one of the leading causes of death among people infected with HIV worldwide. Among people living with HIV, TB is the most frequent life threatening opportunistic disease, even in those receiving anti-retroviral therapy. There are three mechanisms relevant to the development of TB in the people with HIV infection: reactivation of latent TB, progression of recent infection and re-infection.

Patients with HIV infection have a higher risk of developing TB compared to the general population. TB may accelerate the natural progression of HIV infection by activating HIV replication and expediting the depletion of CD4 T-lymphocytes count. The occurrence of TB including multi-drug resistant disease, may accelerate the progress of HIV infected patients to active TB after a recent infection with *Mycobacterium tuberculosis*. TB infection among HIV patients is strongly associated with immune status in which it rises sharply if the patient had worsening immune status. The risk of progression of *Mycobacterium tuberculosis* infection to TB disease increases if the patient is suffering from immune suppression. In addition, the rate of progression of recent or latent MTB infection to TB disease is also increased. In patients with advanced HIV disease, they can also have an exogenous reinfection with other strains of *Mycobacterium tuberculosis* (WHO, 2004).

Pulmonary TB is still the major type of presenting disease in TB/HIV co-infection. However, the frequency of extrapulmonary TB increases with the worsening immune compromise because there is increased susceptibility of reactivation and dissemination of TB in these patients. In a study in the United States, the researchers found that the most common site of extrapulmonary TB was lymphatic (28%), disseminated (23%) and central nervous system/meningeal (22%) disease. HIV-infected patients with CD4 count less than 100 cells/uL were more likely to have a severe form of extrapulmonary TB (AOR: 1.6, 95% CI: 1.0-2.4) (Leeds et al., 2012).

2.4 Diagnosis of TB in HIV Co-infected Patients

The approach to diagnose TB is the same regardless of underlying HIV status. TB disease can be diagnosed by medical history, physical examination, chest x-ray and laboratory investigation. Diagnosis is confirmed by isolating *Mycobacterium tuberculosis* from clinical samples. In extrapulmonary TB or in situations where clinical samples are difficult to obtain, certain procedures should be carried out in order to establish the diagnosis of TB.

2.4.1 Clinical presentations

WHO recommends that all adults and adolescents living with HIV should be screened for TB at the time when HIV infection is diagnosed, before the initiation of antiretroviral therapy and at regular intervals during follow-up (WHO, 2008a). Based on the guidelines of the WHO International Expert Committee in 2007, screening for TB should be done by the combination of symptoms rather than only chronic cough. A meta-analysis of 12 studies involving 8,148 participants, which evaluated the combinations of symptoms as screening rules for TB found that the best performing rule was the presence of any one of the symptoms as current cough, fever, night sweats or weight loss. This screening rule has an overall sensitivity of 79 percent, which increases to 90 percent among participants selected from clinical settings (Getahun, H. et al., 2011).

In the WHO Clinical Staging of HIV Infection, HIV-infected patients who are diagnosed with active TB are categorised as WHO clinical stage 3 (if pulmonary TB) or stage 4 (if extrapulmonary TB) (WHO, 2007). WHO Clinical Staging of HIV Infection was developed by the WHO in the 1990 and has been revised in 2007. It is based on clinical findings that guide the HIV/AIDS patients to make a diagnosis, to manage, to evaluate HIV patients and do not require a CD4 count. This staging has been used by

many countries to determine those patients who are eligible for antiretroviral therapy, particularly in settings in which CD4 testing is not available. There are four categories of clinical stages; stage 1, 2, 3 and 4, progressing from HIV infection till AIDS infection. These stages are defined by symptoms or specific clinical conditions. According to the WHO staging system, adolescents and adults are defined as individuals aged 15 years (WHO, 2007). WHO clinical staging detail is found in Appendix D.

2.4.2 Laboratory investigation

In patients with symptoms and signs suggestive of TB, sputum smear microscopy and sputum culture for mycobacteria should be done to rule in or to rule out TB. Sputum smear microscopy is the most widely used test to diagnose TB in which sputum samples are examined under a microscope to look for bacteria. The diagnosis of TB is based on the detection of acid fast bacilli (AFB) on smears and cultures from clinical specimens. Specimens that are smear-positive should be considered to be due to *M. Tuberculosis* until proved otherwise. WHO recommended that all patients suspected of having pulmonary TB should submit at least two sputum specimens for microscopic examination in a quality-assured laboratory. At least one early morning specimen should be obtained when possible, as sputum collected at this time has the highest yield.

The diagnosis of pulmonary TB in PLWHIV is more difficult because they tend to have non-specific symptoms and sputum smear microscopy is often negative, particularly in advanced HIV infection. Hence, TB culture should be obtained in all TB suspects to enable early diagnosis of TB in sputum smear negative cases.

If an initial sputum smear microscopy is negative in a person with HIV infection, a CXR should be examined, sputum smear microscopy repeated and sputum sent for bacterial culture and AFB culture. Results of sputum culture for AFB would be available in four to six weeks or earlier. Therefore, clinical judgement is made in the

interim as to whether the patient has TB and managed as appropriate. The culture results confirm or refute the clinical diagnosis.

The diagnosis of extrapulmonary TB is challenging as they have a lower bacterial load compared to PTB and sample collection is problematic. A relatively low proportion of cases have positive microscopy and culture for *Mycobacterium tuberculosis*, even with rapid culture methods. In clinically suspected cases of extrapulmonary TB, any relevant procedures such as lumbar puncture, thoracocentesis, fine needle aspiration and biopsy, pleuroscopy, colonoscopy and cystoscopy are required in order to support or confirm the diagnosis and to get the drug susceptibility profile of the organism. Presence of caseating granulomas, or granulomas with Langerhan's giant cells on histology or cytology of the specimen is highly suggestive of TB but they are not specific.

2.4.3 Chest X-ray

In a patient who has clinical features suggestive of TB, but negative on sputum smear microscopy, the patient should be reassessed clinically and send for chest x-ray. If the chest x-ray shows a typical presentation of TB, TB treatment should be started as soon as possible.

The clinical presentation of TB in an HIV-infected person may differ from that in persons with relatively normal cellular immunity who develop reactivation TB. The classic finding in immunologically normal persons which is the cavitation at the apex of the lung, is less common. Chest x-ray changes in TB/HIV patients reflect the degree of immune-suppression. Patients may present with infiltrates in any lung zone, often associated with mediastinal and/or hilar lymphadenopathy. In the early phase of HIV disease, TB/HIV patients usually present with typical chest radiographic findings, such as cavitation and upper lobe infiltrates; because the immune system is still relatively intact (CD4 > 500 cells/uL). In patients with advanced HIV disease that are severely immune-suppressed, the appearance is often atypical with intrathoracic adenopathy and

lower lobe involvement. However, HIV infected patients with pulmonary TB may have a normal chest radiograph.

In HIV-infected patients, it might be difficult to distinguish pulmonary TB from other HIV-related pulmonary infection such as pneumocystic carinii which is the most common pulmonary pathogen in AIDS patients. The poor specificity of the chest X-ray in TB/HIV cases emphasized the need of sputum analysis for acid-fast bacilli as an essential diagnostic tool for TB. The other indications of chest x-ray include suspected complications of PTB; for example pleural effusion, pneumothorax, pericardial effusion and severe or on-going haemoptysis.

2.4.4 The tuberculin skin test (TST)

Tuberculin skin test (TST) or Mantoux test is the standard method of screening to identify individuals who may have been infected by the tuberculosis bacteria. TST is a useful method of diagnosing TB infection, however, it is not as helpful in the diagnosis of active TB disease. Tuberculin is a mixture of antigens obtained from the culture of *M. Tuberculosis*. Antigens are foreign particles or proteins that stimulate the immune system to produce antibodies. The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm (intradermally); about halfway between the wrist and the elbow where a small bubble will form as the tuberculin is injected. The injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter. The injection site should be examined between 48 and 72 hours after administration by a trained person for evidence of swelling. People who have been exposed to tuberculosis will develop an immune reaction, causing a slight swelling at the injection site. In any person, including persons with no known risk factors for TB a reaction of 15 or more millimetres induration is considered positive. However, this method has many limitations. It is highly dependent on the operator for

correct administration and interpretation of the test. TST is also associated with false-positive results stemming from cross-reactivity with non-tuberculous mycobacteria.

2.4.5 New diagnostic tests for TB

Over the past few years, development of T-cell based interferon-gamma release assays (IGRAs) becomes an alternative to TST in diagnosing latent TB infection. In HIV-infected individuals, a positive TST is defined as an induration of at least 5 mm in response to intradermal placement of PPD. IGRAs are more recently developed assays that use highly *M. Tuberculosis*-specific antigens which are not present in most non-tuberculous mycobacteria or in the bacillus Calmette-Guérin vaccine. It detects in vitro interferon-gamma release by peripheral blood monocytes in response to MTb-specific peptides (Mazurek et al., 2010).

One important new advance in the diagnosis of TB is the use of molecular techniques to speed up the diagnostic process as well as to improve its accuracy. Molecular techniques are increasingly used in laboratories around the world. They include polymerase chain reaction to detect mycobacterial DNA in patient's specimens; nucleic acid probes to identify mycobacteria in culture; restriction fragment length polymorphism analysis to compare different strains of TB for epidemiological studies and genetic-based susceptibility testing to identify drug resistant strains of mycobacteria (Senol, 2013).

2.5 TB treatment and management of HIV-infected patients

HIV-infected patients with active pulmonary TB or extrapulmonary TB require prompt initiation of TB treatment. Treatment should be initiated as soon as TB is suspected because delays in the diagnosis of TB will be associated with poor outcomes.

2.5.1 Standard TB treatment

TB treatment is classified as first-line or second line drug treatments. First-line drugs are the drugs of choice administered to patients after their diagnosis of TB. These drugs are generally more effective, less toxic, cheaper and easier to administer than the second line agents. The most common first-line drugs are isoniazid (INH), rifampicin, streptomycin, ethambutol, and pyrazinamide. The primary purpose of TB treatment is to eliminate the infection in the body, prevent resistant strains and control transmission of the disease. If TB remains untreated, 50% of the cases with active TB disease would die within two years.

TB treatment offered to HIV-infected adults are essentially the same as for HIV-uninfected patients. TB treatment requires a minimum of six month regimen consisting daily treatment of isoniazid, rifampicin, pyrazinamide and ethambuthol for two months of intensive phase; followed by four month daily treatments of isoniazid and rifampicin in the maintenance phase. If the cultures are still positive after two months of therapy, the continuation phase should be prolonged to seven months with a total of nine months treatment. For patients with extrapulmonary TB, a six to nine month regimen consisting of two months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by four to seven months of isoniazid and rifampicin is recommended. For CNS disease (tuberculoma or meningitis) and bone or joint TB, nine to twelve months of anti-TB treatment is recommended.

The WHO had promoted Directly Observed Treatment short course (DOTS) as a treatment strategy for the global control of TB mainly to ensure adherence and minimize the development of resistant strains. It requires drugs intake to be directly observed by a healthcare worker or a community health worker for at least the first two months of therapy.

2.5.2 Drug Resistant TB

The main challenge in treating HIV-associated TB patients is the rising cost of drugs and the risk of developing drug resistance. The most common cause of drug resistance is treatment interruption which results from the decision taken by a person to stop the drugs once he/she feels better before completion of the six-months drug course. Drug-resistant strains of TB can also be transmitted to others.

The cost of treatment increases dramatically as the second or third line therapies are much more expensive and requires a longer treatment period. Drug resistant TB is a form of TB in which the bacteria have become resistant to the first-line TB medicines. Resistance to TB drugs occurs when these drugs are misused or mismanaged.

Multi-drug resistant (MDR-TB) and extensively drug resistant (XDR-TB) are much more complicated to treat and contribute to increase mortality. Multidrug-resistant (MDR) TB is the TB bacteria which are resistant to the two most common TB medications, isoniazid and rifampin. The most dangerous form is Extensively Drug-Resistant (XDR) TB where the bacteria is resistant to many common TB medicines such as, isoniazid, rifampin, fluoroquinolone, and at least one of three injectable medicines (capreomycin, kanamycin and amikacin).

All patients should also be assessed regarding risk factors for drug-resistant TB including previous TB treatment (especially if it was incomplete), close contact with a person who has multidrug-resistant TB, history of living in a country where drug-resistant TB is common, and previous residence in an institution such as prison, drug rehabilitation centers or homeless shelter which has documented transmission of a drug-resistant strain of TB. HIV seropositive patients should be asked about antiretroviral therapy use. Their CD4 lymphocyte count and viral load should be measured to assist the treatment of the underlying HIV infection. In patients with active TB, the viral load will be increased; but it will decrease with appropriate therapy.

2.5.3 Co-trimoxazole (CTX) Prophylaxis in TB/HIV co-infection

Co-trimoxazole (CTX) also known as Sulfamethoxazole-Trimethoprim (SMX-TMP) is a broad spectrum antimicrobial agent that targets a variety of aerobic Gram-positive and Gram-negative organisms and protozoa. Co-trimoxazole prophylaxis should be given to patients with TB/HIV co-infection to prevent opportunistic infections. Provision of CTX as primary or secondary prophylaxis for prevention of Pneumocystis jiroveci pneumonia (PCP) (formerly Pneumocystis carinni pneumonia) and toxoplasmosis has been the part of standard care in the management of HIV-infected individuals in developed countries since the early 1990s. CTX is safe, well tolerated, widely available and inexpensive.

Nunn et al. (2008) conducted a randomized controlled trial in Zambia that showed CTX prophylaxis in TB/HIV co-infected adults was associated with a 21% reduction in all-cause mortality (AHR: 0.79; 95% CI 0.63 to 0.99) (Nunn et al., 2008). A meta analysis conducted by Suthar A B et al., that examined the effect of cotrimoxazole on mortality and morbidity in individuals aged 13 years or more, confirmed that CTX significantly increased survival in HIV-infected adults on ART (Suthar, Granich, Mermin, & Van Rie, 2012).

2.5.4 Issues in the management of TB and HIV co-infection

Co-infection with HIV may complicate the diagnosis and worsen the course of TB. There are a few issues that need to be addressed in the management of these two diseases (TB and HIV) in a co-infected patient. Issues that are related to the management of TB/HIV co-infected patients include: drug-drug interactions; immune reconstitution inflammatory syndrome (IRIS); overlapping drug toxicities; pill burden and drug adherence and coordinating care between TB and AIDS control programmes.

i) Drug-drug interactions

The timing of initiation of antiretroviral therapy in patients with TB/HIV co-infection is challenging as potential drug interactions can occur between HAART and anti-TB. Rifampicin, an important drug for TB treatment reduces the blood level of antiretroviral drug groups, non-nucleoside reverse transcriptase (NNRTI) and protease inhibitors (PI) by stimulating the activity of the cytochrome P450 liver enzyme system, which metabolizes the PIs and NNRTIs. On the other hand PIs and NNRTIs can also alter blood levels of rifampicin by enhancing or inhibiting this same enzyme system. These potential drug-drug interactions may result in ineffective treatment of TB, ineffective of ART drugs or an increased risk of drug toxicity.

ii) Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution syndrome (IRIS) is an adverse consequence of the restoration of pathogen-specific immune responses during the initial months of HAART and anti-TB. IRIS usually occurs within three months of TB treatment, typically between two to twelve weeks after the initiation of HAART. The major manifestation are fever (40%) followed by lymphadenitis (38%).

A prospective observational cohort study conducted in Mozambique (Letang et al., 2011) found that predictors of IRIS were pre-ART CD4 count < 50 cells/ml (AHR 2.3, 95% CI 1.19–4.44) and body mass index (BMI) < 18.5 (AHR 2.15, 95% CI 1.07–4.3). Another study found that hemoglobin < 100 g/l (OR=2.2, 95% CI 1.1-4.6) and baseline CD4 count < 50 cells/ml (OR=4.1; 95% CI 1.8-9.5) are predictors of IRIS. A 4-week course of prednisolone (1.5mg/kg/day) for two weeks, followed by 0.75 mg/kg/day for two weeks is recommended to improve symptoms. IRIS may cause clinical deterioration, but does not primarily contribute to mortality. HAART and anti-TB should not be stopped while managing IRIS.

iii) Overlapping toxicities of antiretroviral therapy and TB drugs

Anti-TB and ART drugs have similar side effect profiles therefore overlapping drug toxicities such as skin rash, hepatotoxicity and peripheral neuropathy can be difficult to differentiate. Furthermore, there is a potential of added toxicity when given together. When the side effects occur during concomitant treatment of TB and HIV, it makes difficult to differentiate the causative drug. The overlapping or additive toxicities due to antiretroviral drugs and first line anti-TB drugs are summarised in the Table 2.1.

Table 2.1: Overlapping or additive toxicities due to antiretroviral drugs and first line anti-TB drugs

Toxicity	ART Drugs	AntiTB Drugs
Peripheral neuropathy	Stavudine and didanosine	Isoniazid and etambutol
Gastrointestinal intolerance	All	All
Hepatotoxicity	Nevirapine, efavirenz, all NRTIs and Pis	Isoniazid, rifampicin, rifabutin and pyrazinamide
Central nervous system toxicity	Efavirenz	Isoniazid
Bone marrow suppression	Zidovudine	Rifabutin, rifampicin
Skin rash	Abacavir, nevirapine and efavirenz	Isoniazid, rifampicin and pyrazinamide
Ocular effects	Didanosine	Ethambutol and rifabutin

Source: (Kwara, Flanigan, & Carter, 2005)

iv) Pill burden and drug adherence

Concomitant treatment of both TB and HIV entails the use of multiple drugs especially during the intensive phase of TB therapy. On the top of that, usually patients are also on micronutrient supplements and prophylaxis for opportunistic infections. These put patients on a higher strain to adhere to their medications. To reduce pill burden, it is recommended to use a fixed - dose combination of anti-TB drugs if possible. Necessary

support and encouragement to adhere to treatment should be given to all TB/HIV co-infected patients.

v) Coordinating care between TB and AIDS control programmes

Co-infection with TB and HIV not only affects the individual patient, but it may also have an impact on TB control in a population. Better coordination and communication between the TB and AIDS control programs is required in the management of the patient co-infected with TB and HIV. Screening of all HIV-infected persons for TB and vice-versa should be in place to ensure the best care of TB/HIV co-infected patients.

2.6 TB Prevention

2.6.1 Prevention of TB in people living with HIV

To reduce the occurrence of HIV-associated TB, preventive therapy with isoniazid is recommended for asymptomatic patients infected with *M. Tuberculosis.* Although isoniazid is commonly used for treating TB, it is also effective as preventive therapy. IPT has been recommended since 1998 by WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) as part of a comprehensive HIV and AIDS care strategy. Isoniazid treatment is generally safe, well tolerated and cost effective.

A systematic review reported that isoniazid reduces the risk of clinical TB in HIV-infected people by 32% (Akolo & Adetifa, 2010). Concerning drug resistant TB, a recent systematic review reported that IPT has not been convincingly associated with the emergence of isoniazid resistance (Balcells, Thomas, Godfrey-Faussett, & Grant, 2006).

There is a strong scientific evidence base to show that ART, by lowering a person's viral load and restoring the immune system, significantly reduces the impact of HIV and TB. A retrospective study in Brazil demonstrated that risk of TB in HIV-infected

patients was reduced by 52% with antiretroviral therapy alone, 68% with IPT alone, and 80% with both (Golub et al, 2007).

2.7 TB/HIV Policies

2.7.1 Global TB control

TB control aims to block transmission of the disease, to reduce morbidity and mortality and to prevent the development of drug resistance TB. The essential strategies to control TB include preventing the infection, stopping the progression from latent to active TB; and treating the active disease. Prior to the development of anti-TB drugs, TB control focused mainly on prevention (Daniel, 2006). The discovery of anti-TB drugs in the 1940s provided a significant change to TB control strategy and from the 1950s, truly effective public health measures became possible with treatment to cure being the goal of TB control globally. Following the development of improved anti-TB drugs in the 1970s, TB treatment was initially consisted of a standard 18 months regimen was reduced to 6 months with a combination of anti-TB drugs. TB control became effective in most developed and industrialised countries as a result of improved living conditions and the availability of anti-TB drugs. Subsequently, TB was neglected from the world public health agenda and effective control became the responsibility of each country (Daniel, 2006).

The emergence of HIV/AIDS pandemic in the 1980s led to the return of TB cases globally. The WHO declared TB as a global emergency in 1993 and later developed the directly observed therapy, short-course (DOTS) strategy in 1994 (WHO, 2002). This strategy was aimed to guide nations towards effective TB control after acknowledging that TB had been a neglected and a poorly managed disease that was associated with HIV. The DOTS strategy remains the core intervention for TB control recommended by WHO globally. The strategy was subsequently adopted by most of the WHO member

states with major expansion in India and China, but its scale-up was constrained by weak political commitment (Atun, Weil, Eang, & Mwakyusa, 2010).

In November 1998, the Stop TB Initiative was launched at the World TB Conference in Bangkok, Thailand after realising that TB was a public health concern with political, social and economic dimensions. This initiative is a coalition of stakeholders in the global fights against TB. It comprised of all of the key partners and countries with heavy TB burdens that called for the development of a global action plan for TB control and addressing HIV-associated TB as well as drug-resistant TB. To accelerate social and political action to stop the spread of TB around the world, The Stop TB Partnership was eventually established in 2000. The partnership's goal is to eliminate TB as a public health problem and ultimately secure the world free of TB. Later in 2001, the "Stop TB Partnership" launched the Global Plan to Stop TB 2001–2005 (WHO, 2005). Building on the success of the first plan,the "Stop TB Partnership" launched the second plan for 2006–2015. Its targets are in line with the Millennium Development Goals (MDGs) which aim to reduce TB prevalence and deaths to 50% by 2015 as compared to the 1990 levels (WHO Stop TB Partnership, 2006). In addition to expanding and enhancing DOTS coverage, the second plan also covers the DOTS-Plus approach which addresses MDR-TB and provides strategies and policies for the countries to implement and monitor TB/HIV collaborative activities through the TB/HIV Working Group (WHO Stop TB Partnership, 2006).

In The Global Plan to Stop TB of 2006-2015, new strategies and approaches were introduced to address the complexities of the TB problem. The challenge of TB-HIV was addressed with TB/HIV collaboration which is a joint activity between TB and HIV/AIDS control programs in reducing the burden of TB in people living with HIV/AIDS and vice-versa (WHO, 2006).

2.7.2 Global HIV control

HIV was first reported in the United States in 1981, and the virus was later isolated in 1983 (Barré-Sinoussi et al., 1983). By 1985, more than 17, 000 cases of AIDS from 71 countries had been reported to WHO (Merson, O'Malley, Serwadda, & Apisuk, 2008). During the early stages of the pandemic, emphasis was rather placed on warning the public about the "danger" of the infection due to the initial lack of knowledge about the modes of transmission and difficulty in diagnosis (Mann, 1998). When the modes of spread and diagnosis were identified, specific risk-reduction programs were designed to change individual behavior. The focus was mainly on information, education and communication (IEC) about HIV/AIDS and providing counselling and testing; and distribution of condoms (Mann, 1998). Later on in the epidemic, it was recognized that socioeconomic, political and cultural factors, including gender inequality, poverty and marginalisation of specific groups of the population were associated with HIV/AIDS (Mann, 1998; Merson et al., 2008). Despite this increasing knowledge about the infection, there was a lack of response from nations to address the infection. Nonetheless, its rapid spread and the global threat it posed prompted the WHO to launch the Global Programme on AIDS (GPA) in 1987 which was tasked with supporting and strengthening national AIDS programmes, and providing global leadership (M.Mann & Kay, 1991). During that same year, the World Health Assembly declared HIV a "worldwide emergency" that required urgent and globally directed action. The human rights framework was later championed by the GPA to analyse and address individual and societal factors, including discrimination and other human rights violations directed towards PLWHA, and also to protect at risk and vulnerable populations to HIV (Mann, 1998). The Joint United Nations Program on HIV/AIDS (UNAIDS) was then established in 1996 to replace GPA. This new body was given the mandate to lead an expanded and coordinated multi-sectoral global response. In 1996,

ART became available as the standard of care (UNAIDS, 2012), though its access was initially limited mainly to developed nations.

The increasing global threat of HIV/AIDS generated more coordinated and enhanced approaches within the global community. In Africa, the situation was referred to as a "state of emergency" and led to the Abuja Declaration in 2001 (Organisation of African Unity, 2001), where African Union member states committed themselves to allocate at least 15% of the health sector budget to tackle HIV/AIDS, TB and other related infectious diseases. In the same year, the UN set up a General Assembly Special Session on HIV/AIDS (UNGASS) where political leaders adopted a declaration of commitment, setting up targets for affected countries and funding levels for donor governments. The Global Fund to fight AIDS, TB and Malaria (Global Fund) was subsequently established in 2002 as a public/private partnership which sources funds and provides money to support countries in preventing and treating HIV/AIDS, TB and Malaria. The United States government also announced the President's Emergency Plan for AIDS Relief (PEPFAR) in 2003 which since then has provided funds for prevention, community outreach and prevention of mother-to-child transmission (PMTCT) of HIV activities and increased access to ART in 15 countries (Merson et al., 2008). The fight against HIV/AIDS has continued to receive global support, since it is regarded as part of the commitments to achieve global health goals as highlighted in the MDGs.

Since WHO launched the "3 by 5" initiative in 2003 to scale-up ART to PLWHA, the number of PLWHA on ART has increased steadily (WHO, 2003a). The "3 by 5" initiative was a global target to provide three million people living with HIV/AIDS in developing countries with life-prolonging antiretroviral treatment (ART) by the end of 2005. This increased coverage prompted the commitment to scale-up universal access to HIV prevention, treatment,care and support services by 2010 (WHO, 2010a). At the end of 2009, an estimated 5.2 million people were on ART in low and middle-income

countries which represented a 30% increase as compared to the previous year. In sub-Saharan Africa, almost 37% of all eligible patients were on treatment in the region. However, there were regional variations with some countries like Botswana, Namibia and Rwanda achieves 80% coverage (UNAIDS, 2012). The incidence of new HIV infections has declined globally, with much of this decline partly attributed to behavioural change including increased condom use, delayed sexual debut and reduction in multiple partnerships (UNAIDS, 2012). Since it is estimated that only 22% of all AIDS spending in 106 low and middle-income countries is on prevention, much effort is still needed in scaling-up HIV prevention strategies.

2.7.3 Development of policies on TB/HIV

During the early stages of the HIV epidemic in 1980s, researchers had demonstrated the association between TB and HIV/AIDS and the devastating impact of the co-epidemic. However, despites the alarming increase in the incidence of TB cases, especially in high HIV-prevalent countries particularly in sub-Saharan Africa, the coordinated responses between TB and HIV programmes globally to curb the associated morbidity and mortality were slow and minimal (Getahun, Gunneberg, Granich, & Nunn, 2010). The first international meeting to discuss modalities for controlling both epidemics was organized by the WHO in 1989. It was concluded that countries with poor TB-control programmes; which include mostly countries with increasing HIV prevalence should prioritise improve TB treatment and cure through DOTS.

In response to this, in 1997 ProTEST Initiative (promotion of voluntary testing) was launched by the WHO at sub-district level in three sub-Saharan Africa countries (Malawi, South Africa and Zambia) as the first step towards exploring TB and HIV collaborative service delivery (Lienhardt et al., 2012). The objective of the project was to promote testing for HIV using voluntary counselling and testing (VCT) as an entry

point to access a range of interventions aimed at decreasing the burden of HIV-related TB. The projects demonstrated that TB and HIV programmes could collaborate effectively in service delivery from sub-district to national levels. The lessons learned from this project prompted calls from participants at the "Global DOTS Expansion Meeting" in Cairo, Egypt in 2000 for the creation of the Global TB/HIV Working Group (WHO, 2001). The Working Group, coordinated by WHO was eventually established in 2001 under the auspices of the Global Stop TB Partnership with the goal to reduce the burden of TB in high HIV-prevalent populations. Guidelines for implementing collaborative TB and HIV programme activities was developed in 2003 (WHO, 2003b). The recommended activities to be carried out under the TB and HIV programs at worldwide, national and local levels have operated separately with separate management and funding streams and with little coordination for many years. The implication of this policy is that patients with HIV and TB have to access different services for screening, testing, care, treatment and adherence support. The Interim Policy on Collaborative TB/HIV Activities was published by the WHO which was intended to assist policy-makers to understand what should be done to decrease the joint burden of tuberculosis and HIV in populations affected by both diseases (WHO Stop TB Partnership, 2004). The term collaboration and integration have been used interchangeably in relation to implement joint TB and HIV control activities. However, collaboration implies that TB and HIV programmes work together on a set of activities in order to achieve certain goals or objectives. For countries in which the HIV prevalence is more than 5%, WHO had recommended collaborative TB/HIV activities as showed in Table 2.2 below:

Table 2.2. Recommended collaborative TB/HIV activities*

A. Establish the mechanism for collaboration between tuberculosis and HIV/AIDS programmes

1. Set coordinating bodies for TB/HIV effectives activities at all levels
2. Conduct surveillance of HIV prevalence among Tuberculosis patients
3. Carry out joint TB/HIV planning
4. Monitor and evaluate collaboration TB/HIV activities

B. Decrease the burden of tuberculosis in people living with HIV/AIDS

1. Establish intensified tuberculosis case-finding
2. Introduce isoniazid preventive therapy
3. Ensure tuberculosis infection control in health and congregate settings

C. Decrease the burden of HIV in tuberculosis patients

1. Provide HIV testing and counselling
2. Introduce HIV prevention methods
3. Introduce co-trimoxazole prevention therapy
4. Ensure HIV/AIDS care and support
5. Introduce antiretroviral

Source: (WHO Stop TB Partnership, 2004)

The Three I's for TB/HIV

In view of the alarming increasing rate of TB among people living with HIV, WHO strongly recommends the implementation of the Three I's in addition to initiating earlier antiretroviral therapy (ART) to be part of a TB prevention package which includes: 1. Intensified TB case finding; 2. Isoniazid preventive therapy and 3. Infection control for TB (WHO, 2008b). WHO emphasizes that they should be the core components of HIV services with AIDS programmes and service providers taking the primary responsibility for the 'Three I's for TB/HIV'. The World Health Organization (WHO) reported that 900,000 lives had already been saved over six years by protecting people living with HIV from TB. In 2010 some 2.3 million people living with HIV were screened for TB and 2.2 million TB patients were tested for HIV.

In Malaysia, TB and HIV programs collaboration was strengthened at the national level by placing all TB and HIV programs under the Disease Control Division, Ministry of Health. Such joint efforts included the formation of a National Committee for TB/HIV, implementation of a joint TB-HIV strategic plan and the development of the National AIDS Registry with a TB data management component. The provision of TB and HIV screening and treatment services are provided by primary health care services and hospitals with specialist expertise. TB-HIV patients were provided with universal access to ARTs at no cost by government health care facilities.

The current structure of Disease Control Division gives an advantage in the management of TB/HIV in which both sectors are located under the same umbrella namely the Communicable Disease Section which is led by a Deputy Director of Disease Control. Therefore the TB and HIV program's collaboration can be strengthened at the national level. Both sectors will be better coordinated and will have same directions.

2.8 Characteristics of TB/HIV Co-infected Patients

TB and HIV co-infection has been characterized as a 'dual epidemic' in view of their serious implications for public health. Results of previous studies have shown that many factors were associated with TB / HIV co-infection. To understand more about the disease, its characteristics are divided into socio-demographic factors, lifestyle factors, TB-related characteristics, HIV-related characteristics and laboratory profile. Published epidemiological studies in TB and HIV co-infection were reviewed to determine the characteristics of TB/HIV co-infection.The following search form terminology in full and implied Boolean keywords were entered into electronic databases such as PubMed Central, Science Direct, ProQuest, Medical Database@EBSCHOHost, Wiley InterScience: tuberculosis, HIV, characteristics, clinical manifestations.

2.8.1 Socio-demographic Factors

a) Age

Age is the most frequently studied variable in determining the characteristics of TB/HIV co-infected patients. Most of the studies found that TB/HIV co-infection was significantly more common among young to middle aged adults (Korzeniewska-Kosela et al., 1992; Mohammad & Naing, 2004; Van Der Werf, Sebhatu, Weldegergis, Tesfazion, & Borgdorff, 2007; Weis, Foresman, Cook, & Matty, 1999). However, one study found that TB patients with HIV infection were more likely to have age less than 35 years (Cain et al., 2007) and another study found that it is more frequent in advanced age (Carvalho, Monteiro, Pires Neto, Grangeiro, & Frota, 2008). The survey done in Delhi during September 1997 to August 1998 period found an increase in age distribution of HIV seroprevalence in TB patients with rising age (Jain, Aggarwal, Rajpal, & Baveja, 2000). The prevalence was 0.51% in 15-24 years group, 1.55% in 25-34 years group and 1.66% in the 35 years and more group.

b) Gender

In most of the studies, including those performed in both developed and developing countries, the highest prevalence of TB/HIV co-infection is among males (Alpert, Munsiff, Gourevitch, Greenberg, & Klein, 1997; de Castro Toledo, Greco, & Antunes, 2000; Kung et al., 2009; Mohammad & Naing, 2004; Weis et al., 1999). In Eritrea, the proportion of female and male TB patients infected with HIV was comparable (Van Der Werf et al., 2007).

c) Ethnic

The risk of TB/HIV co-infection may differ by ethnic group, however the mechanism is still uncertain. It may be due to differences in socioeconomic, cultural, physiological or behavioural factor. There is a variation in ethnic contribution to TB/HIV co-infection in the United States. A study done in the Fort Worth, Tex (Weis et al., 1999) showed that TB/HIV co-infection was significantly more common among Black ($p=0.018$) as compared to White, Hispanic or Asian. However, a study that was conducted in New York found that HIV-infected patients were more likely to be Hispanic (Alpert et al., 1997).

d) Educational level

Studies show that having a lower educational level is an indirect risk factor for the development of TB/HIV co-infection. The patients from this group may be illiterate and it could be a barrier in the health education. A study done in Delhi (Jain et al., 2000) examined the association of educational level and TB/HIV co-infection and they found that the risk of TB/HIV co-infection among illiterate and those educated only up to primary level were significantly more as compared to those with middle or higher education ($p=0.020$). This finding is supported by another study in Brazil (Carvalho et al., 2008) who found that HIV-infected patients with a lower educational level (less than

eight years of schooling) had almost two times higher risk of developing TB ($p<0.0001$, relative risk = 2.36) (Carvalho et al., 2008) compared to HIV-negative patients.

e) Employment status

Patients from low socioeconomic level are prone to get TB compared to the higher socioeconomic level(WHO, 2004). In Brazil, employment was found to be significantly associated with lower risk of death in TB patients (OR:0.32, 95%CI: 0.11-0.94) (Pelaquin, e Silva, & Riberio, 2007).

f) Marital status

Several studies had reported a higher proportion of single patients among TB/HIV co-infected patients (Carvalho et al., 2008; de Castro Toledo et al., 2000; Mohammad & Naing, 2004; Putong et al., 2002).

2.8.2 Lifestyle Factor

a) Smoking

Most of the studies do not include smoking as an independent risk factor for TB/HIV co-infection. A study done in Kathmandu, Nepal in 2008 found that HIV-infected patients who were smoking had an odd of seven times higher risk of developing TB as compared to non-smokers (Govinda Prasad, P, S, & BP, 2008). In resource-poor countries, there are now three interacting epidemics: smoking, TB and HIV. In addition to the interactions between smoking and TB and the known interaction between TB and HIV, smoking may also be associated with HIV infection. Thus, the interaction between smoking and TB–HIV co-infection deserves further study.

b) Alcohol consumption

The data from the United States U.S. National TB Surveillance System for the period1993-2005 reported that the groups of TB patients at greater risk for HIV infection included alcohol abusers (15%). A study done among armed forces who were admitted to a referral chest clinic in India for TB/HIV co-infection found that 80% (48/60) of TB/HIV co-infected patients give a history of alcohol consumption and alcohol is a contributory factor of visiting commercial sex workers. In a study in Thailand, alcohol use was reported in 70% from 769 patients (Mankatittham et al., 2009). However, patients in New York were less likely to have a history of alcohol use (Alpert et al., 1997).

c) HIV risk

An association between TB and HIV is particularly striking among groups with a high prevalence of both tuberculosis and HIV infections, e.g., intravenous-drug users (IDU). However, HIV-related TB is not restricted to IDUs only. It has also been reported in other mode of HIV transmission, including homosexuals, bisexual men, sexual contacts of bisexual men and in person with transfusion-associated AIDS.

In a study in Switzerland (Fenner et al., 2012), among HIV-infected TB patients the most likely sources of HIV infection were heterosexual transmission (57.3%), followed by injecting drug users (12.6%) and men having sex with men (9.7%). Where as in British, Columbia, Canada; homosexual men had the highest risk of TB/HIV co-infection which constitute 75% of all 40 cases (Korzeniewska-Kosela et al., 1992).

2.8.3 TB-related characteristics

a) Types of TB

Most of previous studies reported that HIV-infected patients were two to three times more likely to have extra-pulmonary disease (Alpert et al., 1997; Cain et al., 2007; Kung et al., 2009). However, a study in Kota Bharu, Malaysia reported that the highest number of patients (78.5%) had pulmonary TB while an additional four patients (2.7%) had both pulmonary and extra-pulmonary TB (Mohammad & Naing, 2004). Similarly, in a study that was conducted in 769 HIV-infected TB patients in Thailand, most of the patients were diagnosed with Pulmonary TB (60%) and another 40% had extrapulmonary TB. Among the patients with extrapulmonary TB, 75% had extra-pulmonary TB only and the rest (35%) had both extra-pulmonary and pulmonary TB (Mankatittham et al., 2009).

b) Chest x-ray at TB diagnosis

Generally, chest x-ray changes in TB/HIV co-infected patients show the degree of immune-compromise. In mild immune-compromise patients, the chest x-ray appearance is often classical with cavitation and upper lobe infiltrates whereas in severe immune-compromise, the appearance is often atypical (WHO, 2004). From an observational study in Rwanda (Batungwanayo et al., 2000), HIV-positive patients were found to be significantly less likely to develop cavitary lesion than HIV-negative TB patients ($p=0.002$). Mohammad & Naing (2004) identified that the majority of the cases (55.0%) were found to have either typical or atypical pulmonary lesions in their study in Kota Bharu (Mohammad & Naing, 2004).

c) Bacillus Calmette-Guerin (BCG)

BCG is the only vaccine available today for protection against tuberculosis. BCG was first used as a vaccine to protect humans against tuberculosis in 1921. Conventionally,

the site of BCG vaccination is the left shoulder of a person. After ten to twelve weeks of vaccination, a tiny scar is formed at the injection site. The scar serves as a guide if one wants to know whether a person has been BCG vaccinated or not. Several studies examined BCG scars in their research. In Kota Bharu, BCG scars were present in 89% of HIV-infected TB patients in the study (Mohammad & Naing, 2004). In a study done in Malawi , 73.1% were found to have a BCG scar from a total of 491 patients that were examined for BCG scars in 1999 and 2000. Where as Mankatitthamet al found that

514 (67%) TB/HIV co-infected patients had a BCG scar in Thailand (Mankatitthamet al., 2009).

d) Tuberculin skin test

In populations with a high prevalence of TB, tuberculin skin test (TST) does not give accurate results in the diagnosis of TB. A positive tuberculin skin test does not by itself distinguish M. tuberculosis infection from TB disease. A person who was exposed to environmental mycobacteria also may have a false positive test result. On the other hand, in certain circumstances, TST may produce negative results even when the patient has TB such as in HIV patients. Twenty-five cases (16.8%) of TB/HIV in Kota Bharu had a documented history that TST were done with a median of 6.0 mm, ranging from 0 to 25 mm (Mohammad & Naing, 2004).

e) Symptoms at TB diagnosis

Fever, cough and weight loss were the most consistent TB symptoms at presentation reported by HIV-infected patients (Batungwanayo et al., 2000; Korzeniewska-Kosela et al., 1992; Mankatitthamet al., 2009). Apart from that, Batungwanayo et al also found that diarrhoea, oral candidiasis, active or past history of candidiasis were significantly more common in HIV-positive than HIV negative patients in Rwanda (Batungwanayo et al., 2000).

f) Lymph node enlargement

Lymphadenopathy was common in both HIV positive and HIV-negative patients but significantly more often seen in HIV-positive cases ($p < 0.001$) (Nauclér et al., 1996). Similar finding was found in a study in Rwanda (Batungwanayo et al., 2000).

2.8.4 HIV-related characteristics

a) Antiretroviral Therapy (ART)

The fact that antiretroviral therapy improves the quality of life and greatly improves survival for people living with HIV/AIDS is well established. The availability of antiretroviral therapy can serve as an incentive for people to be tested for HIV and can prolong the life expectancy of HIV patients. In South Africa, a study on the impact of antiretroviral therapy among TB patients with HIV infection showed that it can reduce the incidence of tuberculosis in HIV-positive person by more than 80% (Badri, Wilson, & Wood, 2002). Antiretroviral therapy is more beneficial if initiated at an early stage of the disease and it requires a high rate of compliance. In the developed countries, transient worsening of tuberculosis symptoms and signs were seen in up to 30% of the patients after the initiation of antiretroviral in HIV-infected tuberculosis patients. The directly observed treatment programs (DOT) for tuberculosis could be used as a model for antiretroviral therapy in some situations to ensure patient's compliance.

b) Regime of antiretroviral therapy

WHO had updated the guidelines for antiretroviral therapy for HIV infection in adults and adolescent in 2010. If in previous guideline, ART is indicated in TB/HIV co-infected patients with CD4 $\leq$ 350 cells/mm^3, but based on the current guidelines ART should be started as soon as possible irrespective of CD4 cell count, preferably within eight weeks after the initiation of TB treatment. First line therapy should consist of an

NNRTI and two NRTIs. The recommended first line ART in these patients is the combination of Zidovudine (AZT), Lamivudine (3TC) and Efavirenz (EFV).

c) CD4 cell counts

A case-control study in Switzerland (1996) found that immune suppression, as indicated by low CD4+ cell count, was an independent risk factor for tuberculosis in HIV positive patients (OR 7.8; 95% CI 7.3–8.3 for patients with CD4+ <50 cells/mm^3 as compared to those with CD4+ >500 cells/mm^3) (Sudre, Hirschel, Toscani, Ledergerber, & Rieder, 1996). In a study conducted in Brazil, it was found that CD4+ cell counts of less than 200 cells/μL were observed in 71.9% of the TB/HIV co-infected patients with the mean of 169 cells/μL(Carvalho et al., 2008). In HIV-infected patients receiving HAART, the study by Lawn et al (2005) showed that the risk of TB was independently associated with CD4 cell count < 100 cells/ml (adjusted risk ratio [ARR]: 2.38; 95%CI: 1.01–5.60)(Lawn, Badri, & Wood, 2005).

c) Opportunistic infections/ AIDS-defining illnesses

AIDS-defining illness is a clinical marker of immunodeficiency, which has a good correlation with high risk of opportunistic infections, included tuberculosis (Ackah et al., 1995; P. P. Nunn, Elliott, & McAdam, 1994; Shafer et al., 1996). Opportunistic infections (OIs) that are considered as AIDS-defining conditions by the CDC are as follows:

- Bacterial infections, multiple or recurrent (only for children less than 13 years old)
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive (only among people 13 years old or older)
- Coccidioidomycosis, disseminated or extrapulmonary

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (for longer than 1 month)
- Cytomegalovirus disease (other than liver, spleen, or nodes), beginning when older than one month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (lasting longer than 1 month); or bronchitis, pneumonitis, or esophagitis (beginning when older than one month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (for longer than 1 month)
- Kaposi sarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex (only for children less than 13 years old)
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, of any site, pulmonary (only among people 13 years old or older), disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia (PCP)
- Pneumonia, recurrent (only among people 13 years old or older)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent

- Toxoplasmosis of the brain, beginning when older than one month
- Wasting syndrome due to HIV

A study done in Brazil found that the presence of HIV related symptoms; or AIDS-related complex (ARC) is the only risk factor for tuberculosis development in HIV-infected patients (OR: 3.5; CI 95% - 1.2-10.8) after adjusting for the past history of pneumonia, past history of hospitalization, CD4 count and no anti-retroviral use (de Castro Toledo et al., 2000).

d) RNA Viral load

In a study that was conducted in Thailand, among 87 patients with HIV RNA viral load result, the median HIV RNA viral load was 308,000 copies/ml (IQR, 51,900- 759,000) at the time of TB diagnosis (Mankatittham et al., 2009).

2.8.5 Laboratory profiles

a) Haemoglobin

No study reported any association between low hemoglobin level or anemia and risk of developing TB in HIV-infected patients, but a study conducted in Zambia (Elliott et al., 1995) found that it was associated with higher risk of dying in this group of patients. Another study that was done in Zambia and Malawi (Ciglenecki et al., 2007) demonstrated that in HIV-infected TB patients, the hemoglobin level that is 10 g/dl is associated with lower mortality both during (HR:0.22; 95%CI:0.1–0.4) and after (HR:0.25; 95%CI: 0.1–0.5) tuberculosis treatment.

b) Albumin

In several studies, albumin level was examined as an indices of malnutrition. Serum albumin level is a well known marker for HIV disease progression (Mehta,

Astemborski, Sterling, Thomas, & Vlahov, 2006; Shah et al., 2007). In Brazil, high serum albumin was found to be associated with lower in-hospital mortality (HR:0.16; 95%CI:0.05-0.56) in disseminated TB patients who were infected with HIV (dos Santos, Deutschendorf, Scheid, & Zubaran Goldani, 2011).

c) Hepatitis viral serology

Only one study reported viral serology assessment in TB/HIV co-infected patients (Kingkaew et al., 2009). From 769 HIV-infected patients in the study, 9% were HbsAg reactive and 31% were anti-HCV reactive.

2.9 Systematic review: TB treatment outcomes in TB/HIV co-infected patients

Treatment outcome results serve as an indirect measure of the quality of TB management and care provided by a health care system. World Health Organization (WHO) had recommended that tuberculosis treatment outcomes should be monitored using standardized categories by the epidemiological surveillance system- cure, treatment completed, treatment failure, died, defaulted or transferred out. In line with that recommendation, National TB Control Programs (NTCP) in all countries routinely report treatment outcomes for all TB patients to the World Health Organization (WHO), but there was limited information on outcomes of tuberculosis treatment in HIV-infected patients.

A systematic review was conducted to evaluate the TB treatment outcomes in TB/HIV co-infected patients based on published articles.

Search strategy

A systematic search of studies dealing with TB treatment outcomes in TB/HIV co-infected patients were conducted using three electronic databases (Pubmed, Science Direct and Medline via EBSCOhost). Various combinations of the terms “tuberculosis”, “HIV”, “AIDS”, “co-infection” and “outcome” were used to screen for potentially relevant studies. Additional studies were also identified using cross-referencing.

Inclusion and exclusion criteria

Original articles after 1993, the year that WHO launched the surveillance of TB treatment outcomes; were included in this review. The inclusion criteria is an article that estimated both successful and unsuccessful treatment outcomes in the total population of HIV-infected TB patients who started treatment. Studies conducted in children, case reports, editorials or reviews were not included. If the article dealt with specific group; such as extra-pulmonary TB alone or with only specific risk factor such as MDR-TB, then the study was also excluded. The selection process of the studies is summarized in Figure 2.1.

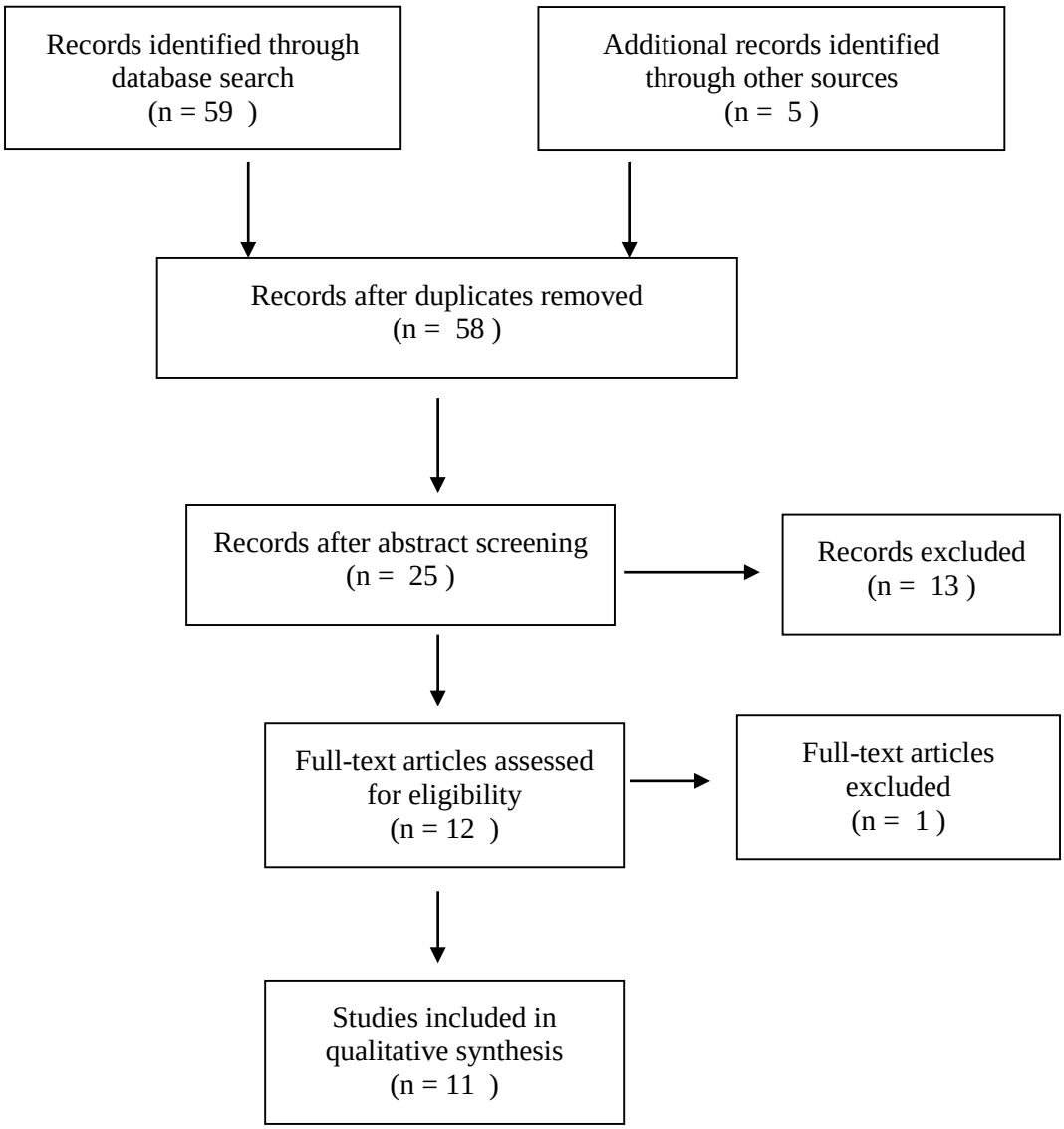


Figure 2.1: Flow chart of study selection process.

Definitions of outcome measures

The TB treatment outcomes in TB/HIV co-infected patients were measured as percentages of successful and unsuccessful outcomes among all patients who started therapy. As suggested by the WHO, successful outcomes included cured patients and those who completed TB treatment. Some studies that used other terms for successful treatment, such as 'favorable outcome'(Klautau & Kuschnaroff, 2005; S Vijay, Kumar, Chauhan, Rao, & Vaidyanathan, 2011) were also included in this group. For this review, defaulted or treatment interrupted; failed treatment and died were pooled into unsuccessful outcomes. Transferred out cases are classified as outcome not evaluated.

Critical appraisal

Critical appraisal is a useful tool in assessing the comprehensivity of the whole paper as well as it allows researcher to systematically review the research papers' relevance, results and validity. It also identifies the strengths and difficulties of the research papers. The critical appraisal that was undertaken in this review is using the Glasgow Critical Appraisal Checklist for Cohort Studies (adapted from Jaeschke, 1994). An overall score was given to each study by allocating one point for each positive result on the checklist. All the papers had clear research questions and a well-defined representative population. Most studies provided estimates of the accuracy of the outcomes measured (Table 2.3).

Table 2.3 Critical appraisal of studies on TB treatment outcomes in TB/HIV co-infected patients.

(Appendix F)

Data extraction

For all included studies, the following data was extracted from original publications: first author and year of publication; study site, study design, types of TB, category of TB diagnosis (new case or recurrent) and the proportion (%) of each category of

treatment outcomes (cured, completed treatment, treatment failure, treatment default, died and not evaluated).

Findings

As shown in Figure 2.1, the literature search identified 59 potentially relevant articles published in English. An additional five articles were identified from the cross referencing. After reading the full text, twelve studies satisfied the inclusion criteria for review and one study was excluded because almost half of the cases loss of follow up. Finally, eleven studies from nine different countries, addressing TB treatment outcomes in TB/HIV co-infected patients were included in this review. The findings from this review is presented in the Table 2.4 below.

Table 2.4: Tuberculosis treatment outcomes in TB/HIV co-infected patients for articles included in the review

Study, year	Country	Study design	Cases			Treatment outcome (%)							
						Successful			Unsuccessful				Not evaluated
			Type	Category	Total (N*)	Total	Cured	Completed	Total	Failure	Default	Died	
Broek, 1998	Tanzania	Prospective	All	All	146	59.0	NR	NR	18.0	3.0	NR	16.0	22
Harries, 1998	Malawi	Prospective	All	New cases only	554	50.9	NR	NR	40.7	0.5	6.3	33.9	8.3
Murray, 1999	South Africa	Prospective	SP and SN	All	190	77.4	NR	NR	21.1	5.3	2.1	13.7	1.6
Mwaungulu, 2004	Malawi	Retrospective Prospective	All	All	220	61.8	NR	NR	35.4	1.8	4.1	29.5	2.7
Klautau, 2005	Brazil	Prospective	All	All	78	78.0	NR	NR	22.0	5.1	11.0	6.4	NR
Thuy,2006	Vietnam	Retrospective	All	All	637	71.0	59.0	12.0	28.0	1.0	1.0	26.0	1.0
Quy, 2006	Vietnam	Prospective	All	All	39	56.5	53.9	2.6	38.4	7.7	5.1	25.6	5.1
Maruza, 2008	Brazil	Retrospective	All	All	262	58.8	NR	NR	41.2	0.8	11.5	29.0	NR
Kingkaew, 2009	Thailand	Prospective	All	All	769	64.0	NR	NR	26.0	1.0	8.0	17.0	10.0
Vijay, 2012	India	Prospective	All	All	281	75.0	NR	NR	24.4	0.4	15.0	9.0	NR
Girardi, 2012	Italy	Prospective	All	All	246	52.8	30.5	22.4	24.8	0.8	10.2	14.6	21.6

N*= Total number of HIV-positive cases in the study; NR: not reported; SP: smear positive; SN: smear negative
Type, All: Smear positive pulmonary TB, smear negative pulmonary TB and extrapulmonary TB
Category, All: New and recurrent cases.

Eight were prospective studies, two retrospective studies and one study manipulate retrospective and prospective study design. All included studies were population-based study. The sample size of HIV-infected TB patients in the reviewed studies ranged from 39 (Quy et al., 2006) to 769 (Kingkaew et al., 2009).

Success rates were ranging from 50.9% (Harries et al., 1998) to 78% (Klautau & Kuschnaroff, 2005). Results from two different regions in Vietnam gave a variation in treatment success rate; which is 56.5% (Quy et al., 2006) and 71% (Thuy et al., 2007) respectively. Among the unsuccessful outcomes group, patients who died attribute the largest proportion. The highest reported death rate in the included studies was 33.9% in Malawi (Harries et al., 1998). However, the mortality rate is declining to 9% as reported by a study in India (S Vijay et al., 2011).

Completion of TB treatment is the most important priority of TB control programs. From the included studies, the study in India (S Vijay et al., 2011) reported the highest defaulter rate in TB/HIV co-infected patients (15%). (Van den Broek et al., 1998) did not report the number of HIV patients who defaulted TB treatment but analyse them as 'uncertain outcome'; together with patients who were transferred out. In this study, 22% of the cases were evaluated as uncertain outcome.

The World Health Organization (WHO) reported that globally, a total of 14,188 people living with HIV/AIDS (PLWH) were registered with TB in 2004 as compared to 123,297 in 2008 showing an increase of 88%. In HIV negative patients, the registered TB cases increased from 4,380,029 in 2004 to 5,457,800 in 2008 (20% increase). The treatment success rate in PLWH was improved from 47% in 2004 to 71% in 2008 and the mortality rates declined over years from 16% in 2004 to 12% in 2008.

In this review the successful TB treatment outcomes in HIV-infected patients were ranged between 48.4% to 78%; which is below the 85% threshold that was suggested by

the WHO. Further, this review also shown that TB/HIV-infected persons have an alarming default rate. An urgent attention from the health care system is needed as co-infected persons who default from TB treatment can lead to treatment failures and the emergence of drug-resistant TB in the community. Patient non-compliance to treatment can be interpreted as a failure of the health care system in dealing with the natural tendency of humans to stop treatment as soon as they feel better.

Generally, the mortality rates of TB/HIV co-infected patients are higher than TB patients who are HIV negative. HIV co-infected TB patients respond to anti-TB drugs as well as HIV negative TB patients, but they may have a higher short-term mortality. In South Africa, the probability of death for TB with HIV-positive patients were greatest in two weeks following the start of treatment. It continued to increase throughout the treatment period in HIV-positive patients at an average of three percent per month (Murray, Sonnenberg, Shearer, & Godfrey-Faussett, 1999).

To ascertain TB treatment outcomes among HIV-infected patients, appropriate recording and reporting in both TB and HIV clinics is important, especially information about deaths. It is also crucial to monitor the progress in the prevention and control of TB.

2.10 Risk factors for TB treatment default

Defaulting from treatment is one of the unfavourable outcomes for patients on DOTS and represents an important challenge for the TB control program. Default is defined by the WHO as a treatment interruption of two consecutive months or more after at least one month of treatment but the definition of defaulters can vary within national programs. Defaulting TB treatment can lead to prolonged periods of infectiousness, recurrent TB infections, emergence of drug-resistance, and increased morbidity and mortality.

A total of 18 studies were identified, all of which were conducted in developing countries and published between 2000 and 2013. Out of 18 studies, only four studies specifically looked at the risk factors for defaulting TB treatment among TB/HIV co-infected patients (Amuha, Kutyabami, Kitutu, Odoi-Adome, & Kalyango, 2009; Elbireer, Guwatudde, Mudiope, Nabbuye-Sekandi, & Manabe, 2011; Kittikraisak et al., 2009; M Maruza et al., 2011). Table 2.4 shows the results of the search studies carried on risk factors for defaulting TB treatment. Each study included different characteristics, therefore the factors identified are heterogeneous. Overall, available literature identified several factors associated with defaulting from TB treatment which includes socioeconomic, treatment related factors and health system factors.

Table 2.5: Independent factors for TB treatment default.

(Appendix G)

Socioeconomic factors

Socioeconomic factors were identified as predictors for TB treatment default. Gender, alcoholism, smoking, homelessness, illiteracy and low income are some of the socioeconomic factors which have been found to be associated with higher default rates. Alcoholism has been cited as one of the major factors contributing to default by most of the studies (Amuha et al., 2009; Garrido et al., 2012; Hasker et al., 2008; Jakubowiak, Bogorodskaya, Borisov, Danilova, & Kourbatova, 2007; Muture et al., 2011; Naidoo et al., 2013; Sophia Vijay, Balasangameswara, Jagannatha, Saroja, & Kumar, 2003). The altered behaviour under the influence of alcohol and other substances is believed to be the reason for such observations. When one is under the influence of alcohol, he is likely to forget to take the medicines, and the chances that it may subsequently lead to poor compliance are high. Smoking was found to be significant predictive factor of TB

treatment default in Thailand (Kittikraisak et al., 2009), Brazil (Magda Maruza, Arraes, & Ximenes, 2008) and South Africa (Naidoo et al., 2013).

Another factor implicated with defaulting among TB patients is the distance of the residence of the patient from the treatment facility which was reported by studies done in Southern Euthopia (Shargie & Lindtjørn, 2007) and Uganda (Elbireer et al., 2011). The continuation phase of treatment is the most crucial time for defaulting from treatment and future interventions should take this into consideration. (Shargie & Lindtjørn, 2007).

In Nepal, Mishra et al. (2005) examined the contribution of socio-economic status to non-adherence to treatment. The results of their study revealed that unemployment (AOR: 9.2; 95%CI: 2.8–29.8), low status occupation (AOR 4.4; 95%CI:1.5-12.5), low annual income (AOR: 5.4, 95%CI: 1.0-30.0), and cost of travel to the TB treatment facility (AOR: 3.0; 95%CI 1.2–7.3) are significantly associated with non-adherence to treatment. They concluded that low socioeconomic status and particularly lack of money are important risk factors for nonadherence to treatment in a poor country as Nepal.

Personal factors

The contribution of previous history of defaulting has been demonstrated in several studies (Chan-Yeung, Noertjojo, Leung, Chan, & Tam, 2003; Garrido et al., 2012; Muture et al., 2011). Chan et al. (2003) in Hong Kong evaluated the contribution of side effects of treatment to defaulting and found that treatment side effects were associated with default (AOR 13.30, 95%CI 3.23–54.79) (Chan-Yeung et al., 2003). This finding was also supported by Elbireer et al. (2011) who found that side effects of treatment were almost six times associated with TB treatment default (Elbireer et al., 2011).

In patients who were co-infected with HIV, CD4 counts lower than 200 cells/mm were found to be associated with TB treatment default (M Maruza et al., 2011). They also found that the use of HAART was a protective factor for defaulting TB treatment (AOR: 0.12; 95%CI: 0.05-0.33).

Health system factors

Factors related to the health system have also been identified as reasons for non-completion of treatment. A study by Elbireer S (2011) looked at the health facility factors and their contribution for TB treatment default in TB/HIV co-infected patients. They found that long waiting time at the clinic (AOR 4.18; 2.18-8.02), poor drug availability (AOR 4.75; 2.29-9.84), conduct of staff (AOR 2.72; 1.02-7.25), lack of opportunity to express feeling (AOR 3.47; 1.67-7.21) and lack of health education (AOR 5.31; 1.94–14.57) were significantly associated with TB treatment default (Elbireer et al., 2011).

Supervised TB treatment was one of the protective factors for treatment discontinuation. In Brazil, DOT was associated with a lower risk of TB treatment default (Garrido et al., 2012) . Likewise, another study in China also found that direct observation by village doctors had protective effect to non-adherence (Xu et al., 2009). This suggests that direct supervision reduces the risk of dropout. This could be explained by the fact that those who received anti TB treatment by the health staff would also receive more education about the disease, its duration and the outcome of care and are therefore more motivated to continue treatment for the required duration.

In sum, defaulting from treatment is a multi-factorial issue that has organizational and socio-economic implications. It is important to understand predictive factors for treatment default so that programs can implement specific measures to target the population at risk which is important not only to improve the patient's life expectancy, but also preventing disease transmission to the general population. Most importantly

inadequate treatment adherence is considered as a potential cause for the development of multidrug-resistant TB (MDR-TB) which is more difficult and costly to treat.

2.11 Survival time of TB/HIV co-infected patients

Time taken from TB diagnosis or TB treatment initiation to death in TB/HIV co-infected patients may vary in each individual. In most studies, the median survival time was calculated as the period between the date of TB treatment initiation and the date of death.

From the literatures, the median survival time in TB/HIV co-infected patients ranged from 7.3 months as documented from a study in India (S Vijay et al., 2011); to 22 months in Zambia (Elliott et al., 1995). Four studies assessed six-month survival in TB/HIV co-infected patients and found that the six-month survival rates were 71% (Sanguanwongse et al., 2008), 76% (Elliott et al., 1995), 78% (Palmieri et al., 1999) and 79% (P. Nunn et al., 1992) respectively. A study in Southern Euthopia that comparing the survival between HIV positive and HIV negative patients found that the survival rate at the end of the intensive phase was similar between both groups (93.7% and 94.0%, respectively). In HIV-infected TB patients, the survival rate decreased to 85.7% at the end of the study period (eight months). However, HIV negative TB patients in this study had better survival with the survival rate of 92.2% at the end of the eight months (Shaweno & Worku, 2012).

In a study done by Whalen *et al*., the median survival for the entire cohort of TB/HIV co-infected patients were 18.1 months with 1-year survival of 64% (Whalen et al., 1997). Manosuthi *et al*. reported that in TB/HIV co-infected patients who were on antiretroviral therapy, the survival rates at one (1), two (2) and three (3) years after TB diagnosis were much higher (96.1%, 94.0%, 87.7% respectively) as compared to patients without antiretroviral therapy (44.4%, 19.2%, 9.3% respectively) (Manosuthi, Chottanapand, Thongyen, Chaovavanich, & Sungkanuparph, 2006). The summary of

median survival time in TB/HIV co-infected patients from published articles is presented in Table 2.6.

Table 2.6: Median survival time from TB diagnosis to death in TB/HIV co-infected patients.

Citation	Study Design	N	Outcome
(P. Nunn et al., 1992)	Retrospective, Kenya	281	6-month survival probability in TB with HIV positive was 79% (95% CI = 69-85%)
(Elliott et al., 1995)	Prospective, Zambia	239	The probability of survival for HIV-positive patients at 2,6, 12 and 18 months was 89%, 76%, 66% and 55% respectively. Median survival time was 22 months.
(Whalen et al., 1997)	Retrospective cohort study in four US academic medical centers	112	The median survival for the entire cohort was 18.1 months with a 1-year survival of 64%. The median survival was shorter in TB/HIV co-infected patients with both pulmonary and extra-pulmonary disease (8.4 months).
(Palmieri et al., 1999)	Retrospective, Rome, Italy	118	The median survival time was 15.2 months. 6-month survival was 78% 1-year survival rate was 57%.
(Chaisangcharoen, 2005)	Retrospective, Thailand	310	The median survival time was 10.9 months (95% CI = 8.42-13.45)
(S Vijay et al., 2011)	Prospective, India	281	The median survival time between the date of TB treatment initiation and the date of death was 7.3 months.
(Shaweno & Worku, 2012)	Retrospective, Ethiopia	370	The survival probabilities at 2 months was 93.7% and 85.7% at seven months.

2.12 Systematic reviews: Predictors of survival in TB/HIV Co-infected Patients

Many factors may potentially contribute to shorter survival of HIV-infected TB patients, particularly in poor resource setting. A large number of observational studies conducted among patients with TB-HIV co-infection reported that several factors can predict unfavourable outcomes. However, these factors have not been consistent across studies and settings. This review aims to identify the most consistent variables which are predictive of mortality among TB-HIV co-infected patients based on findings from observational studies. Understanding the prognostic factors of poor outcome in TB-HIV co-infection can help clinicians to identify a patient's level of risk; thus facilitating clinical decision making.

Search strategy

A literature search was done using five major databases including PubMed, ScienceDirect, CINAHL, Scopus and Ovid. All prognostic studies predicting death in Tuberculosis and HIV co-infection were considered eligible for this review. Data for the present review were identified using the following terms: (Tuberculosis OR TB) AND (Human Immunodeficiency Virus OR HIV) AND (survival OR mortality). The titles and abstracts identified from the search were independently assessed by two reviewers against the inclusion criteria. Full text of all studies that meet the inclusion criteria were retrieved and read by the same two reviewers and subsequently discussed during a consensus meeting. Any disagreement between the two reviewers was addressed through consensus, otherwise the third reviewer was asked to act as an arbiter.

Literature selection

The titles which were related to our domain, determinants and outcome (DDO) were scanned to determine eligibility and relevance. Relevant titles were selected by two independent reviewers. The abstracts of the selected titles were read and only abstracts

that met the inclusion criteria; which were defined prior to the search; were selected. Any disagreement regarding eligibility of the abstracts was resolved by consensus. Included studies were articles that met these criteria: the primary aim was to investigate prognostic factors or risk factors for death in TB-HIV patients, studies designed as longitudinal cohort; either prospective or retrospective, studies conducted in adults and that were published in English.

The exclusion criteria were case series or case studies, articles published as abstracts only, articles without detailed description of methods, where the primary objective was not to investigate predictors for death in TB-HIV patients, where the analysis of risk factors for death were very specific; for example co-trimoxazole prophylaxis (Mwaungulu et al., 2004), where multivariate analysis regarding the strength of association was not reported, studies conducted in children, editorials, reports or unpublished reports and studies that were done before 1996. We selected only original articles. Articles were also screened for duplicate publication.

Data extraction and analysis

Data extraction was done to collect information on the participants, characteristics of the study, methods and outcomes. A standardized form was used to extract data from full text articles. From the included articles, the following information was extracted: country, period of enrollment, the sample size, the characteristics of study population (age, sex); study design; duration of follow up; the outcome measures (total death, %) and prognostic variables assessed in each study; and quality of the regression model. Quantitative analysis was not performed due to heterogeneity in study population and analyses of the included studies.

Findings

Studies selection

Figure 2.2 summarizes the selection process of the studies. A total of 3695 were identified using search strategy in PubMed (57), ScienceDirect (124), CINAHL (34), Scopus (34) and Ovid (3446). Of these, 209 articles were selected after reading the titles. All abstracts were reviewed and 147 were excluded because they did not meet inclusion criteria by the reading of abstracts. After reading the entire article, 47 articles were excluded because they did not meet the eligibility criteria. Finally, 15 studies satisfied the pre-determined criteria and were retained for this review.

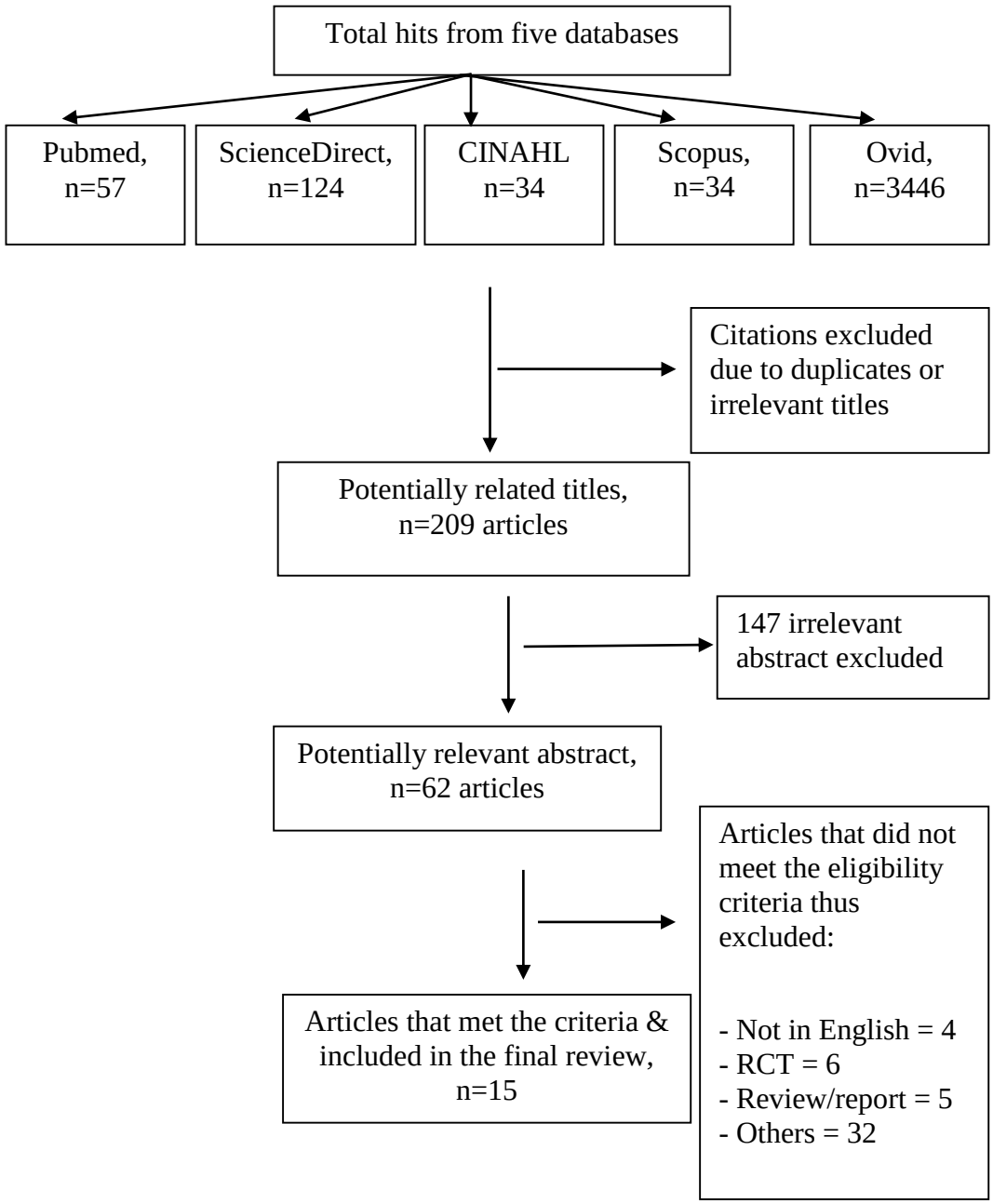


Figure 2.2: Flow chart of study selection process

Studies Characteristics and Patients

The characteristics of the fifteen studies that assessed factors potentially associated with mortality in TB/HIV co-infection are summarized in Table 2.3. Year of publication ranged from 1996 to 2013. Six studies (dos Santos et al., 2011; Manosuthi et al., 2006; Sanguanwongse et al., 2008; Sileshi, Deyessa, Girma, Melese, & Suarez, 2013; Sungkanuparph, Eampokalap, Chottanapund, Thongyen, & Manosuthi, 2007; Varma et al., 2009) were from high TB burden countries and covered 3668 patients and nine studies (Catala et al., 2011; Dheda, Lampe, Johnson, & Lipman, 2004; Gadkowski et al., 2009; Girardi et al., 2001; Palmieri et al., 1999; Podlekareva et al., 2009; Shafer et al., 1996; Velasco et al., 2009; Whalen et al., 1997) were from intermediate or low TB burden countries and covered 3230 patients. There was considerable variation with respect to population size (54 – 1269) and follow-up duration between the studies.

Mean or median ages of patients varied from 33 to 40 years. In most studies the predominant gender was male. Most studies (87.5%) were retrospective studies and only two were prospective.

Statistical quality and the presentation of methods and results were acceptable for many studies according to the PRISMA (preferred reporting items for systematic review and meta-analysis) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). All studies performed regression analysis, and reported the probability value or the survival curves, or both. Only one article did not provide the values of hazard ratios and 95% confidence intervals (Shafer et al., 1996). No studies clearly stated that collinearity was assessed or developed a risk score based on the multivariate analysis results. One study (Varma et al., 2009) reported that interaction effects were evaluated.

The majority of reviewed studies measured the primary outcome as all-cause mortality; which is consistent with World Health Organization guideline. This guideline defined

TB death as any death that occurred during TB treatment, irrespective of cause. Only five studies discussed causes of death (Catala et al., 2011; Dheda et al., 2004; Girardi et al., 2001; Manosuthi et al., 2006; Sungkanuparph et al., 2007). The case fatality rates ranged from 4% to 84%.

None of the studies included post-mortem findings in their reports. Only post-mortem studies can determine the cause of death definitively.

From 15 studies included in this review, demographic (in 4 studies), clinical (in 14 studies) and laboratory (in 13 studies) variables were most frequently evaluated by multivariable modelling (Tables 2.7).

Table 2.7(a): Independents predictors of death in TB/HIV co-infected patients.

Factors	Catala et al., 2011	Dos-Santos et al, 2011	Gadkowski et al, 2009	Girardi et al, 2001	Manosuthi et al, 2006	Palmieri et al, 1999	Podlekareva et al, 2009	Sanguanwongse et al, 2008
Socio-demographic Factors								
Increasing age	+		+	+				+
Non-citizen								+
Inner-city residence	+							
Injecting Drug User	+							
Clinical factors								
Fever on admission		+						
Time of TB diagnosis								
Extrapulmonary TB					+			
Disseminated TB							+	+
Non-cavitary radiological pattern	+							
AIDS-defining illnesses	+			+		+	+	
History of previous AIDS								
No appropriate anti-TB						+		
TB treatment not containing RHZ							+	
No ART			+	+	+			+
No Fluconazole use								+
No CPT								
Laboratory factors								
Low serum albumin		+						
Low CD4 counts	+		+	+		+	+	+
Anti-TB drug resistant					+	+	+	+

RHZ indicates Rifamycin, Isoniazid & Pyrazinamide; ART: Antiretroviral therapy; CPT: Cotrimoxazole prophylactic therapy

Table 2.7(b): Independents predictors of death in TB/HIV co-infected patients.

Factors	Shafer et al, 1996	Sungkanuparph et al, 2006	Varma et al, 2009	Velasco et al,2009	Whalen et al, 1997	Dheda et al., 2004	Sileshi et al., 2013
Socio-demographic factors							
Increasing age							
Non-citizen							
Inner-city residence							
Injecting Drug User							
Clinical factors							
Fever on admission							
Time of TB diagnosis				+		+	
Extrapulmonary TB		+			+		
Disseminated TB							
Non-cavitary radiological pattern							
AIDS-defining illnesses					+		
History of previous AIDS						+	
No appropriate anti-TB							
TB treatment not containing RHZ							
No ART		+	+	+			+
No Fluconazole use							
No CPT							+
Laboratory factors							
Low serum albumin							
Low CD4 counts	+			+		+	+
Anti TB drug resistant		+					

RHZ indicates Rifamycin, Isoniazid & Pyrazinamide; ART: Antiretroviral therapy; CPT: Cotrimoxazole prophylactic therapy

Deaths during anti-tuberculosis treatment

Six studies focused on deaths occurring during anti-tuberculosis treatment. The case fatality rates in these studies ranged between 19% and 72%. These studies found disseminated TB, (Podlekareva et al., 2009; Sanguanwongse et al., 2008), resistance to anti-tuberculosis drugs (Manosuthi et al., 2006; Palmieri et al., 1999; Podlekareva et al., 2009; Sanguanwongse et al., 2008), presence of acquired immune-deficiency syndrome (AIDS)-defining illnesses, (Palmieri et al., 1999; Podlekareva et al., 2009) and low CD4 counts (Dheda et al., 2004; Palmieri et al., 1999; Podlekareva et al., 2009; Sanguanwongse et al., 2008; Sileshi et al., 2013) to be major determinants of poor outcome. Palmieri *et al.* (Palmieri et al., 1999) found that patients without appropriate anti-tuberculosis therapy within the first few weeks after TB diagnosis had a survival rate of 48% at six months. One study focused only on hospitalized patients (dos Santos et al., 2011) demonstrated that fever on admission and low serum albumin to be independent predictors of early death.

Deaths after completion of anti-tuberculosis treatment

Nine studies assessed deaths occurring in patients more than one year after TB treatment. These studies found that socio-demographic factors including increasing age (Catala et al., 2011; Gadkowski et al., 2009; Girardi et al., 2001; Sanguanwongse et al., 2008), injecting drug user (Catala et al., 2011), extra-pulmonary TB (Manosuthi et al., 2006; Sungkanuparph et al., 2007; Whalen et al., 1997) and immunological features of advanced immune suppression (Catala et al., 2011; Gadkowski et al., 2009; Girardi et al., 2001; Shafer et al., 1996; Sungkanuparph et al., 2007; Velasco et al., 2009) to be independent predictors of death in TB-HIV co-infected patients.

Predictors of death in TB-HIV co-infected patients

Socio-demographic factors

There were some variations in socio-demographic factors being analysed across studies due to the unique character of different countries. In Thailand, mortality was independently associated with Thai nationality as compared to non-Thai (Sanguanwongse et al., 2008) In Spain, residence in a socio-economically deprived neighborhood or categorized as inner-city residents, were more likely to die (Catala et al., 2011).

Several studies described an association between increasing age and death in TB/HIV co-infection. Gadkowski *et al.*(Gadkowski et al., 2009) found that during TB treatment, age more than 45 (RR: 2.18, 95% CI 1.11, 4.29) was independently associated with increased death. These findings could be explained by the association of age with a rise in co-morbidity which frequently accounted for death.

One study (Catala et al., 2011) have demonstrated that history of injection drug use resulted in higher risk of death in TB/HIV co-infected patients (AHR:1.4; 95%CI: 1.1–1.8). Injection drug users are prone to have social problems including unemployment, incarceration and homelessness, which may affect their access to health care. They are also having a higher risk of non-adherence to treatment.

Clinical characteristics

As shown in Table 2.7 ((a) and (b)), the clinical variables found to be the most common independent predictor of death were types of tuberculosis (extra-pulmonary TB and disseminated TB), not on ART and the presence of other acquired immune-deficiency syndrome (AIDS) defining illnesses. Other variables found to be predictive of mortality were no fever on admission (one study), presumptive TB diagnosis (one study), time of TB diagnosis (two studies), non-cavitary radiological pattern (one study), history of previous AIDS (one study), no appropriate anti-TB (one study), TB treatment not

containing RHZ (two studies), no Fluconazole use and no cotrimoxazole prophylactic therapy in one study, respectively.

Whalen and his colleague (Whalen et al., 1997) have demonstrated that HIV-infected patients with extra-pulmonary TB had shorter survival time. This finding may be explained by the fact that patients with extra-pulmonary TB have more severe immunodeficiency status and higher bacterial load of *Mycobacterium tuberculosis*. Manosuthi *et al.* (2006) had demonstrated that gastrointestinal TB is an independent predictor of death in TB-HIV co-infected patients (AHR: 9.22; 95%CI 1.10-78.02) in Thailand (Manosuthi et al., 2006).

In the study done by Dos santos *et al.*(dos Santos et al., 2011), TB-HIV co-infected patients who had fever at admission had better prognosis (HR 0.18, 95%CI 0.06-0.54) which could be due to secretion of several cytokines as a result of adaptive cell-mediated immune response to *Mycobacterium tuberculosis*.

Catala *et al*. (Catala et al., 2011) found that presentation with an abnormal non-cavitary chest x-ray pattern was associated with lower survival as compared to a cavitary chest x-ray pattern. Patients who develop cavitations have better survival because they have better immunity (Geng, Kreiswirth, Burzynski, & Schluger, 2005).

Five studies demonstrated that patients who suffered a prior AIDS-defining illness are associated with increased risk of death (Catala et al., 2011; Girardi et al., 2001; Palmieri et al., 1999; Podlekareva et al., 2009; Whalen et al., 1997).

Several studies demonstrated that TB/HIV co-infected patients who were not on ART were associated with higher risk of death. A study (Whalen et al., 1997) that was done before ART was widely available showed a much higher mortality rate (84%) as compared to 4% to 43.7% in other studies. This finding support the facts that ART can save patients' live.

Among patients with ART, Manosuthi *et al.*(Manosuthi et al., 2006) found that fifty percent of patients who did not receive ART in this study died within 10.7 months after they were diagnosed with TB. They also concluded that those who started ART less than six months after they were diagnosed with TB had a longer survival as compared to the patients who delayed ART more than six months after their TB diagnosis (HR 2.65, 95% CI 1.15-6.10). Whereas Velasco *et al.*(Velasco et al., 2009) proved that HIV-associated TB patients will have better survival if HAART and TB treatment were started concurrently (AHR 0.37, 95% CI 0.17 – 0.66). Only one study (Palmieri et al., 1999) analyzed the association of appropriate anti-tuberculosis therapy with survival in TB/HIV co-infected patients which reported that those who were not on appropriate anti-tuberculosis therapy had higher mortality rates (AHR 2.6, 95%CI 1.5-4.4).

Laboratory factors

Low CD4 lymphocytes count ($\leq$ 200cells/mm^3) (Catala et al., 2011; Dheda et al., 2004; Gadkowski et al., 2009; Girardi et al., 2001; Palmieri et al., 1999; Podlekareva et al., 2009; Sanguanwongse et al., 2008; Shafer et al., 1996; Sileshi et al., 2013; Velasco et al., 2009) and anti-TB drugs resistant (Alpert et al., 1997; Manosuthi et al., 2006; Palmieri et al., 1999; Podlekareva et al., 2009; Sungkanuparph et al., 2007) have been reported as consistent predictors of mortality in HIV-associated tuberculosis.

In studies where drug susceptibility testing was performed, resistance to anti-tuberculosis drugs was independently associated with an increased risk of death (Manosuthi et al., 2006; Palmieri et al., 1999; Podlekareva et al., 2009; Sanguanwongse et al., 2008; Sungkanuparph et al., 2007). Palmieri *et al* (Palmieri et al., 1999) found that median survival of patients with multi-drug resistant tuberculosis (MDR-TB) was 4.6 months from their TB diagnosis. Low serum albumin (hypoalbuminaemia) was

associated with poorer prognosis in only one study (dos Santos et al., 2011). However, other studies did not reproduce this finding.

The most important finding of this review is that it confirms the degree of immuno-suppression influences survival in TB/HIV co-infected patients both during anti-tuberculosis treatment and even after the completion of anti-tuberculosis treatment. Most of the studies demonstrated that variables associated with immunodeficiency, such as low CD4 lymphocyte count and the presence of AIDS defining illnesses were important independent predictors of mortality. The fact that low CD4 lymphocyte count is a potent predictor of death in TB-HIV co-infected patients leads to the inevitable conclusion that early access to ART has huge potential to improve immune function and to save lives.

Resistance to anti-tuberculosis drugs as a predictor of mortality in TB patients has been well described (Amnuaiphon et al., 2009; Garcia-Garcia et al., 2002; Kawai et al., 2006; Lefebvre & Falzon, 2008; Low et al., 2009; Mathew et al., 2006; Quy et al., 2006). HIV/AIDS was also associated with the current emergence of drug resistant tuberculosis, thus drug susceptibility testing in TB patients co-infected with HIV is important. In view of the high mortality among patients with HIV and drug-resistant TB co-infection, empiric second-line TB therapy should be considered for previously treated and hospitalized patients particularly in settings with a high-burden of MDR/XDR-TB; while awaiting confirmatory drug susceptibility testing results (Andrews et al., 2010).

HIV-associated morbidity and mortality has significantly reduced with the use of ART. It has also improved the survival of TB-HIV co-infected patients during and after completion of TB treatment. The World Health Organization (WHO) currently

recommends that ART should be given to all HIV-infected TB patients regardless of CD4 cell count (WHO, 2011c).

Documented benefits of ART in HIV-infected TB patients and appropriate anti-tuberculosis drugs and HAART combinations have been recommended by the Centre for Disease Control and Prevention (CDC). Unfortunately, still it is not widely used in many countries (Sanguanwongse et al., 2008). Patients were not prescribed with ART or delayed initiation of ART during TB treatment possibly due to physicians' concerns about the number of pills to be taken, overlapping drug toxicities, drug-drug interactions between rifamycins and antiretroviral drugs and the possible immune reconstitution syndrome (McIlleron, Meintjes, Burman, & Maartens, 2007). The findings that deaths were less common among HIV-infected TB patients receiving ART should convince physicians that the benefits of ART outweigh the risks of toxicity when these drugs are used in combination.

Collaborations between TB and HIV services and interventions to improve HIV-related health care utilization is needed to increase survival and reduce AIDS-related and non-AIDS-related death among TB-HIV co-infected patients (Catala et al., 2011; Gadkowski et al., 2009).These interventions include improving access to health services, expansion of laboratory services to ensure early detection of TB and drug-resistant TB, adherence to ART and anti-tuberculosis treatment and improvements in clinical management, such as early and continuous ART during TB treatment. Preventive measures such as prevention of HIV transmission, harm reduction programme among injecting drug users, as well as early hepatitis B and hepatitis C treatment in co-infected patients are also necessary (WHO, 2004).

This review has several important limitations. First, all studies included in this review were observational studies which are affected by selection bias. Secondly, there was substantial variability in settings, patients' characteristics, variables and outcome assessed, which resulted in considerable heterogeneity. The wide range of reported mortality rates across the study, which vary from 4% to 84% in part could have resulted from the heterogeneity of the included patients. Third, most studies were conducted at single centres, which affect the generalisability of the results. In addition two studies (dos Santos et al., 2011; Shafer et al., 1996) had a limited sample size (less than 100 subjects). The search strategy was restricted to articles that were available in the used electronic databases and full reports that were published in English. Relevant studies might be missed and resulted in language or publication bias.

This systematic review proposes some important prognostic factors for the prediction of mortality in TB-HIV co-infected patients. Low CD4 lymphocyte count (≤ 200cells/mm^3), drug-resistant tuberculosis and not on ART is the most consistent predictors of mortality in HIV-associated TB patients. Early initiation of ART prior to the development of clinical markers of survival will help to maximize clinical outcome. Identification of predictors of death in TB-HIV co-infected patients may allow closer clinical monitoring of high-risk individuals.

2.13 Summary

In this chapter, an overview about TB and HIV infection, including the pathogenesis, epidemiology, characteristics, treatment and survival were reviewed from many evidences of research that have been done in various places in the world. TB among HIV patients is unique in that while it is contagious, both diseases can be treated with standard drugs and potentially preventable. HIV seropositive patients with TB will develop AIDS faster and die earlier than HIV-infected patients without TB. The early diagnosis and prompt management of TB among HIV patients may ensure longer life and reduced morbidity.

CHAPTER 3: METHODOLOGY

About this chapter

This chapter provides details of work done related to collection and processing of data. Section 3.1 and 3.2 introduces the topic of study design and the study area where the data collection was conducted. Section 3.3 to 3.7 explains the methodology used in this study, which includes study duration, study population, sample size calculation, sampling procedure and study variables and the definitions of outcome measures. Section 3.8 introduces the conceptual framework of this study. Section 3.9 to 3.11 provides a detailed account of the data extraction process and ethic clearance. Section 3.12 and 3.13 explains the data management and data analysis process.

3.1 Study Design

The design of this study is a prospective observational, multi-centre study. In the hierarchy of epidemiological studies, Randomized Controlled Trial (RCT) is the best study design because randomization can reduce biases to facilitate isolation of the true treatment effect. However, for a prognostic research question, the highest evidence come from a systematic review then followed by a cohort study. A prospective cohort study is the best design to determine risk factors.

This is a prognostic study which assesses several variables to determine the predictors of an outcome. Prognostic studies begin with observation at a specified point in time the course of a disease and follow-up patients for an adequate period of time and measure all relevant outcomes (Fletcher and Fletcher, 2005).

3.2 Study Area/ Site

This study was conducted at four public hospitals in the Klang Valley including the Institute of Respiratory Medicine, Kuala Lumpur and three hospitals in Selangor namely Kajang Hospital, Hospital Tuanku Ampuan Rahimah, Klang and Sungai Buloh Hospital.

The Klang Valley is an area in Malaysia that consists of Kuala Lumpur and neighbouring cities and towns in the state of Selangor. In the year 2006, the population in this area was estimated to be 6.0 million. Being the most urbanized area with major industrial and commercial activities in Malaysia, the Klang Valley became a focus for a large number of migrants from other states within Malaysia and foreign immigrants especially from Indonesia, India and Nepal.

In 2008, the proportion of TB/HIV among all TB cases in Klang Valley was 24.4%; ranked the second highest TB/HIV in Malaysia after Kelantan (31.3%).

Figure 3.1: Map shows the location of Klang Valley

The Institute of Respiratory Medicine is the main TB treatment centre in Kuala Lumpur. Kajang Hospital, Hospital Tuanku Ampuan Rahimah, Klang and Sungai Buloh Hospital were selected as study sites because they are specialist hospitals that have both TB Clinic and HIV Clinic. They are the only public hospitals that offer HIV treatment and care in the state of Selangor.

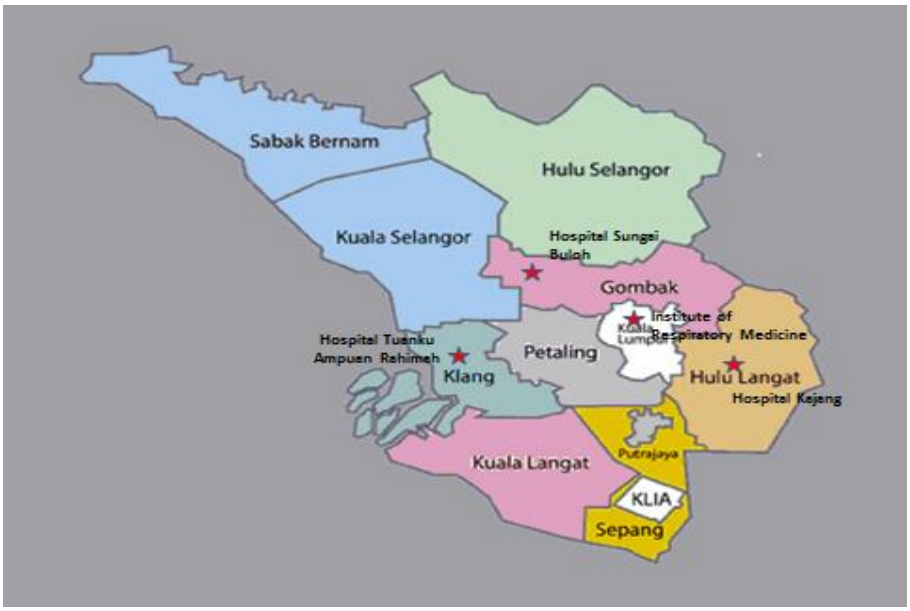


Figure 3.2: Map of four participating hospitals in Klang Valley.

3.2.1 Institute of Respiratory Medicine, Kuala Lumpur

Institute of Respiratory Medicine or better known as IPR was established in 1958 as a small clinic called Klinik Jalan Pahang. New structures were built in 1960 to house the country's National Tuberculosis Program and Tuberculosis Hospital. The new establishment was then named National Tuberculosis Centre (NTBC). It served as the nerve centre for TB control activity and its laboratory served as the National Reference Laboratory for Tuberculosis. With the decline of tuberculosis, in 1996 the MOH upgraded the NTBC and expanded its services to cater for other respiratory diseases too. Since then the NTBC was renamed as the Institute of Respiratory Medicine (IPR)

and now functions as a hospital providing specialized care in all areas of respiratory medicine including tuberculosis. The bed strength of this hospital is 104 with four high dependency beds and four newly built negative pressure isolation rooms. The patients at this health facility are managed by Chest Physicians and medical officers.

The Institute of Respiratory Medicine (IPR) was chosen for this study because it is the main hospital for TB management in Kuala Lumpur. Based on the National TB Control Programme (NTCP), IPR has been categorized as a TB Treatment Centre (1) where new cases are diagnosed and TB treatment initiated for patients after physical examination and investigation. TB patients who do not need specialist care and management will be transferred to the TB Treatment Centre (2) for continuation of their TB treatment and follow-up. This clinic receives walk-in patients, referrals from the Out-patient Department, Hospital Kuala Lumpur and from Community Health Clinics. There are also referrals from private hospitals and general practitioners. The majority of TB notifications received by the Health Department of Kuala Lumpur Federal Territory are from the Institute of Respiratory Medicine. The TB Clinic in IPR is scheduled weekly every Monday and Thursday. TB cases found to be HIV positive are referred to the Infectious Disease Unit of Hospital Sungai Buloh.

3.2.2 Kajang Hopital

Kajang Hospital is a district hospital located in the district of Hulu Langat in Selangor, Malaysia about 30 km Southeast of Kuala Lumpur. According to historical records, Kajang Hospital was initially founded in 1889 with the founding of the town. It is located on 16 acres of land and since 2010 has been able to accommodate 306 inpatients.

The TB Clinic in Kajang Hospital is scheduled for every Wednesday. HIV positive TB patients will be referred to the HIV Clinic for HIV management and care including

initiation of antiretroviral therapy. Both these clinics are managed by the Medical Department personnel.

The Medical Department of Hospital Kajang has been established since the 1980's. However, the medical specialist service was only made available in the 1990's. Currently Hospital Kajang has five in-house medical specialists and a visiting consultant from Hospital Sungai Buloh who provides his services one day a week at the HIV clinic.

3.2.3 Hospital Tuanku Ampuan Rahimah, Klang (HTAR)

The Tengku Ampuan Rahimah Hospital (HTAR) in Klang is a government tertiary hospital with 28 wards and 893 beds. The HTAR which is located in South Klang in the Klang district has about twenty clinical disciplines and functions as the main referral hospital for many peripheral district hospitals, including Sabak Bernam, Petaling, Kuala Langat, Kuala Selangor and Sepang.

The TB Clinic in HTAR is also known as the Chest Clinic. The TB Clinic is conducted every Tuesday. TB patients who are HIV positive will be referred to the HIV Clinic, which is located adjoining to the Chest Clinic. Methadone replacement therapy is also offered to intravenous drug users at this clinic.

3.2.4 Hospital Sungai Buloh

Hospital Sungai Buloh is a hospital with 646 inpatient beds. It is located in the district of Gombak, Selangor, about 25 km away from Kuala Lumpur. It is located on a 130-acre (0.53 km^2) site and provides a variety of secondary and tertiary medical services. It was initially built to reduce patient overcrowding at the Kuala Lumpur General Hospital.

The catchment areas of this hospital include the districts of Gombak, Petaling, Hulu Selangor and Kuala Selangor. The population in these three districts form 40% of the population of the state of Selangor, which totals approximately 2.18 million residents.

Sungai Buloh Hospital is the National Referral Centre for Infectious Diseases. The TB clinic in Hospital Sungai Buloh is located at the National Leprosy Centre, opposite the main hospital building. The TB Clinic of Hospital Sungai Buloh is scheduled for every Friday. This TB clinic is managed by medical officers and supervised by an Infectious Disease Specialist. Even though the Sungai Buloh Hospital is equipped with the Electronic Hospital Information System (EHIS), records at the TB Clinic still use the conventional method of reporting. TB patients are treated and managed based on the MOH Guidelines for Tuberculosis treatment. After successful completion of TB treatment, patients will be referred to the infectious disease clinic for continuation of their follow-up.

3.3 Study Duration

The recruitment phase of the subjects was between 1st January 2010 and 30th September 2010 (9 months). Additional follow up period was from 1st October 2010 until 30th September 2011 (12 months). This duration was chosen in line with WHO guidelines which recommended that all National TB Control Programs evaluate patients' treatment outcome 12 months after initiating TB treatment.

Data collection was carried out in two phases. The first phase was between 1st January 2010 and 30th September 2010 where data on socio-demographic background, lifestyle factors, clinical characteristics, pharmacological information and laboratory profiles were collected. The second phase of data collection was between 1st October 2010 and 30th September 2011 where the TB treatment outcome data were collected and efforts were made to complete missing data.

3.4 Study Population

The study population consisted of all patients who had registered for TB treatment as a result of clinical suspicion or laboratory confirmation and were tested positive for HIV in Institute of Respiratory Medicine, Kuala Lumpur and at three public hospitals in Selangor (Kajang Hospital, Klang Hospital and Sungai Buloh Hospital)from January 2010 until September 2010 (nine months).

3.4.1 Definition

Cases were newly diagnosed TB patients who were HIV positive and who registered at the Institute of Respiratory Medicine, Kuala Lumpur and at three public hospitals in Selangor (Kajang Hospital, Klang Hospital and Sungai Buloh Hospital) during the study period. World Health Organization defines a newly diagnosed TB patient as a patient in whom tuberculosis had been diagnosed by a clinician or was bacteriologically confirmed, had never received treatment for tuberculosis or who had taken anti-tuberculosis drugs for less than 30 days (WHO, 2010b).

3.4.2 Inclusion criteria

The inclusion criteria were:

1. TB patients aged 15 years and above who tested positive for HIV.

2. Sputum-smear positive or sputum-smear negative and/or having extra-pulmonary tuberculosis.

3.4.3 Exclusion criteria

The exclusion criteria were:

1. Pregnant mothers

2. Patients who were transferred out to other centres during tuberculosis treatment.

3. Patients who had their TB diagnosis changed to other diagnosis after starting anti- tuberculosis treatment.

3.5 Sample Size Estimation

The estimation of sample size was calculated according to the objectives of the study.

For the descriptive objectives, the sample size was calculated by using the formula for cross sectional study to estimate how many TB patients who are HIV positive required for the study. The formula is as below:

$$n = \frac{Z_{1-\alpha/2}^{2}\, p(1-p)}{d^2}$$

n = sample size

$Z_{1-\alpha/2}$ = Standard normal variate (at 5% type 1 error (p<0.05) it is 1.96)

p = expected proportion in population

d = absolute error of precision.

Based on literature review, the proportion of HIV cases among TB patients in Malaysia in 2008 was 10.4% ( ). In this study, used values are $Z_{1-\alpha/2}$ = 1.96, p = 0.10 and d = 0.05.

Therefore,

$$n = \frac{(1.96)^2 \times 0.10\,(1-0.10)}{(0.05)^2}$$

n = 139

Assuming 30% of missing data, the number of the sample size should be at least 181.

3.5.1 Sample size calculation for risk factors of TB treatment default in HIV-infected patients

The calculation of sample size was done using Power and Sample Size Calculation (PS) software version 2.1.31 (Dupont and Plummer, 1997). The estimation of sample size was based on the alpha level of 0.05, with desired statistical power of 80%

Table 3.1: Sample size calculation for risk factors of TB treatment default

Significance level (α)	0.05
Power (1- β)	0.8
P_0 (the probability of the outcome for a control patient.)	0.08 (Kittikraisak, 2009)
P_1 (the probability of the outcome in an experimental subject.)	0.20
m (the ratio of control to case patients.)	1:2
n	276
Total sample size (+30% lost to follow-up)	276 + (276 x 30%) = 359

3.5.2 Sample size calculation for predictors of survival in HIV-infected TB patients during TB treatment.

The significance level α was set at 0.05 and the power of the study was set at (1- β) of 80%. The median survival time of those without the prognostic factor(m_1) and the ratio of those without prognostic factor to those with prognostic factor (m) were obtained from the literature. Patients were recruited during accrual period of length A. After recruitment ended, there was an additional follow-up of length F. Patients remained in the study from the time they were recruited until the end of the study. Therefore, the first patient in was followed for time A + F; and last patient in was followed for F.

Table 3.2: Sample size calculation for predictors of survival in HIV-infected TB patients

Significance level (α)	0.05
Power (1- β)	0.8
R (The hazard ratio both pulmonary and extra-pulmonary TB compared to pulmonary TB only)	4.0 (Whalen, 1996)
m_1 (Median survival time of pulmonary TB only)	30.4 months (Whalen, 1996)
m (Ratio of both pulmonary and extra-pulmonary TB to pulmonary TB only) Both pulmonary and extra-pulmonary TB = 54 Pulmonary TB only = 36	1.5 : 1
A (The accrual time during which patients were recruited)	9 months
F (Additional follow-up after end of recruitment)	12 months
n (Sample size determined by the PS Software)	49
n + n(m)	49 + (49 x 1.5) = 122.5
Total sample size (+30% lost to follow-up)	123 + (123x 30%) = 159.9

Overall, the calculated sample size ranged from 181 to 359.

3.6 Sampling Procedure

All eligible patients seen between January and September 2010 at Institute of Respiratory Medicine and three public hospitals in Selangor (Kajang Hospital, Klang Hospital and Sungai Buloh Hospital), who were registered for TB treatment and were also documented to have concomitant HIV infection were included in the study.

According to the National TB Control Program, for TB management and care, health centres are designated as, TB Treatment Centre (1) and TB Treatment Centre (2). TB Treatment Centres (1) are health centres which are manned by Family Medicine Specialists or Medical Officers trained in TB management and have laboratory and x-ray facilities for the diagnosis of TB. These health centres function as centres for TB diagnosis and initiation of treatment. TB Treatment Centres (2) do not have these

facilities, and they can only function as Directly Observed Treatment (DOT) centres for continuation of TB treatment. Every patient diagnosed with TB will be offered routine HIV testing. Patients confirmed to have TB and who are HIV positive will be referred to the nearest public hospital for further management and care.

The National TB Control Program requires that patients who were diagnosed with TB and who had started treatment should be registered at their treatment centre. Since there were only 267 TB/HIV co-infected cases registered in the four centres between 1st January 2010 and 30th September 2010, all the identified patients were included in the study due to the limited number of patients available to meet the calculated sample size.

3.7 Operational definitions

3.7.1 Independent variables (Patients' characteristics)

The selected independent variables were based on the literature review. Independent study variables were grouped into socio-demographic, lifestyle, TB-related characteristics, HIV-related characteristics and laboratory profile.

a) Socio-demographic:

1. Age.

Age was categorised into three groups: ≤ 34, 35-54 and more than 55 years old.

2. Gender.

Male or female.

3. Ethnicity

Ethnicity was grouped into four: Malay, Chinese, Indian and Others.

4. Marital status.

Marital status was grouped into single, married and divorced.

5. Nationality.

Nationality was categorized into Malaysian and non-Malaysian. Non- Malaysians comprised a small number of patients originating from Indonesia, Myanmar, Thailand and Nepal.

6. Employment status

Occupation status was classified as ‘employed’ and ‘unemployed’. Housewives, students, pensioner or patients who were not working were included in the unemployed group.

b) Lifestyle:

1. Smoking status.

Smokers were defined as people who smoked, regardless of the number of sticks, duration and type of cigarette. Nonsmokers were those who had never smoked in their lifetime.

2. Alcohol consumption

Ever take alcohol were defined as people who took alcohol, regardless of the number of glasses and duration. Never take alcohol were those who had never drunk in their lifetime.

3. Mode of HIV transmission

Mode of HIV transmission was grouped into intravenous drug user (IDU), heterosexual, homosexual and others. The Centre for Disease Control and Prevention (CDC)

suggested that cases of HIV infection and AIDS are counted only once in a hierarchy of exposure categories. Persons with more than one reported mode of exposure to HIV are classified in the exposure category listed first in the hierarchy. For example, injecting drug use is accepted as the highest risk activity even though there may also be risk of HIV infection through sexual activity.

4. Body weight

Body weight recorded at the time of TB diagnosis (in kilogram (kg)).

c) TB-related characteristics:

1. Types of TB

Type of TB was categorized into three groups:

i) Pulmonary TB – TB disease involving the lung parenchyma

ii) Extrapulmonary TB - TB disease in the organs through lympho-haematogenous spread. For example: miliary TB, TB meningitis, TB lymphadenitis, TB of the pleura, genitourinary TB, TB of the bones.

iii) Both Pulmonary TB and extra-pulmonary TB- Patients suffering from both Pulmonary TB and Extra-pulmonary TB at the same time.

2. Status of TB diagnosis

Status of TB diagnosis was categorized into two groups:

i) New TB Case – Patient who was newly diagnosed with TB and had not received any previous TB treatment; or TB patients who have taken TB treatment, but less than four weeks; or patient who claims to have taken TB treatment but has no evidence of registration.

ii) Ever had TB before – Whether patients had relapsed TB, treatment after interruption or treatment after failure.

- Relapsed TB cases - TB cases that have been cured or completed TB treatment but became active again with positive sputum or based on bacteriological examination, histological or clinical-radiological (re-diagnosed as TB and treated as a new episode).
- Treatment after interruption – TB cases that were re-started TB treatment after previous treatment had stopped.
- Treatment after failure- TB cases that were re-started TB treatment after previous treatment had failed.

3. TB case detection

Active or passive case detection.

4. Presence of BCG scar

Bacillus Calmette–Guérin (BCG) scar was grouped into three categories:

i) Presence – Scar measuring more than 2 mm including keloid scars that arise above the surface of the skin.

ii) No scar – No scar at all or a small 'pinpoint' scar measuring less than 2 mm.

iii) Not recorded – if both of the above columns in TBIS-10A1 form were left blank.

5. Chest x-ray at TB diagnosis.

Chest x-ray at TB diagnosis was grouped into:

i) No lesion

ii) Minimal lesion – Slight lesions without demonstrable cavitation confined to a small part of one or both lungs. The total extent of the lesions should not exceed the volume of lung on one side which lies above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra.

iii) Moderately advanced lesion – One or both lungs may be involved, but the total extent of the lesions should not exceed the following limits:

a. Disseminated lesions of slight to moderate density not exceeding the total volume of one lung or the equivalent in both lungs.

b. Dense and confluent lesions not exceeding one third the volume of one lung.

c. Total diameter of cavitation, if present, not more than 4cm.

iv) Far advanced lesion – Lesions are more extensive than moderately advanced.

6. Tuberculin skin testing (TST)

The TST result values for each patient were coded as negative, positive or missing.

7. TB treatment

TB treatment is divided into two phases which is the Intensive Phase and the Maintenance Phase.

i) **Intensive phase** or initial phase is defined as standard TB treatment on a daily basis during the first two months of initiating TB treatment. For certain cases, the intensive phase may extend up to three months.

The treatment regimen can be 2SHRZ or 2EHRZ or 2HRZ

ii) **Maintenance Phase** or continuation phase is usually for the next four months but can be more than four months in certain cases.

The treatment regimen for maintenance phase can be $4S^2H^2R^2$ or $4R^2H^2$ or $4H^3R^3$ or 4HR or $4S^3H^3R^3$

(E= Ethambuthol, S = Streptomycin, H = Isoniazid, R = Rifampicin, Z = Pyrazinamide)

8. Co-morbidities/past medical histories

Co-morbidities and past medical histories that were assessed in the form TBIS 10A1 include diabetes mellitus, congenital heart disease, liver disease, chronic renal failure, malabsorption syndrome, steroid therapy, history of gastrectomy and cancer.

d) HIV-related characteristics

1. Date of HIV diagnosis

The date when the patient was first diagnosed as HIV positive based on the laboratory results.

2. Timing of HIV diagnosis in relation to TB diagnosis.

Timing of HIV diagnosis was classified as pre-TB diagnosis or post-TB diagnosis. It was later classified as HIV diagnosis before the year 2010 or after 2010.

3. Status of anti-retroviral therapy

Status of anti-retroviral therapy was grouped into ‘Yes’ for patients who were initiated ART or ‘No’ for those who were not on ART.

4. Timing of anti-retroviral therapy

Timing of anti-retroviral therapy was grouped into three categories: not on anti-retroviral therapy, anti-retroviral therapy started before TB diagnosis and anti-retroviral therapy started during TB treatment.

5. Regime of Anti-retroviral Therapy (ART)

Following the guidelines by the Malaysian Ministry of Health (MOH), the regime of anti-retroviral therapy in TB/HIV co-infection is categorized into:

i. No ART

ii. 2NRTIs + NNRTI

iii. 2NRTIs + PI

(NRTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, PI= Protease Inhibitor)

Table 3.2: Selection of antiretroviral therapy

Group	Drug
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	• Lamivudine (3TC) • Stavudine (d4T)
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	• Efavirenz (EFV) • Nevirapine
Protease Inhibitor (PI)	• Ritonavir • Indinavir

6. Opportunistic infections

Infections caused by a microorganism that does not normally in humans, such as Pneumocystic Carinii Pneumonia (PCP), candidiasis; and other infections occurs in AIDS patients.

7. Number of opportunistic infections (OI)

How many OIs occur in AIDS patients. Categorized into ‘No OI’, ‘One OI’, ‘two OIs’ and ‘three or more OIs’

8. Baseline CD4+ T-lymphocytes count

Categorised into '< 200 cells/µl', '≥ 200 cells/µl' and 'not available'.

e) Laboratory profile

Baseline laboratory results that were collected for each patient are as follows:

- Haemoglobin (g/dL)
- Total white blood cell count (10^3/µl)
- Platelet (10^3/µl)
- Urea (mmol/L)
- Natrium (mmol/L)
- Potassium (mmol/L)
- Creatinine (mmol/L)
- Total protein (g/L)
- Serum albumin (g/L)
- Total bilirubin (µmol/L)
- Alkaline Phosphatase (ALP) (U/L)
- Alanine Transaminase (AST) (U/L)
- CD4 T-lymphocytes count (cells/µl)
- HIV RNA viral load (copies/ml)
- HbsAg – reactive, non-reactive
- Anti-HCV– reactive, non-reactive
- Toxoplasma IgG – reactive, non-reactive
- Rapid Plasma Reagen (RPR) – reactive, non-reactive

3.7.2 Dependent variable (Outcomes).

a) Tuberculosis Treatment Outcomes

TB treatment outcomes were classified according to WHO recommendations - cure, treatment completed, treatment failure, died, defaulted or transferred out; and 'still on treatment'. The outcomes were assessed twelve (12) months after the TB diagnosis was made.

- **Cured:** Former smear-positive patient who was smear-negative in the last month of treatment, and on at least one previous occasion.
- **Completed treatment:** A patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
- **Treatment success:** A patient who is cured and who has completed treatment.
- **Treatment Failure:** A smear-positive patient who has remained smear-positive at five months or later during treatment.
- **Defaulted/Treatment Interrupted:** A patient who has interrupted treatment for two consecutive months or failure of the patient to attend the clinic after the date that the patient was due for follow-up.
- **Died:** A patient who dies for any reason during the course of treatment
- **Still on treatment:** The patient is still on treatment at the end of the study period and did not meet any other outcome during treatment. This category includes patients whose treatment were prolonged because of side effects or complications or whose initial regimen had been planned for more than twelve months.

b) Survival time

Survival time at 2 months (end of intensive phase of TB treatment), 6 months, 9 months and 12 months after starting TB treatment.

c) Survival probabilities

Survival probabilities or survival function is the probability that the individual survives from the date of diagnosis until 30th September 2011. The 2, 6, 9 and 12-month survival rate refers to the percentage of patients who were still alive at least 2, 6, 9 and 12 months respectively after the TB treatment was initiated. Hazard is the probability that patients under observation experience the event (death).

The event in this study was death regardless of the cause. The outcome was survival time, which refers to the time in months from the date of TB diagnosis until the patients died due to TB or other related causes or until when data were censored.

Patients were considered as censored if (1) they had not experienced the event (death) at the end of the study period (30th September 2011); (2) they were still alive at the end of the study period; (3) lost to follow up during the study period. For patients who were still alive when discharged, then subsequently lost to follow up, the date of their last follow up visits written in the medical records was the date of censoring.

3.8 Conceptual framework

Figure 3.3 shows the conceptual framework of risk factors for TB treatment default in TB/HIV co-infected patients. The conceptual framework shows that treatment behavior is influenced or shaped by personal, socioeconomic and treatment related factors. These factors are interrelated, and may affect behavior positively or negatively. The resulting behavior is determined by the ultimate balance of the negative and positive effects of these factors in an individual.

Figure 3.4 displays the conceptual framework of predictors of survival in TB/HIV co-infected patients. Survival among TB/HIV co-infected patients are affected by several factors that influence the risk of death identified as prognostic factors. In this study,

patients who were diagnosed with TB associated with HIV were followed up until they died or were censored at the end of the study period. The patients' survival times were calculated from the date their TB treatment were initiated.

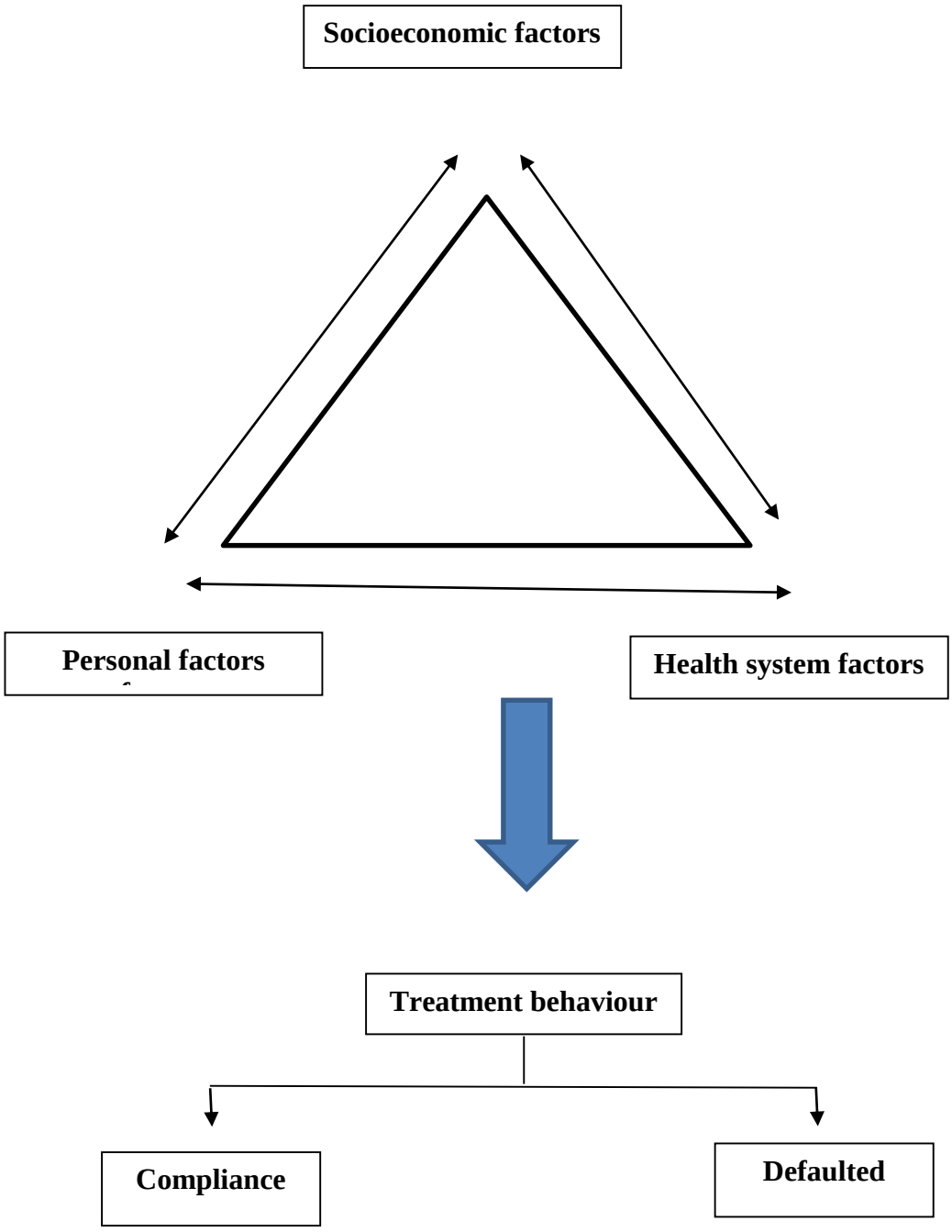


Figure 3.3: Conceptual framework of risk factors for TB treatment default in TB/HIV co-infected patients.

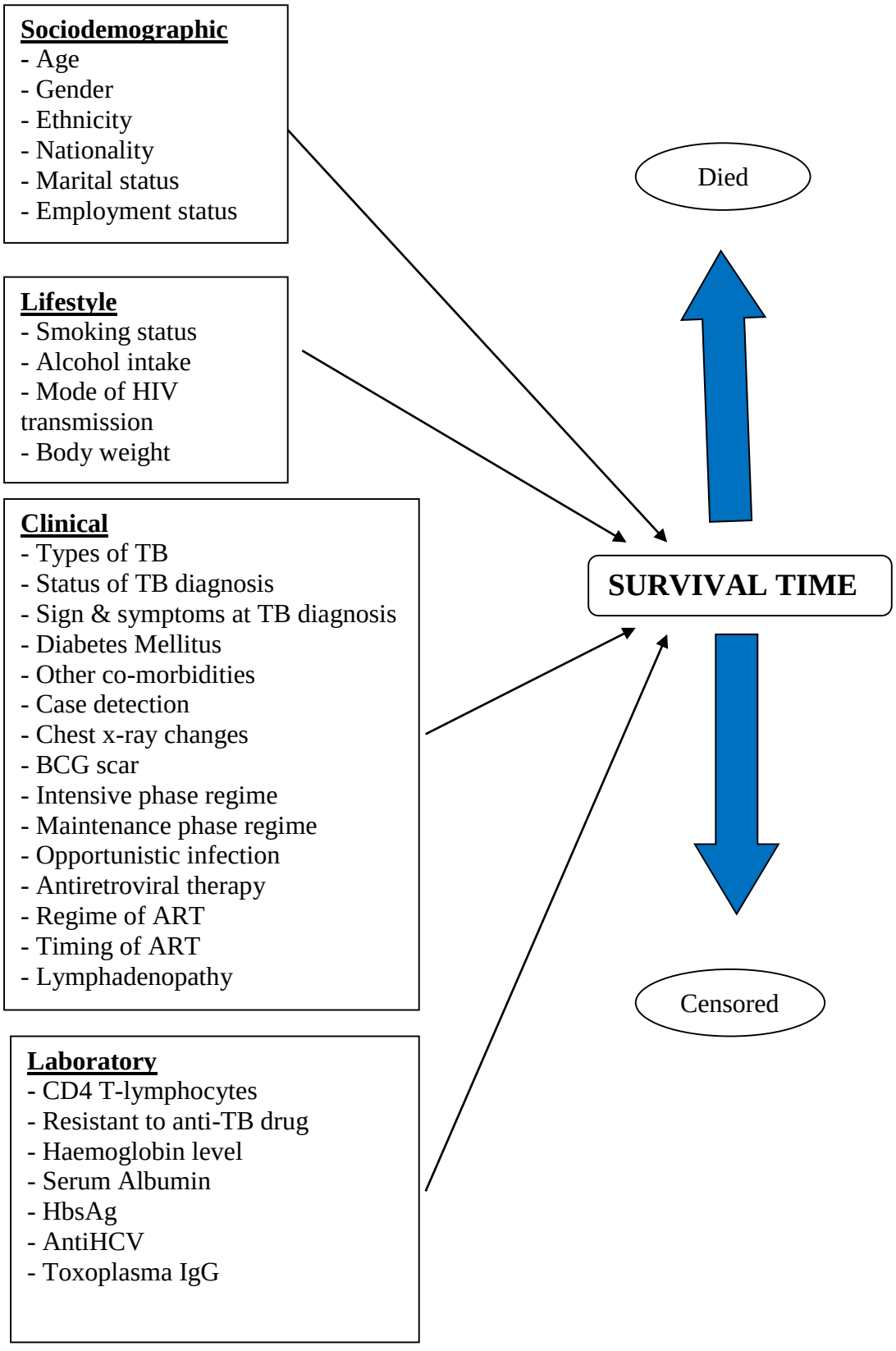


Figure 3.4: Conceptual framework of predictors of survival in TB/HIV co-infected patients.

3.9 Methods of Data Collection

3.9.1 Patient's recruitment

All TB patients who were tested positive for HIV, registered between January 2010 and September 2010 in Institute of Respiratory Medicine and three public hospitals in Selangor (Kajang Hospital, Klang Hospital and Sungai Buloh Hospital) were included in the study. In Malaysia, all TB patients were screened for HIV routinely, based on the guidelines by the Ministry of Health. HIV Enzyme-linked immunosorbent assay (ELISA) test results for these patients were traced and those who had positive results were included in the study.

The list of patients diagnosed with TB and HIV positive was obtained from the TB registration book (TBIS 101B) which was kept at each TB clinic. The patient's registration number or National Registration Identity Card (NRIC) number was used to retrieve their medical records. For non-citizens, their passport numbers or hospital registration numbers were used. Patients' medical records and TBIS documents were reviewed to obtain all the dependent and independent variables including information on socio-demographic data, lifestyle factors, clinical characteristics, pharmacological information and laboratory profiles.

3.9.2 Follow-up and exclusion

Data on further follow-up were reviewed and the required information was retrieved in the data collection form. Patients who were transferred out to other treatment centres or had their initial TB diagnosis changed to other diagnosis by the attending physician were excluded from the study. Then, patients' survival status and their survival times were determined. For this purpose, patients were followed up until 30thSeptember 2011. The date and cause of death of patients who died during hospitalization were extracted

from medical records. Survival status for those who were discharged alive and on regular appointment were also determined from their medical records. There were also patients who either defaulted treatment or follow-up appointment or were lost to follow-up. For these patients, their survival status was obtained by contacting the patients or relatives through the phone number or address as recorded in their medical records. For confirmation, the survival status was also obtained through the Department of National Registry. Further matching with the Electoral Register of 2011 was done to confirm their mortality status.

Date of initial diagnosis was defined as the first time individuals were diagnosed with TB diagnosis and specific treatment was initiated. Treatment outcomes were assessed at the end of TB treatment according to WHO guidelines. Survival time was defined as time in months from the date of initial diagnosis to death, or in the case of individuals who did not die, the last follow up recorded by the health centres. The ascertainment of mortality data was done by reviewing hospital records and data was matched with the National Registration Department using the identity card number.Information gathered from the medical records and TBIS documents were used to complete a standard data collection form. To ensure confidentiality, each case was assigned a study identification number that was included on all records as personal identifiers.

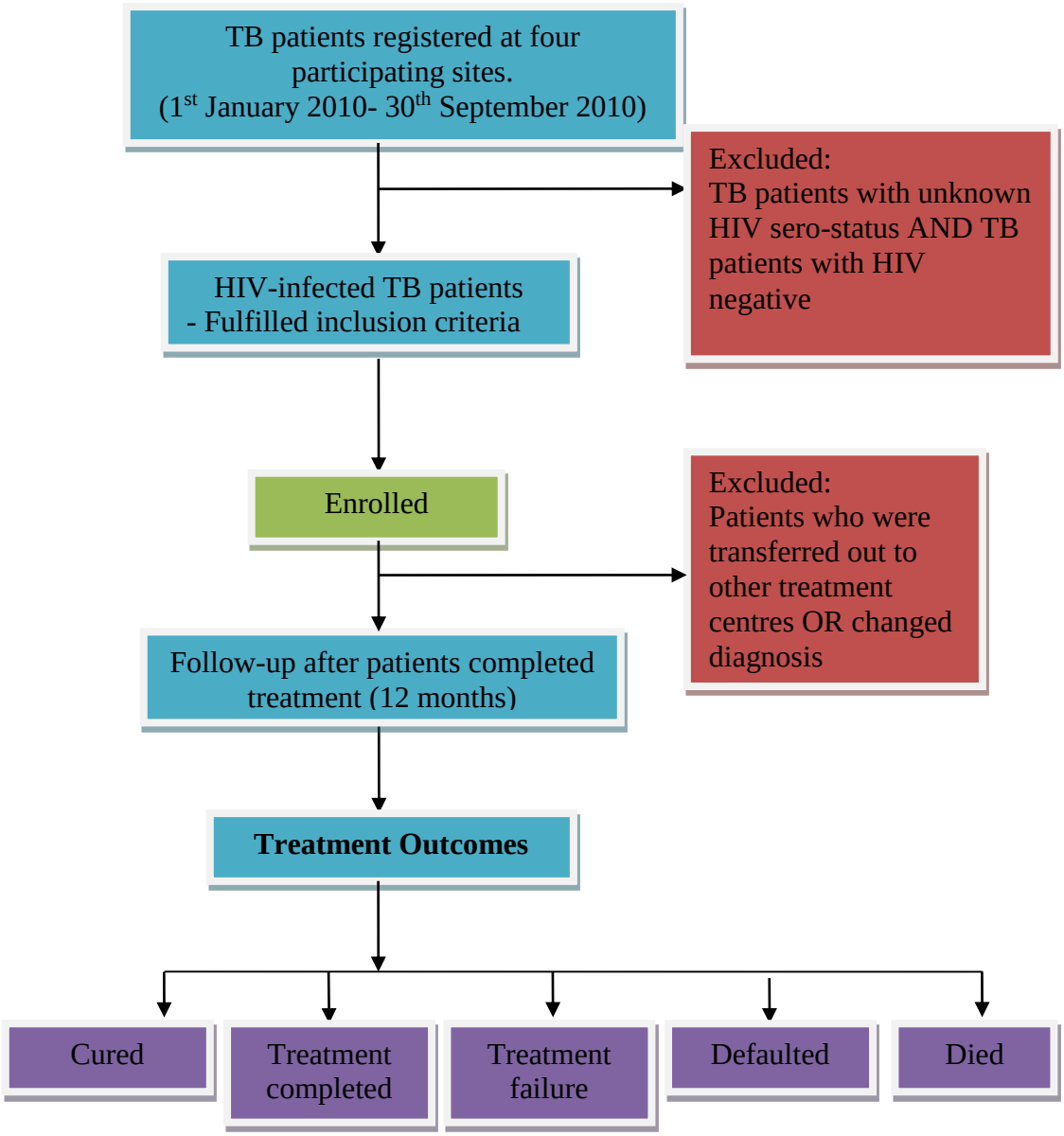


Figure 3.5: Flow chart of data collection process.

3.10 Study Instruments

Socio-demographic data, clinical and laboratory information and treatment outcome information were extracted from the patient's medical record and TBIS documents (TBIS 10A1, TBIS 10A2and TBIS10-I); HIV clinic records and in-patient records. All this information was documented in a standard data collection form.

3.10.1 National Tuberculosis Information System (TBIS) documents.

The National TB Information System is a system of reporting TB cases in Malaysia which was implemented in 2003. Through this system, TB data are collected and reported uniformly by all TB clinics or treatment centres across the country using standardized forms. In this system, all TB cases are notified to the District Health Office, which also functions as the data centre for the collection, supervision, monitoring and reporting of all TB activities of a district.

These data were used for the purpose of monitoring TB cases not only in the treatment centres, but also at the district, state, and at the national level. This allows for comparison of data made at the national and at the international level through the annual reports to the World Health Organization (WHO).

TBIS documents prepared for three major activities of TB control programs, include: 1) patient and contact management, 2) laboratory services and 3) BCG vaccination. Each one has three different formats which include accessories (for daily operational use), TB registers and TB reports. For the purpose of data collection for this study, document TBIS that were used are TBIS 101B (TB patients registration book), TBIS 10A1 (Initial information on TB treatment) and TBIS 10A2 (Information on follow-up treatment) and TBIS 10I (TB patient's treatment card).

TBIS 101B (TB registration book)

This book is available and maintained in all Treatment Centers (1). This register contains all cases treated at the concerned treatment centre. Among the important information contained in this register are patient information and records of specific events during the treatment; particularly the transfer of patients to other treatment centres. It also documents patient's records of missing treatment and treatment outcome.

TBIS 10A1

This form contains TB patients' data and is designed for the purpose of registration of TB patients and input to the national TBIS database, Ministry of Health Malaysia. It contains basic information on individual TB patients including aspects of socio-demographic, clinical, laboratory test results and the initiation of TB treatment.

TBIS 10A2

This form is records the progress of patients during follow-up and their treatment outcomes.

TBIS 10I

The TBIS 10-I or TB treatment card records all information pertaining to the treatment of each patient, sputum status monitoring, DOT and treatment outcomes. The TB treatment card is coloured either orange or white. The Orange coloured card is designed for cases that are TB positive (sputum smear positive) and white coloured card for TB negative (sputum smear negative) cases. This treatment card is filled in the TB Treatment Centre (1) immediately after a TB diagnosis is made. For patients who are transferred out to other treatment centres, the 10-I TBIS copy will be sent by post to the new treatment centre. Data contained in this card include:

i. Name of treatment centre that started TB treatment and continued treatment

ii. Category of TB cases, status of TB diagnosis and serial sputum status.

iii. Regime of TB treatment received, the date of TB treatment regime changed and the reasons for changing treatment regime.

iv. TB treatment outcomes

Medical Records

Other medical records were reviewed to obtain information that could not be retrieved from the above TBIS documents. The records included medical records in TB clinics, medical records in HIV clinics, medical records during admission, which were filed in a record office, laboratory results and death certificate.

As Hospital Sungai Buloh utilizes Information and Communication Technology (ICT) applications in its clinics, patient information in the Electronic Hospital Information System (e-HIS) was also reviewed to retrieve the missing data.

3.10.2 Data Collection Form

The data collection form was developed based on TBIS documents, particularly TBIS-10A1 and information for literature review. The data collection forms have three parts. Part A collected details about each patient's socio-demographic characteristics, mainly their age, gender, ethnicity, marital status and employment status. It also included patient's lifestyle practices, including their smoking status and alcohol consumption. Part B documented the clinical information of each patient, which included details about the date of TB diagnosis, type of TB, status of TB diagnosis, TB treatment received (intensive and maintenance phase), date of HIV diagnosis, chest x-ray changes, lymphadenopathy, co-morbidities, antiretroviral therapy, opportunistic infection; and

clinical signs and symptoms at the time of TB diagnosis. Section E in Part B recorded their laboratory results which included a full blood count, Renal Profile, Liver Function Test, CD4+ T-lymphocytes count, Hepatitis B serology (HbsAg), Hepatitis C serology (AntiHCV), Toxoplasma serology (Toxo IgG) and Rapid Plasma Reagin for the screening of syphilis. Part C recorded TB patient's treatment outcome after they completed treatment.

3.11 Ethical Consideration and Confidentiality

The main ethical issue was patients' privacy since their medical records were retrieved to obtain information. Instead of using the patient's name in the data collection sheet, the researcher used a confidential code to represent each patient. Ethical clearance was obtained from the Medical Ethics Committee of University of Malaya on 24 March 2010 (MEC Ref No. 776.11) and from Ministry of Health Research and Ethics Committee (MREC) with the reference number NMRR-10-1201-6599. The requirement to obtain informed written consent from each individual was waived by the institutional review board as the study was limited to review of existing medical records.

3.12 Data Management

The data were entered into the personal computer using a Statistical Package for Social Sciences (SPSS) Version 16.0 at the end of the day after the data collection or if time did not permit, it was entered no more than a week from data collection day. Entry was double checked immediately against the raw data to exclude typing errors. The double data entry method was done to check the consistency of data whereby data were entered by two persons and saved in two different files. Data were compared using Epi Info to check for dissimilar records in the two different files. Where the data did not match, it was checked with the original data set. Duplicate entries were identified and eliminated. Data was also checked for outliers by running the 'frequencies' of all variables. After

that, data transformation was performed using SPSS for Windows (version 22.0) by creating new variables using the Transform, Recode or Compute commands; when necessary. The data cleaning such as validation, editing and tracing the missing data was carried out before commencing the data analysis. For the purpose of safekeeping, all files were backed up regularly.

3.13 Data analysis and interpretation of results

SPSS for Windows (version 16.0) was used for data entry and all statistical analyses. The data analysis was divided into descriptive and inferential analysis.

3.13.1 Descriptive analysis

In the descriptive analysis, the frequency distribution, measures of central tendencies and measures of distribution were produced. Continuous data were checked for normality by testing for the presence of skewness and kurtosis. The skewness value gives information about the symmetry of the distribution. Kurtosis gives information about the 'peakedness' of the distribution. Positive skewness values mean clustering of scores on the left at the low values or known as positive skew. Negative skewness values mean scores are clustered at the right-hand side of the graph. Positive kurtosis values mean that the distribution is slightly peaked or clustered in the center; with long thin tails. Kurtosis values below 0 indicate a distribution that is relatively flat (too many cases in the extremes). Kolmogorov-Smirnov statistic results were also reviewed to assess for normality. A non-significant result ('Sig.' value of more than 0.05) indicates normality.

Data exploration was done mainly to acquire the descriptive statistics that describe all the variables and to examine the distribution of the data graphically. Following data

exploration the tables were constructed. The continuous variable with normal distribution was summarized using mean and standard deviation and the skewed distribution was summarized using the median and interquartile range (IQR). Certain continuous variables such as age, hemoglobin level, albumin level and CD4 T-lymphocytes count were transformed into categorical variables for further analysis.

All the categorical variables were summarized using counts and percentages (%). After examining the data, some categories of certain variables were collapsed due to small numbers of the sample. For continuous variables, the Student t test was performed for normally distributed variables and Mann-Whitney U test for non-normally distribution. For categorical variables, the Pearson chi square test or Fisher's exact test was used depending on the expected values in the cells. Simple logistic regression was used for categorical data with more than two categories.

Some of the independent variables were re-categorized when it was deemed necessary. For variables which had more than two categories, dummy variables were created before further bivariate analyses were done. An example of the dummy table is shown in table 3.2.

Table 3.3: Dummy variable for the independent groups which have more than two categories

Variables	**Reference**		**Dummy variable**		
Ethnicity	Others		**Ethnic(1)**	**Ethnic(2)**	**Ethnic(3)**
		Malay	1	0	0
		Chinese	0	1	0
		Indian	0	0	1
		Others	0	0	0

Student t test

There are three types of t-test, namely one sample t-test, paired t-test and independent t-test. In this study, independent t-test was used for data analysis. The independent t test is a statistical test used to compare the means of two groups. It is performed when there is one nominal variable and one measurement variable with the following assumptions:

i) Normal distribution in each group (if the sample size is 30 or more in each group, the need for normality is reduced)

ii) Equality of variances (if the sample sizes are equal, this assumption may be ignored)

iii) Independence of observations

The equation for independent t-test is as follows:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s\sqrt{\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

Where,

$s\sqrt{(1/n_1 + 1/n_2)}$ is the estimated standard error of the difference between the means.

't' is considered to be statistically significant if it's calculated value is sufficiently different from 0.

3.13.2 Inferential analysis

Inferential analysis was performed to examine the relationship between each independent variable with the outcome. In this study, survival analysis was conducted to determine the association of all independent variables with the following dependent variables, namely, (i) defaulted TB treatment (defaulters and non-defaulters) and (ii) survival of TB/HIV co-infected patients (mortality status : alive/dead).

Survival Analysis

Survival analysis was developed to estimate the survival of a cohort over time. It can be applied to any outcomes that are dichotomous and occur only once during follow-up. The time to event or survival time can be measured in days, weeks or years. In survival analysis, subjects are usually followed over a specified time period and the focus is on the time at which the event of interest occurs. Observations are called censored when the information about their survival time is incomplete.

Kaplan Meier analysis

Kaplan Meier is a non-parametric method that is widely used to estimate and graphically plot survival probabilities as a function of time. It can be used to obtain univariate descriptive statistics for survival data, including the median survival time; and compare the survival experience for two or more groups of subjects. The log-rank test was used to estimate the probability of survival and compare the survival curves between the various categories. Survival probabilities across the groups were plotted for each variable using Kaplan-Meier Product Limit estimates of survivorship function method.

The survival probability at any particular time is calculated by the formula given below (Kleinbaum & Klein, 1996):

$$S(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i}$$

Where;

S(t) = proportion of individuals surviving until time t.

n_i = the number of survivors just prior to time t_i or the number of survivors less the number of losses/censored cases

d_i = the number of deaths at time t_i

Cox proportional hazards regression

Univariable Cox proportional hazards analysis was conducted for all independent variables to get the independent effects of each variable and to have a preliminary idea of which variable(s) that might be of prognostic importance. The Cox proportional hazards model assumes that the time to event and the covariates are related through the following equation:

$$h_i(t) = [h_0(t)] \times [\exp(\beta_1 X_{i1} + \beta_2 X_{i2} + \ldots\ldots\ldots\ldots + \beta_p X_{ip})$$

Where

$h_i(t)$ represents the hazard, or the risk of suffering the event of interest, of patient *i* at time *t*,

$h_0(t)$ is the baseline hazard at time t

p is the number of covariates

Multiple Cox Regression

Multivariable Cox hazard regression was applied to identify the independent prognostic variables of TB/HIV co-infection. A combination of variables will produce a more accurate prognosis than any of these variables examined one at a time. The log rank p-value less than 0.25 was set as cut off value to choose predictors for entry into multiple Cox proportional hazards regression analysis. The cut off value of *p* less than 0.25 was

chosen in order not to miss significant predictors which may have been confounded during univariate analysis. This is similar to the Hosmer-Lemeshow approach in logistic regression.

Predictors with p-value less than 0.25 from the univariate analysis were then fitted jointly into a Cox regression model. In the presence of multiple variables, some variables may not be significant anymore. Each variable starting from the least statistically significant was dropped individually from the model and the -2 log likelihood (-2LL) from the nested models were compared with and without that variable. If the value of the difference in -2LL was not increased significantly, the variable was dropped. Once a variable was discarded, the effect of omitting each of the remaining covariates in turn was examined. Here, "preliminary main effect model" was obtained.

Interaction

To refine the model, all possible two-ways interactions of independent variables in the preliminary main effect model were checked. The inclusion of the interactions was to improve inferences and to obtain a more realistic model. Interactions among the covariates were examined by creating a new covariate as a product of the original covariates. For example, the interaction of X_1 and X_2 can be defined as X_1X_2 and represented as X_3. There will be a new term $\beta_3X_1X_2$ in the hazard function.

1) If $X_1=0$, one additional unit of X_2 has a hazard ratio of $\exp(\beta_2)$
2) If $X_1=1$, one additional unit of X_2 has hazard ratio of $\exp(\beta_2+ \beta_3)$

Positive β_3 enables X_2 to have more effect in group 1 of X_1than in group 0. If β_3 is negative the effect of X_2 could be less in group 1 than in group 0. A similar explanation can be achieved by exchanging the positions of X_1 and X_2.

Then, the independent variables were fitted into linear regression model and Variation Inflation Factor (VIF) was obtained to assess the multicolinearity (MC). The VIF value of more than 10 was considered to indicate a problem of multicollinearity, which required remedial action.

Model Fitness

Model fitness was done by testing the assumption of proportional hazards and diagnostics statistics using two ways (Rosner B., 2006):

1. Graphical approach using Log-Minus-Log plot

Hazard regression models for survival involved the proportional hazards assumptions, where the variables were independent with respect to time, hazards were proportional and their hazards ratios should be constant across time, that is, the proportionality of hazards from one case to another should not vary over time. The assumption was verified graphically by inspection of the cumulative hazards curves (log minus log plots) and hazard plots in all categorical independent variables in the preliminary final model. The almost parallel curves indicate that the hazards of dying were proportional over time. Thus, the assumption of the proportional hazards model would be fulfilled and the Cox regression model would be valid.

2. Goodness-of-fit (GOF)

The implementation of the test is by correlating the partial residuals and the survival time rank. This is a more confirmatory test because it provides a test statistic and p-value for assessing the proportional hazard assumption for a given predictor of interest. Thus, a more objective decision can be done using a statistical test. This is done by performing a Cox regression model and saving the partial residuals for each predictor. The time variable is ranked from 1 for the subject who has the earliest event, to the

largest value and then correlated with the residuals. The tests will suggest that the proportional hazard assumption is violated if the p-value is less than 0.05.

The results from the final model were summarized with regression coefficient, adjusted hazard ratio (AHR), which described the risk of death, its 95% confidence interval (CI) and its corresponding p-value. The significant level was set at 0.05, two-tailed. An HR is a ratio of the risks for different subgroups of a co-variate. For example, for a binary co-variate such as gender where males are coded as 1 and female 0, a hazard ratio of 2.00 would imply that the risk of dying among male is 2.00 times higher than among female.

3.14 Summary

This chapter details the study design and work done in extracting the data from four study centres, namely Institute of Respiratory Medicine, Kajang Hospital, HTAR Klang and Sungai Buloh Hospital. The data collection process took longer than expected due to various logistic issues. Data cleaning, transformation and data analysis were also performed.

CHAPTER 4: RESULTS

About this chapter

The results of this report will be presented following the sequence of the specific objectives as in Chapter 3. This chapter is divided into five sub-sections which describe the following information in detail: Section 4.1 is the descriptive analysis which describes the socio-demographic, lifestyle, TB-related characteristic, HIV-related characteristics and laboratory profiles of TB/HIV co-infected patients in this study. Section 4.2 presents the results on TB treatment outcomes in TB/HIV co-infected patients. The factors associated with default from TB treatment in TB/HIV co-infected patients are also described in detail. Section 4.3 describes the mortality rate and the causes of death in TB/HIV co-infected patients in this study, the survival curves and finally the predictors of death in TB/HIV co-infected patients. Section 4.5 is the summary of this chapter.

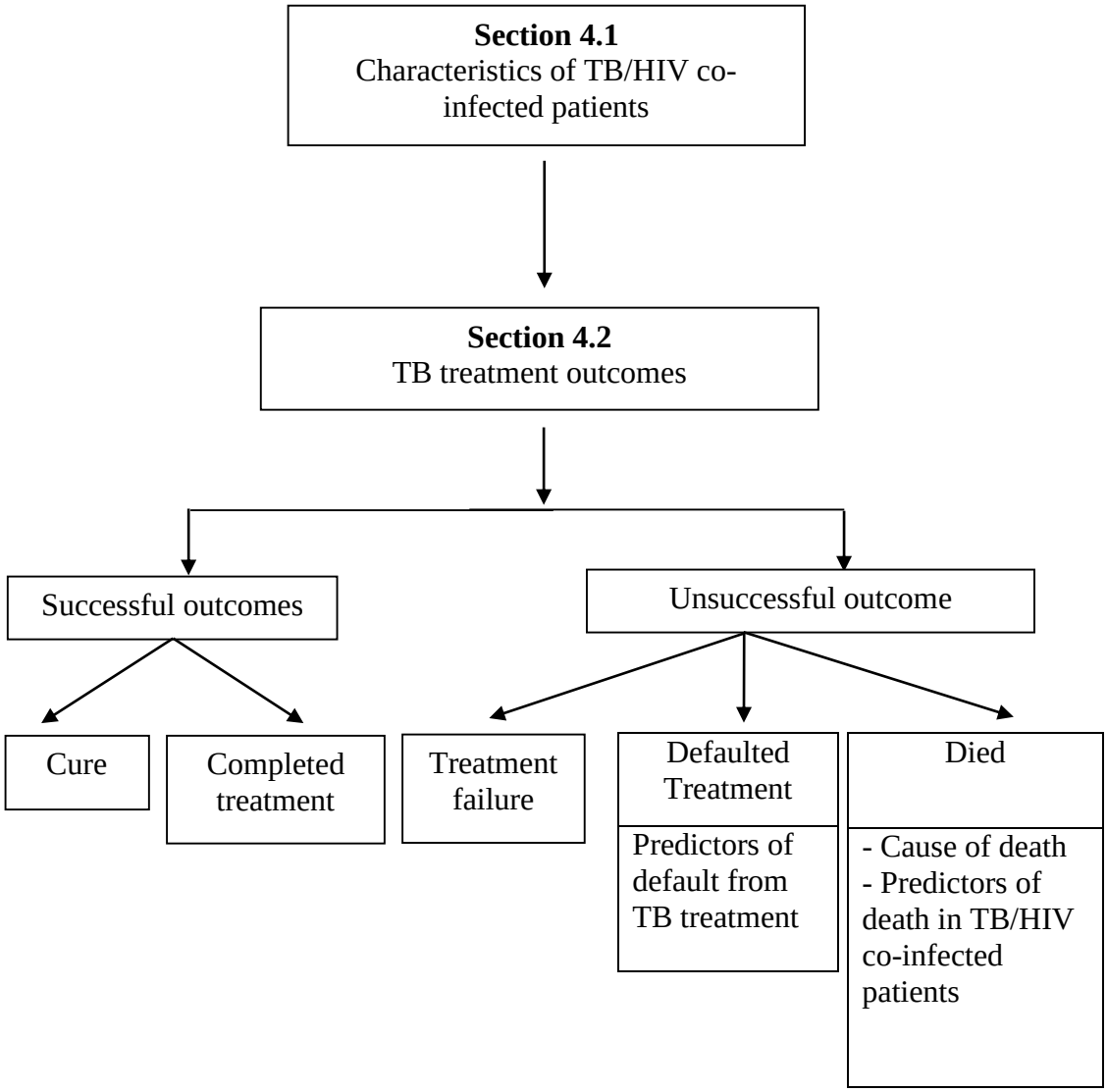


Figure 4.1 Flowchart of data analysis.

4.1 Descriptive Analysis

A total of 2262 tuberculosis patients were registered between 1st January 2010 and 30th September 2010 in Hospital Sungai Buloh, Hospital Kajang, Hospital Tuanku Ampuan Rahimah, Klang; and Institute of Respiratory Medicine, Kuala Lumpur. Among these patients, 267 patients were co-infected with HIV, 32 patients (12.0%) were transferred out to other treatment centres and 8 patients (3.0%) had their diagnosis changed because they were later found to have a different diagnosis and were thus excluded. Finally, 227 patients were eligible for analyses according to the inclusion criteria. The mean follow-up duration was 14.3 months (SD 6.3) months and the median was 15.9 (IQR 5.8) months.

Table 4.1: No of TB Cases and TB with HIV positive registered in four centres between 1st January 2010 and 30th September 2010.

Location	Total TB Cases (n)	TB with HIV-positive (n, %)
Hosp. Sungai Buloh	381	193(50.7)
Hosp. Kajang	208	17 (8.2)
HTAR Klang	371	19 (5.1)
Inst. Respiratory Medicine	1302	38 (2.9)
TOTAL	**2262**	**267 (11.8)**

The characteristics of patients included in the analyses and those who were excluded (transferred out and changed diagnosis) by age, gender and ethnicity in the control group is illustrated in table 4.2. There was no statistically significant difference in the age group, gender and ethnic distribution between the two groups.

Table 4.2: Characteristics of patients included in analyses compared to transferred out and changed diagnosis.

Variables		Included (n = 227) No (%)	Excluded (n = 40) No (%)	*p* value
1. Age group, year	< 34	73 (32.2)	13 (32.5%)	0.279
	35-54	141 (62.1)	22 (55.0%)	
	≥ 55	13 (5.7)	5 (12.5%)	
2. Gender	Male	200 (88.1)	35 (87.5%)	0.921
	Female	27 (11.9)	5 (12.5%)	
3. Race	Malay	110 (48.5)	20 (50.0%)	0.517
	Chinese	37 (16.3)	8 (20.0%)	
	Indian	37 (16.3)	3 (7.5%)	
	Others	43 (18.9)	9 (22.5%)	

4.1.1 Socio-Demographic Distribution

Table 4.3 displays the distribution of socio-demographic characteristics of TB/HIV co-infected patients. The mean age of TB/HIV co-infected patients were 39.1(SD 8.6) years old and ranged from 16 to 62 years old. The peak age group was patients from 35 to 54 years old (62.1%). Male to female ratio was 7:1. The TB/HIV co-infected patients were predominantly Malays (48.5%) followed by Chinese (16.3%), Indians (16.3%) and Others (18.9%). Other race includes indigenous ethnic groups born in Sabah and Sarawak; those who were born from interracial marriages and also non-citizens. A total of 182 (81.5%) Malaysians formed the majority of TB/HIV co-infected patients while there were only 42 (18.5%) non-Malaysians patients who originated from Myanmar, Indonesia, Nepal and Thailand. More than half the patients were unemployed (57.3%). The majority of TB/HIV co-infected patients were single or divorced (67.0%).

Table 4.3: Distribution of socio-demographic characteristics of 227 TB/HIV patients.

Variables		N (%)
Age group, years	< 34	73 (32.2)
	35-54	141 (62.1)
	≥ 55	13 (5.7)
Age (mean (SD))	39.1 ± 8.6 years	
Gender	Male	200 (88.1)
	Female	27 (11.9)
Race	Malay	110 (48.5)
	Chinese	37 (16.3)
	Indian	37 (16.3)
	Others	43 (18.9)
Nationality	Malaysian	185 (81.5)
	Non- Malaysian	42 (18.5)
Employment status	Employed	97 (42.7)
	Unemployed	130 (57.3)
Marital status	Single/divorced	152 (67.0)
	Married	75 (33.0)
Religion	Islam	121 (53.3)
	Buddhist	38 (16.7)
	Hindu	30 (13.2)
	Others	38 (16.8)
Incarceration*	Yes	21 (18.5)
	No	206 (81.5)

*Incarceration: Prisoners/Drug Rehabilitation Centre inmates at the time of TB diagnosis.

4.1.2 Lifestyle Factors

Lifestyle factors referred to the smoking status, alcohol consumption mode of HIV transmission and body weight. The lifestyle characteristic of TB/HIV co-infected patients are highlighted in Table 4.4.

The majority of the respondents in this study were smokers (74%) and non-consumers of alcohol (76.2%). Mode of HIV transmission was mainly through injecting drugs (55.9%) followed by heterosexual (35.7%) homosexual (3.5%) and others (4.8%, n=11). The median body weight of these patients was 49.7 (SD 9.0) kg.

Table 4.4: Distribution of lifestyle factors of 227 TB/HIV patients.

Variables		N (%)
Smoking status	Smoker	168 (74.0)
	Non-smoker	59 (26.0)
Alcohol intake	No	173 (76.2)
	Yes	54 (23.8)
Mode of HIV transmission	Intravenous drug users	127 (55.9)
	Heterosexual	81 (35.7)
	Homosexual	8 (3.5)
	Others[a]	11 (4.8)
Body weight (Mean (SD))	49.7 (±9.0)kg	

[a] Others: Blood transfusion (n=1) and Unknown (n=10).

4.1.3 TB-related Characteristics

TB related characteristics referred to the type of TB, status of TB diagnosis, TB treatment, status of BCG immunization and other co-morbidities. The TB-related characteristics are illustrated in Table 4.5. Pulmonary TB occurred in 48.9% of patients, followed by extra-pulmonary TB (28.2%) and 22.9% had both pulmonary and extra-pulmonary TB. The majority of patients (70.9%) were newly diagnosed TB cases whereas another 29.1% had previous history of TB. Among 227 patients, only 62.6% of cases had at least one specimen collected at any time before or during treatment which was positive for acid-fast bacilli and/or culture-positive for *Mycobacterium tuberculosis* (MTB) in the sputum, or other type of samples (blood, pleural fluid, cerebro-spinal fluid etc.).

Among all patients, 85.9% were on anti-tuberculosis regimes that contained rifampicin, as recommended by the WHO. The median time of the intensive phase was 61 days or 2.0 months. Patients who developed adverse drug reactions to rifampicin, were prescribed another drug regimen such as isoniazide (H) and pyrazinamide (Z) (3.5%) and others (10.6%). Maintenance phase was continued for 71.9% of patients with 137 (60.4%) on isoniazid (H) and rifampicin (R) regime. Another 28.8% were not on maintenance therapy mainly because they defaulted follow-up. In patients who were on maintenance therapy, the median time of maintenance phase was 149 days (5.0 months).

All TB types were included in this study. Smear positive pulmonary TB was reported in 40.5% of patients, in which 29.5% of total cases had smear positive TB only. Another 11.0% had smear positive and extra-pulmonary TB. Smear negative PTB only was diagnosed in 18.9%, smear negative PTB and extrapulmonary TB in 12.3% and 28.2% had extrapulmonary TB only.

Among those with extrapulmonary TB, 32.2% had disseminated or miliary TB, 10.1% had TB lymphadenitis, 5.3% had TB meningitis, 1.3% had intra-abdominal TB and pleural TB respectively and another 3.5% were at other sites.

Co-morbidities that were assessed included diabetes mellitus, congenital heart disease, malabsorption syndrome, malignancies, chronic liver disease and history of gastrectomy. The frequencies of other co-morbidities were low in these patients. Overall, only 41 (18.1%) cases had co-morbidities. Diabetes mellitus was present in only 2.6% (n=6) of cases.

Case detection was classified as ‘Passive’, if the patient came to hospital for TB investigation by himself (self-referral) and ‘Active’ if household and other close contacts of infectious case subjects were identified and tested for TB infection or via screening of high risk individuals. Among 227 patients, 11 (4.9%) were diagnosed as

having TB through active case finding while 10 patients (4.4%) were detected through screening of inmates in prisons and drug rehabilitation centres. One patient was identified by contact tracing of a TB case.

Table 4.5: Distribution of TB-related characteristics in 227 TB/HIV co-infected patients

Variables		N (%)
Types of TB	Pulmonary TB	111 (48.9)
	Extra-pulmonary TB	64 (28.2)
	Both	52 (22.9)
Status of TB diagnosis	Newly diagnosed TB	161 (70.9)
	Ever had TB before	66 (29.1)
Case detection	Passive	216 (95.2)
	Active	11 (4.9)
Intensive phase regime	HRZ[a]	195 (85.9)
	HZ	8 (3.5)
	Others	24 (10.6)
Maintenance phase	No maintenance therapy	64 (28.2)
	HR	137 (60.4)
	Others	26 (11.4)
Changed in treatment[b]	Yes	37 (16.4)
	No	190 (83.7)
Median time of intensive phase (days)		61.0 (IQR 52 -78)
Median time of maintenance phase (days)		149.0 (IQR 111-210)
BCG scar	Scar present	197 (86.8)
	No scar/ NR	30 (13.2)
Co-morbidities[c]	Yes	41 (18.1)
	No	186 (81.9)
Diabetes Mellitus	Yes	6 (2.6)
	No	221 (97.4)

[a]HRZ: Isoniazid, Ryfampycin & Pyrazinamide; HZ: Isoniazid & Pyrazinamide only; HR: Isoniazid &Ryfampycin
[b]Change in diagnosis: change from the initial TB regime (HRZ) to another due to side effects of treatment or adverse reaction.
[c]Co-morbidities: Include diabetes mellitus, congenital heart disease, malabsorption syndrome, malignancies, chronic liver disease and history of gastrectomy

4.1.4 Clinical Presentation

Table 4.6 displays the clinical presentations in TB/HIV co-infected patients. Sign and symptoms assessed were based on TBIS 10A form which included cough more than two weeks, cough with sputum, hemoptysis, loss of weight, fever, night sweat and loss of appetite. The frequency distribution of symptoms presented among TB/HIV co-infected patients in study sites are shown in Table 4.6. At diagnosis, most of the patients presented with fever (74.9%), followed by loss of weight (69.2%), cough more than two weeks (67.0), loss of appetite (66.1%), cough with sputum (48.5%) and night sweats (43.2%). Hemoptysis was experienced by only 13.7% of the patients.

Table 4.6: Distribution of clinical presentations in 227 TB/HIV co-infected patients

Variables		N (%)
Cough more than two weeks	Yes	152 (67.0)
	No	75 (33.0)
Cough with sputum	Yes	110 (48.5)
	No	117 (51.5)
Hemoptysis	Yes	31 (13.7)
	No	196 (86.3)
Loss of weight	Yes	157 (69.2)
	No	70 (30.8)
Fever	Yes	170 (74.9)
	No	57 (25.1)
Night sweats	Yes	98 (43.2)
	No	129 (56.8)
Loss of appetite	Yes	150 (66.1)
	No	77 (33.9)
Chest x-ray changes	No lesion	52 (22.9)
	Minimal lesion	109 (48.0)
	Advanced lesion	66 (29.1)
Lymph node enlargement	No lymphadenopathy	120 (52.9)
	Lymphadenopathy	107 (47.1)

4.1.5 HIV-related Characteristics

Table 4.7 showed the distribution of characteristics of HIV in TB/HIV co-infected patients. The majority of the patients (67.3%) was diagnosed to have HIV before TB diagnosis. There were 140 (61.7%) patients on anti-retroviral therapy, whereas 87 (38.3%) were not on any anti-retroviral therapy. Among them, antiretroviral therapy was initiated before TB diagnosis in 39 (17.2%) patients and another 101 (44.5%) patients were started on antiretroviral therapy after they were diagnosed with TB. For these patients, the median time from TB diagnosis to initiating ART was 51.5 (SD 62.2) days. In terms of ART regimen for 140 (61.7%) who were on ART during TB

treatment, 127 (56.2%) were on two NRTI and an NNRTI, ten patients (4.4%) on NtRTI + NNRTI, two patients (0.9%) on two NRTI + PI and only one patient (0.4%) received NtRTI + PI.

Table 4.7:Distribution of HIV-related characteristics in 227 in TB/HIV co-infected patients

Variables		N (%)
Timing of HIV diagnosis in relation to TB diagnosis	Same year (2010)	74 (32.6)
	Before 2010	153 (67.4)
Opportunistic infection	Yes	108 (47.6)
	No	119 (52.4)
Anti-retroviral therapy	Yes	140 (61.7)
	No	87 (38.3)
Anti-retroviral regime	No ART	87 (38.3)
	2NRTI + NNRTI	127 (56.2)
	NtRTI + NNRTI	10 (4.4)
	2NRTI + PI	2 (0.9)
	NtRTI + PI	1 (0.4)
Timing of antiretroviral therapy	No ART	87 (38.3)
	Before TB diagnosis	39 (17.2)
	During TB treatment	101 (44.5)
Median time starting antiretroviral during TB treatment[a]	51.5 (IQR 62.2) days	

[a]**n**= 101
IQR:Interquartile range;NRTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, PI = Protease Inhibitor

4.1.6 Laboratory Investigations

Table 4.8 describes the frequency distribution of laboratory characteristics among TB/HIV co-infected patients in the study sites. A total of 178 (78.4%) of the patients had a low hemoglobin level (<12 g/DL). CD4 counts were available for only 208 patients (91.6%). The mean CD4 count was 109.8 (SD 131.3) cells/µl with a median of 59 (IQR 133.5) cells/µl. Among the 95 patients with available HIV RNA viral load

result, the median HIV RNA viral load was 204,638.0 copies/ml (IQR 828,620.0). CD4 count and HIV RNA viral load test were not available for all patients because those tests are expensive and were done on a case by case basis.

From a total of 227 patients, 167 isolates (73.6%) were tested for anti-TB drug sensitivity. One isolate was resistant to pyrazinamide, one was resistant to streptomycin and another one was resistant to rifampicin. None of the isolates had multidrug resistant tuberculosis (MDR-TB). Co-infection with Hepatitis B were reported in 15 patients (6.6%), Hepatitis C in 127 patients (55.9%), Toxoplasmosis in 51 patients (22.5%) and syphilis in 11 patients (4.8%).

Table 4.8: Distribution of laboratory profiles in 227 TB/HIV co-infected patients

Variables		N (%)
Hemoglobin level	< 12 g/dL	178 (78.4)
	≥ 12 g/dL	49 (21.6)
(Mean (SD))	10.5(±1.9)g/dL	
Total White Blood Cell (Mean (SD))	6.3 (±3.3) 10^3/µl	
Platelet (Mean (SD))	268.8 (±112.4) 10^3 /µl	
Urea (Mean (SD))	3.8 (±1.6) mmol/L	
Natrium (Mean (SD))	133.1 (±4.3) mmol/L	
Potassium(Mean (SD))	5.6 (±21.4) mmol/L	
Creatinine (Mean (SD))	69.0 (±36.8) mmol/L	
Total Protein (Mean (SD))	76.7 (±10.7) g/L	
Serum albumin (Mean (SD))	26.5 (±7.5)g/L	
Total bilirubin (Mean (SD))	13.7 (±17.3)µmol/L	
Alkaline Phosphatase (Mean (SD))	162.0 (±121.4)U/L	
Alanine Transaminase (Mean (SD))	45.0 (±87.0)U/L	
CD4 T-lymphocytes count[a]	< 200 cells/µl	168 (74.0)
	≥ 200 cells/µl	39 (17.2)
	Not available	20 (8.8)
(Median (IQR))	59 (IQR 133.5)cells/µl	
[a]HIV RNA viral load (Median (IQR))	204638.0 (IQR 828620.0) copies/ml	
HbsAg	Reactive	15 (6.6)
	Non-reactive	212 (93.4)
Anti-HCV	Reactive	127 (55.9)
	Non-reactive	89 (39.2)
	Not available	11 (4.8)
Toxoplasma IgG	Reactive	51 (22.5)
	Non-reactive	62 (27.3)
	Not available	114 (50.2)
Rapid Plasma Reagen (RPR)	Reactive	11 (4.8)
	Non-reactive	125 (55.1)
	Not available	91(40.1)

[a] Available for 95 patients only.

4.2 Tuberculosis treatment outcomes in TB/HIV co-infected patients

4.2.1 Tuberculosis treatment outcomes

During this study, a total 227 patients were found to have TB-HIV co-infection in four centres from 1st January 2010 till 30th September 2010. At the end of TB treatment, patients were classified into five groups according to outcomes. They were classified as 'cured' if they were smear-negative at, or one month prior to the completion of treatment and on at least one previous occasion; as 'treatment completed' if patients completed treatment but did not have proof of cure;as 'treatment failure' if patients remained or became again smear positive at five months or later during treatment; as 'treatment defaulted ' if the treatment was interrupted for two months or more and as 'death' if a patient died for any reason during the course of treatment.

Among 227 patients analysed, successful outcomes were achieved in 117 patients (53.4%) with 18.1% of patients cured and another 33.5% completed treatment. The unsuccessful outcomes were those patients who 'defaulted' (24.7%, n=56) and 'died' (20.3%). There was no cases of treatment failure identified.

However, 8 (3.4%) were still on treatment and did not meet any other outcome at the end of the study period (30thSeptember 2011). Patients who were categorized as still on treatment at the end of 12 months included patients whose treatment was prolonged because of side effects or complications or whose treatment was re-started several times because of multiple episodes of defaulting treatment.

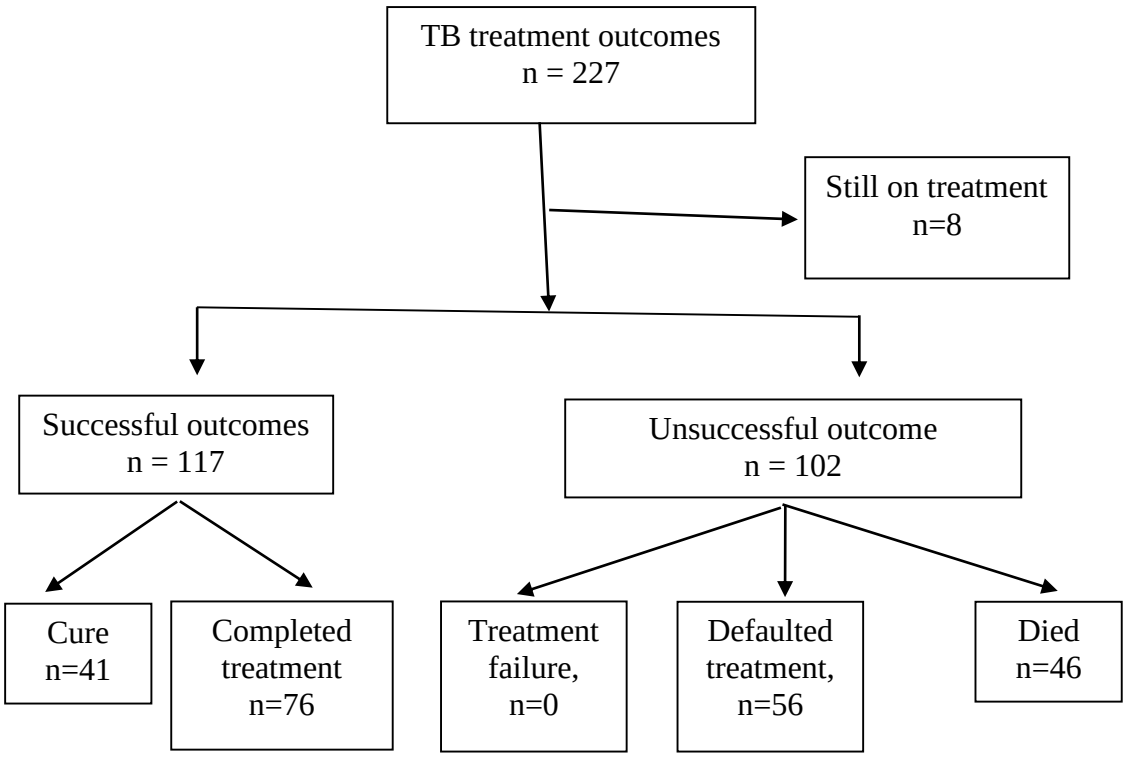


Figure 4.2: Flowchart of TB treatment outcomes in 227 TB/HIV co-infected patients.

4.2.2 Factors associated with tuberculosis treatment default

For this analysis, treatment outcomes were divided into two groups; defaulters and non-defaulters. Four variables (cure, completed treatment, still on treatment, died) were combined into one variable named 'non-defaulters' and were compared with 'defaulters' to identify factors associated with treatment default.

Table 4.9 below displays the socio-demographic and lifestyle characteristics of 227 TB/HIV co-infected patients stratified by TB treatment outcomes (non-defaulters and defaulters).

Table 4.9: Socio-demographic and lifestyle characteristics of 227 TB/HIV co-infected patients in Klang Valley stratified by non-defaulters and defaulters.

Characteristics	Non-defaulters* n (%)	Defaulters n (%)
Age group		
< 34	56 (32.7)	17 (30.4)
35-54	105 (61.5)	36(64.2)
≥ 55	10 (5.8)	3 (5.4)
Gender		
Male	146 (85.4)	54 (96.4)
Female	25 (14.6)	2 (3.6)
Ethnicity		
Malay	86 (50.3)	24 (42.9)
Chinese	31 (18.1)	6 (10.7)
Indian	22 (12.9)	15 (26.8)
Others	32 (18.7)	11 (19.6)
Nationality		
Malaysian	140 (81.9)	45 (80.4)
Non-Malaysian	31 (18.1)	11 (19.6)
Employment		
Employed	96 (56.1)	34 (60.7)
Unemployed	75 (43.9)	22 (39.3)
Incarceration[#]		
Yes	154 (90.1)	52 (92.9)
No	17 (9.9)	4 (7.1)
Marital status		
Single/Divorced	113 (66.1)	39 (69.6)
Married	58 (33.9)	17 (30.4)
Religion		
Islam	92 (53.8)	29 (51.8)
Buddhism	32 (18.7)	6 (10.7)
Hindu	19 (11.1)	11 (19.6)
Others	28 (16.4)	10 (17.9)
Smoking		
Ever smoked	124 (72.5)	44 (78.6)
Never smoked	47 (27.5)	12 (21.4)
Alcohol intake		
Ever take alcohol	35 (20.5)	19 (33.9)
Never take alcohol	136 (79.5)	37 (66.1)
Mode of HIV transmission		
Intravenous drug users	90 (52.6)	37 (66.1)
Sexual	73 (42.7)	17 (30.4)
Other/unknown	8 (4.7)	2 (3.6)

[#]Incarceration: Prisoners/Drug Rehabilitation Centre inmates at the time of TB diagnosis.

Table 4.10 to Table 4.13 below displays the TB-related, HIV-related characteristics and laboratory profiles of 227 TB/HIV co-infected patients stratified by TB treatment outcomes (non-defaulters and defaulters).

Table 4.10: TB-related characteristics of TB/HIV co-infected patients in Klang Valley stratified by non-defaulters and defaulters.

Characteristics	Non-defaulters n (%)	Defaulters n (%)
Types of TB		
Pulmonary TB	83 (48.5)	27 (48.2)
Extrapulmonary TB	48 (28.1)	17 (30.4)
Both	40 (23.4)	12 (21.4)
Status of TB diagnosis		
Newly diagnosed TB	125 (73.1)	36 (64.3)
Ever had TB before	46 (26.9)	20 (35.7)
Case detection		
Passive	161(94.2)	55 (98.2)
Active	10 (5.8)	1 (1.8)
Intensive phase regime		
[a]HRZ	145 (84.8)	50(89.3)
HZ	6 (3.5)	2 (3.6)
Others	20 (11.7)	4 (7.1)
[b]Changed in treatment		
Yes	141 (82.5)	49 (87.5)
No	30 (17.5)	7 (12.5)
Lymph node enlargement		
Yes	72 (42.1)	35 (62.5)
No	99 (57.9)	21 (37.5)
Cough more than two weeks		
Yes	59 (34.5)	16 (28.6)
No	112 (65.5)	40 (71.4)
Cough with sputum		
Yes	86 (50.3)	31 (55.4)
No	85 (49.7)	25 (44.6)
Haemoptysis		
Yes	24 (14.0)	7 (12.5)
No	147 (86.0)	49 (87.5)
Loss of weight		
Yes	120 (70.2)	37 (66.1)
No	51 (29.8)	19 (33.9)
Fever		
Yes	126 (73.7)	44 (78.6)
No	45 (26.3)	12 (21.4)

Table 4.10, continued.

Characteristics	Non-defaulters n (%)	Defaulters n (%)
Night sweats		
Yes	73 (42.7)	25 (44.6)
No	98 (57.3)	31 (55.4)
Loss of appetite		
Yes	109 (63.7)	41 (73.2)
No	62 (36.3)	15 (26.8)
BCG scar		
Scar present	149 (87.1)	48 (85.7)
No scar/ NR	22 (12.9)	8 (14.3)
Diabetes Mellitus		
Yes	4 (2.3)	2 (3.4)
No	167 (97.7)	54 (96.6)
[c]Co-morbidities		
Yes	32 (18.7)	9 (16.1)
No	139 (81.3)	47 (83.9)
Chest x-ray changes		
No lesion	39 (22.8)	13 (23.2)
Minimal lesion	81 (47.4)	28 (50.0)
Advanced lesion	51 (29.8)	15 (26.8)

Note:-[a]HRZ: Isoniazid, Ryfampycin & Pyrazinamide; HZ: Isoniazid & Pyrazinamide only; HR: Isoniazid &Ryfampycin
[b]Change in diagnosis: change from the initial TB regime (HRZ) to another due to side effects of treatment or adverse reaction.
[c]Co-morbidities: Include diabetes mellitus, congenital heart disease, malabsorption syndrome, malignancies, chronic liver disease and history of gastrectomy

Table 4.11: HIV-related characteristics of TB/HIV co-infected patients in Klang Valley stratified by non-defaulters and defaulters.

Variables	Non-defaulters n (%)	Defaulters n (%)
Timing of HIV diagnosis in relation to TB diagnosis		
Same year (2010)	60 (35.1)	14 (25.0)
Before 2010	111 (64.9)	42 (75.0)
Opportunistic infection		
Yes	89 (52.0)	19 (33.9)
No	82 (48.0)	37 (66.1)
Anti-retroviral therapy		
Yes	55 (32.2)	32 (57.1)
No	116 (67.8)	24 (42.9)
Anti-retroviral regime		
No ART	55 (32.2)	32 (57.1)
2NRTI + NNRTI	105 (61.4)	22 (39.3)
Others	11 (6.4)	2 (3.6)
Timing of antiretroviral therapy		
No ART	55 (32.2)	32 (57.1)
Before TB diagnosis	29 (17.0)	10 (17.9)
During TB treatment	87 (50.8)	14 (25.0)

NRTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non- Nucleoside Reverse Transcriptase Inhibitor

Table 4.12:Laboratory profiles (categorical variables) of TB/HIV co-infected patients (N=227) in the Klang Valley stratified by non-defaulters and defaulters.

Variables	Non-defaulters n (%)	Defaulters n (%)
Hemoglobin level		
< 12 g/dL	131 (76.6)	47 (83.9)
≥ 12 g/dL	40 (23.4)	9 (16.1)
Serum albumin		
< 35 g/L	137 (80.1)	50 (89.3)
≥ 35 g/L	34 (19.9)	6 (10.7)
HbsAg		
Reactive	12 (7.0)	3 (5.4)
Non-reactive	159 (93.0)	53 (94.6)
CD4 count		
< 200cells/µl	128 (74.9)	40 (71.4)
≥ 200cells/µl	29 (17.0)	10 (17.9)
Not available	14 (8.2)	6 (10.7)
Anti-HCV		
Reactive	91 (53.2)	36 (64.3)
Non-reactive/NA	80 (46.8)	20 (35.7)
Toxoplasma IgG		
Reactive	38 (22.2)	13 (23.2)
Non-reactive/NA	133 (77.8)	43 (76.8)
Rapid Plasma Reagen (RPR)		
Reactive	10 (5.8)	1 (1.8)
Non-reactive/NA	161 (94.2)	55 (98.2)

NA: Not available

Table 4.13:Laboratory profiles (continuous variables) of TB/HIV co-infected patients (N=227) in the Klang Valley stratified by non-defaulters and defaulters.

Variables	Non-defaulters (n=171) Mean (SD)	Defaulters (n=56) Mean (SD)
Hemoglobin, g/dL	10.63 (1.84)	10.11 (1.84)
Total White Blood Cell, 10^3/µl	6.44 (3.30)	5.96 (3.12)
Platelet, 10^3/µl	275.70 (114.74)	248.02 (103.07)
Urea, mmol/L	3.74 (1.56)	4.03 (1.60)
Natrium, mmol/L	133.68 (3.73)	131.34 (5.22)
Potassium, mmol/L	6.13 (24.61)	3.81 (0.45)
Creatinine,mmol/L	68.82 (40.91)	69.72 (19.51)
Total Protein, g/L	76.26 (11.25)	77.10 (8.78)
Serum albumin, g/L	26.80 (7.55)	25.72 (7.20)
Total bilirubin, µmol/L	14.00 (19.20)	12.75 (9.15)
Alkaline Phosphatase, U/L	156.95 (123.28)	177.16 (115.28)
Alanine Transaminase, U/L	48.83 (99.01)	33.36 (24.27)

4.2.3 Time to tuberculosis treatment default.

Time analysis of default from treatment was performed using the Kaplan-Meier survival method. Survival time was measured from the date of starting TB treatment until the date of defaulting TB treatment. Among the 227 TB/HIV co-infected patients on TB treatment, 56 (24. 7%) defaulted. The mean survival time was 390.8 (95% CI: 363.1, 418.6) days or 13.0 (95%CI: 12.1, 14.0) months. The median survival time was not calculated because the cumulative proportion of survival was still more than 50%. The KM survival curve for patients who defaulted from TB treatment is displayed in Figure 4.3.

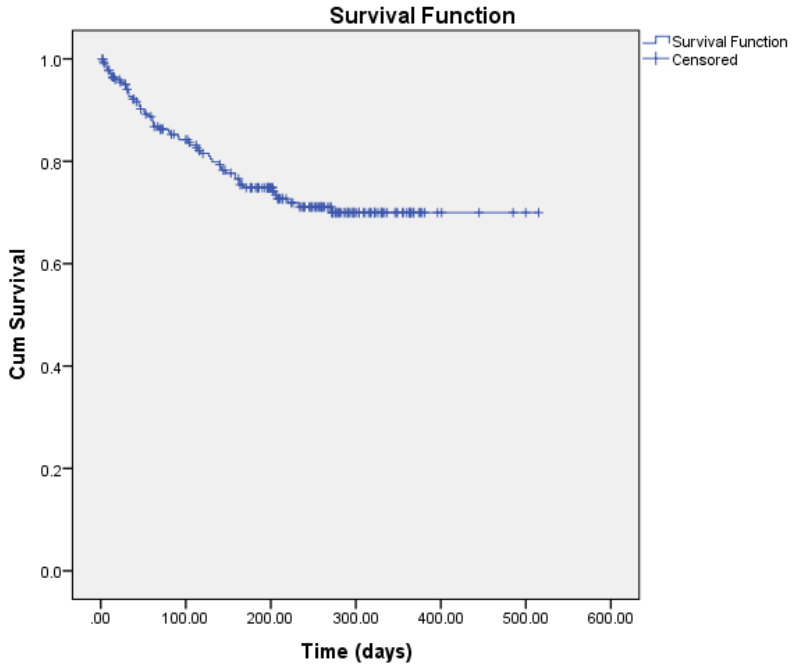


Figure 4.3: Kaplan-Meier curve for TB/HIV co-infected patients who defaulted TB treatment (n=227).

4.2.4 Univariate analysis

Univariate Cox proportional hazards analysis was performed on each independent variable to determine the crude estimate of the predictor of tuberculosis treatment outcome. It was also to determine which of the characteristics were significantly associated with TB treatment default and which should be selected for the multivariate analyses if the p-value was less than 0.25.

4.2.5 Socio-demographic and lifestyle characteristics of defaulters of TB treatment.

The association between the socio-demographic characteristics and lifestyle characteristics with TB treatment default in TB-HIV co-infected patients are displayed in Table 4.14. There was a significant association between TB treatment defaulters and

alcohol intake. Patients who had history of alcohol intake had a higher risk of defaulting from TB treatment than patients who gave no history of alcohol intake (HR: 1.79; 95%CI: 1.03-3.11). The other socio-demographic and lifestyle characteristics variables were not statistically significant.

Table 4.14: Univariate analysis of sociodemographic and lifestyle predictors for defaulting tuberculosis treatment in 227 TB/HIV co-infected patients.

Characteristics		N	Crude HR	95% CI
Age group	< 34	73	1.00	-
	35-54	141	1.15	0.65-2.05
	≥55	13	1.19	0.35-4.06
Gender	Male	200	3.97	0.97-16.27
	Female	27	1.00	-
Nationality	Malaysian	185	0.96	0.50-1.86
	Non-Malaysian	42	1.00	-
Ethnicity	Malay	110	0.89	0.43-1.81
	Chinese	37	0.62	0.23-1.67
	Indian	37	1.81	0.83-3.94
	Others	43	1.00	-
Employment status	Employed	97	0.74	0.43-1.27
	Unemployed	130	1.00	-
Incarceration	Yes	21	0.87	0.31-2.39
	No	206	1.00	-
Marital status	Single/Divorced	152	1.22	0.69-2.15
	Married	75	1.00	-
Smoking	Yes	168	1.44	0.76-2.72
	No	59	1.00	-
Alcohol	Yes	173	1.79	1.03-3.11*
	No	54	1.00	-
Mode of HIV Transmission	Sexual	89	1.00	-
	IDU	127	1.73	0.42-7.19
	Others	11	0.96	0.22-4.13
Body weight	< 50kg	133	0.86	0.51-1.44
	≥ 51kg	94	1.00	-

*p<0.05; HR: hazards ratio; CI: Confidence Interval, IDU: Intravenous drug user

4.2.6 Clinical characteristics and laboratory profile; and default from TB treatment.

Table 4.15 to Table 4.18 displays the association of patient's clinical characteristics and laboratory profiles with TB treatment default. In univariate analysis, only lymph node enlargement and ART were significantly associated with default from TB treatment ($p<0.05$). TB/HIV co-infected patients who had lymphadenopathy had two times risk of default from TB treatment than patients who do not have lymphadenopathy (HR:2.01; 95%CI:1.17-3.46). Patients who were not on ART had more than three times risk of default from TB treatment than those who were on ART (OR: 3.47; 95%CI: 2.04- 5.90). The other clinical characteristics and laboratory variables were not found to be statistically significant.

Table 4.15: Univariate analysis of TB-related characteristics as predictors for defaulting tuberculosis treatment in 227 TB/HIV co-infected patients

Characteristics	N	Crude HR	95% CI
Types of TB			
Pulmonary TB	111	1.21	0.61-2.39
Extra-pulmonary TB	64	1.26	0.60-2.65
Both	52	1.00	-
Status of TB diagnosis			
Newly diagnosed TB	161	0.69	0.40-1.18
Ever had TB before	66	1.00	-
CXR Changes			
No lesion	52	1.00	-
Minimal lesion	109	1.01	0.52-1.94
Advanced lesion	56	0.99	0.47-2.08
Intensive Phase Regime			
HRZ	195	1.86	0.67-5.15
HZ	8	1.58	0.29-8.62
Others	24	1.00	-
Changed Treatment			
Yes	37	1.69	0.76-3.73
No	190	1.00	-
BCG Scar			
Yes	197	1.00	-
No	30	1.18	0.56-2.47
Co-morbidities			
Yes	41	0.92	0.45-1.87
No	186	1.00	-
Diabetes mellitus			
Yes	6	1.30	0.32-5.32
No	221	1.00	-

*p<0.05; HR: Hazards ratio; CI: Confidence Interval; CXR: Chest x-ray

Table 4.16: Univariate analysis of initial clinical presentations as predictors for defaulting tuberculosis treatment in 227 TB/HIV co-infected patients.

Characteristics	N	Crude HR	95% CI
Cough more than two weeks			
Yes	152	1.20	0.67-2.14
No	75	1.00	-
Cough with sputum			
Yes	110	0.94	0.56-1.60
No	117	1.00	-
Hemoptysis			
Yes	31	1.01	0.60-1.72
No	196	1.00	-
Loss of weight			
Yes	157	1.25	0.72-2.17
No	70	1.00	-
Fever			
Yes	170	1.27	0.67-2.41
No	57	1.00	-
Night sweats			
Yes	98	1.01	0.60-1.72
No	129	1.00	-
Loss of appetite			
Yes	150	1.46	0.81-2.64
No	77	1.00	-
Lymphadenopathy			
Yes	107	2.01	1.17-3.46*
No	120	1.00	

*p<0.05; HR: Hazards ratio; CI: Confidence Interval ;NA: Not available; RPR: Rapid Plasma Reagin

Table 4.17: Univariate analysis of HIV-related characteristics as predictors for defaulting tuberculosis treatment in 227 TB/HIV co-infected patients.

Characteristics	N	Crude HR	95% CI
Timing of HIV diagnosis in relation to TB diagnosis			
Same year (2010)	74	0.70	0.38-1.28
Before 2010	153	1.00	-
Anti-retroviral therapy			
Yes	140	1.00	-
No	87	3.47	2.04-5.90*
Opportunistic Infection			
Yes	108	0.56	0.32-0.97
No	119	1.00	-
Number of OI			
No OI	119	1.00	-
One OI	79	0.56	0.30-1.03
Two OIs	23	0.54	0.19-1.52
Three or more OIs	6	0.60	0.08-4.40

*p<0.05; HR: Hazards ratio; CI: Confidence Interval

Table 4.18: Univariate analysis of baseline laboratory profile as predictors for defaulting tuberculosis treatment in 227 TB/HIV co-infected patients.

Characteristics	N	Crude HR	95% CI
Hemoglobin level			
< 12 g/dL	178	1.71	0.84-3.49
≥ 12 g/dL	49	1.00	-
Serum albumin			
< 35 g/L	187	2.07	0.89-4.82
≥ 35 g/L	40	1.00	-
CD4 count			
Not available	168	1.13	0.56-2.26
< 200 cells/µl	39	1.76	0.64-4.86
≥ 200 cells/µl	20	1.00	-
HbsAg			
Positive	15	0.90	0.28-2.88
Negative	212	1.00	-
Anti-HCV			
Reactive	127	1.60	0.92-2.76
Non-reactive/NA	89	1.00	-
Toxoplasma IgG			
Reactive	51	1.11	0.60-2.06
Non-reactive/NA	176	1.00	-
Rapid Plasma Reagen			
Reactive	11	0.26	0.04-2.08
Non-reactive/NA	216	1.00	-

*p<0.05; HR: Hazards ratio; CI: Confidence Interval; NA: Not available.

4.2.7 Multivariate analysis

In the multivariate analysis, all covariates with cut-off p-value of less than 0.25 in the univariate analysis and any others that were thought to be of clinical importance, were included. The final model was selected based on the principle of parsimony and best fit using the Hosmer-Lemeshow approach of using -2 log likelihood ratios. The variable with the largest p-value was deleted from the model. This step was continued until no covariates could be deleted from the model. At this point, each of the deleted covariates

were added back into the model one at a time to ensure that none of them were significant or showed evidence of being a confounder.

The significant independent factors associated with TB treatment default after multivariate analysis are presented in Table 4.20. The outcome variable is classified into 'defaulter' and 'non-defaulter'. In the unadjusted (univariate analysis), we identified nineteen possible predictive factors for default from TB treatment (univariate $p<0.25$ to avoid missing out possible predictors) including employment status, alcohol intake, body weight, mode of HIV transmission, status of TB diagnosis, intensive phase regime, changed in TB treatment regime, loss of appetite, lympadenopathy, presence of opportunistic infection, number of opportunistic infection, status of antiretroviral therapy, haemoglobin level, platelet count, serum albumin, alkaline phosphatase (ALP), urea, Rapid Plasma Reagin and anti-HCV serology.

After adjusting for other predictors in multiple Cox regression analysis, the significant predictors of default from TB treatment in HIV-infected patients were alcohol intake, presence of lymphadenopathy, status of antiretroviral therapy and serum albumin level. All possible two way interactions between the variables in the main effect model were checked and no significant interaction term was identified. The proportional hazard assumption was checked by two methods. First, the proportional hazards assumption was tested univariately using log minus log plot (LML) and hazard plot for all significant variables. All variables showed parallel lines which indicated the proportional hazard assumption were fulfilled. Second, the proportional hazard assumption was checked by the correlation test between partial residuals and survival time rank. The correlation test showed correlation was very small (less than 0.3) and p-value more than 0.05 which indicated that the proportional hazard assumption was met. All these are summarized in Table 4.19.

Table 4.19: Pearson's correlation between variables and survival time rank of TB/HIV patients defaulting TB treatment.

Variables	Pearson's *r*-value	*P-value*
Alcohol intake		
Ever drink	0.076	0.579
Lymphadenopathy		
Yes	0.045	0.690
Antiretroviral therapy		
No ART	-0.018	0.315
Serum albumin		
< 35 g/L	-0.032	0.815

Note: n=56

The strongest predictor of default from TB treatment was not being put on anti-retroviral therapy, with a hazard ratio of 3.75 (95%CI:2.19-6.42). This indicated that patients who were not on antiretroviral therapy were almost four times more likely to default from TB treatment than those who were on anti-retroviral therapy. A TB/HIV co-infected patient who had an albumin level less than 35 g/L were about three times more likely to default from TB treatment (HR: 2.89; 95%CI: 1.22-6.84).

Patients with lymphadenopathy were twice more likely to default TB treatment (HR: 2.03; 95%CI: 1.18-3.49). Alcohol intake was also an independent predictor of default from TB treatment in TB/HIV co-infected patients (HR: 1.93, 95%CI:1.10-3.38). The employment status, body weight, mode of HIV transmission, status of TB diagnosis, intensive phase regime, change in TB treatment regime, loss of appetite, presence of opportunistic infections, number of opportunistic infections, haemoglobin level, platelet count, alkaline phosphatase (ALP), urea, Rapid Plasma Reagin and anti-HCV serology showed no significant association with default from TB treatment in the multivariate analysis.

Table 4.20: Significant independent predictors of default from TB treatment in 227 TB/HIV co-infected patients in the Klang Valley.

Characteristics	Crude HR	95% CI	[a]Adjusted HR	95% CI
Alcohol intake				
Ever drink	1.79	1.03-3.11	1.93	1.10-3.38*
Never drink	1.00	-	1.00	-
Lymphadenopathy				
Yes	2.01	1.17-3.46	2.03	1.18-3.49*
No	1.00	-	1.00	-
Antiretroviral therapy				
Yes	1.00	-	1.00	-
No	3.47	2.04-5.90	3.75	2.19-6.42*
Serum albumin				
< 35 g/L	2.07	0.89-4.82	2.89	1.22-6.84*
≥35 g/L	1.00	-	1.00	-

HR: Hazards Ratio, CI: Confidence Interval, * $p < 0.05$

[a]Adjusted for employment status, body weight, mode of HIV transmission, status of TB diagnosis, intensive phase regime, changed in TB treatment regime, loss of appetite, presence of opportunistic infections, number of opportunistic infections, hemoglobin, platelet, alkaline phosphatase (ALP), urea, Rapid Plasma Reagin and anti-HCV serology

4.3 Survival of TB/HIV co-infected patients during TB treatment

4.3.1 Mortality rate

To determine the survival of TB/HIV co-infected patients during TB treatment, the survival status of all patients (n = 227), including those who were still on TB treatment were assessed at the end of the study period. To verify the patient's status, patient data was linked to the National Registration Department database. Patients who died during treatment default were reclassified as having died instead of having defaulted treatment. In total, seven (7) patients who were originally classified as defaulters were later reclassified as having died, meaning the total number of deaths during TB treatment was 53 (23.3%).

4.3.2 Cause of death

Information on the cause of death was available for 45 patients (84.9% of all deceased). The cause of death is summarized in the Table 4.21 below.

Table 4.21: Cause of death in 53 TB/HIV co-infected patients

Causes of death	n	%
Opportunistic infections associated with HIV	8	15.1
Pneumonia	8	15.1
Hospital acquired pneumonia	6	11.3
Acute coronary syndrome	1	1.9
Fungal septicaemia	2	3.8
Septicaemia	7	13.2
Hospital acquired pneumonia	6	11.3
TB meningitis	5	9.4
Nosocomial infection	2	3.8
Hepatic encephalopathy	2	3.8
Hypoglycaemia	1	1.9
Neuroglycopaenic shock	1	1.9
Neuroleptic malignant syndrome	1	1.9
Opium overdose	1	1.9
Not available	8	15.1
TOTAL	53	100.0

4.4 Predictors of Mortality in TB/HIV co-infected patients

4.4.1 Mean survival time of TB/HIV co-infected patients.

Survival time was measured from the date of starting TB treatment until the date of the patient's death or the end of the study. There were 53 (23.3%) deaths among the 227 TB/HIV co-infected patients. The overall mean survival time from TB diagnosis to death was 11.07 months (95% CI: 10.35, 11.78) as shown in Figure 4.4 below. Median survival time was not calculated because the cumulative proportion of survival was still more than 50%.

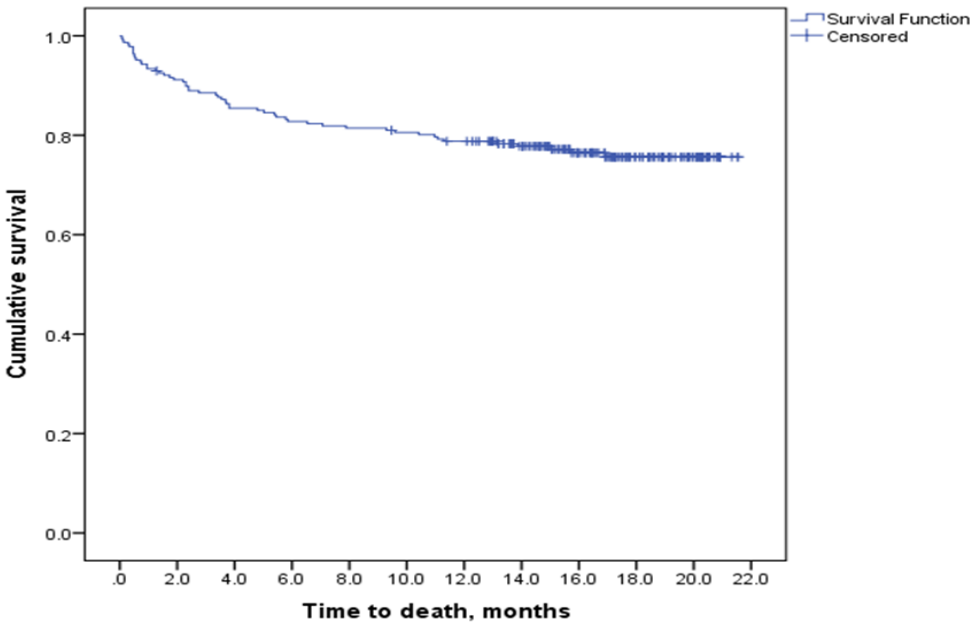


Figure 4.4: Kaplan-Meier curve for overall survival estimate among TB/HIV co-infected patients (n=227)

4.4.2 Survival Time

Survival at 2, 6 and 12 months after initiating TB treatment were 90.7% (95%CI: 90.3-91.1), 82.8% (95%CI: 82.6-83.1) and 78.8% (95%CI: 78.3-79.3) respectively (Table 4.22). The range of survival time was 1.3 months to 21.6 months.

Table 4.22: Summary of KM estimates for 227 TB/HIV co-infected patients

Time	Number of deaths	% Survival	95% Confidence Interval
2 months	21	90.7	90.3-91.1
6 months	40	82.8	82.6-83.1
12 months	48	78.8	78.3-79.3

4.4.3 Kaplan Meier Estimates

The Kaplan Meier (KM) estimates and log rank for the estimation of the univariate association between socio-demographic and lifestyle characteristics with survival time is shown in Table 4.23. As shown in Table 4.23, there were statistically significant differences in the mean survival time for ethnicity (p=0.036), employment status (p=0.002), imprisonment (p=0.006) and mode of HIV transmission (p=0.031). Other variables were not statistically significant. The mean survival time for Malay patients was 16.30 months (95%CI 14.79,17.81) which was the shortest duration compared to other ethnic groups. Those who were employed had significantly longer mean survival time (19.12 months, 95%CI: 17.96,20.29) compared to those who were unemployed (19.12 months; 95%CI: 17.96,20.29). Those infected via the homosexual route had significantly longer mean survival time (15.06 months; 95%CI: 9.53, 20.60) compared to infections via injecting drugs, heterosexual and other routes.

Table 4.23: K-M estimate and log rank test between socio-demographic and lifestyle characteristics.

Variables	N	N of event	Censored, n	Mean survival time, months (95% CI)	Log-rank *p* value
Age group (years)					
< 34	73	12	61	18.13 (16.64,19.61)	0.267
35-54	141	38	103	17.02 (15.73,18.30)	
≥ 55	13	3	10	15.54 (12.17,20.91)	
Gender					
Male	200	47	153	17.53 (16.48,18.57)	0.992
Female	27	6	21	17.13 (14.40,19.86)	
Nationality					
Malaysian	185	48	137	17.14 (16.03, 18.26)	0.074
Non-Malaysian	42	5	37	19.30 (17.43,21.16)	
Ethnicity					
Malay	110	35	75	16.30 (14.79,17.81)	0.036*
Chinese	37	5	32	18.28 (16.12,20.45)	
Indian	37	8	29	17.37 (15.14, 19.60)	
Others	43	5	38	19.35 (17.52, 21.17)	
Employment					
Employed	97	13	84	19.12 (17.96,20.29)	0.002*
Unemployed	130	40	90	16.19 (14.77, 17.62)	
Imprisonment					
Yes	21	10	11	13.40 (10.01, 16.80)	0.006*
No	206	43	163	17.90 (16.90, 18.90)	
Marital status					
Single/divorced	152	41	111	16.97 (15.73, 18.21)	0.075
Married	75	12	63	18.64 (17.09, 20.19)	
Smoking					
Yes	168	42	126	17.23 (16.06,18.40)	0.323
No	59	11	48	18.38 (16.64,20.12)	
Alcohol intake					
Yes	54	12	42	17.67 (15.78, 19.56)	0.777
No	173	41	132	17.44 (16.30, 18.58)	
Mode of HIV transmission					
IDU	127	40	87	16.24 (14.83, 17.66)	0.012*
Heterosexual	81	9	72	19.39 (18.04, 20.73	
Homosexual	8	1	7	19.18 (17.06, 21.30)	
Others	11	3	8	16.43 (11.94,20.92)	
Body weight					
< 50kg	133	36	97	16.71 (15.32, 18.11)	0.08
≥50kg	94	17	77	18.66 (17.38, 19.94)	

* The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)

Table 4.24 displays the univariate association between TB-related and HIV-related characteristics with survival time. There were statistically significant differences in the survival time of patients who had maintenance therapy, opportunistic infection and antiretroviral therapy.

The mean survival time for patients who received maintenance regime for TB treatment was much longer than those who were not on any maintenance therapy. The mean survival time for patients who received isoniazid and rifampicin was 19.77 months (95%CI: 19.00,20.54). Patients who were on maintenance therapy had improved the mean survival time by almost 43%.

The mean survival time among patients who did not have opportunistic infection was longer (18.72 months, 95%CI: 17.54, 19.89) compared to patients with opportunistic infection (16.23months; 95%CI: 14.67,17.79). TB/HIV co-infected patients who received concurrent antiretroviral therapy were also having longer mean survival time (19.03 months; 95%CI: 18.05, 20.02) compared to those who were not receiving ART (15.12 months; 95%CI: 13.22, 17.02).

Table 4.24: K-M estimate and log rank test to determine the univariate association between clinical characteristics and survival time.

Variables	N	N of event	Censored, n	Mean survival time, months (95% CI)	Log-rank *p* value
Types of TB					
Pulmonary	110	24	86	17.55 (16.18, 18.93)	0.851
Extrapulmonary	65	15	50	17.37 (15.47, 19.26)	
Both	52	14	38	17.32 (15.32,19.31)	
Status of TB diagnosis					
Newly diagnosed TB	161	36	125	17.68 (16.54, 18.83)	0.574
Ever had TB before	66	17	49	17.13 (15.25, 19.01)	
Intensive phase regime					
HRZ	195	44	151	17.54 (16.48,18.62)	0.863
HZ	8	2	6	16.08 (10.69,21.47)	
Others	24	7	17	17.11 (14.61,19.62)	
Maintenance phase regime					
No maintenance	64	35	29	11.32 (8.97, 13.68)	< 0.001*
HR	137	15	122	19.77 (19.00,20.54)	
Others	26	2	24	19.37 (17.61,21.12)	
Changed in TB treatment					
Yes	37	9	28	17.58 (15.54, 19.61)	0.982
No	189	44	145	17.42 (16.32, 18.52)	
Case detection					
Passive	216	48	168	17.70 (16.70, 18.69)	0.008
Active	11	5	6	13.95 (9.26, 18.65)	
Cough more than two weeks					
Yes	152	33	119	17.65 (16.50,18.80)	0.41
No	75	20	55	16.95 (15.16, 18.74)	
Cough with sputum					
Yes	110	31	79	16.53 (16.56,18.52)	0.889
No	117	22	95	18.46 (17.24, 19.67)	
Haemoptysis					
Yes	31	7	24	17.05 (14.48, 19.63)	0.078
No	196	46	150	17.53 (16.48, 18.59)	
Loss of weight					
Yes	157	37	120	17.56 (16.40, 18.72)	0.96
No	70	16	54	17.45 (15.63, 19.27)	

Table 4.24, continued.

Variables	N	N of event	Censored, n	Mean survival time, months (95% CI)	Log-rank *p* value
Fever					
Yes	170	40	130	17.53 (16.40,18.66)	0.904
No	57	13	44	17.09 (15.21,18.97)	
Night sweats					
Yes	98	18	80	18.53 (17.21, 19.84)	0.122
No	129	35	94	16.76 (15.37, 18.15)	
Loss of appetite					
Yes	150	36	114	17.52 (16.32,18.72)	0.75
No	77	17	60	17.08 (15.44,18.71)	
Co-morbidities					
Yes	41	13	28	16.07 (13.54, 18.61)	0.158
No	186	40	146	17.69 (16.65, 18.72)	
Diabetes mellitus					
Yes	6	3	3	13.29 (7.94, 18.64)	0.152
No	221	50	171	17.63 (16.64, 18.61)	
Presence of BCG scar					
Yes	197	48	149	17.44 (16.39, 18.49)	0.436
No	30	5	25	17.66 (15.04, 20.28)	
Opportunistic infections					
Yes	108	33	75	16.23 (14.67,17.79)	0.014*
No	119	20	99	18.72 (17.54, 19.89)	
Timing of HIV diagnosis					
Same year	74	16	58	16.60 (14.88,18.32)	0.857
Before 2010	153	37	116	17.60 (16.45, 18.76)	
Antiretroviral therapy					
Yes	140	23	117	19.03 (18.05, 20.02)	< 0.001*
No	87	30	57	15.12 (13.22, 17.02)	

* The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)

Table 4.25 displays the univariate association between laboratory profiles with survival time. Only CD4 count (p=0.047) and Toxoplasma serology (p=0.049) showed statistically significant difference in the survival time.

Patients who had CD4 count more than 200 cells/µl had better mean survival time (19.90 months; 95%CI: 18.69, 21.14) compared to those with CD4 count less than 200 cells/µl (16.97 months; 95%CI: 15.78, 18.16) and those whose CD4 count were not available (16.13 months; 95%CI: 12.46, 19.79). Patients with non-reactive Toxoplasma test or whose Toxoplasma test was not available had better survival than patients who had reactive (positive) Toxoplasma serology test (18.07 vs. 15.69 months).

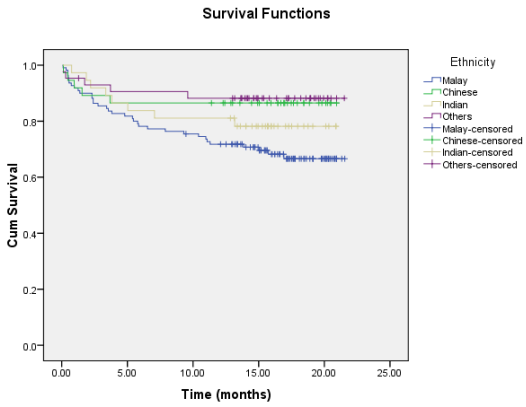
Table 4.25: K-M estimate and log rank test to determine the univariate association between laboratory independent variables and survival time

Variables	N	N of event	Censored, n	Mean survival time (months) (95% CI)	Log rank p-value
Hemoglobin level					
< 12 g/dL	178	45	133	17.26 (16.13,18.39)	0.216
≥ 12 g/dL	49	8	41	18.04 (16.18,19.91)	
Serum albumin level					
< 35g/dL	187	46	141	17.37 (16.29, 18.46)	0.369
≥ 35g/dL	40	7	33	17.79 (15.60, 19.98)	
CD4 T-lymphocytes count					
< 200 cells/µl	168	45	123	16.97 (15.78, 18.16)	0.047*
≥ 200 cells/µl	39	3	36	19.90 (18.69, 21.14)	
Not available	20	5	15	16.13 (12.46, 19.79)	
HbsAg					
Reactive	15	3	12	17.39 (14.19, 20.59)	0.736
Non-reactive	212	50	162	17.48 (16.46, 18.50)	
Hepatitis C serology					
Reactive	127	36	91	16.75 (15.37, 18.13)	0.059
Non-reactive/NA	100	17	83	18.53 (17.19, 19.87)	
Toxoplasma IgG					
Reactive	51	17	34	15.69 (13.35, 18.04)	0.049*
Non-reactive/NA	176	36	140	18.07 (17.02, 19.12)	
RPR					
Reactive	11	1	10	19.69 (17.80, 21.58)	0.240
Non-reactive/NA	216	52	164	17.39 (16.36,18.41)	

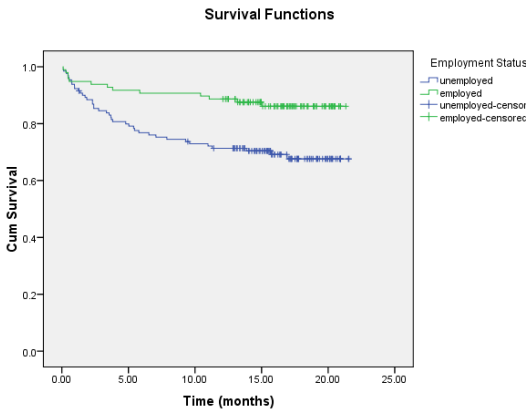
* The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)

4.4.4 Kaplan Meier Survival Curve

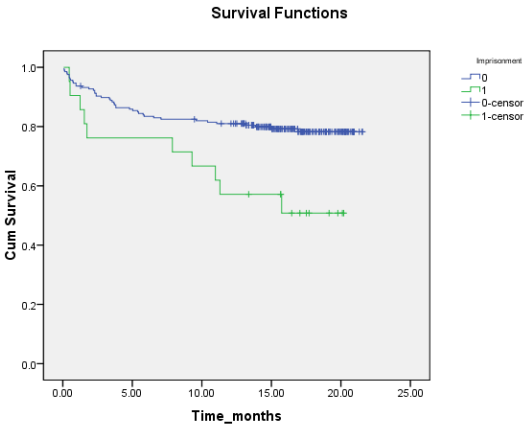
In general, there were significant differences in survival rates in terms of ethnicity, employment status, imprisonment, mode of HIV transmission, the maintenance phase of tuberculosis treatment, concurrent opportunistic infection, anti-retroviral therapy, CD4 T-lymphocytes and Toxoplasma serology. Survival curves for these significant variables are shown in Figure 4.5.



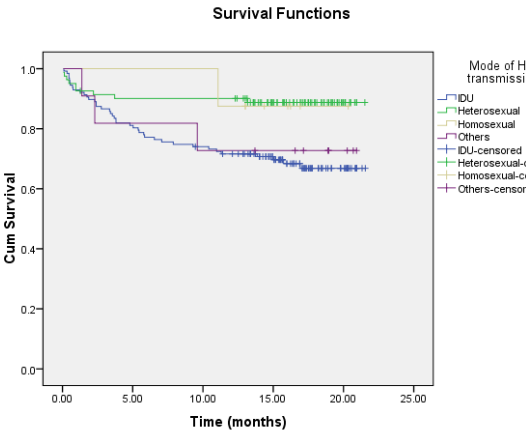
a) Ethnicity (p=0.036)



b) Employment (p=0.002)

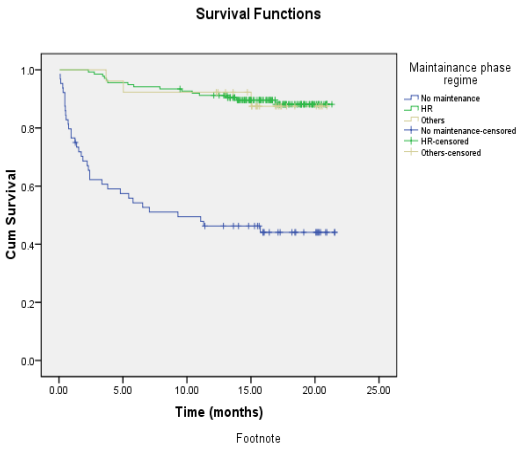


(c) Imprisonment (p=0.006)

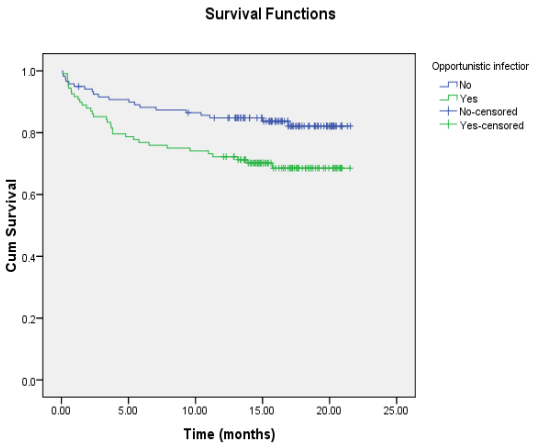


(d) Mode of HIV transmission

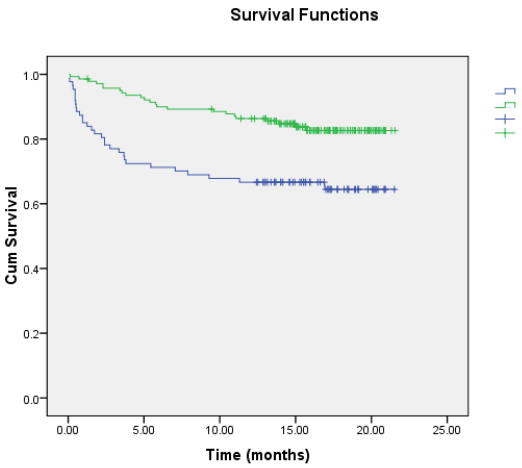
(p=0.012)



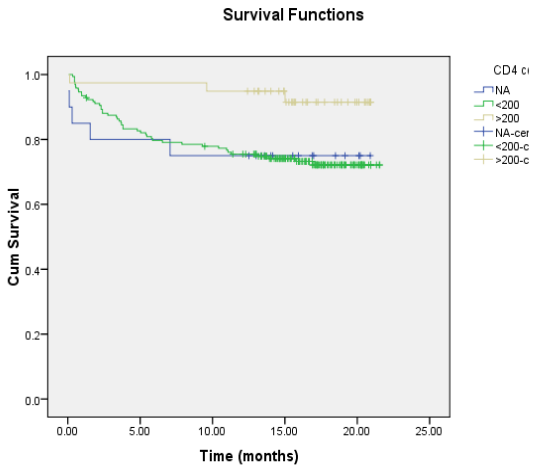
(e) Maintenance phase (p< 0.001)



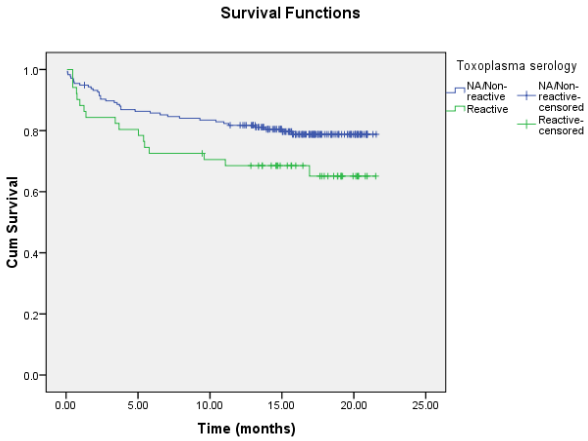
(f) Opportunistic infection (p=0.014)



(g) Anti-retroviral therapy (p< 0.001)



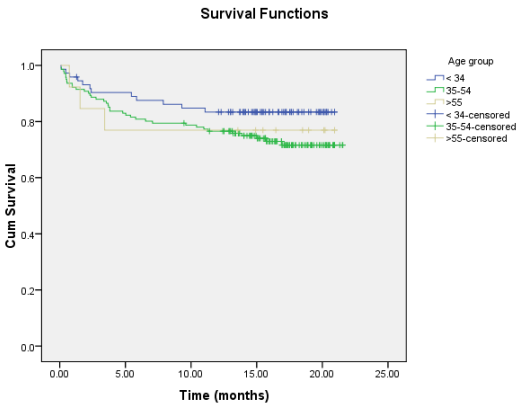
(h) CD4 counts (p=0.047)



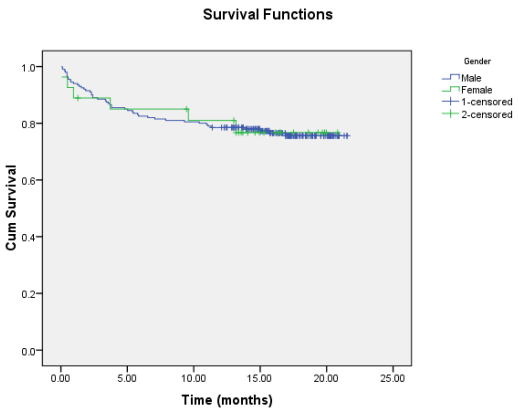
(i) Toxoplasma serology (p=0.049)

Figure 4.5: The survival plot of significant variables using Kaplan Meier Survival Curves

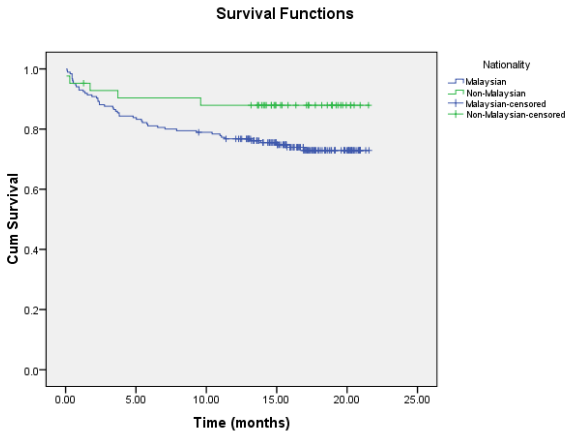
There were no significant difference in the survival distributions according to age group, gender, nationality, marital status, smoking status, alcohol intake, types of TB, status of TB diagnosis, case detection, TB symptoms at diagnosis (cough more than two weeks, cough with sputum, hemoptysis, night sweats, loss of weight,loss of appetite), co-morbidities, lymphadenopathy, chest x-ray changes, haemoglobin level, serum albumin level, HbsAg, anti-HCV serology or Rapid Plasma Reagin (RPR) serology test (Figure 4.6).



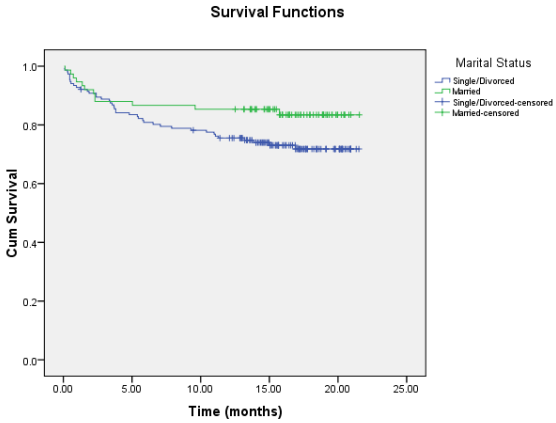
(a) Age group (p=0.267)



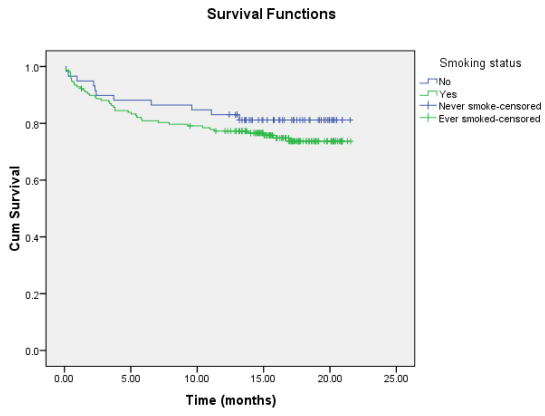
b) Gender (p=0.992)



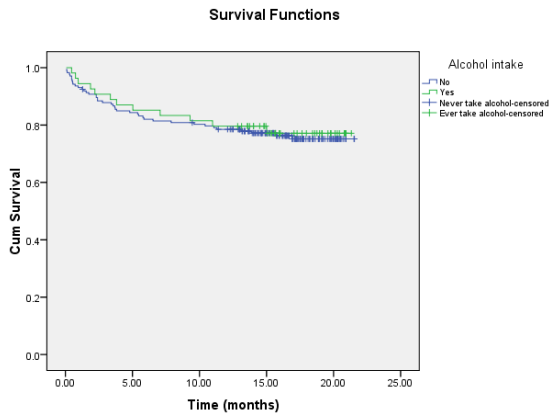
c) Nationality (p=0.074)



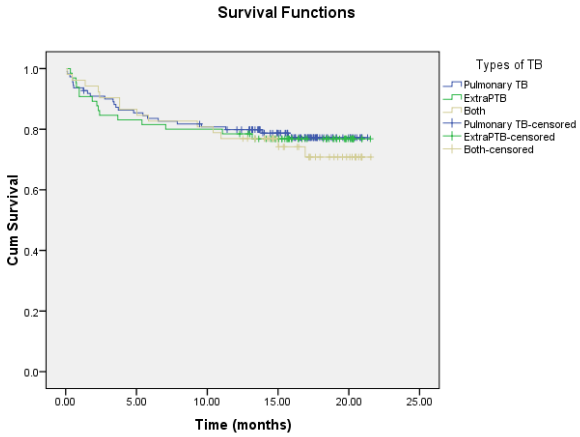
d) Marital status (p=0.075)



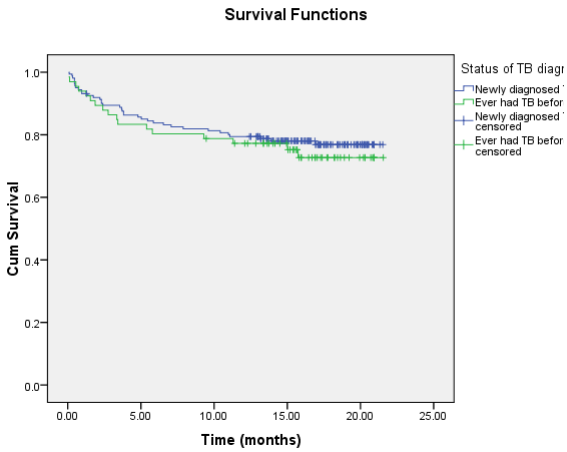
(e) Smoking status (p=0.323)



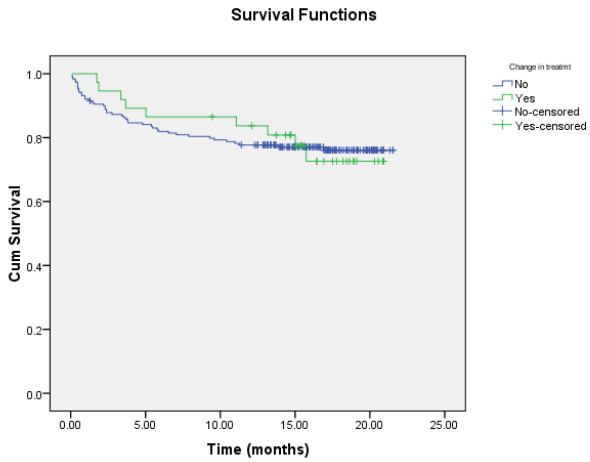
(f) Alcohol intake (p=0.777)



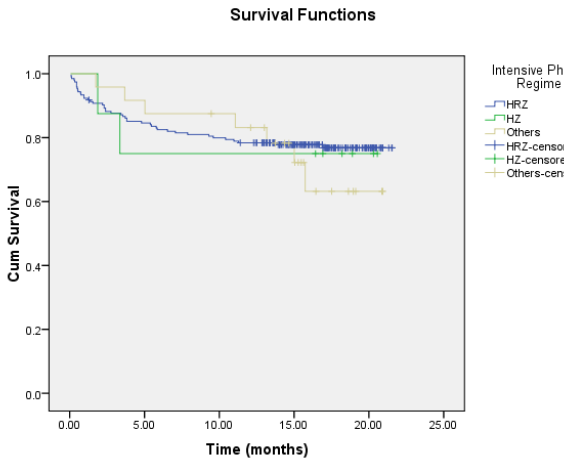
(g) Types of TB (p=0.851)



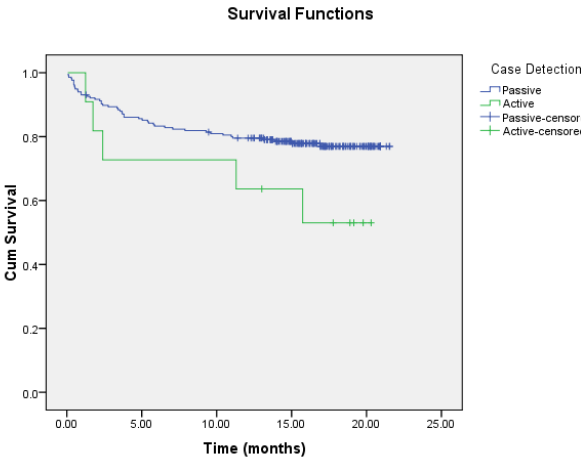
(h) Status of TB diagnosis (p=0.574)



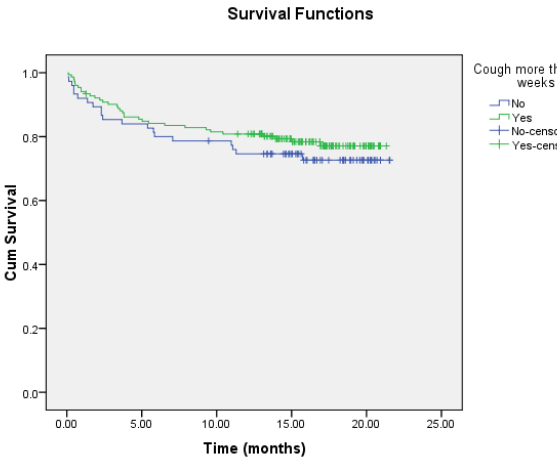
(i) Change in TB treatment (p=0.982)



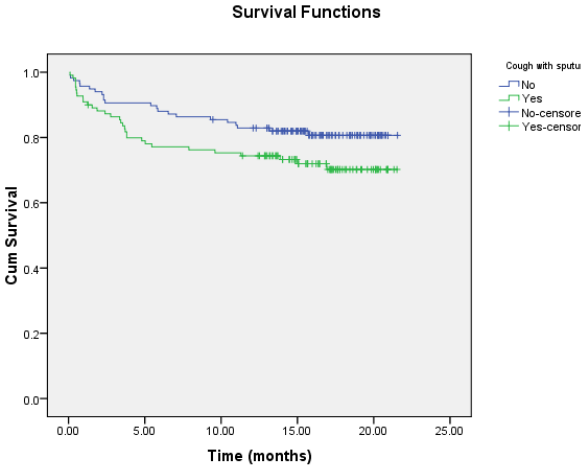
(j) Intensive phase regime (p=0.863)



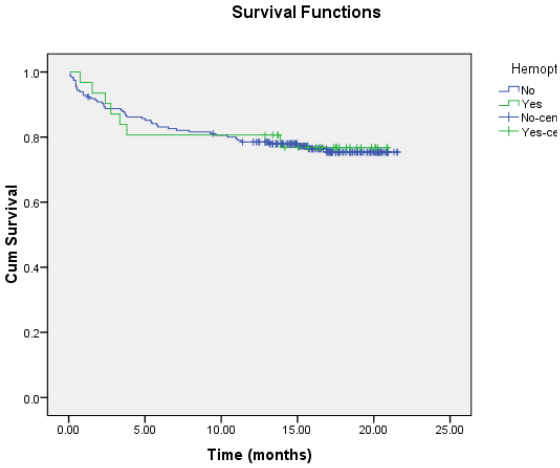
(k) Case detection (p=0.088)



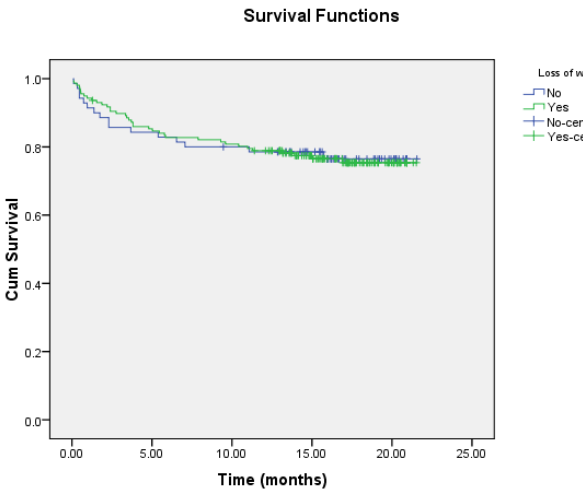
(l) Cough more than two weeks (p=0.410)



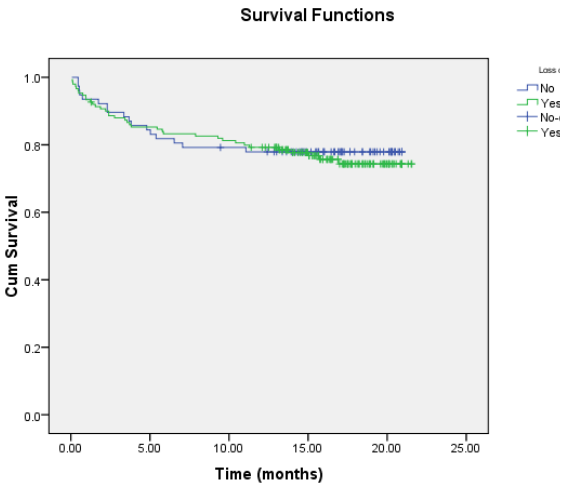
(m) Cough with sputum (p=0.078)



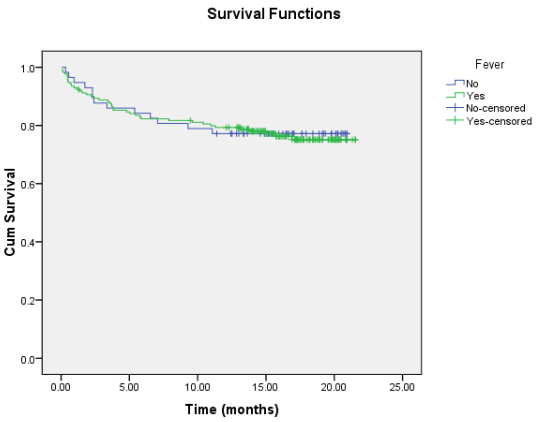
(n) Hemoptysis (p=0.889)



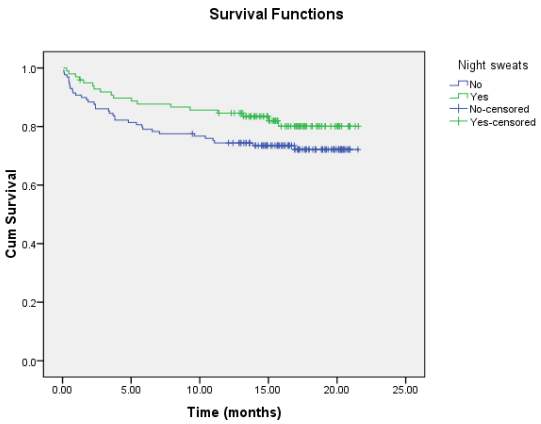
(o) Loss of weight (p=0.889)



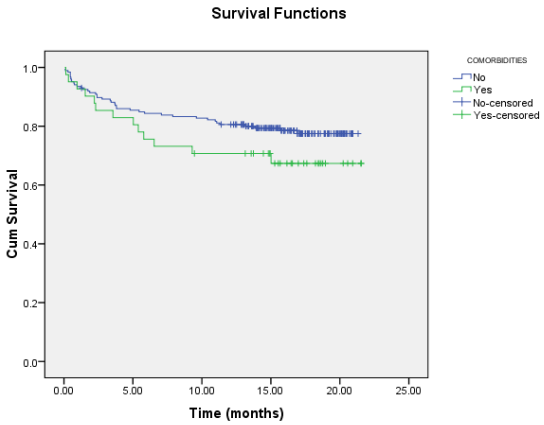
(p) Loss of appetite (p=0.750)



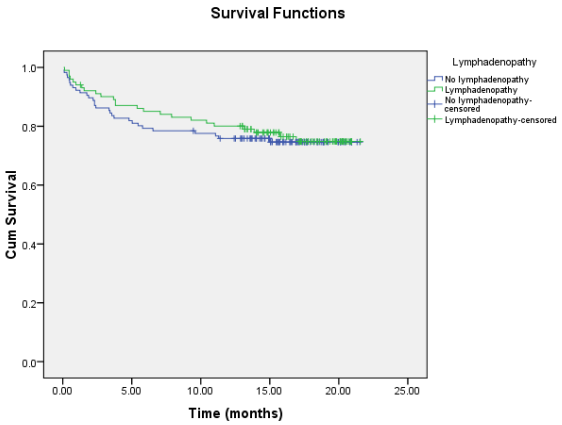
q) Fever



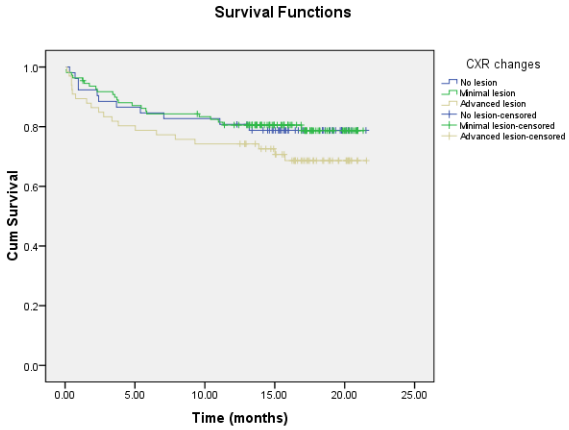
r) Night sweats (p=0.122)



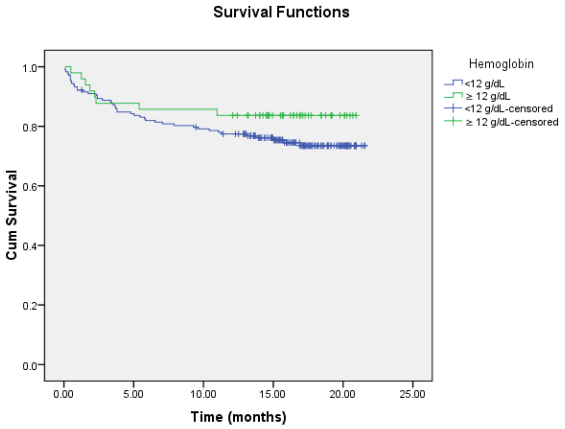
s) Co-morbidities (p=0.158)



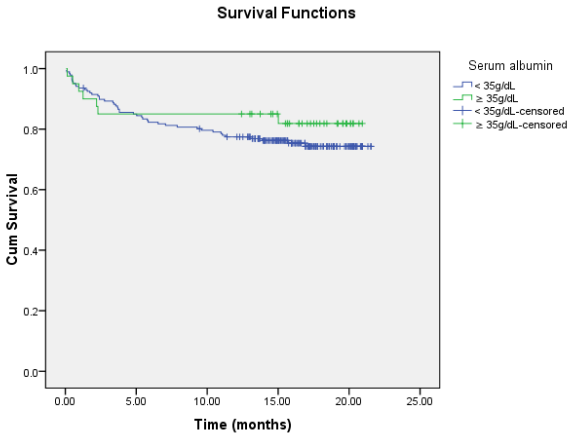
t) Lymphadenopathy (p=0.728)



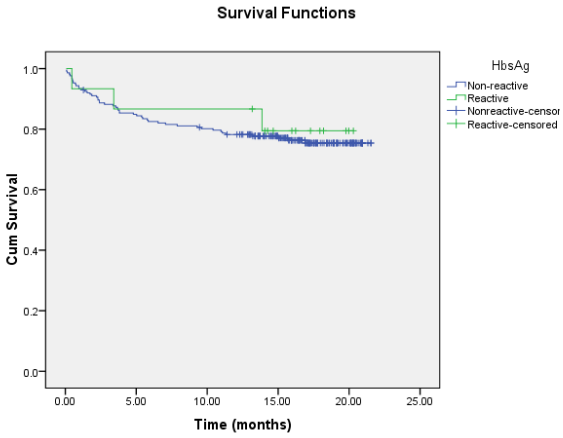
u) Chest x-ray changes (p=0. 285)



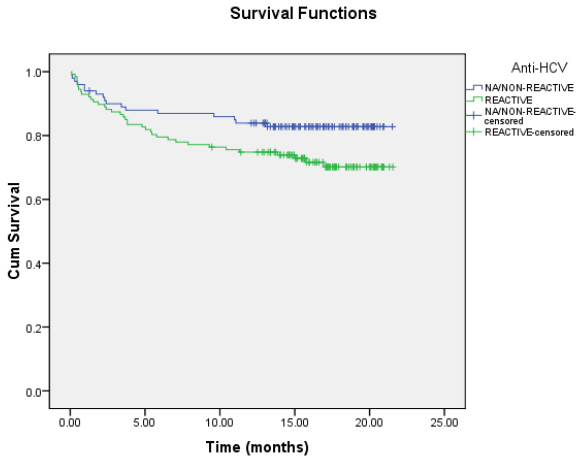
v) Hemoglobin level (p=0.216)



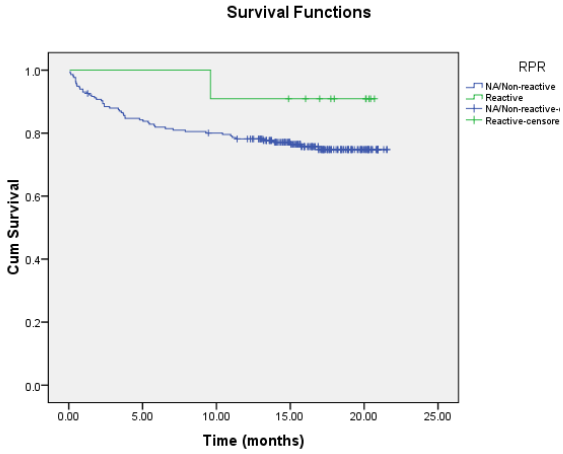
w) Serum albumin (p=0.369)



x) HbsAg (p=0.736)



y) Anti-HCV serology (p=0.059)



z) Rapid Plasma Reagin (p=0.240)

Figure 4.6: The survival plot of non-significant variables using Kaplan Meier Survival Curves

4.4.5 Univariate analysis

The univariate Cox Proportional Hazard (CPH) Regression analysis was performed to assess the effect of multiple co-variates on survival. The association between the socio-demographic and lifestyle characteristics with the survival status of TB-HIV co-infected

patients are displayed in Table 4.26. Only ethnicity shows a significant association with survival status. The Malays had a higher risk of dying (HR: 2.90; 95%CI: 1.14,7.41) compared to other ethnic groups. The other background characteristics were not statistically significant.

Table 4.26: Univariate socio-demographics and lifestyle predictors of death in TB/HIV co-infected patients.

Variables		Crude HR (95% CI)
Age group	< 34	1
	35-54	1.70 (0.89, 3.26)
	≥55	1.48 (0.42, 5.24)
Gender	Male	1.01 (0.43, 2.35)
	Female	1
Nationality	Malaysian	1.75 (0.40, 7.76)
	Non-Malaysian	1
Ethnicity	Malay	2.90 (1.14,7.41)*
	Chinese	1.17 (0.34,4.03)
	Indian	1.89 (0.62,5.77)
	Others	1
Employment	Employed	1
	Unemployed	0.39 (0.21, 0.73)
Incarceration	Yes	0.39 (0.20, 0.78)
	No	1
Marital status	Single/divorced	1.78 (0.94, 3.39)
	Married	1
Smoking	Ever smoking	0.72 (0.37,1.39)
	Never smoking	1
Alcohol intake	Ever take alcohol	0.91 (0.46,1.86)
	Never take alcohol	1
Mode of HIV transmission	Intravenous drug users	1.08 (0.33, 3.48)
	Sexual	0.35 (0.10,1.27)
	Others	1
Body weight	< 50 kg	1.67 (0.94,2.97)
	≥ 51 kg	1

*Incarceration: Prisoners/Drug Rehabilitation Centre inmates at the time of TB diagnosis.

Table 4.27 displays the association of patient's clinical characteristics and laboratory profiles with their survival status. Maintenance therapy regime, opportunistic infection, number of opportunistic infections and antiretroviral therapy were significantly associated with survival status.

Table 4.27: Univariate clinical predictors of death in TB/HIV co-infected patients.

Variables		Crude HR (95% CI)
Types of TB	Pulmonary	1.06 (0.56, 2.02)
	Extrapulmonary	1.21 (0.63, 2.34)
	Both	1
Status of TB diagnosis	Newly diagnosed TB	0.85 (0.48,1.51)
	Ever had TB before	1
Intensive Phase Regime	HRZ[a]	0.80 (0.36, 1.79)
	HZ	0.88 (0.18, 4.25)
	Others	1
Maintenance Phase Regime	No maintenance	7.11(2.18, 23.15)*
	HR	0.95 (0.27, 3.27)
	Others	1
Changed in treatment[b]	Yes	0.99 (0.48, 2.03)
	No	
Case detection	Passive	0.97 (0.29, 3.28)
	Active	1
Cough more than two weeks	Yes	0.79 (0.46, 1.38)
	No	1
Cough with sputum	Yes	1.63 (0.94, 2.81)
	No	1
Hemoptysis	Yes	0.94 (0.43, 2.09)
	No	1
Loss of weight	Yes	1.02 (0.57, 1.83)
	No	1
Fever	Yes	1.04 (0.56, 1.94)
	No	1
Night sweats	Yes	0.64 (0.36, 1.13)
	No	1
Loss of appetite	Yes	1.10 (0.62, 1.96)
	No	1

Table 4.27, continued.

Variables		Crude HR (95% CI)
Co-morbidities[c]	Yes	1.13 (0.15, 8.77)
	No	
Diabetes mellitus	Yes	0.44 (0.14, 1.40)
	No	1
Presence of BCG scar	Yes	0.70 (0.28,1.75)
	No scar/ NR	1
Lymphadenopathy	Yes	0.91 (0.53,1.56)
	No	1
Opportunistic infection	Yes	1.98 (1.14,3.46)
	No	1
Chest x-ray changes	No lesion	1
	Minimal lesion	0.96 (0.47, 1.98)
	Advanced lesion	1.52 (0.73, 3.17)
Number of Opportunistic Infection (OI)	No OI	1
	One OI	1.86 (1.02, 3.39)
	Two OIs	2.02 (0.85, 4.78)
	More than two OI	3.72 (1.10,, 12.52)
Antiretroviral Therapy	Yes	1
	No	2.50 (1.45, 4.31)

[a]HRZ: Isoniazid, Ryfampycin & Pyrazinamide; HZ: Isoniazid & Pyrazinamide only; HR: Isoniazid &Ryfampycin
[b]Change in diagnosis: Change from the initial TB regime (HRZ) to another due to side effects of treatment or adverse reaction.
[c]Co-morbidities: Include diabetes mellitus, congenital heart disease, malabsorption syndrome, malignancies, chronic liver disease and history of gastrectomy

There were statistically significant associations between serum albumin level and CD4 T-lymphocytes count with survival status of TB/HIV co-infected patients.

Table 4.28: Univariate laboratory predictors of death in TB/HIV co-infected patients.

Variables	Crude HR (95% CI)
Haemoglobin level	
< 12 g/dL	1.60 (0.75,3.40)
≥ 12 g/dL	1
Total White Blood Cell, 10^3/µl	1.12 (1.05, 1.18)
Platelet, 10^3/µl	0.10 (0.99,1.00)
Urea, mmol/L	1.05 (0.89, 1.25)
Natrium, mmol/L	1.06 (0.99, 1.15)
Potassium, mmol/L	1.00 (0.99, 1.02)
Creatinine, mmol/L	1.00 (0.99, 1.01)
Total Protein, g/L	0.99 (0.96, 1.02)
Serum albumin level	
< 35 g/L	1.44 (0.65, 3.18)
≥ 35 g/L	1
Total bilirubin, µmol/L	0.98 (0.98, 1.02)
Alkaline Phosphatase (ALP), U/L	1.00 (0.995, 1.001)
Alanine Transaminase (ALT), U/L	1.00 (0.998, 1.004)
CD4 T-lymphocytes count	
Not available	3.95 (0.94, 16.53)
< 200 cells/µl	3.90 (1.21,12.54)
≥ 200cells/µl	1
HbsAg	
Reactive	1.22 (0.38, 3.92)
Non-reactive	1
Hepatitis C serology	
Reactive	1.73 (0.97, 3.08)
Non-reactive/unknown	1
Toxoplasma IgG	
Reactive	1.77 (0.99, 3.15)
Non-reactive/unknown	1
Rapid Plasma Reagin (RPR)	
Reactive	0.33 (0.05, 2.35)
Non-reactive/unknown	1

*Ref: Reference value

4.4.6 Multivariate analysis

The log rank p-value less than 0.25 was set as cut off value to choose variables for multiple Cox proportional hazards regression analysis.The outcome is a single outcome variable with two categories (alive or dead). Eighteen variables that had a log rank *p-val*ue of less than 0.25 including age group, marital status, ethnicity, employment status, incarceration,body weight, cough with sputum at diagnosis, night sweats, co-morbidity with diabetes mellitus, presence of opportunistic infections, number of opportunistic infections, ART, haemoglobin level, serum albumin level, total white blood cell count, Toxoplasma serology test, anti-HCV serology and CD4 T-lymphocytes counts were all associated with survival in the univariate analyses.

During the multivariate analysis using Cox proportional hazards regression model; ethnicity, number of opportunistic infections, anti-retroviral therapy, total white blood cell count (WBC) and CD4 T-lymphocytes were found to be associated with death in TB/HIV co-infected patients. Ethnicity is the strongest risk factor for death in this study. The risk of dying among Malay patients was almost five times higher than ethnic group classified as 'Others' (HR: 4.48; 95%CI: 1.73-11.64).

Low CD4 T-lymphocytes count is the strongest clinical predictors of death in TB/HIV co-infected patients. Patients with CD4 T-lymphocytes count less than 200 cells/µl had almost four times higher risk of death compared to CD4 T-lymphocytes count more than 200 cells/µl (HR 3.89; 95% CI:1.20-12.63). Patients with three or more opportunistic infections had 3.61 times higher risk of death than patients who did not have any opportunistic infection (HR: 3.61; 95%CI:1.04-12.55). However, this group has a wide confidence interval because of the small number (n=6). The risk of death in patients who were not on antiretroviral therapy was 3.21 times compared to patients on antiretroviral therapy (HR: 3.21; 95%CI: 1.76-5.85). For every 1000 cells per microliter

unit increase in total white blood cell (WBC), the risk of death increased by 12% (HR: 1.12; 95%CI: 1.05-1.20). Based on the Pearson's correlation, WBC has an inverse relationship with number of opportunistic infections, but it was not significant and the r-value was low (*r-value* = 0.06; *p-value*=0.366). The crude and adjusted hazard ratios are displayed in Table 4.29.

Table 4.29: Significant predictors of death in TB/HIV co-infected in the Klang Valley.

Characteristics	Crude HR	95% CI	[a]Adjusted HR	95% CI
Race				
Malay	2.90	1.14-7.41	4.48	1.73-11.64*
Chinese	1.17	0.34-4.03	1.78	0.51-6.25
Indian	1.89	0.62-5.77	2.40	0.76-7.56
Others	1.00	-	1.00	-
Number of Opportunistic infections (OI)				
No OI	1.00	-	1.00	-
One OI	1.86	1.02-3.39	2.68	1.40-5.13
Two OIs	2.02	0.85-4.78	3.32	1.33-8.29
More than two OIs	3.72	1.10-12.52	3.61	1.04-12.55*
Anti-retroviral therapy				
Yes	1.00	-	1.00	-
No	2.50	1.45- 4.31	3.21	1.76-5.85*
Total White Blood Cells (TWBC)	1.12	1.05-1.18	1.12	1.05-1.20*
CD4 T-lymphocytes count				
Not available	3.95	0.94-16.53	2.21	0.50-9.81
< 200 cells/µl	3.90	1.21-12.54	3.89	1.20-12.63*
≥ 200cells/µl	1.00	-	1.00	-

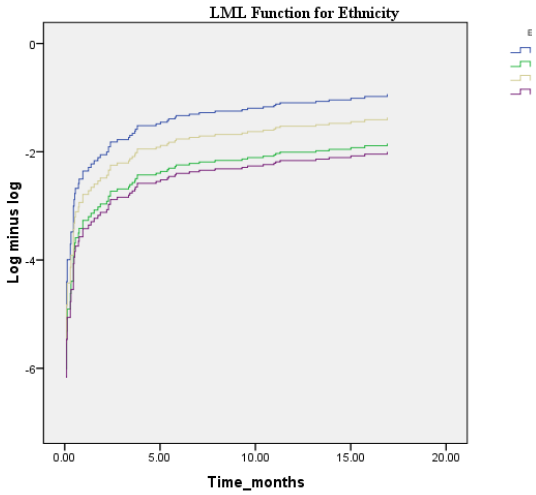
HR: Hazards Ratio, CI: Confidence Interval, * $p < 0.05$

[a]Adjusted for age group, marital status, employment status, incarceration, body weight, cough with sputum at diagnosis, night sweats, co-morbidity with diabetes mellitus, haemoglobin level, serum albumin level, toxoplasma serology test and anti-HCV serology.

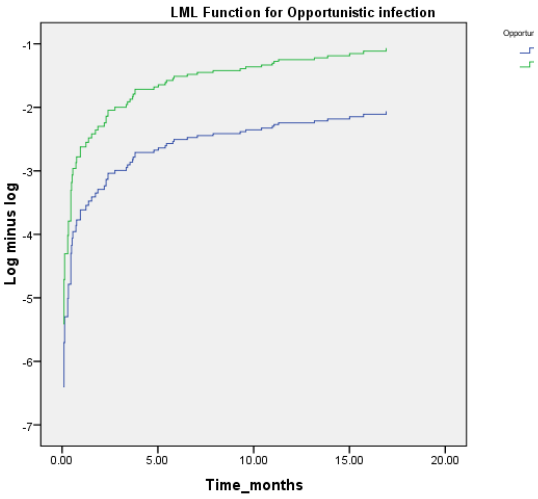
The final model was checked for model assumptions to ensure that it is fit enough to predict death.

Proportional hazards assumption

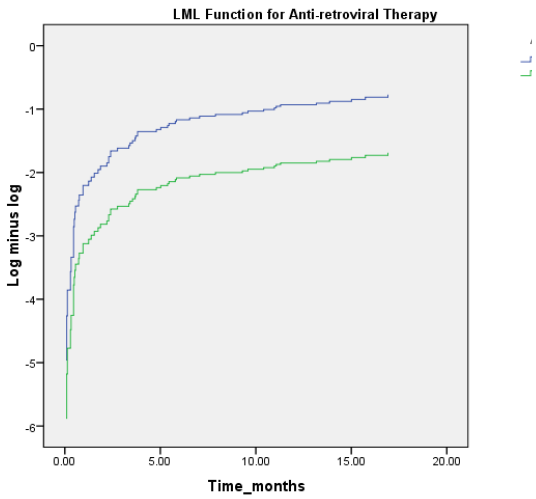
The assumption of the proportional hazards was checked by examining the hazard function and the Log-Minus-Log (LML) plots for all the statistically significant predictors of death in TB/HIV co-infected patients. The log minus log hazard curves plotted against survival time in all categorical variables that were included in the final model were parallel (Figure 4.7). For these four categorical predictors, all the plots showed parallel lines and were not crossing with each other. Hence it can be concluded that the proportional hazards assumption is met. Hazard plot against survival time also showed the parallel pattern, which indicated the proportional hazard assumption was fulfilled (Figure 4.8).



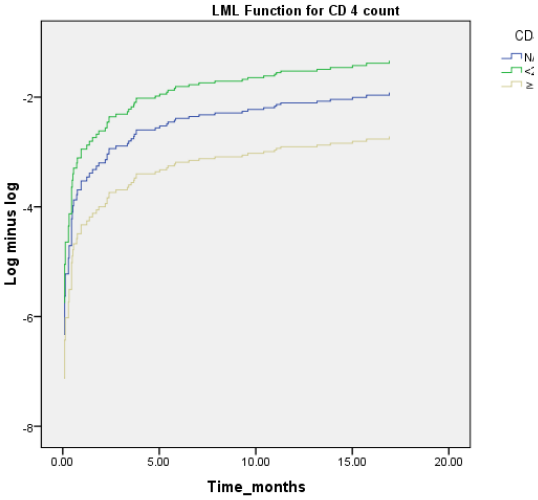
a) Ethnicity



b) Opportunistic Infection

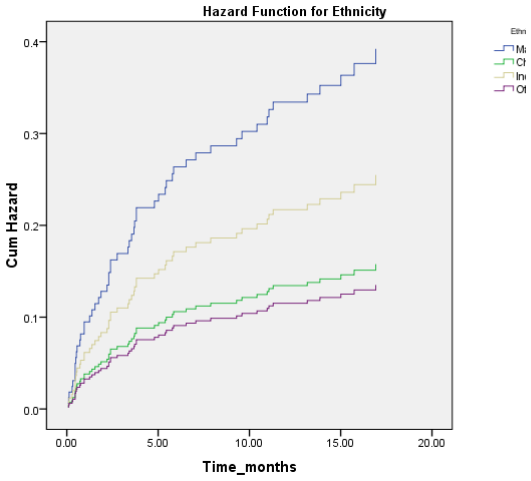


c) Antiretroviral therapy

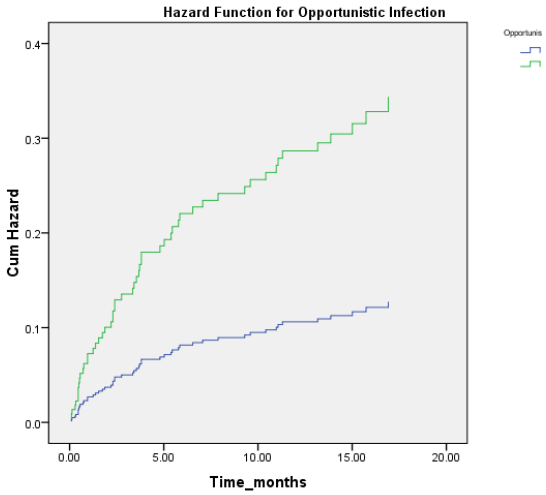


d) CD4 count

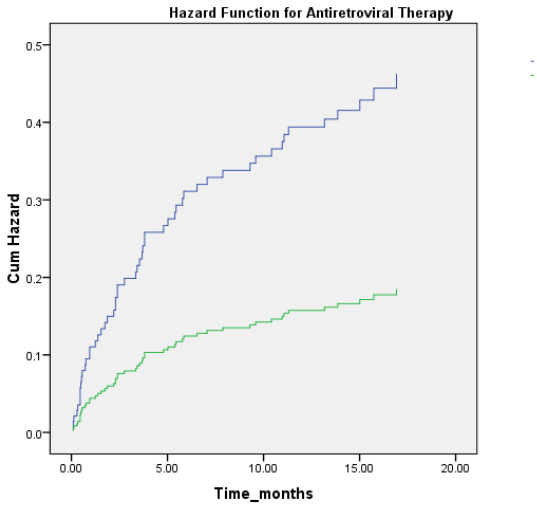
Figure 4.7: The Log-minus-log cumulative hazard curve plotted against survival time in all categorical variables in the final model



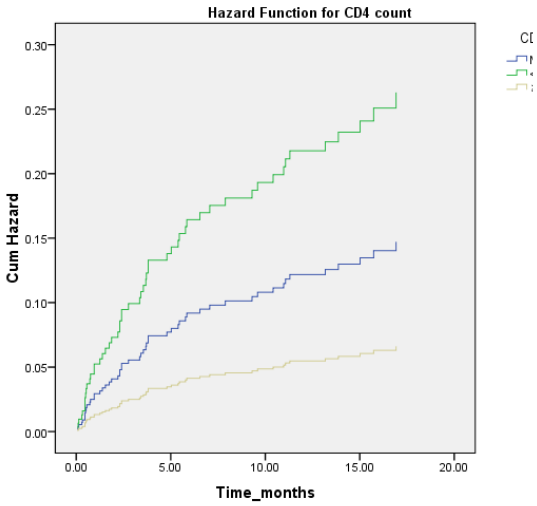
a) Ethnicity



(b) Opportunistic Infection



b) Antiretroviral therapy



d) CD4 counts

Figure 4.8: The hazard function curve plotted against survival time in all categorical variables in the final model

The second way was by correlation of the partial residuals for all the statistically significant predictors with the survival time rank of TB/HIV co-infected patients to death. If the p-values were more than 0.05, it indicated that proportional hazards assumption was met. The correlation is summarized in Table 4.30.

Table 4.30: Pearson's correlation between variables and survival time of TB/HIV co-infected patients to death

Variables	Pearson's *r*-value	*P-value*
Race		
Malay	0.087	0.237
Chinese	0.034	0.292
Indian	0.094	0.501
Number of Opportunistic infections (OIs)		
One OI	0.097	0.489
Two OIs	-0.051	0.717
More than two OIs	-0.013	0.927
Anti-retroviral therapy		
No ART	-0.012	0.341
Total White Blood Cells (TWBC)	-0.070	0.617
CD4 T-lymphocytes count		
Not available	-0.028	0.301
< 200 cells/µl	0.116	0.219

Note: N=53

4.5 Summary

This chapter presents the results from the study of TB/HIV co-infected patients in Klang Valley. The socio-demographic, lifestyle, clinical characteristics and laboratory profiles of TB/HIV co-infected patients were presented in detail. Among the 227 patients eligible for analysis, 51.6% (117) achieved successful outcomes (cure, completed treatment), while 24.7% (56) of patients defaulted treatment and 20.3% (46) died. Another 3.4% (8) were still on treatment. After adjusting for other factors, default TB treatment in TB/HIV co-infected patients was associated with ever take alcohol (AHR 1.93; 95% CI 1.10-3.38), not receiving antiretroviral therapy (AHR 3.75; 95% CI 2.19-6.42), lymphadenopathy (AHR 2.03; 95% CI 1.18-3.49) and low serum albumin (AHR 2.89; 95% CI 1.22-6.84).

Results

At the end of the study period, the total number of deaths was 53 (23.3%) out of 227 patients with 40% of deaths occurring within two months of TB diagnosis. Survival at 2, 6 and 12 months after initiating TB treatment were 90.7%, 82.8% and 78.8% respectively. After adjusting for other factors, poor survival was associated with being Malay (AHR: 4.48; 95%CI: 1.73-11.64), number of opportunistic infections more than two (AHR: 3.61; 95%CI:1.04-12.55), not receiving antiretroviral therapy (AHR: 3.21; 95%CI: 1.76-5.85), increase per 1000 total white blood cell count per microliter (AHR: 1.12; 95%CI: 1.05-1.20) and CD4 T-lymphocytes count < 200 cells/µl (AHR 3.89; 95% CI:1.20-12.63).

CHAPTER 5: DISCUSSION

About this chapter

This chapter synthesises the results of the research in comparison with other studies and finally discusses the strengths and limitations of the research. The aim of this study was to describe and determine HIV infection among active TB cases, TB treatment outcomes, survival probabilities and prognostic factors affecting survival among a cohort of HIV-infected TB patients in Malaysia which is an intermediate TB burden country with a TB incidence of 65 per 100, 000 populations per year during the study period (WHO, 2012). Identifying the prognostic factors will help us in the management of patients and provide vital information for clinical and public health intervention programs.

5.1 Characteristics of TB/HIV co-infected patients

5.1.1 Socio-demographic

TB is a common opportunistic infection and cause of death in HIV-infected patients in many parts of the world, particularly in developing countries. The results of our study estimated that the proportion of TB-HIV in the Klang Valley to be 11.0%, which was slightly higher than the national prevalence of HIV-infected patients among tested TB patients in Malaysia (7.2%) in 2010 (WHO, 2012). HIV prevalence in TB patients in Asia ranged from 0.9% to 38% in 2010 (WHO, 2012). TB-HIV co-infection is still relatively low in Malaysia compared to other countries in Asia.

The majority of the patients were males. The male to female ratio was 7:1. The finding that males were at risk for TB/HIV co-infection is in agreement with other studies. In Malaysia, the proportion of TB among males was higher compared to females. In a

recent report, the proportion of TB among males in Malaysia was 67.7% compared to females, which was 32.3% (WHO, 2012).

In this study, the age groups with most frequent HIV infection were 35-54 years with the mean age of 39.1 (SD 8.6) years; which is the age range in which most cases of intravenous drug users were reported and sexually active age group. This is consistent with the report from the Malaysian Ministry of Health that documented an increasing trend of HIV cases among older adult in this country. In year 2011, about 60% of new HIV infection were reported among people aged 30-49 years (MOH, 2012b). The age distributions among the TB/HIV co-infected cases were consistent with findings in other studies. Most of the studies found that TB/HIV co-infection was significantly more common among young and middle aged adults (Korzeniewska-Kosela et al., 1992; Van Der Werf, Sebhatu, Weldegergis, Tesfazion, & Borgdorff, 2007; Weis, Foresman, Cook, & Matty, 1999). A study in An Giang province, Vietnam reported that the TB/HIV co-infected TB patients in this study were among younger age groups, in which 74% of cases were between 25 to 44 years of age (Thuy et al., 2007).

The race distribution was Malays (48.5%), Chinese (16.3%) and Indians (16.3%). The rest (18.9%) consisted of indigenous ethnic groups born in Sabah and Sarawak; those who were born from interracial marriages and non-citizens. Surprisingly, the proportion of TB/HIV patients among Indians was higher than expected as Indians form only 7-8% of the population. However the reason for this was unclear. A previous study conducted in Kota Bharu, Kelantan, Malaysia had shown a higher proportion of Malays (94%) with TB/HIV co-infection (Mohammad & Naing, 2004). This is to be expected because Kelantan has the highest percentage of Malays (93%) with the Chinese making up only 5% and Indians only 1% of its total population. Therefore, it would not be a good representation of Malaysia.

The most common mode of HIV infection was through IDU (55.9%), followed by sexual transmission: 35.7% heterosexual and 3.5% homosexual. In the earlier phase of HIV pandemic in Malaysia until the year 2010, IDU was the main mode of HIV transmission. However, with intensive implementation of harm reduction programmes including Methadone Maintenance Therapy (MMT) and Needle Syringe Exchanged Programme (NSEP) since 2005, the number of HIV infections transmitted through sharing needles was successfully reduced. In 2011, the percentages of sexual transmission had superseded IDU as the main driving factor of the HIV epidemic in Malaysia. Overall, the number of new HIV infections reported to the Ministry of Health in 2011 had decreased to 3,479 cases; which is approximately half of what was reported in 2002 (MOH, 2012b).

Previous studies demonstrated that IDUs were associated with both risks of unsuccessful TB treatment outcomes and mortality in HIV-infected TB patients. Girardi et al. found that IDUs was associated with four times higher risk of unsuccessful outcomes (AOR:4, 95%CI: 1.35-12.5) compared to other modes of HIV infection (Enrico Girardi et al., 2012). In this study, IDUs remain an independent factor for unsatisfactory outcome of TB treatment despite adjustment for other socio-economic factors including years of education, place of origin (born in Italy or foreign born), age at TB diagnosis, history of imprisonment and type of housing. The researchers related this to the high proportion of intravenous drug users (48%) in their study population. Another study that was conducted in Spain (Ruiz-Navarro et al., 2005) found that the odds of potentially unsatisfactory outcomes (treatment failure and transferred out) were increased in intravenous drug users (AOR: 1.71, 95%CI: 1.06-2.75) after adjusting for age, gender and alcohol abuse. However the researchers did not provide possible explanations for this result. Two other studies (Alpert et al., 1997; Catala et al., 2011) have revealed that a history of intravenous drug use resulted in poor survival in HIV-

infected TB patients. Drug users are exposed to the risk of contracting TB because this group is usually associated with poor nutrition, sanitation and hygiene; social displacement and high risk sexual behaviour. They also live in seclusion to avoid being caught by the police or anti-drugs authority. Therefore, they do not seek treatment unless they are seriously ill or institutionalized. Furthermore, TB treatment involves a number of medications which require a longer duration to complete the treatment. Their homeless condition and nomadic lifestyle make it difficult for health authorities to conduct contact tracing, to monitor their treatment and to track them if they do not come for further follow-up.

A study in New York that assessed the socio-demographic characteristics and TB treatment outcomes of HIV-infected TB patients found that previous incarceration was more common among HIV- infected patients compared to HIV-negative individuals in this study with 41.6% of 92 HIV-infected TB patients having a history of incarceration (Alpert et al., 1997). Another study by Kittikraisak et al. (2009) also found that incarceration history was an independent factor for TB treatment default among HIV-infected patients in Thailand (AOR: 2.0; 95% CI: 1.1-3.7). The researchers were unsure of the reasons for default but expected that some patients may have been re-incarcerated without informing the TB clinic in which they were treated (Kittikraisak et al., 2009).

In our study, only 21 (18.5%) patients were living in prisons or drug rehabilitation centres at the time of their TB diagnosis. A systematic review and meta-analysis that assessed population at highest risk for recent TB transmission (Nava-Aguilera et al., 2009) found that a history of incarceration was an independent predictor of recent TB transmission with a combined estimated risk of 2.21 (95% CI 1.71–2.86) perhaps due to overcrowding and poor hygiene conditions in most detention centres.

Existing guidelines of the Ministry of Health Malaysia require that all persons with active TB should be screened for HIV infection and vice versa. This policy had benefited at least 10 patients (4.4%) in this study in which they were diagnosed via TB screening in prisons or drug rehabilitation centres where they were detained. TB screening not only give them an opportunity for earlier access to TB treatment but also hinder the TB transmission to other inmates in such closed settings.

5.1.2 TB-related characteristics

This study included all types of TB including smear positive PTB; smear negative PTB and extra-pulmonary TB. The majority of TB in HIV-infected patients is still pulmonary TB but extra-pulmonary TB is now becoming more common particularly in those with advanced immune suppression. Patients with HIV infection were more likely to have smear positive PTB, alone or in combination with extrapulmonary TB. The total number of smear positive pulmonary TB was 40.5%. Smear negative pulmonary TB was diagnosed in 31.3% and extrapulmonary TB in 28.2% of patients. This finding in this study was different from other studies that reported extra-pulmonary TB as the most common type of TB among the TB/HIV co-infected patients (Alpert et al., 1997; K P Cain et al., 2007; Kung et al., 2009). Extrapulmonary TB becomes more common in HIV-infected patients because as the immunity declines, the body is unable to prevent the growth and spread of *Mycobacterium tuberculosis*, thus changing the clinical presentation of TB. However, a study in Vietnam reported a higher proportion of smear-positive TB in HIV-infected TB patients with 83% from a total of 637 patients being diagnosed with smear-positive pulmonary TB (Thuy et al., 2007). This is an important finding as smear positive TB is the most infective type and people with smear positive TB can trigger a chain of transmission within the community. If smear positive TB patients are correctly diagnosed and successfully treated, in the long term it will help to reduce the burden of TB in the country.

The most common TB symptoms presented by the patients at diagnosis were cough of more than two weeks duration (67.0%), fever (74.9%), loss of appetite (66.1%) and loss of weight (69.2%). This is consistent with the finding that most of the patients in this study had pulmonary TB. Therefore, physicians should pay more attention and have a high index of suspicion with HIV-infected patients who present with symptoms of fever and cough by carrying out the appropriate tests to diagnose TB. Early diagnosis and immediate initiation of treatment are essential for an effective TB control program. Delay in diagnosis will significantly affect both disease prognoses at the individual level and transmission within the community because most transmissions occur between the onset of cough and initiation of treatment.

Abnormal chest x-ray was reported in 77.1% of patients, with 48.0% having minimal lesion and another 29.1% already having an advanced lesion. In this study, minimal lesion is defined as slight lesions without demonstrable cavitation in both lungs. In HIV-infected patients, the common finding of cavitation at the apex of the lung as seen in immunologically normal persons is less common. Although radiographic findings in HIV-infected patients may reflect the degree of immune suppression, but they may also have a normal chest radiograph. The finding in this study is consistent with a report that chest x-rays in TB/HIV co-infected patients may show little change or there may be diffuse pulmonary infiltrates without cavitation (Shafer & Edlin., 1996). Very frequently, presentation of atypical chest X-ray appearance makes it difficult to diagnose TB in this group of patients.

The majority of TB/HIV patients in this study had no co-morbidity (81.9%). This was probably due to a higher proportion of patients in this study being in the young to middle age group. Therefore, they were less likely to have other co-morbidities seen in older patients. Although diabetes mellitus is also a known risk factor for TB, only 2.6% of the patients in this study were reported to have diabetes mellitus and their age ranged

between 39 to 57 years old.. This finding concurs with the prevalence of diabetes in Malaysia as documented in the National Health Morbidity Survey III (NHMS III) that was conducted in 2006. Data from NHMS III reported that there was a sharp increase of diabetes for those aged 40 years and above with the highest prevalence in the 60 to 64 age group (25.2%) (Letchuman GR et al., 2010).

The patients received standard therapy in accordance with the Clinical Practice Guidelines on the Control and Management of TB in Malaysia that recommended that patients with a first episode of tuberculosis be treated with a 2-month intensive combination-drug regimen of rifampicin (a rifamycin derivative), isoniazid, ethambutol, and pyrazinamide, followed by a maintenance phase for an additional four to seven months (based on WHO guidelines). The drug doses in every patient were determined according to pre-treatment weight. The mean duration of TB treatment in this study was 6.2 (SD 3.8) months and the median was 6.6 (IQR 6.8) months. A change in therapy mainly due to adverse reactions to anti-TB drugs occurred in 26% of patients. The data from a systematic review suggested that TB patients that were co-infected with HIV required at least eight months duration of rifamycin therapy with an initial daily dosing to ensure a better outcome (Khan et al., 2010). If this report is referred to, the duration of TB treatment of TB/HIV co-infected patients in Malaysia is not optimal. Furthermore, they reported that there were trends toward higher relapse rates if rifamycins were used for only six months, compared with eight months.

From a total of 227 patients, 167 isolates (73.6%) were tested for anti-TB drug sensitivity and only three mono-resistant cases were identified. One isolate was resistant to pyrazinamide, one resistant to streptomycin and another one resistant to rifampicin. No MDRTB case was reported in this study. National data recently reported by WHO documented that MDRTB in Malaysia still at a low level of 1.3% in 2011 (WHO, 2012).

5.1.3 HIV-related Characteristics

Most TB/HIV co-infected patients had concurrent opportunistic infection at the time of TB diagnoses. This is consistent with other findings that have been described in other studies (Thuy et al., 2007; Wobeser et al., 1999). The presence of opportunistic infection other than TB at the time of TB diagnosis in most HIV-infected TB patients suggests that patients in this study already had advanced HIV at the time of diagnosis. This condition will increase their risk of dying from either TB or HIV. Thus, we strongly support the administration of isoniazid prophylaxis to prevent TB in HIV-infected patients; which has been recommended by previous studies (Moreno et al., 1997, Akolo & Adetifa, 2010). In Malaysia, Isoniazid Preventive Therapy (IPT) started in September 2011. Further research should be carried out to evaluate the effect of IPT in HIV-infected patients in this country.

The median CD4 count at diagnosis for TB/HIV co-infected patients in this study were 59 cells/µl (IQR 133.5). One study of HIV-infected TB patients in Malaysia in 2005 found similar low CD4 counts with a median of 57 cells/µl (Nissapatorn et al., 2005). The median CD4 counts are similar to other studies in Thailand, which was reported to range between 54 cells/µl to 63 cells/µl (Cain et al., 2009; Mankatittham et al., 2009; Manosuthi et al., 2006; Sanguanwongse et al., 2008). However, published studies in sub-Saharan Africa reported a higher median CD4 count. The median CD4 count in sub-Saharan Africa ranged between 106 cells/µl to 317 cells/µl (Komati et al., 2010; Lawn, Badri, & Wood, 2005; Perriëns et al., 1995). This result supported the findings that TB/HIV co-infected patients in Asia were more immuno-suppressed than those in sub-Saharan Africa. A possible explanation for this is that patients presented late to the health centre to seek treatment because of perceived stigma and discrimination. Stigma prevents them from seeking medical treatment and utilise HIV-related services

(Mahajan et al, 2008). Generally, people in Malaysia are still not open to accept PLWH and AIDS because the feeling of suspicion and prejudice is still strong in them.

Among the 95 patients with an available HIV RNA viral load result, the median HIV RNA viral load was 204,638.0 copies/ml (IQR: 828,620.0). A study in Thailand reported a higher median HIV RNA viral load which is 308,000 copies/ml (IQR: 707,000). Higher HIV viral loads increase the rate of disease progression and also increase HIV infectiousness. The predominance of low CD4 counts and a high HIV RNA viral load suggests that TB is a late presentation of HIV disease in Malaysia. This finding is also related to delay in diagnosis due to their self-stigma and health seeking behaviour.

In Malaysia, ART was introduced through the national health system in 1996. The first line ART is given at no cost for those who need it and the second line regimen is also heavily subsidised by the government. This study reflected the implication of free ART policy by the Malaysian government. The policy for starting ART follows international recommendations. Despite the well documented benefit of ART in TB/HIV co-infected patients and the widely available ART in this country, 38.3% of cases in this study were not on ART. Although there are guidelines by WHO, but the decision to start ART invariably depends on the attending physician. The timing of initiating the ART after starting anti-TB therapy has been controversial. The initiation of ART may be deferred until completion of tuberculosis therapy because of concerns about potential drug interactions between rifampicin and some classes of antiretroviral drugs, the immune reconstitution inflammatory syndrome (Schiffer & Sterling, 2007), overlapping side effects and high pill burden. However, recent observational studies (Velasco et al., 2009) and randomised control trial (Abdool Karim et al., 2010) provided evidence that the initiation of antiretroviral therapy during TB therapy significantly improved survival in TB/HIV co-infected patients.

Recent international guidelines recommend that HIV-infected persons initiate treatment with nevirapine (NVP), zidovudine (AZT), and lamivudine (3TC) (WHO, 2011c). Rifampicin can alter drug levels of nevirapine, thus the guidelines recommend that in patients receiving rifampicin, nevirapine should be replaced with efavirenz (EFV). In this study, most of the patients (56.2%) received the combination of stavudine (d4T), lamivudine (3TC) and efavirenz (EFV). However, in this guidelines WHO had advised all countries to progressively reduce the use of d4T in first line regiments because of its well-recognised toxicities.

Early diagnosis of both TB and HIV, will not only promise an earlier access to appropriate treatment, but also provide more opportunities for deciding the proper timing of ART initiation and then better prognosis by saving lives (WHO, 2008).

5.2 Poor treatment outcome

Monitoring the outcome of TB treatment is an essential part of TB disease surveillance. This is to ensure that the disease is successfully eliminated. The treatment success has been reported to differ between the HIV-positive and HIV-negative TB patients. Previous studies that evaluated TB treatment outcomes found that HIV co-infections were associated with poorer outcomes compared to HIV-negative patients (Anunnatsiri, Chetchotisakd, & Wanke, 2005; Ruiz-Navarro et al., 2005). The researchers in Spain related the high number of HIV-positive TB patients in their study being intravenous drug users (58.6%) with high co-morbidity as the most likely explanation for treatment interruption (Ruiz-Navarro et al., 2005). In Thailand, the majority of HIV-infected TB patients had advanced HIV disease and were not treated effectively for their HIV infection, therefore, they were also at risk of contracting other opportunistic infections related to death as an outcome (Anunnatsiri et al., 2005).

Consistent with other findings, the results of this study indicated that HIV-infected TB patients in the Klang Valley have poor treatment outcomes with a treatment success rate only 53.4% compared to the 85% treatment success rate targeted by the WHO. The treatment success rate in the present study was similar to that found in other studies conducted in the city of Recife, Brazil (58.8%) (Magda Maruza, Arraes, & Ximenes, 2008), in Vietnam (56.5%) (Quy et al., 2006), in Tanzania (59.0%) (Van den Broek et al., 1998) and in Malawi (50.9%) (Harries et al., 1998). A higher percentage was found in another study involving TB/HIV co-infected patients in India (Vijay et al., 2011) with the treatment success rate of 75.0% and in Sau Paulo, Brazil (78.0%) (Klautau & Kuschnaroff, 2005).

This study reported a high default rate or non-adherence to TB treatment (25.6%) among the TB/HIV co-infected patients. However, this finding shows a substantial improvement as compared to a single centre study done in Kuala Lumpur which reported 40.5 % of non-adherence (defaulted and absconded) among 252 TB/HIV cases between January 2001 and December 2002 (Nissapatorn et al., 2005). The high default rate observed in our study could perhaps be due to patients stopping medication once they felt better; or other reasons which require further studies. A systematic review of qualitative studies that assessed patient adherence to TB treatment had identified patients' adherence to their treatment regimens as being influenced by the interaction of a number of factors. These included health service factors such as the organization of treatment and care; social context (family, community and household influences); personal factors (including attitudes towards treatment and illness) and the financial burden of treatment (SA Munro et al., 2007).

There are variations in the rates of non-adherence to TB treatment among TB/HIV co-infected patients as reported by previous studies. The percentage of noncompliance ranged from 1.0% in Vietnam (Thuy et al., 2007) to 21.7% as observed in a study in in

Pernambuco, Brazil (M Maruza et al., 2011). Male gender, smoking and CD4 T-cell count less than 200 cells/mm^3 were found to be associated with treatment default in the study among Brazilians (M Maruza et al., 2011) whereas age older than 29 years, having complete or incomplete secondary or university education, and using ART were identified as protective factors against TB treatment default. The association between DOTS and improved survival as reported by Alpert et al. proved that compliance with TB treatment was important an important factor (Alpert et al., 1997).

Non-adherence not only contributed to the spread of TB, but also the emergence of drug resistant TB. Although the drug resistant cases in Malaysia are still considered low, the numbers are actually increasing each year. Based on the results of the sensitivity test for *Mycobacterium TB* isolates reported by the National Public Health Laboratory, Sungai Buloh; there was an average of 500 mono-resistant cases seen every year from 2004 to 2008. The number of multidrug resistant cases was reported to be around 40 cases yearly and this contributes to less than 1% of total TB cases (MOH, 2010).

5.3 Risk factors for default from TB treatment in HIV-infected patients

TB treatment default is defined as an interruption of treatment for two or more months. It is an important public health problem because patients who default treatment may continue to transmit infection to others and may acquire drug-resistant TB strains. On the other hand, completing TB treatment is not easy for patients because TB treatment takes a minimum of six months and thus may require frequent clinic visits for medication monitoring and refills. They may also develop unpleasant side effects of the anti-TB drugs.

The identification of risk factors for default from TB treatment is crucial in order to improve TB treatment outcomes among HIV-infected patients. In a recent study in

Brazil, the default rate was 21.7% among males. Smoking and CD4 T-cell count less than 200 cells/mm3 were identified as risk factors for default in HIV-infected individuals. Age over 29 years, complete or incomplete secondary or university education and the use of highly active antiretroviral therapy (HAART) was identified as associated with lower rate of TB treatment default (M Maruza et al., 2011). In an earlier study in Thailand, factors associated with TB treatment default among HIV-infected TB patients included a history of incarceration, smoking and having a symptom complaint (Kittikraisak et al., 2009).

Apart from individual characteristics, health facility and patient-specific factors are also associated with TB treatment default in HIV-infected patients as shown by a study in urban Uganda (Elbireer et al., 2011). In this study, they found that the distance from home to clinic, long waiting time at the clinic, poor drug availability, conduct of staff, lack of opportunity to express feelings were all associated with treatment default. Other patient-related factors were lack of health education. Not being aware of the duration of treatment or the risk of discontinuing it, not knowing that TB can be cured, length of TB treatment and side effects of treatment were also associated with defaulting from TB treatment.

During our study, we found that 56 (25.6%) of TB/HIV co-infected patients had defaulted TB treatment. After adjusting for other factors in the multivariate analysis; alcohol intake, presence of lymphadenopathy, status of antiretroviral therapy and serum albumin level were significantly associated with default from TB treatment in HIV-infected patients.

In this study, patients who ever consumed alcohol were two times more likely to default from TB treatment than those who did not give a history of alcohol intake (AHR: 1.93, 95%CI: 1.10-3.38). The finding that alcohol consumption was associated with TB treatment default was consistent with other previous studies (Hasker et al., 2008;

Jakubowiak et al., 2007; Muture et al., 2011). In a systematic review, alcohol was shown to have a pathogenic impact on the immune system making patients more susceptible to active TB infection as well as to the reactivation of latent disease among heavy drinkers with a pooled relative risk of 2.94 (95%CI: 1.89-4.59) (Rehm et al., 2009). Alcohol abuse leads to forgetting the taking of medications and eventual default. The association of alcohol intake with default from TB treatment needs to be better understood to plan for a more appropriate intervention program to reduce default rate in this group of patients.

An association between lymphadenopathy and default from TB treatment (AOR: 2.03, 95%CI: 1.18-3.49) was observed in this study. This finding has not been reported elsewhere, but TB lymphadenitis is the most common form of extrapulmonary TB in both HIV infected and non-HIV patients and is generally associated with a higher degree of immune-suppression. Extrapulmonary TB has been found in the past to be significantly associated with death in HIV-infected patients compared to patients with pulmonary TB only (AHR: 5.1; 95%CI: 1.9-25.9) perhaps due to a higher bacterial load of *Mycobacterium tuberculosis* and have much more severe immunodeficiency status (Sungkanuparph et al., 2007).

This study also found that TB/HIV co-infected patients who were not on antiretroviral therapy were 3.75 times more likely to default from TB treatment than those who received antiretroviral therapy (AOR: 3.75, 95% CI 2.19-6.42). This is in line with findings by Maruza et al. (M Maruza et al., 2011) in Brazil. A study in India also reported that non initiation of ART is significantly associated with unfavourable outcome (AOR: 4.90, 95% CI 1.85–12.96) (Vijay et al., 2011). In a study that was conducted in twelve HIV centres in Greater London and Southeast England, the researchers reported that treatment interruption is more likely to occur in patients with concomitant TB treatment and HAART due to adverse events (Gillian L. Dean et al.,

2003). Although patients who received HAART had shown to have significant decreased of viral load, AIDS-defining illness and death; but patients with concomitant treatment commonly experienced adverse events (gastrointestinal disturbances, seizures, memory loss, psychosis, and pancreatitis) which eventually lead to discontinuation or interruption of TB therapy.

This study suggested that lower serum albumin (less than 35 g/L) is a predictor of TB treatment default (AOR: 2.89, 95% CI 1.22-6.84). However, there are no previous studies that reported similar findings. Poor nutritional status, which is associated with both TB disease and HIV can account for low levels of albumin. Their mean body weight, 49.7 (SD 9.0)kg is 21% lower than the mean body weight for Malaysian adult (Azmi et al., 2009) suggested that they probably have poor general well being and nutritional status. The anthropometric assessment of the Malaysian Adults Nutrition Survey (MANS) involving 6,775 men and 3,441 women aged 18 to 59 years showed that the overall mean body weight and BMI of Malaysian adult were 62.65 kg (95%CI: 62.20-63.09) and 24.37 kg/m2 (95%CI: 24.21-24.53) respectively. Other studies have reported that albumin level is also a strong prognostic marker of HIV disease progression (Mehta et al., 2006; Shah et al., 2007) and can be used as an alternative marker of disease progression, particularly in resource-limited settings.

In this study, we found that patients with lymphadenopathy, lower serum albumin level and not receiving antiretroviral therapy were all associated with a high rate of default from TB treatment in HIV-infected TB patients. These patients were probably severely ill due to poor immune status, as supported by low mean haemoglobin level (10.5 (SD 1.9) g/dL) and were thus unable to tolerate their medications making it difficult for them to comply with their follow-up schedules at health centres. Hemoglobin and serum albumin levels are conventionally thought to be proxies for general nutritional status (Forse & Shizgal, 1980).

The finding that receiving antiretroviral therapy was protective against treatment default reinforces the need for early initiation of antiretroviral therapy in HIV-infected TB patients. The results also indicate that the strategy to reduce rates of TB treatment default should be targeted to specific high risk groups and in particular to alcohol drinkers. This requires further research since failure to complete TB treatment is a risk factor for TB transmission to others, especially those who are smear positive. Poor adherence to TB treatment is also associated with higher rates of TB recurrence (Korenromp et al., 2003) and the emergence of drug resistance TB.

5.4 Mortality in TB/HIV co-infected patient

TB is the leading direct cause of death among people living with HIV (PLWH) in Africa and a major cause of death elsewhere. A meta-analysis of fifteen cohort studies comparing mortality in PLWH with and without TB revealed that PLWH with TB had approximately two times higher risk of death from all causes compared to PLWH without TB (HR: 1.8; 95%CI: 1.4-2.3) which indicates that PLWH with TB die earlier compared to PLWH without TB (Straetemans et al., 2010). In sub-Saharan Africa, a region with a high prevalence of HIV, up to 30% of HIV-positive TB patients (all forms) die before the end of treatment. Early deaths are defined as deaths that occur within less than 30 days of TB treatment which often are due to TB while later deaths are related to complications of HIV. HIV-positive patients who are smear-negative have a worse prognosis than smear-positive TB patients because they are likely to get more severe forms of TB.

HIV infection as a predictor of death in TB patients has been established in many previous studies (Elliott et al., 1995; Harries et al., 1998; Kawai et al., 2006; Mugusi et al., 2009; Quy et al., 2006; Van den Broek et al., 1998). In this study, death during TB treatment occurred in 53 (23.3%) of TB/HIV co-infected patients with 40% of deaths

occurring within two months of TB diagnosis. This finding is similar to case fatality rates during TB treatment that was reported in previous studies in Thailand, which was 29% (Sanguanwongse et al., 2008) and Vietnam (26%) (Thuy et al., 2007). Data from the National TB Control Programme showed that the rate of TB death in Malaysia in 2011 was 8.0% of the total notified TB cases in that year (MOH, 2012a). Our study findings indicate that HIV increases the risk of death in our cohort of patients.

In a prospective study that was conducted in Africa, 31% from a total of 827 adult TB patients were dying at the end of TB treatment. It is surprising to note that almost fifty percent of deaths occurred in the first month of treatment. However, there is no information about availability of ART in the study which could be the reason for that scenario.

5.5 Survival probabilities of TB/HIV co-infection

The overall survival at 2, 6 and 12 months after initiating TB treatment in this study was 90.7%, 82.8% and 78.8% respectively. The survival probabilities are considered good as they were higher compared to the overall survival at 2, 6 and 12 months in Zambia (Elliott et al., 1995); with their overall survival rates being 89%, 76% and 66% respectively. Another study done in Rome, Italy also showed lower survival probabilities with their 6-month survival being 78% and 1-year survival rate was 57% (Palmieri et al., 1999). However, both studies were done before the HAART were widely available and with the old regime of ART. A recent study in Southern Ethiopia reported that their HIV positive TB patients (n=370) had almost similar survival probabilities to our study; with their survival rate of 93.7% at 2 months which decreased to 85.7% after seven months of treatment. In this study, 33.2% of HIV-infected TB patients were known to have started CPT and 14.1% were known to have started ART (Shaweno & Worku, 2012) .

The mean survival time in our study was 11.07 months (95% CI: 10.35, 11.78). The median survival time was not calculated in this study because the cumulative proportion of survival was still more than 50%. In previous studies, the median survival time in HIV-infected TB patients ranged from 7.3 months (Vijay et al., 2011) to 22.0 months (Elliott et al., 1995). The median survival time in our study is quite similar to the median survival time reported in Thailand (Chaisangcharoen, 2005) which was 10.9 months (95% CI: 8.42, 13.45). This may be because conditions in Thailand, which is also a developing country, may be similar to that in Malaysia. Thailand also implemented free access to HAART which is similar to Malaysia. In order to reduce the cost and to facilitate drug supply management, the Thai Ministry of Public Health used fixed-dose combination of generic drugs generic stavudine, lamivudine, and nevirapine; known as "GPO-VIR" (Sungkanuparph, Techasathit, Utaipiboon, & Chasombat, 2010).

5.6 Prognostic factors for TB/HIV survival

Among HIV-infected patients, age group, marital status, ethnicity, employment status, imprisonment, mode of HIV transmission, cough with sputum at diagnosis, night sweat, co-morbidity with diabetes mellitus, opportunistic infection, ART, haemoglobin and serum albumin level, total white blood cell count, Toxoplasma serology test and CD4 T-lymphocytes counts were all associated with survival in univariate analyses. In the multivariate analysis the significant independent predictors of survival were ethnicity, opportunistic infections, antiretroviral therapy, total white blood cell count and CD4 T-lymphocytes.

In this study it was established that the only social risk factor for survival was ethnicity. Malays had almost five times higher risk of death than the ethnic group classified as 'Others' (HR: 4.48; 95%CI: 1.73-11.64) even after adjusting for potential confounders which included employment status, body weight and serum albumin level in

multivariate analysis. Malays patients have the shortest mean survival time compared to other ethnic groups which was 16.30 months (95%CI 14.79,17.81). This is the first published study on TB/HIV survival in Malaysia; therefore comparison about survival status among ethnic groups with other Malaysian studies cannot be made. This warrants further research as reasons for this finding are not clear. Thus, future research needs to focus on the ethnic differences in relation to treatment adherence and access to care.

The finding that every 10^3 increase in total white blood cell per microliter (HR: 1.12; 95%CI: 1.05-1.20) is associated with higher mortality in HIV-infected TB patients finding is novel. We have not found any study in the literature that presents a similar association. Most previous studies have focused on T lymphocyte subsets, particularly $CD4^+$, and generally reported depressed $CD4^+$ T cells in peripheral blood of TB patient. In this study, the total white blood cell results were that documented at the time of TB diagnosis (pre-TB treatment). This finding may reflect that the risk of dying is increased with the severity of infection at TB diagnosis.

The immune responses against HIV-infected TB have not been fully clarified. Generally, infection will cause white blood cells to be elevated. The major types of white blood cells; neutrophils, lymphocytes, monocytes, eosinophils and basophils play a different role in the immune system with a different disease-fighting activity. In active TB disease, neutrophils and monocytes are the main components of white blood cell that response to mycobacterial infection (Morris, Bird, & Nell, 1989). A recent study by Berry et al supported that neutrophils play a role in the pathogenesis of TB which resulted from over-activation by IFN-gamma and type I IFNs (Berry et al., 2010). A study in South Africa found that patients at the time of TB diagnosis had high absolute neutrophil and monocyte counts, which were depleted during treatment, but low lymphocyte subset counts which increased with TB treatment (Veenstra et al., 2006). However, in TB patients who were co-infected with HIV, HIV viruses will attack

lymphocytes and cause further depletion of $CD4^+$ T cells. There is conflicting evidence of the effect of *Mycobacterium tuberculosis* (MTB) on HIV replication, but several studies had shown that MTB infection may increase HIV replication and worsen the patient's immune status (Pawlowski et al., 2012).

Another factor that was independently associated with decreased survival in this study was the number of opportunistic infections. Patients with three or more types of opportunistic infections had 3.61 times higher risk of death than patients who did not have any opportunistic infection (HR: 3.61; 95% CI:1.04-12.55). The finding that opportunistic infection was associated with death were consistent with other studies in this area (Catala et al., 2011; Enrico Girardi et al., 2012; Palmieri et al., 1999; Podlekareva et al., 2009; Whalen et al., 1997). Although these studies demonstrated a positive association between opportunistic infections and death in TB/HIV co-infected patients, the investigators did not examine the relationship between the number of opportunistic infections and risk of death. To our knowledge, this is the first study to report that the number of opportunistic infections is associated with death in TB/HIV co-infection. TB is known to be the most common opportunistic infection in HIV patients. A study by Wong et al in South Africa who investigated the cause of death of TB/HIV patients on antiretroviral therapy by needle biopsy found that TB was the main cause of death regardless of antiretrovirals status (pre-ART, early-ART or late-ART); with disseminated TB being responsible for 87% of deaths in the first three months of ART (Wong et al., 2012).

In addition to concurrent opportunistic infections, not receiving antiretrovirals (HR: 3.21; 95% CI: 1.76-5.85) was also associated with death in TB/HIV co-infected patients. This study demonstrated that ART can improve both the TB treatment outcome and also survival. The mean survival time of patients on ART was 19.0 months (95% CI: 18.1-20.0) and the mean survival time of patients who were not on ART was 15.1

months (95% CI: 13.2-17.0). The survival probability at 12 months for patients on ART was 86.3% compared to 66.7% in patients who were not on ART. This finding shows that HIV-infected TB patients treated with ART had almost 23% better survival compared with those who were not treated with ART. The benefit of ART in reducing the death rates of TB/HIV co-infected patients have been well documented in other studies (Gadkowski et al., 2009; E Girardi et al., 2001; Manosuthi et al., 2006; Sanguanwongse et al., 2008; Varma et al., 2009). The widespread use of antiretroviral therapy since 1996 has markedly improved the survival of HIV-infected patients in both developing and developed countries by reducing the number of deaths due to many opportunistic infections. In TB/HIV co-infected patients, the decision to introduce antiretroviral therapy is not an easy decision because of concerns about treatment-related complications. However, Dheda et al. (Dheda, Lampe, Johnson, & Lipman, 2004) compared outcomes in patients starting TB treatment during the pre-HAART era (before 1996) with those in patients starting treatment during the HAART era (during or after 1996) and found that the risk of death during the follow-up period was reduced by 60% for the latter (during HAART era) (HR 0.40, 95%CI: 0.19-0.84). Velasco et al. (Velasco et al., 2009) proved that HIV-associated TB patients will have better survival if HAART and TB treatment were started concurrently (HR 0.37, 95% CI 0.17 – 0.66). Furthermore, there were clinical trials that showed timely initiation of antiretroviral therapy in TB/HIV co-infected patients saved lives particularly those with low CD4 (Abdool Karim et al., 2010; Blanc, Sok, & Laureillard, 2011; Havlir et al., 2011; Nanteza et al., 2011). A recent clinical trial by Abdool Karim et al. comparing the outcomes in early versus late ART concluded that in severely immune-compromised patients with CD4 counts less than 50/mm^3, ART should be started as soon as possible after the start of TB treatment. Although earlier initiation of ART is associated with a higher risk of IRIS, but the finding that it is also associated with two thirds lower risk of

death than later ART is far more important (incidence rate ratio, 4.7). However, for those with a higher CD4 count, they recommended that the initiation of ART be deferred until the first four weeks of continuation phase of TB treatment in order to reduce the risk of IRIS (Abdool Karim et al., 2011).

This study adds to the literature that low CD4 T-lymphocytes are associated with higher risk of death in TB/HIV co-infected patients during TB treatment. In our study, patients with CD4 T-lymphocytes count lower than 200 cells/µl had almost four times higher risk of death compared to those with CD4 T-lymphocytes count more than 200 cells/µl (HR 3.89; 95% CI: 1.20-12.63). This finding has been well established in other previous studies (Alpert et al., 1997; Catala et al., 2011; Gadkowski et al., 2009; E Girardi et al., 2001; Podlekareva et al., 2009; Sanguanwongse et al., 2008; Shafer et al., 1996; Velasco et al., 2009). The mean survival time of patients with CD4 < 200 cells/µl is 17.0 months (95% CI: 15.8-18.2) which is lower than the mean survival time for patients with CD4 > 200 cells/µl (20.0 months; 95% CI: 18.7-21.1). The mean survival time for patients whose CD4 counts were not available was 16.1 months (95% CI: 12.5-19.8). This finding is similar to those with CD4 < 200 cells/µl; suggesting that this group of patients might have had lower CD4 counts as well. The numbers of CD4 T-lymphocytes and their activities decrease in HIV infection, but the mechanisms underlying this progressive reduction are still not well understood. Even though opportunistic infections usually occur at less than 200 CD4+ cells/µl, TB is commonly thought to occur at a higher concentration.

Other variables in the literature review that was found to be predictors of mortality in TB/HIV infected patients like increasing age, extra-pulmonary TB and TB drug resistant were not reproduced in this study, probably due to the small sample size. For example, our sample size was not powerful enough to evaluate the association between

drug resistant TB and death because only three cases of resistance to anti-TB drug was found in our study.

The high mortality rate in this study (23.3%) despite the use of rifampicin for two months of intensive phase could possibly be contributed by patients with immune-suppression. These patients had low CD4 counts and opportunistic infection and were not treated with anti-retroviral therapy.

5.7 Strengths of the study

This study present findings of much needed research in TB/HIV co-infection. To our knowledge, this study is the first report in Malaysia to identify the risk factors for mortality during TB treatment in and determine the survival time. This study supports Malaysia's target in the Millenium Development Goal, which aims to reduce the burden of HIV/AIDS and TB disease as a public health problem by 50% by the year 2015 compared to the mid 1990 levels. Malaysia is currently on track to achieve this.

We believe that this study will provide benefits to TB/HIV co-infected patients in Malaysia. The results of this study will help policy makers to estimate the burden of HIV infection among active TB cases in Malaysia thus enabling them to make informed decisions on treatment and program priorities. The results of this study will also help to engage policy makers, researchers and communities to collaborate to generate the knowledge that is needed for better care for TB/HIV co-infected patients in Malaysia; as well as to promote further research in this area. Such interventions and care may include access to improved tools for TB screening in people living with HIV, better linkages between TB and HIV clinics, careful monitoring for drug-resistant TB and prevention of TB occurrence in HIV infected persons.

5.8 Limitations of the study

There are a few limitations to be considered in relation to the findings in our study. The study was only carried out in Kuala Lumpur and Selangor; which are the central parts of Malaysia and can be considered as the most urbanised area in Malaysia. The results from this study may not be generalizable to the whole of Malaysia.

This study is limited by its observational study design. In this study, some of the predictors that had been related to observed survival in other studies of TB/HIV co-infected patients, such as DOT supervision, Tuberculin skin testing (TST), co-trimoxazole preventive therapy, and complication regarding treatment were not assessed. It would also be interesting to know the differential for the WBC particularly the absolute neutrophil count. However, these predictors were excluded from the analysis because data related to these predictors were incomplete or unavailable in many of the patients' records. The reason was to avoid too many missing values which might have affected the results of the study. These variables might have affected the result of our study by making our estimation more complete.

Another limitation of this study arose from dealing with secondary data. Patient information was retrieved from their medical records or folders available in the TB clinic and the medical records unit of the respective hospitals. Some reports were not clear and confusing since different doctors reported in different ways. However, the problem of missing data was minimized by carrying out the study prospectively whereby the participants were 'active' patients who were still on follow-up. This study design avoided the possibility that patients' folders were discarded because patients did not turn up for follow-up for a long time. Data verification was done by cross-checking the data in TB Clinic with patients' records at HIV Clinic and their medical records during admission.

The transferred-out patients (n=32, 12%) who were subsequently excluded in our analysis may slightly bias our results. However, there was no statistically significant difference in the age group, gender and ethnic distribution between the patients included in analyses compared to transferred out patients. We were unable to include these patients because their records were not available and their treatment outcomes were unknown.

In this study, the mean follow-up duration was 14.3 months (±6.3) months and the median was 15.9 (IQR 5.8) months, therefore the survival rate may be underestimated. The follow-up time should be longer to enable accurate estimation of survival time of these patients. A larger sample size may be required to further support the findings obtained from the present study. In many TB patients, multiple causes of death may act simultaneously, so the cause of death may not be determined accurately as there were no post-mortem reports.

5.9 Summary

Tuberculosis is a preventable and curable disease regardless of a patient's HIV status. The characteristics of HIV-positive patients in this study may represent the actual situation in Malaysia, where the majority of them are males, of Malay ethnicity and intravenous drug users. The prognosis for TB/HIV co-infected patients during TB treatment was poor, which was contributed by the underlying immune-suppression induced by HIV infection rather than complications from active TB. The findings in this study may differ from reports of studies done in other countries due to differences in the countries' socio-demographic profile, cultural practices and beliefs.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

About this chapter

This final chapter summarizes the major findings in this thesis; propose the likely implications of the findings, recommendations and finally make suggestions for future research based on the data analyses in this thesis. As TB/HIV co-infections become more common across the globe, it is important to know how far one can make broad generalizations concerning characteristics of TB patients with HIV co-infection and factors that predict TB treatment success rates as well as survival. A prospective cohort study was used to characterize TB/HIV co-infected patients, to determine the risk factors for TB treatment default and to identify predictors of survival in order to establish generalizations and comparisons with findings from other countries. This thesis explored the predictors of survival of TB/HIV co-infected patients by evaluating a large number of variables.

6.1 Reviews of main findings

6.1.1 Characteristics of TB/HIV co-infected patients

Analysis of the socio-demographic data showed that 62.1 percent of TB/HIV co-infected patients in the Klang Valley were 35-54 years old with a mean age of 39.1 (standard deviation 8.6). The majority were male, Malay, single and unemployed. The most common mode of HIV transmission was through injecting drug use. Pulmonary TB occurred in 48.9 percent of patients, followed by extra-pulmonary TB (28.2 percent) and 22.9 percent had both pulmonary and extra-pulmonary TB. The majority of TB/HIV co-infected patients had haemoglobin level less than 12 g/dL and baseline CD4 less than

200 cells/μL. These laboratory readings indicate that these patients were in the advanced HIV infection stage. Patients who received antiretroviral therapy constitute 61.3 percent. The most common antiretroviral regimens were two NRTI with one NNRTI (56.2 percent).

6.1.2 TB treatment outcomes and predictors of defaulted TB treatment

Among the 227 patients eligible for analysis, 51.6 percent (117) achieved successful outcomes (cure, completed treatment), while 25.6 percent (56) of patients defaulted treatment and 20.3 percent (46) died.

Alcohol intake, not receiving antiretroviral therapy, presence of lymphadenopathy and low serum albumin were independent predictors of defaulted TB treatment in TB/HIV co-infected patients. These predictors are comparable to those identified in other studies with the exception of the presence of lymphadenopathy and low serum albumin.

Concurrent anti-retroviral treatment and good immune status are vital to achieving success in the treatment of HIV-infected TB patients. The high default rate (25.6 percent) warrants a detailed review of the implementation of Directly Observed Therapy (DOT) with priority to be directed to those most at risk patients in order to improve treatment outcomes.

In general, HIV-infected tuberculosis patients in the Klang Valley had poor treatment outcomes except for those who were prescribed concurrent anti-retroviral treatment and had good immune status.

6.1.3 Predictors of death

This study identified the independent significant predictors of survival in TB/HIV co-infected patients. These factors include being Malay, having more than two opportunistic infections (OI), not receiving antiretroviral therapy, increase per 1000

total white blood cell count per microliter and CD4 T-lymphocytes count less than 200 cells/µl.

In this study, antiretroviral therapy is one of the modifiable factors that was associated with survival in TB/HIV co-infected patients. This is the main finding of this study which supports the fact that the degree of immune-suppression influences survival in TB-HIV co-infected patients during TB treatment. Early initiation of antiretroviral therapy in these patients can improve survival by restoring immune function and preventing opportunistic infections. It was found that HIV-infected TB patients who were treated with ART had almost 23 percent better survival compared with those who were not treated with ART.

In conclusion, our study highlights important issues about the factors that are associated with TB treatment default and survival of TB/HIV co-infected patients in the Malaysian population. This study contributes mainly to the building of knowledge in the management of TB/HIV co-infected patients. It is a significant contribution as it provides evidence for the formulation of public health policy.

6.2 Implication to clinical /hospital care

The results of this study highlight the patients' characteristics that affect their treatment success rate and survival. Early recognition and management of risk factors or predictors of mortality will help to decrease morbidity and ultimately the TB/HIV co-infected patients will achieve better chances for survival.

The high degree of immune-suppression and high case fatality rates during the early stage of the disease among people with TB/HIV co-infection warrants that co-infected people should be diagnosed as early as possible. TB is more difficult to detect in HIV infected patients due to its unique and myriad presentations. Therefore, a high index of suspicion is required to make a timely diagnosis of TB in this group of patients.

Clinicians should be encouraged to offer HIV testing to all TB patients and to assess HIV risk factors in patients who present with TB. Any intervention designed to improve treatment outcomes for such patients must focus on early diagnosis and treatment of both TB and HIV infection. This will require improvements in current levels of TB screening among people living with HIV and HIV testing among TB patients, along with improvements in the quality of TB diagnosis.

The finding that almost 74 percent of patients had a CD4 count less than 200 suggests that all TB/HIV patients should have early access to appropriate opportunistic infection prophylaxis and ART. Furthermore, in our study, we found that increasing number of opportunistic infections are associated with death in TB/HIV co-infection. The timely implementation of these two treatment interventions is critical to decrease case fatality rates. Unless contraindicated, co-trimoxazole prophylactic therapy (CPT) should be provided to all TB/HIV patients during TB treatment because of its value in prevention of PCP, toxoplasmosis and bacterial infections. CPT has been shown to reduce overall mortality during TB treatment (Raizada, 2009).

The outcome of this study will guide clinicians and health care providers to have a better understanding of risk factors for TB treatment default and recognise the predictors of mortality due to TB/HIV co-infection in the local context. This is potentially useful in the development of Malaysian Clinical Practice Guidelines (CPG) for the management of TB/HIV co-infection and revision of current CPG for Management of Tuberculosis. Successful TB treatment and better survival in TB/HIV co-infected patients largely depend on an individualized approach, with emphasis on treatment adherence, lifestyle factors and timely monitoring of laboratory markers. Proper management and monitoring of the patient after initiation of the treatment are important to interrupt further spread of TB. Drug interactions, drug side effects and the immune reconstitution inflammatory syndrome (IRIS) should be managed well. Patients

who present with characteristics identified as high risk for death should be closely monitored to ensure early recognition and management of complications.

6.2.1 Recommendations

Defaulting TB treatment is a complex issue with various factors impacting on treatment compliance behaviour. Patients who adhere poorly to TB treatment regimen should be traced and given intensive drug counselling to improve their survival. General TB health education and counselling stressing on the duration of treatment, side effects and the risk of discontinuing TB treatment should be given to these patients. Integration of TB and HIV services and counselling may allow for efficient delivery of important information. Collaboration with shelter homes and Non-governmental Organizations (NGOs) as well as community volunteers need to be enhanced to ensure that TB/HIV co-infected patients adhere to both TB treatment and antiretroviral therapy.

Ideally, treatment for both TB and HIV infections should be conducted by personnel in the same department who will be responsible for monitoring the patient. This scenario will contribute towards reducing the default rate in the study population. However, due to inadequate space in the public hospitals, TB and HIV units are still being operated in separate buildings. If a proper tracking system and referral mechanism are not put in place, this can hamper inter-unit referrals of co-infected patients and may lead to delays for these patients to seek treatment and hence loss to follow up. Lack of infrastructure was seen as a general problem within treatment centres. HIV positive patients can be easily exposed to TB patients waiting in over-crowded outpatient clinics as well as in the wards. Improvements in the infrastructure of the health system together with appropriate infection control measures are required to address these challenges in order to prevent the spread of nosocomial TB infection to HIV positive patients who are high risk.

The findings of this study support the concomitant use of ART with anti-TB drugs to improve survival in TB/HIV co-infected patients. Early initiation of ART prior to the development of clinical markers will help to maximize a more favourable clinical outcome. The benefits of ART should be made available by dissemination of information through the electronic media such as television advertisements and distribution of pamphlets, posters, to assist TB/HIV co-infected patients to have a better understanding of their need for treatment adherence which ultimately will improve their quality of life.

6.2.2 Future research

Future work that includes more TB-related characteristics, including Tuberculin skin testing (TST), bacterial culture and information on drug resistant TB should be conducted.

TB disease diagnosis in Malaysia relies on sign and symptom screening, chest radiography and acid fast bacilli sputum smear which have a poor sensitivity in HIV patients. More rapid tests for TB are needed for early and accurate diagnosis of TB in HIV-infected patients to provide timely specific treatment for patients in need, minimize TB transmission in the community and reduce mortality. Further research is needed in order to explore the benefits of prescribing fluconazole and cotrimoxazole, in addition to ART to all HIV-infected TB patients.

Another area for future research should investigate total white blood cell count as a predictor of death. More information is needed on differential count of WBC in particular to examine the role of the absolute neutrophil count in relation to survival.

6.3 Implication to policy makers

The available data have important implications for TB/HIV control in Malaysia. The Ministry of Health Malaysia is committed to achieve the MDG targets to reduce the TB incidence and the TB mortality rate. The findings of this analysis are useful to TB and HIV/AIDS programme managers within the Ministry of Health Malaysia as it provides important data on the magnitude of TB/HIV co-infection scenario in this country. The findings from this study can be translated into programmes or policies to improve the health and living status of TB/HIV co-infected patients. TB mortality ranked the highest among all other infectious diseases in Malaysia. Assessment of the survival rate and predictors of death will enable the policy makers to see the weaknesses in the system that need to be rectified and improved. The policy makers can identify correctly the patients who are at high risk. Thus future interventions will be more target-driven and cost-effective.

6.3.1 Recommendations

The results of the present study indicate a need for a coordinated TB control program which should include active case surveillance, effective care and treatment, and directly observed therapy. Strengthening the TB program will help to reduce TB/HIV co-infection cases. The current national TB and HIV programs remain largely separated and fragmented; with varying levels of communication and interaction. There is a need for more coordination and focus on the management of patients with TB/HIV co-infections rather than viewing the two diseases as two separate entities. Collaborative efforts are necessary to implement strategies and interventions to reduce TB/HIV related morbidity and mortality in line with WHO's guidelines (WHO, 2008).

TB/HIV case management should be optimized further. A much more comprehensive data collection system is required which ideally will link the TB and HIV clinics. In Malaysia, web-based TB case notification was implemented in 2008. This application should be upgraded further by including variables essential for TB/HIV monitoring such as CD4 counts, viral load, status of antiretroviral therapy, fluconazole and co-trimoxazole used. There must also be a way to monitor the quality of the completeness and reliability of baseline and follow up data that are being collected. The communication between the National TB Control Program and hospitals in case-holding process should also be strengthened.

Malaysia has had greater availability of antiretroviral drugs since 2005. However, a substantial number of HIV-infected patients are still not receiving ART treatment despite the WHO recommendations that all HIV-infected TB patients should be given ART regardless of their CD4 count (WHO,2010). It was believed that stigma and discrimination towards HIV-infected people, especially injecting drug users is one of the biggest barriers. Self-stigma prevent many patients from accessing treatment and care. There is a need to increase accessibility and improved utilization of ART for HIV-infected patients; particularly those who are co-infected with TB. Creation of an enabling environment through public education and well-trained health care workers are essential in ensuring greater and sustainable access to ART.

Developing a multi-sectoral approach has been seen to improve patients' survival. Although TB treatment and antiretroviral therapy are provided free of charge by the Malaysian government, but some laboratory testing recommended by the WHO guidelines to monitor patients' progression are chargeable and the cost has to be borne by the patients. Collaboration with NGOs are needed to decrease the financial burden of TB/HIV co-infected patients. In addition, integrating the TB and HIV care with other developmental organizations and community members such as religious leaders and

community supporters should help to remove barriers that directly or indirectly affect survival.

6.3.2 Future research

To complement this study, further qualitative study on TB treatment defaulters will be helpful to have a better understanding of why they default treatment which will also affect their survival.

Further study in different areas and using other study designs are needed to determine the main reason for poor TB treatment outcome and to further assess TB/HIV mortality situation in Malaysia. The compilation of medication history can be made more comprehensive by including documented barriers to DOTS or reasons for non-adherence and tolerance of TB treatment. There is a need to strengthen the documentation of the medical records system to ensure completeness of the registry which currently is a common problem in practice.

Future studies should be carried out over a longer period. It will give invaluable information about the long term survival of TB/HIV co-infected patients including the recurrence rate of TB.

6.4 Implication to patients

The findings of this study highlight several things. TB/HIV co-infected patients had poor nutritional status as shown by low body weight, low serum albumin and haemoglobin levels. Previous studies had reported that malnutrition is a strong risk factor for progression from latent TB to active TB disease. On the other hand, TB itself is a risk factor for malnutrition; and TB patients who are malnourished (BMI less than 18.5) had an increased risk of death even with appropriate antibiotic therapy.

Although unemployment was not found to be significantly associated with either TB treatment default or death in this study, however, this factor should not be viewed

lightly as 57.3 percent of patients in this cohort were unemployed. It is well known that unemployment is strongly related to health and has socioeconomic implications for the patients and their family. Patients may not work because they are severely ill or do not want to go out to work because of the stigma of HIV and TB. Both HIV and TB are stigmatizing diseases that can cause them to lose self-confidence to deal with people. The employers may not want to keep them in the organization because of their poor health status or fear that the disease is contagious to others.

6.4.1 Recommendation

There is need for nutrition-related interventions to maintain optimal nutritional status that includes counselling and support to improve food intake, counselling to manage nutrition-related symptoms of HIV-related illnesses, counselling on management of treatment-related side-effects and therapeutic feeding to manage moderate and severe malnutrition among TB and HIV-infected adults.

Alcohol intake is the only modifiable socioeconomic risk factor that was associated with TB treatment default. Patients who take alcohol should be assessed properly to determine the level of alcohol consumption because it can complicate the management of TB/HIV co-infected patients. Alcohol-dependence therapy should be given to those who are found in need for treatment. They may also require a longer duration of hospital admission; at least after completing their intensive phase of TB treatment to ensure treatment compliance.

Unemployed patients should be empowered either by providing them with job-training or other income- generating activities. Those who are severely ill and unable to work should be channelled to the relevant authorities for financial assistance.

6.4.2 Future research

More studies are required to understand why the risk of defaulting TB treatment is higher among alcohol drinkers. Further research is recommended to look into why Malay patients had lower survival compared to Chinese and Indian patients. There may be ethnic differences in relation to treatment adherence and access to care which requires further study.

Quality of life in TB/HIV co-infected individuals need to be researched further, particularly in terms of depression and self-stigma. Further research is needed to determine whether reducing self-stigma and increasing TB and HIV knowledge among the general community and patients will reduce delay in diagnosis and hence improve patient outcomes.

References

Abdool Karim, S. S., Naidoo, K., Grobler, A., Padayatchi, N., Baxter, et al. (2010). Timing of initiation of antiretroviral drugs during tuberculosis therapy. *The New England Journal of Medicine*, *362*(8), 697–706.

Abdool Karim, S. S., Naidoo, K., Grobler, A., Padayatchi, N., Baxter, et al. (2011). Integration of antiretroviral therapy with tuberculosis treatment. *The New England Journal of Medicine*, *365*(16), 1492–501.

Ackah, A. N., Coulibaly, D., Digbeu, H., Diallo, K., Vetter, K. M., Coulibaly, I. M., et al. (1995). Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet*, *345*(8950), 607–610. Retrieved 15th April 2012, from http://www.ncbi.nlm.nih.gov/pubmed/7898177

Akolo, C., Adetifa, I., Shepperd, S., Volmink, J. (2010).Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000171. DOI: 10.1002/14651858.CD000171.pub3.

Alpert, P. L., Munsiff, S. S., Gourevitch, M. N., Greenberg, B., & Klein, R. S. (1997). A prospective study of tuberculosis and human immunodeficiency virus infection: clinical manifestations and factors associated with survival. *Clin Infect Dis*, *24*(4), 661–668.

Alwood, K., Keruly, J., Moore-Rice, K., Stanton, D. L., Chaulk, C. P., & Chaisson, R. E. (1994). Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *AIDS*, *8*(8), 1103–1108.

Amnuaiphon, W., Anuwatnonthakate, A., Nuyongphak, P., Sinthuwatanawibool, C., Rujiwongsakorn, S., Nakara, P., et al. (2009). Factors associated with death among HIV-uninfected TB patients in Thailand, 2004-2006. *Tropical Medicine & International Health*, *14*(11), 1338–1346.

Amuha, M. G., Kutyabami, P., Kitutu, F. E., Odoi-Adome, R., & Kalyango, J. N. (2009). Non-adherence to anti-TB drugs among TB/HIV co-infected patients in Mbarara Hospital Uganda: prevalence and associated factors. *African Health Sciences*, *9 Suppl 1*(August), S8–15.

Andrews, J. R., Shah, N. S., Weissman, D., Moll, A. P., Friedland, G., & Gandhi, N. R. (2010). Predictors of Multidrug- and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community. *Plos One*, *5*(12). Retrieved 28th July 2012, from doi:ARTN e15735 DOI 10.1371/journal.pone.0015735

Anunnatsiri, S., Chetchotisakd, P., & Wanke, C. (2005). Factors associated with treatment outcomes in pulmonary tuberculosis in northeastern Thailand. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *36*(2), 324–330.

References

Atun, R., Weil, D. E. C., Eang, M. T., & Mwakyusa, D. (2010). Health-system strengthening and tuberculosis control. *Lancet*, *375*(9732), 2169–78.

Azmi, M. Y., Junidah, R., Siti Mariam, A., Safiah, M. Y., Fatimah, S., Norimah, a K., et al. (2009). Body Mass Index (BMI) of Adults: Findings of the Malaysian Adult Nutrition Survey (MANS). *Malaysian Journal of Nutrition*, *15*(2), 97–119.

Badri, M., Wilson, D., & Wood, R. (2002). Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa : A cohort study. *The Lancet*, *359*, 2059–2064.

Barré-Sinoussi, F., Chermann, J. C., Rey, F., Nugeyre, M. T., Chamaret, S., Gruest, J et al. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). 1983. *Science*, *220*, 868–871.

Batungwanayo, J., Taelman, H., Bogaerts, J., Clerinx, J., Kagame, A., Deun, A. Van et al. (2000). Impact of Human Berry, M. P. R., Graham, C. M., McNab, F. W., Xu, Z., Bloch, S. A A, et al., (2010). An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature*, *466*(7309), 973–7.

Blanc, F., Sok, T., & Laureillard, D. (2011). Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *New England Journal of Medicine*, 365: 1471–1481.

Cain, K. P, Kanara, N., Laserson, K. F., Vannarith, C., Sameourn, K., et al,. (2007). The epidemiology of HIV-associated tuberculosis in rural Cambodia. *The International Journal of Tuberculosis and Lung Disease*, *11*(9), 1008–13.

Cain, K. P., Anekthananon, T., Burapat, C., Akksilp, S., et al,. (2009). Causes of Death in HIV-infected Persons Who Have Tuberculosis, Thailand. *Emerging Infectious Diseases*, *15*(2), 258–264.

Carvalho, B. M. De, Monteiro, A. J., Pires Neto, R. D. J., Grangeiro, T. B., & Frota, C. C. (2008). Factors related to HIV/tuberculosis coinfection in a Brazilian reference hospital. *The Brazilian journal of infectious diseases an official publication of the Brazilian Society of Infectious Diseases*, *12*(4), 281–286.

Catala, L., Orcau, A., Garcia de Olalla, P., Millet, J. P., Rodriguez-Mondragon, et al. (2011). Survival of a large cohort of HIV-infected tuberculosis patients in the era of highly active antiretroviral treatment. *Int J Tuberc Lung Dis*, *15*(2), 263–269.

Chaisangcharoen, N. (2005). *Survival of tuberculosis patients with HIV infection at Yala Hospital and Tuberculosis Centre 12*. Unpublished master's thesis. Mahidol University, Thailand.

Chan-Yeung, M., Noertjojo, K., Leung, C. C., Chan, S. L., & Tam, C. M. (2003). Prevalence and predictors of default from tuberculosis treatment in Hong Kong. *Hong Kong Medical Journal, Hong Kong Academy of Medicine*, *9*(6), 1076–1082.

Ciglenecki, I., Glynn, J. R., Mwinga, A., Ngwira, B., Zumla, A., Fine, P. E. M., et al. (2007). Population differences in death rates in HIV-positive patients with tuberculosis. *Int J Tuberc Lung Dis*, *11* (December 2006), 1121–1128.

References

Daniel, T. M. (2006). The history of tuberculosis. *Respiratory Medicine, 100*(11), 1862–70.

De Castro Toledo, a C., Greco, D. B., & Antunes, C. M. (2000). Risk factors for tuberculosis among human immunodeficiency virus-infected persons. A case-control study in Belo Horizonte, Minas Gerais, Brazil (1985-1996). *Memórias do Instituto Oswaldo Cruz, 95*(4), 437–43.

Dheda, K., Lampe, F. C., Johnson, M. A., & Lipman, M. C. (2004). Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *The Journal of Infectious Diseases, 190*(9), 1670–6.

Dos Santos, R. P., Deutschendorf, C., Scheid, K., & Zubaran Goldani, L. (2011). In-hospital mortality of disseminated tuberculosis in patients infected with the human immunodeficiency virus. *Clin Dev Immunol, 2011*. Retrieved 18th April 2012 from http://www.hindawi.com/journals/jir/2011/120278/

Dunlap, N., Bass, J., & Fujiwara, P. (2000). Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med, 161*, 1376–1395.

Elbireer, S., Guwatudde, D., Mudiope, P., Nabbuye-Sekandi, J., & Manabe, Y. C. (2011). Tuberculosis treatment default among HIV-TB co-infected patients in urban Uganda. *Tropical Medicine & International Health: TM & IH, 16* (8), 981–7.

Elliott, A. M., Halwiindi, B., Hayes, R. J., Luol, N., Mwinga, A. G., et al,. (1995). The impact of human immunodeficiency virus on mortality of patients treated for tuberculosis in a cohort study in Zambia. *Trans R Soc Trop Med Hyg, 89*(1), 78–82.

Fenner, L., Gagneux, S., Janssens, J.-P., Fehr, J., Cavassini, M., Hoffmann, M., Egger, M.,et al.(2012). Tuberculosis in HIV-negative and HIV-infected patients in a low-incidence country: clinical characteristics and treatment outcomes. *PloS One, 7*(3), e34186. Retrieved 23rd June, 2013 from http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0034186

Forse, R., & Shizgal, H. (1980). Serum albumin and nutritional status. *Journal of Parenteral and Enteral Nutrition, 4*(5), 450–454.

Gadkowski, L. B., Hamilton, C. D., Allen, M., Fortenberry, E. R., Luffman, J., Zeringue, E., et al. (2009). HIV-specific health care utilization and mortality among tuberculosis/HIV coinfected persons. *AIDS Patient Care and STDs, 23*(10), 845–851.

Garcia-Garcia, M. D., Ponce-de-Leon, A., Garcia-Sancho, M. C., Ferreyra-Reyes, L., Palacios-Martinez, M., Fuentes, J., et al. (2002). Tuberculosis-related deaths within a well-functioning DOTS control program. *Emerging Infectious Diseases, 8*(11), 1327–1333.

Garrido, M. D. S., Penna, M. L., Perez-Porcuna, T. M., de Souza, A. B., Marreiro, L. D. S., Albuquerque, B. C., et al. (2012). Factors associated with tuberculosis treatment

default in an endemic area of the Brazilian Amazon: a case control-study. *PloS One*, *7*(6), e39134. Retrieved 23rd June 2013, from http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0039134

Geng, E., Kreiswirth, B., Burzynski, J., & Schluger, N. W. (2005). Clinical and radiographic correlates of primary and reactivation tuberculosis - A molecular epidemiology study. *JAMA-Journal of the American Medical Association*, *293*(22), 2740–2745.

Getahun, H., Gunneberg, C., Granich, R., & Nunn, P. (2010). HIV infection-associated tuberculosis: the epidemiology and the response. *Clinical Infectious Diseases*, *50 Suppl 3*, S201–7.

Getahun, H., Kittikraisak, W., Heilig, C.M., Corbett, E.L., Ayles, H., et al. (2011) Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. *PLoS Med* 8(1): e1000391.

Gillian L. Dean, Simon G. Edwards, Natalie J. Ives, Gail Matthews, Emma F. Fox, et al,. (2003). Treatment of tuberculosis in HIV infected persons in the era of highly active antiretroviral therapy. *AIDS*, *17 Suppl 4* (July 2001), S112–4.

Girardi, E., Palmieri, F., Cingolani, A., Ammassari, A., Petrosillo, N., Gillini, L., et al. (2001). Changing clinical presentation and survival in HIV-associated tuberculosis after highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*, *26*(4), 326–331.

Girardi, Enrico, Palmieri, F., Angeletti, C., Vanacore, P., Matteelli, A., et al. (2012). Impact of previous ART and of ART initiation on outcome of HIV-associated tuberculosis. *Clinical & Developmental Immunology*, *2012*, 931325.

Golub, J. E., Saraceni, V., Cavalcante, S. C., Pacheco, A. G., Moulton, L. H., King, B. S., et al. (2007). The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* (London, England), *21*(11), 1441–1448.

Govinda Prasad, D., P, G., S, S., & BP, R. (2008). Characterization of Mycobacteria in HIV / AIDS Patients of Nepal. *J Nepal Med Assoc*, *47*(1), 18–23.

Harries, D., Nyangulu, D. S., Kang'ombe, C., Ndalama, D., Glynn, J. R., et al. (1998). Treatment outcome of an unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba Hospital, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *92*(3), 343–7.

Hasker, E., Khodjikhanov, M., Usarova, S., Asamidinov, U., Yuldashova, U., et al. (2008). Default from tuberculosis treatment in Tashkent, Uzbekistan; Who are these defaulters and why do they default?. *BMC Infectious Diseases*, *8*(97), 97.

Havlir, D. V, Kendall, M. a, Ive, P., Kumwenda, J., Swindells, S., Qasba, et al. (2011). Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *The New England Journal of Medicine*, *365*(16), 1482–91.

References

Hauck, F. R., Neese, B. H., Panchal, A. S., & El-Amin, W. (2009). Identification and management of latent tuberculosis infection. *American Family Physician*, *79*(10), 879–86. Retrieved 15th October 2012, from http://www.ncbi.nlm.nih.gov/pubmed/19496388

Jain, S. K., Aggarwal, J. K., Rajpal, S., & Baveja, U. (2000). Prevalence of HIV infection among tuberculosis patients in Delhi - a sentinel surveillance study. *Indian Journal of Tuberculosis*, 21–26.

Jakubowiak, W. M., Bogorodskaya, E. M., Borisov, S. E., Danilova, I. D., & Kourbatova, E. V. (2007). Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. *The International Journal of Tuberculosis and Disease*, *11*(1), 46–53.

Kassim, S., Sassan-Morokro, M., Ackah, A., Abouya, L. Y., Digbeu, H., Yesso, G., et al. (1995). Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa. *AIDS*, *9*(10), 1185–1192.

Kawai, V., Soto, G., Gilman, R. H., Bautista, C. T., Caviedes, L., Huaroto, L., et al. (2006). Tuberculosis mortality, drug resistance, and infectiousness in patients with and without HIV infection in Peru. *American Journal of Tropical Medicine and Hygiene*, *75*(6), 1027–1033.

Khan, F. a, Minion, J., Pai, M., Royce, S., Burman, W., Harries, A. D., & Menzies, D. (2010). Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clinical Infectious Diseases*, *50*(9), 1288–99.

Kingkaew, N., Sangtong, B., Amnuaiphon, W., Jongpaibulpatana, J., Mankatittham, W., Akksilp, S., et al. (2009). HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death. *International Journal of Infectious Diseases : IJID : official publication of the International Society for Infectious Diseases*, *13*(6), 722–9.

Kittikraisak, W., Burapat, C., Kaewsa-ard, S., Watthanaamornkiet, W., Sirinak, C., Sattayawuthipong, W., et al. (2009). Factors associated with tuberculosis treatment default among HIV-infected tuberculosis patients in Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *103*(1), 59–66.

Klautau, G. B., & Kuschnaroff, T. M. (2005). Clinical forms and outcome of tuberculosis in HIV-infected patients in a tertiary hospital in São Paulo - Brazil. *The Brazilian Journal of Infectious Diseases*, *9*(6), 464–78.

Kleinbaum, D. G., & Klein, M. (1996). *Survival Analysis. A self-Learning Text. Statistics in the Health Sciences*. New York: Springer.

Komati, S., Shaw, P. A, Stubbs, N., Mathibedi, M. J., Malan, L., Sangweni, P., et al. (2010). Tuberculosis risk factors and mortality for HIV-infected persons receiving antiretroviral therapy in South Africa. *AIDS (London, England)*, *24*(12), 1849–55.

Korenromp, E. L., Scano, F., Williams, B. G., Dye, C., & Nunn, P. (2003). Effects of human immunodeficiency virus infection on recurrence of tuberculosis after

rifampin-based treatment: an analytical review. *Clinical Infectious Diseases.*, *37*(1), 101–12.

Korzeniewska-Kosela, M., FitzGerald, J. M., Vedal, S., Allen, E. a, Schechter, M. T., Lawson, L., et al. (1992). Spectrum of tuberculosis in patients with HIV infection in British Columbia: report of 40 cases. *CMAJ : Canadian Medical Association Journal*, *146*(11), 1927–34.

Kung, H.C., Sun, H.Y., Chen, M.Y., Hsieh, S.M., Sheng, W.H., Chen, Y.C., et al. (2009). Human immunodeficiency virus testing among patients with tuberculosis at a university hospital in Taiwan, 2000 to 2006. *Journal of the Formosan Medical Association*, *108*(4), 320–7.

Kwara, a, Flanigan, T. P., & Carter, E. J. (2005). Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. *The International Journal of Tuberculosis and Lung Disease*, *9*(3), 248–57.

Lawn, S. D., Badri, M., & 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), 2109–16.

Leeds, I. L., Magee, M. J., Kurbatova, E. V, del Rio, C., Blumberg, H. M., Leonard, M. K., & Kraft, C. S. (2012). Site of extrapulmonary tuberculosis is associated with HIV infection. *Clinical Infectious Diseases : An official publication of the Infectious Diseases Society of America*, *55*(1), 75–81.

Lefebvre, N., & Falzon, D. (2008). Risk factors for death among tuberculosis cases: analysis of European surveillance data. *European Respiratory Journal*, *31*(6), 1256–1260.

Letchuman, G.R., Wan Nazaimoon, W.M., Wan Mohamad, W.B., Chandran, L.R., Tee, G.H., e al. (2010). Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *The Medical Journal of Malaysia*, *65*(3), 180–6.

Letang, E., Miro', J.M., Nhampossa, T., Ayala, E., Gascon, J., et al. (2011) Incidence and Predictors of Immune Reconstitution Inflammatory Syndrome in a Rural Area of Mozambique. *PloS One* 6(2): e16946. doi:10.1371/journal.pone.0016946.

Lienhardt, C., Glaziou, P., Uplekar, M., Lönnroth, K., Getahun, H., & Raviglione, M. (2012). Global tuberculosis control: lessons learnt and future prospects. *Nature reviews. Microbiology*, *10*(6), 407–16.

Low, S., Ang, L. W., Cutter, J., James, L., Chee, C. B. E., Wang, Y. T., & Chew, S. K. (2009). Mortality among tuberculosis patients on treatment in Singapore. *International Journal of Tuberculosis and Lung Disease*, *13*(3), 328–334.

M.Mann, J., & Kay, K. (1991). Confronting the pandemic: the World Health Organization's Global Programme on AIDS, 1986-1989. *AIDS*, *5* (Suppl. 2), S221–S229.

Malaysia Demographic Profiles 2013. (2013). Retrieved 19th March 2013, from http://www.indexmundi.com/malaysia/demographics_profile.html

Mankatittham, W., Likanonsakul, S., Thawornwan, U., Kongsanan, P., Kittikraisak, W., et al. (2009). Characteristics of HIV-infected Tuberculosis Patients in Thailand. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *40*(1), 93–103.

Mann, J. (1998). Responding to HIV/AIDS: a historical perspective. *Health and Human Rights*, *2*(4), 5–8. Retrieved 23rd March 2012, from http://www.jstor.org/stable/10.2307/4065182

Manosuthi, W., Chottanapand, S., Thongyen, S., Chaovavanich, A., & Sungkanuparph, S. (2006). Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*, *43*(1), 42–46.

Maruza, M., Albuquerque, M. F., Coimbra, I., Moura, L. V, Montarroyos, U. R., Miranda Filho, D. B., et al. (2011). Risk factors for default from tuberculosis treatment in HIV-infected individuals in the state of Pernambuco, Brazil: a prospective cohort study. *BMC Infect Dis*, *11*, 351.

Maruza, Magda, Arraes, R., & Ximenes, D. A. (2008). Treatment outcome and laboratory confirmation of tuberculosis diagnosis in patients with HIV/AIDS in Recife, Brazil. *J Bras Pneumol*, *34*(6), 394–403.

Mathew, T. A., Ovsyanikova, T. N., Shin, S. S., Gelmanova, I., Balbuena, D. A., Atwood, S., et al. (2006). Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. *International Journal of Tuberculosis and Lung Disease*, *10*(8), 857–863.

Mazurek, M., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., Castro, K. (2010). Updated guidelines for using interferon γ release assays to detect Mycobacterium tuberculosis infection – United States. *MMWR Recomm Rep*, 59, 1-25.

McIlleron, H., Meintjes, G., Burman, W. J., & Maartens, G. (2007). Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *Journal of Infectious Diseases*, *196 Suppl* , S63–75.

Mehta, S. H., Astemborski, J., Sterling, T. R., Thomas, D. L., & Vlahov, D. (2006). Serum albumin as a prognostic indicator for HIV disease progression. *AIDS Res Hum Retroviruses*, *22*(1), 14–21.

Merson, M. H., O'Malley, J., Serwadda, D., & Apisuk, C. (2008). The history and challenge of HIV prevention. *Lancet*, *372*(9637), 475–88.

MOH. (2002). Practice guidelines for the control and management of tuberculosis. Kuala Lumpur: Ministry of Health Malaysia.

MOH. (2010). National Strategic Plan for TB in Malaysia. Kuala Lumpur: Ministry of Health Malaysia.

References

MOH. (2011). National Strategic Plan for TB Control in Malaysia, 2011-2015. Kuala Lumpur: Ministry of Health Malaysia.

MOH. (2012a). Annual Report 2011: TB Control Programme in Malaysia. Kuala Lumpur: Ministry of Health Malaysia.

MOH. (2012b). *Global AIDS Response 2012: Country Progress Report* (p. 110). Retrieved 21st May 2013 from http://www.moh.gov.my/images/gallery/Report/GLOBAL_AIDS_Endorsed_DG.pdf

Mohammad, Z., & Naing, N. N. (2004). Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, from 1998 to 2001. *Southeast Asian J Trop Med Public Health*, *35*(1), 140–143.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*, *62*(10), 1006–1012.

Moreno, S., Miralles, P., Diaz, M. D., Baraia, J., Padilla, B., Berenguer, J., et al. (1997). Isoniazid preventive therapy in human immunodeficiency virus-infected persons. Long-term effect on development of tuberculosis and survival. *Archives of Internal Medicine*, *157*(15), 1729–1734

Morris, C. D., Bird, R., & Nell, H. (1989). The haematological and biochemical changes in severe pulmonary tuberculosis. *The Quarterly Journal of Medicine*, *73*(272), 1151–9.

Mugusi, F. M., Mehta, S., Villamor, E., Urassa, W., Saathoff, E., Bosch, R. J., et al. (2009). Factors associated with mortality in HIV-infected and uninfected patients with pulmonary tuberculosis. *BMC Public Health*, *9*, 409.

Munro, S.A., Lewin S.A., Smith H.J., Engel M.E., Fretheim A., et al. (2007) Patient adherence to tuberculosis treatment: A systematic review of qualitative research. PLoS Med 4(7): e238. doi:10.1371/journal.pmed.0040238

Murray, J., Sonnenberg, P., Shearer, S. C., & Godfrey-Faussett, P. (1999). Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. American journal of respiratory and critical care medicine, 159(3), 733–40.

Muture, B. N., Keraka, M. N., Kimuu, P. K., Kabiru, E. W., Ombeka, V. O., & Oguya, F. (2011). Factors associated with default from treatment among tuberculosis patients in Nairobi province, Kenya: a case control study. *BMC Public Health*, *11*(1), 696.

Mwaungulu, F. B., Floyd, S., Crampin, A. C., Kasimba, S., Malema, S., Kanyongoloka, H., et al. (2004). Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi. *Bull World Health Organ*, *82*(5), 354–363.

References

Naidoo, P., Peltzer, K., Louw, J., Matseke, G., McHunu, G., & Tutshana, B. (2013). Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. *BMC Public Health*, *13*, 396.

Nanteza, M. W., Mayanja-Kizza, H., Charlebois, E., Srikantiah, P., Lin, R., Mupere, E., et al. (2011). A randomized trial of punctuated antiretroviral therapy in Ugandan HIV-seropositive adults with pulmonary tuberculosis and $CD4^+$ T-cell counts of ≥ 350 cells/μL. *The Journal of Infectious Diseases*, *204*(6), 884–92.

Nauclér, a, Winqvist, N., Dias, F., Koivula, T., Lacerda, L., Svenson, S. B., et al. (1996). Pulmonary tuberculosis in Guinea-Bissau: clinical and bacteriological findings, human immunodeficiency virus status and short term survival of hospitalized patients. *Tubercle and Lung Disease: The official journal of the International Union against Tuberculosis and Lung Disease*, *77*(3), 226–32.

Nava-Aguilera, E., Andersson, N., Harris, E., Mitchell, S., Hamel, C., et al. (2009). Risk factors associated with recent transmission of tuberculosis: systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease*, *13*(1), 17–26.

Nissapatorn, V., Kuppusamy, I., Sim, B. L. H., Quek, K. F., & Khairul Anuar, A. (2005). Tuberculosis in HIV/AIDS patients: a Malaysian experience. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *36*(4), 946–953.

Nunn, A. J., Mwaba, P., Chintu, C., Mwinga, A., Darbyshire, J. H., & Zumla, A. (2008). Role of co-trimoxazole prophylaxis in reducing mortality randomised clinical trial. *BMJ*, 337:a257. doi:10.1136/bmj.a257

Nunn, P., Brindle, R., Carpenter, L., Odhiambo, J., Wasunna, K., Newnham, R., et al. (1992). Cohort Study of Human-Immunodeficiency-Virus Infection in Patients with Tuberculosis in Nairobi, Kenya - Analysis of Early (6-Month) Mortality. *American Review of Respiratory Disease*, *146*(4), 849–854.

Nunn, P. P., Elliott, a M., & McAdam, K. P. (1994). Impact of human immunodeficiency virus on tuberculosis in developing countries. *Thorax*, *49*(5), 511–8.

Organisation of African Unity. (2001). The Abuja declaration on HIV/AIDS, tuberculosis and other related infectious diseases. Abuja, Nigeria.

Palmieri, F., Pellicelli, A. M., Girardi, E., De Felici, A. P., De Mori, P., Petrosillo, N., & Ippolito, G. (1999). Negative predictors of survival in HIV-infected patients with culture-confirmed pulmonary tuberculosis. *Infection*, *27*(6), 331–334.

Pawlowski, A., Jansson, M., Sköld, M., Rottenberg, M. E., Källenius, G., World Health Organization, & WHO. (2012). Tuberculosis and HIV Co-Infection. (T. C. Hobman, Ed.) *PLoS Pathogens*, *8*(2), e1002464. doi:10.1371/journal.ppat.1002464

Pelaquin, M. H. H., e Silva, R. S., & Riberio, S. A. (2007). Factors associated with death from tuberculosis in the eastern part of the city of Sao Paulo, 2001. *J Bras Pneumol*, *33*(3), 311–317.

References

Perriëns, J. H., St Louis, M. E., Mukadi, Y. B., Brown, C., Prignot, J., et al. (1995). Pulmonary Tuberculosis in HIV-Infected Patients in Zaire - A Controlled Trial of Treatment for Either 6 or 12 Months. *New England Journal of Medicine*, *332*(12), 779–784.

Podlekareva, D. N., Mocroft, A., Post, F. A., Riekstina, V., Miro, J. M., et al. (2009). Mortality from HIV and TB coinfections is higher in Eastern Europe than in Western Europe and Argentina. *AIDS*, *23*(18), 2485–2495.

Putong, N. M., Pitisuttithum, P., Supanaranond, W., Phonrat, B., Tansuphasawadikul, S., Silachamroon, U., et al. (2002). Mycobacterium Tuberculosis infection among HIV / AIDS patients in Thailand. *The Southeast Asian Journal of Tropical Medicine and Public Health*, *33*(2), 1–6.

Quy, H. T., Cobelens, F. G. J., Lan, N. T. N., Buu, T. N., Lambregts, C. S. B., & Borgdorff, M. W. (2006). Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. *International Journal of Tuberculosis and Lung Disease*, *10*(1), 45–51.

Raizada, N., Chauhan, L.S., Babu, B.S., Thakur, R., Khera A., et al. (2009) Linking HIV-infected TB patients to Cotrimoxazole prophylaxis and antiretroviral treatment in India. *PloS One* 4(6): e5999. doi:10.1371/journal.pone.0005999

Rehm, J., Samokhvalov, A. V, Neuman, M. G., Room, R., Parry, C., Lönnroth, K., e al. (2009). The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health*, *9*, 450.

Rosner, B. (2006). Fundamentals of biostatistics, 7th edition. Boston, USA: Brooks/Cole.

Ruiz-Navarro, M. D., Espinosa, J. A., Hernandez, M. J., Franco, A. D., Carrillo, C. C., Garcia, A. D., et al. (2005). Effects of HIV status and other variables on the outcome of tuberculosis treatment in Spain. *Arch Bronconeumol*, *41*(7), 363–370.

Sakula, A. (1982). Robert Koch: centenary of the discovery of the tubercle bacillus, 1882. *Thorax*, *37*(4), 246–251.

Sanguanwongse, N. M. D., Cain, K. P. M. D., Suriya, P. M. S., Nateniyom, S. M. D., Yamada, N. M. D., et al. (2008). Antiretroviral therapy for HIV-infected tuberculosis patients saves lives but needs to be used more frequently in Thailand. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *48*(2), 181–189.

Santin, M., Muñoz, L., & Rigau, D. (2012). Interferon-γ release assays for the diagnosis of tuberculosis and tuberculosis infection in HIV-infected adults: a systematic review and meta-analysis. *PloS One*, *7*(3), e32482. doi:10.1371/journal.pone.0032482

Schiffer, J. T., & Sterling, T. R. (2007). Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *44*(2), 229–34.

References

Senol, G. (2013). Laboratory Diagnosis of Tuberculosis-Latest Diagnostic Tools. In *Tuberculosis - Current Issues in Diagnosis and Management*. Retrieved 21st January 2014, from http://www.intechopen.com/books/tuberculosis-current-issues-in-diagnosis-and-management/laboratory-diagnosis-of-tuberculosis-latest-diagnostic-tools.

Shafer, R. W., & Edlin, B. R. (1996). Tuberculosis in patients infected with human immunodeficiency virus: perspective on the past decade. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *22*(4), 683–704. Retrieved 14th May 2012, from http://www.ncbi.nlm.nih.gov/pubmed/8729208.

Shafer, R. W., Bloch, A. B., Larkin, C., Vasudavan, V., Seligman, S., Dehovitz, J. D., et al. (1996). Predictors of survival in HIV-infected tuberculosis patients. *AIDS*, *10*(3), 269–272.

Shah, S., Smith, C. J., Lampe, F., Youle, M., Johnson, M. a, Phillips, a N., & Sabin, C. a. (2007). Haemoglobin and albumin as markers of HIV disease progression in the highly active antiretroviral therapy era: relationships with gender. *HIV Med*, *8*(1), 38–45.

Shargie, E. B., & Lindtjørn, B. (2007). Determinants of treatment adherence among smear-positive pulmonary tuberculosis patients in Southern Ethiopia. *PLoS medicine*, *4*(2), e37. doi:10.1371/journal.pmed.0040037

Shaweno, D., & Worku, A. (2012). Tuberculosis treatment survival of HIV positive TB patients on directly observed treatment short-course in Southern Ethiopia: a retrospective cohort study. BMC research notes, 5, 682. doi:10.1186/1756-0500-5-682

Sileshi, B., Deyessa, N., Girma, B., Melese, M., & Suarez, P. (2013). Predictors of mortality among TB-HIV Co-infected patients being treated for tuberculosis in Northwest Ethiopia: a retrospective cohort study. *BMC infectious diseases*, *13*(1), 297. doi:10.1186/1471-2334-13-297

Straetemans, M., Bierrenbach, A. L., Nagelkerke, N., Glaziou, P., & van der Werf, M. J. (2010). The effect of tuberculosis on mortality in HIV positive people: a meta-analysis. (M. Pai, Ed.) *PloS One*, *5*(12), e15241. doi:10.1371/journal.pone.0015241

Sudre, P., Hirschel, B., Toscani, L., Ledergerber, B., & Rieder, H. L. (1996). Risk factors for tuberculosis among HIV-infected patients in Switzerland. *European Respiratory Journal*, *9*(2), 279–283.

Sungkanuparph, S., Eampokalap, B., Chottanapund, S., Thongyen, S., & Manosuthi, W. (2007). Impact of drug-resistant tuberculosis on the survival of HIV-infected patients. *International Journal of Tuberculosis and Lung Disease*, *11*(3), 325–330.

Sungkanuparph, S., Techasathit, W., Utaipiboon, C., & Chasombat, S. (2010). Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents. *Asian Biomedicine*, *4*(4), 515–528.

Suthar, A. B., Granich, R., Mermin, J., & Van Rie, A. (2012). Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review

and meta-analysis. *Bulletin of the World Health Organization*, *90*(2), 128C–138C. doi:10.2471/BLT.11.093260

Thuy, T. T., Shah, N. S., Anh, M. H., Nghia, D. T., Thom, D., Linh, Tet al. (2007). HIV-associated TB in An Giang Province, Vietnam, 2001-2004: epidemiology and TB treatment outcomes. *PloS One*, *2*(6), e507. doi:10.1371/journal.pone.0000507

UNAIDS. (2012). *Report on the global AIDS epidemic* (p. 106). Joint United Nations Programme on HIV/AIDS (UNAIDS).

Van den Broek, J., Mfinanga, S., Moshiro, C., O'Brien, R., Mugomela, A., & Lefi, M. (1998). Impact of human immunodeficiency virus infection on the outcome of treatment and survival of tuberculosis patients in Mwanza, Tanzania. *The International Journal of Tuberculosis and Lung Disease*, *2*(7), 547–52.

Van Der Werf, M. J., Sebhatu, M., Weldegergis, T., Tesfazion, A., & Borgdorff, M. W. (2007). TB-HIV co-infection in Eritrea. *The International Journal of Tuberculosis and Lung Disease*, *11*(7), 823–826.

Varma, J. K., Nateniyom, S., Akksilp, S., Mankatittham, W., Sirinak, C., Sattayawuthipong, W., etal. (2009). HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. *BMC Infect Dis*, *9*, 42.

Veenstra, H., Baumann, R., Carroll, N. M., Lukey, P. T., Kidd, M., Beyers, N., e al. (2006). Changes in leucocyte and lymphocyte subsets during tuberculosis treatment; prominence of CD3dimCD56+ natural killer T cells in fast treatment responders. *Clinical and Experimental Immunology*, *145*(2), 252–60.

Velasco, M. M. D. P., Castilla, V. M. D. P., Sanz, J. M. D. P., Gaspar, G. M. D. P., Condes, E. M. D. P., Barros, C. M. D., et al. (2009). Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *50*(2), 148–152.

Vijay, S., Kumar, P., Chauhan, L. S., Rao, S. V, & Vaidyanathan, P. (2011). Treatment outcome and mortality at one and half year follow-up of HIV infected TB patients under TB control programme in a district of South India. *Plos One*, *6*(7), e21008. doi:10.1371/journal.pone.0021008 PONE-D-11-05379 [pii]

Vijay, Sophia, Balasangameswara, V. H., Jagannatha, P. S., Saroja, V. N., & Kumar, P. (2003). Defaults among tuberculosis patients treated under DOTS in Bangalore city : A search for solution. *Indian Journal of Tuberculosis*, *50*, 185–195.

Weis, S. E., Foresman, B., Cook, P. E., & Matty, K. J. (1999). Universal HIV Screening at a Major Metropolitan TB Clinic : HIV prevalence and high-risk behaviors among TB patients. *American Journal of Public Health*, *89*, 73–75.

Weis, S. E., Foresman, B., Cook, P. E., & Matty, K. J. (1999). Universal HIV Screening at a Major Metropolitan TB Clinic : HIV Prevalence and High-Risk Behaviors Among TB Patients. *American Journal of Public Health*, *89*, 73–75.

References

Whalen, C., Horsburgh Jr., C. R., Hom, D., Lahart, C., Simberkoff, M., Ellner, J., & Horsburgh Jr., C. R. (1997). Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. *AIDS*, *11*(4), 455–460.

WHO. (2001). First Meeting of Global Working Group on TB/HIV. 9–11 April 2001. Geneva, Switzerland.

WHO. (2002). An expanded DOTS framework for effective tuberculosis control. Geneva, Switzerland.

WHO. (2003a). Treating 3 million by 2005: Making it happen: The WHO Strategy 2003.

WHO. (2003b). Guidelines for implementing collaborative TB and HIV programme activities. Geneva, Switzerland.

WHO. (2004). *TB/HIV- A clinical manual.* (2nd Editio., p. 212). Geneva, Switzerland: World Health Organization.

WHO. (2005). Global Plan to Stop TB 2001 to 2005. Geneva, Switzerland.

WHO. (2006). The STOP TB strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals.

WHO. (2007). WHO Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.

WHO. (2008a). A revised framework to address TB-HIV co-infection in the Western Pacific Region. Geneva, Switzerland: World Health Organization. Retrieved 3rd April 2012, from http://www.wpro.who.int/publications/docs/TB_HIV_framework_final.pdf

WHO. (2008b). *WHO Three I's Meeting Report of a Joint World Health Organization* (p. 14). Geneva, Switzerland.

WHO. (2010a). *Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2009.* (p. 162). Retrieved 27th June 2013 from http://www.popline.org/taxonomy/term/54754?page=8883

WHO. (2010b). Treatment of tuberculosis guidelines. doi:WHO/HTM/TB/2009.420

WHO. (2011a). *Global tuberculosis control: WHO report 2011*. (WHO, Ed.)*WHO* (p. 258). World Health Organization. Retrieved 15th August 2012, from http://www.who.int/tb/publications/global_report/en/index.html

WHO. (2011b). *Tuberculosis Control in the Western Pacific Region - 2010 Report*. (p. 116). Geneva: World Health Organization. doi:ISBN 978 92 9061 522 4

WHO. (2011c). Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva: World Health. Retrieved from http://www.who.int/hiv/pub/arv/adult2010/en/index.html

References

WHO. (2012). *Global Tuberculosis Report 2012* (p. 272). Geneva, Switzerland.

WHO Stop TB Partnership. (2004). Interim policy on collaborative TB/HIV activities. Retrieved 15th August 2012, from http://whqlibdoc.who.int/hq/2004/who_htm_tb_2004.330.pdf

WHO Stop TB Partnership. (2006). *The global plan to stop TB, 2006–2015: Actions for life towards a world free of tuberculosis* (p. 167). Geneva, Switzerland.

Wobeser, W., Yuan, L., Naus, M., & Group, C. S. (1999). Outcome of pulmonary tuberculosis treatment in the tertiary care setting - Toronto 1992/93. Tuberculosis Treatment Completion Study Group. *CMAJ*, *160*(6):789-94. Retrieved 26th August 2012, from http://www.ncbi.nlm.nih.gov/pubmed/10189422

Wong, E. B., Omar, T., Setlhako, G. J., Osih, R., Feldman, C., Murdoch, D. M., et al. (2012). Causes of death on antiretroviral therapy: a post-mortem study from South Africa. *PloS One*, *7*(10), e47542. doi:10.1371/journal.pone.0047542

Xu, W., Lu, W., Zhou, Y., Zhu, L., Shen, H., & Wang, J. (2009). Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. *BMC Health Services Research*, *9*, 169. doi:10.1186/1472-6963-9-169.

Appendix A: Ethical Approval

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
OFFICE OF THE DEPUTY DIRECTOR-GENERAL OF HEALTH
(PENYELIDIKAN & SOKONGAN TEKNIKAL)
(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Aras 12, Blok E7, Parsel E, Presint 1
Level 12, Block E7, Parcel E, Precinct 1
Pusat Pentadbiran Kerajaan Persekutuan
Federal Government Administrative Centre
62590 PUTRAJAYA

Tel. : 03 88832543
Faks : 03 88895184

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) dlm.KKM/NIHSEC/08/0804/P11-129
Tarikh : 11 April 2011

Dr Ismawati Ismail
Fakulti Perubatan
Universiti Malaya

Puan,

NMRR-10-1201-6599
Characteristics, Treatment Outcome And Survival Of TB/HIV Co-Infected Patients In Kuala Lumpur And Selangor - A Prospective, Multi-Centre Study

Lokasi Projek: Institut Perubatan Respiratori Kuala Lumpur / Hospital Kajang / Hospital Sungai Buloh / Hospital Tengku Ampuan Rahimah Klang

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut adalah untuk memenuhi keperluan akademik Program Doktor Falsafah Kesihatan Umum, Universiti Malaya (UM).

3. Sehubungan dengan ini, dimaklumkan bahawa pihak JEPP KKM tiada halangan, dari segi etika, ke atas pelaksanaan projek tersebut. JEPP mengambil maklum bahawa kajian ini tidak melibatkan sebarang intervensi dan hanya menggunakan rekod perubatan pesakit dan borang pengumpulan data untuk mengumpul data kajian. Segala rekod dan data pegawai adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Puan perlu akur dan mematuhi keputusan tersebut.

4. Laporan tamat kajian dan sebarang penerbitan dari kajian ini hendaklah dikemukakan kepada Jawatankuasa Etika & Penyelidikan Perubatan selepas tamatnya projek ini.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DATO' DR CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

Appendix B: Funding Approval

UNIVERSITI MALAYA

UM.TNC2/IPPP/UPGP/GERAN(PPP)PS230/2010A

15 April 2010

Ismawati Binti Ismail
Jabatan SPM
Fakulti Perubatan
Universiti Malaya

Tuan/Puan,

KEPUTUSAN PERMOHONAN PERUNTUKAN PENYELIDIKAN PASCASISWAZAH (PPP) DAN KATALALUAN BAGI AGIHAN 1-2010 DI BAWAH PERUNTUKAN UNIVERSITI PENYELIDIKAN 2010

Dengan hormatnya saya merujuk kepada perkara di atas

2. Sukacita dimaklumkan bahawa permohonan tuan/puan telah **diluluskan oleh Jawatankuasa Peruntukan Penyelidikan Pascasiswazah Agihan 1-2010** untuk dibiayai di bawah Peruntukan Universiti Penyelidikan 2010.

3. Butiran kelulusan adalah seperti berikut:

Tajuk	:	Characteristics, Treatment Outcome And Survival Of Tb/Hiv Co-Infected Patients In Kuala Lumpur And Selangor - A Prospective, Multi-Centre Study
No. Akaun	:	PS230/2010A
Password	:	4Kg5us
Tempoh	:	15 April 2010 – 14 April 2011

Pecahan	**RM**
Kelengkapan & Alat Kursus	0.00
Bekalan	2,200.00
Perjalanan & Sara Hidup	4,536.00
Bayaran Saguhati	0.00
Jumlah	**6,736.00**

4. Untuk makluman tuan/puan, **peruntukan untuk menghadiri persidangan** tidak lagi diluluskan di bawah PPP. Sebaliknya pihak Unit Pengurusan Geran Penyelidikan (UPGP) telah menyediakan satu tabung khas di mana pelajar Ijazah Tinggi boleh memohon bantuan kewangan untuk menghadiri persidangan.

5. Tuan/Puan juga layak untuk memohon bantuan dari **tabung** ***page charge*** yang telah disediakan oleh pihak IPPP untuk membantu membiayai kos penerbitan di dalam jurnal ISI.

Unit Pengurusan Geran Penyelidikan
Institut Pengurusan dan Pemantauan Penyelidikan, A205 Bangunan IPS, Universiti Malaya, 50603 Kuala Lumpur, Malaysia
Tel: (603) 7967 4522 / 4647 / 4652 / 4653 / 4654 / 4675 / 4521 / 6952 • **Faks**: (603) 7967 4648
Emel: ketua_upd_ippp@um.edu.my • http://www.ippp.um.edu.my

Appendix B: Funding Approval (cont.)

6. **Urusan perbelanjaan** (pembelian & pembayaran) **dan semakan akaun** boleh dibuat melalui sistem kewangan penyelidikan: http://www.efinance.ippp.um.edu.my. Sebarang **perbelanjaan selain dari kelulusan asal** perlu mendapat kelulusan Ketua UPGP dengan mengisi borang permohonan dan kelulusan yang telah disediakan di laman web IPPP: http://www.ippp.um.edu.my. Satu taklimat berkenaan perkara ini akan dibuat pada minggu kedua bulan Mei. Tarikh sebenar akan diberitahu melalui e-mel tuan/puan.

7. Tuan/Puan dikehendaki menghantar **laporan projek** seperti berikut:

   i) **Laporan Kemajuan Projek** dalam tempoh setiap enam bulan dengan menggunakan borang yang telah ditetapkan.

   ii) **Laporan Akhir Projek** dalam tempoh satu bulan setelah akaun projek tamat dengan menggunakan borang yang ditetapkan.

Kegagalan tuan/puan berbuat demikian akan menyebabkan akaun tuan/puan dibekukan dan akan menjejaskan permohonan peruntukan pada masa akan datang.

8. Sila sahkan **penerimaan tawaran** dengan mengembalikan borang penerimaan tawaran (lampiran 1) **selewat-lewatnya pada 30 April 2010** (Jumaat). Akaun anda hanya akan diaktifkan setelah pihak kami menerima jawapan penerimaan tawaran tersebut. Jika tiada sebarang maklum balas diterima sehingga tarikh tersebut, tawaran ini akan terbatal dengan sendirinya.

9. Tuan/Puan diminta untuk berbelanja mengikut kelulusan yang telah diberikan. Semua inbois dan tuntutan perlu dikemukakan kepada UPGP selewat-lewatnya pada tarikh akhir projek.

Sekian, terima kasih.

Yang benar,

PROF. DR. SHALIZA IBRAHIM
Ketua

s.k. Prof. Awang Bulgiba (Penyelia)
Fakulti Perubatan
Universiti Malaya.

Appendix C: Topic Approval

UNIVERSITI MALAYA

UM.M/PDG/644/29

6 Mac 2014

Dr. Ismawati binti Ismail (MHC090003)
Jabatan Perubatan Kemasyarakatan dan Pencegahan
Fakulti Perubatan
Universiti Malaya

(Email: drismawati@gmail.com)

Tuan/Puan,

KELULUSAN TAJUK TESIS

Dengan ini dimaklumkan bahawa Fakulti dalam mesyuaratnya pada 5.3.2014 telah meluluskan tajuk tesis tuan/puan seperti berikut:-

"TUBERCULOSIS TREATMENT OUTCOMES AND SURVIVAL OF TB/HIV CO-INFECTED PATIENTS IN THE KLANG VALLEY, MALAYSIA".

Sekian, terima kasih.

Yang benar,

RUHANI ZAKARIA
Ketua Penolong Pendaftar Kanan
Fakulti Perubatan.

s.k. Ketua, Jabatan Perubatan Kemasyarakatan dan Pencegahan

Profesor Dr. Awang Bulgiba bin Awang Mahmud - Penyelia
Jabatan Perubatan Kemasyarakatan & Pencegahan

Cik Joan Tang May Yin
Penolong Pendaftar (Unit Tesis)

AHN/hh/kelulusan tajuk tesis/disertasi - 2014

Appendix D: Data Collection Form

TITLE OF RESEARCH: TREATMENT OUTCOMES AND THE PREDICTORS FOR SURVIVAL OF TB/HIV CO-INFECTED PATIENTS IN THE KLANG VALLEY, MALAYSIA

PART A: PATIENT'S INFORMATION

Date of data collection: _____

For office use
CODE (ID) ☐

Name: _____
IC no: _____
RN: _____
Contact no: _____

Date of starting TB treatment: _____

Date of diagnosis of HIV: _____

A) SOCIODEMOGRAPHIC

1. Date of birth	_____	1. Age ☐
2. Gender	☐ 1. Male ☐ 2. Female	2. Gender ☐
3. Nationality	☐ 1. Malaysian ☐ 2. Non-Malaysian	3. Nationality ☐
4. Ethnic	☐ 1. Malay ☐ 2. Chinese ☐ 3. Indian ☐ 4. Others. Specify: _____	4. Ethnic ☐
5. Religion	☐ 1. Islam ☐ 2. Buddhist ☐ 3. Hindu ☐ 4. Others Specify: _____	5. Religion ☐
6. Education Level	☐ 1. Never schooling ☐ 2. Primary school ☐ 3. Secondary school ☐ 4. Tertiary level	6. Educational level ☐
7. Occupation	_____	7. Occupational group 1.Professional ☐ 2.Intermediate ☐ 3.Skilled worker ☐

1

Appendix D

4. Semi-skilled worker
5. Unskilled
6. Unemployed

8. Marital status
1. Married
2. Single
3. Divorce / Widow

8. Marital status
1.Married
2. Unmarried

9. Household income per month

9. Household income group
1. More than 3 000
2. 2000 to 2999
3. 1000 to 1999
4. Less than 1 000

10. Incarceration
1.Yes
2.No

B) LIFESTYLE

11. Smoking status
1.Yes
2.No

11. Smoking status

12. Alcohol consumption
1.Yes
2.No

12. Alcohol consumption

13. HIV exposure
1. Homosexual
2. Heterosexual
3. Injecting Drug User
4. Others

13. HIV exposure

2

PART B: CLINICAL INFORMATION

A) INFORMATION ON TUBERCULOSIS

1. Date of starting TB treatment

2. Type of Tuberculosis

- 1. Smear positive PTB
- 2. Smear negative PTB
- 3. Extrapulmonary TB

3. Status of diagnosis

- 1. Newly diagnosed
- 2. Retreatment
- 3. Recurrent

4. Tuberculosis Treatment

4a. Intensive Phase

- 1. 2SHRZ / 4S2H2R2
- 2. 2EHRZ / 4R2H2
- 3. 2HRZ / 4H2R2
- 4. Others

4b. Maintenance Phase

- 1.4H2R2
- 2.4S2H2R2
- 3.4HR
- 4.4H3R3
- 5.4S3H3R3
- 6. Others

5. Case detection

- 1. Active
- 2. Passive
- 3. Screening

6. Main symptoms

- 1. Cough > 2
- 2. Cough with sputum
- 3. Hemoptysis
- 4. Lost of weight
- 5. Fever
- 6. Night sweats
- 7. Lost of appetite
- 8. Others

2. Type of Tuberculosis

3. Status of diagnosis

4a. Intensive Phase

4b. Maintenance Phase

5. Case detection

3

7. Co-morbidities/Past medical histories

- 1. Diabetes Mell
- 2. Congenital Heart Disease
- 3. Liver Disease
- 4. Chronic Renal Failure
- 5. Malabsorption Syndrome
- 6. Steroid Therapy
- 7. Gastrectomy
- 8. Cancer
- 9. Others

B) PHYSICAL EXAMINATION

8. Body Mass Index

Height
Weight
BMI

9. Presence of BCG scar

- 1. Yes
- 2. No

9. Presence of BCG scar

10. Lymph node enlargement

- 1. Yes
- 2. No

C) RADIOLOGICAL FINDINGS

11. Chest x-ray changes

- 1. no lesion
- 2. minimal lesion
- 3. moderately advanced
- 4. far advanced

11. Chest x-ray changes

D) INFORMATION ON HIV

12. CD4 counts

- 1.< 50 (cell/μL)
- 2.50-199 (cell/μL)
- 3.200- 349 (cell/μL)
- 4. > 350 (cell/μL)

12. CD4 counts

13. Viral load

- 1. ≤100,000 (copies/ml)
- 2. >100,000 (copies/ml)

13. Viral load

14. Antiretroviral therapy

- 1. Before TB treatment
- 2. During TB treatment
- 3. No ART

14. Patient on ART

4

15. Anti-retroviral regime
List:

_____
_____
_____

☐ 2NRTI + NNRTI
☐ NtRTI + NNRTI
☐ 2NRTI + PI
☐ NtRTI + PI

16. Patient was on Isoniazide Preventive Therapy

☐ 1. Yes
☐ 2. No

16. Isoniazide Preventive Therapy ☐

17. Opportunistic infection

☐ 1. Yes
☐ 2. No

17. OI ☐

If yes, type of opportunistic infections:

i. _____
ii. _____
iii. _____
iv. _____

18. Full diagnosis:

_____

5

Appendix D

E) LABORATORY INFORMATION

Baseline laboratory results:

	Unit	Date	Results
Hemoglobin level	g/dL		
Total White Blood Cell	10^3/µl		
Platelet	10^3 /µl		
Urea	mmol/L		
Natrium	mmol/L		
Potassium	mmol/L		
Creatinine	mmol/L		
Total Protein	g/L		
Serum albumin	g/L		
Total bilirubin	µmol/L		
Alkaline Phosphatase	U/L		
Alanine Transaminase	U/L		
Sputum smear:			
Sputum x 1			
Sputum x 2			
Sputum x 3			
Sputum c & s			
HbsAg			
Anti-HCV			
Toxoplasma IgG			
Rapid Plasma Reagen (RPR)			
Others:			

Appendix D

PART C: INFORMATION AT THE END OF TB TREATMENT

Final diagnosis (if different from 'No. 17'):

A) TREATMENT OUTCOME

1. Date of completed TB treatment:

2. Duration of TB treatment

1. < 6 months
2. 6 - 9 months
3. > 9 months

3. Treatment outcome

1. Cure
2. Completed treatment
3. Defaulted treatment
4. Failed treatment
5. Died

If 'died', cause of death:

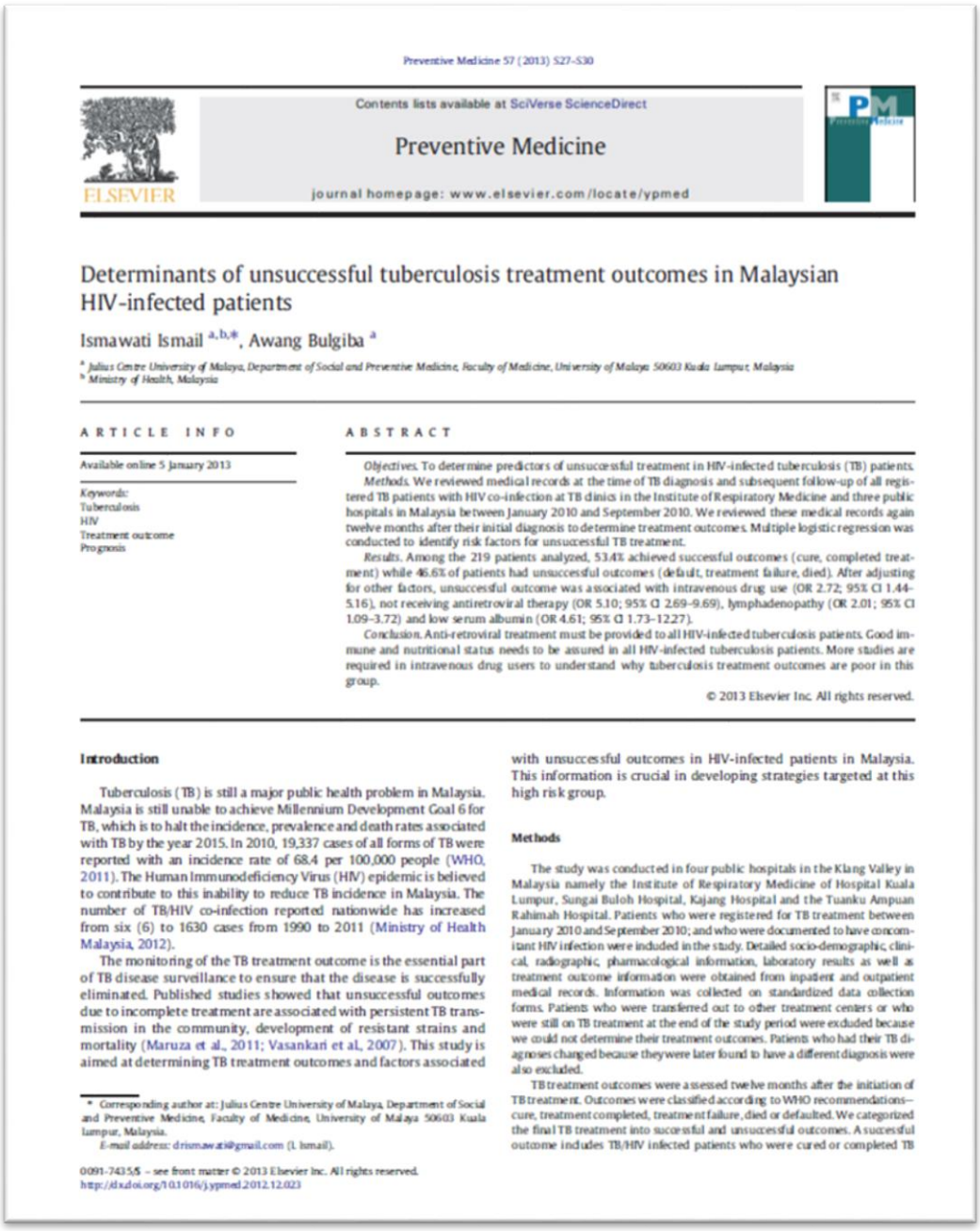
2. Duration of treatment

3. Treatment outcome

7

Appendix E: Publication

1) Ismail I, Bulgiba A (2013) Determinants of unsuccessful tuberculosis treatment outcome in HIV-infected Malaysian patients. Prev Med. 2013;57 Suppl:S27-30. doi: 10.1016/j.ypmed.2012.12.023. Epub 2013 Jan 5.



Preventive Medicine 57 (2013) S27–S30

Contents lists available at SciVerse ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients

Ismawati Ismail [a,b,*], Awang Bulgiba [a]

[a] Julius Centre University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya 50603 Kuala Lumpur, Malaysia
[b] Ministry of Health, Malaysia

ARTICLE INFO

Available online 5 January 2013

Keywords:
Tuberculosis
HIV
Treatment outcome
Prognosis

ABSTRACT

Objectives. To determine predictors of unsuccessful treatment in HIV-infected tuberculosis (TB) patients.

Methods. We reviewed medical records at the time of TB diagnosis and subsequent follow-up of all registered TB patients with HIV co-infection at TB clinics in the Institute of Respiratory Medicine and three public hospitals in Malaysia between January 2010 and September 2010. We reviewed these medical records again twelve months after their initial diagnosis to determine treatment outcomes. Multiple logistic regression was conducted to identify risk factors for unsuccessful TB treatment.

Results. Among the 219 patients analyzed, 53.4% achieved successful outcomes (cure, completed treatment) while 46.6% of patients had unsuccessful outcomes (default, treatment failure, died). After adjusting for other factors, unsuccessful outcome was associated with intravenous drug use (OR 2.72; 95% CI 1.44–5.16), not receiving antiretroviral therapy (OR 5.10; 95% CI 2.69–9.69), lymphadenopathy (OR 2.01; 95% CI 1.09–3.72) and low serum albumin (OR 4.61; 95% CI 1.73–12.27).

Conclusion. Anti-retroviral treatment must be provided to all HIV-infected tuberculosis patients. Good immune and nutritional status needs to be assured in all HIV-infected tuberculosis patients. More studies are required in intravenous drug users to understand why tuberculosis treatment outcomes are poor in this group.

Introduction

Tuberculosis (TB) is still a major public health problem in Malaysia. Malaysia is still unable to achieve Millennium Development Goal 6 for TB, which is to halt the incidence, prevalence and death rates associated with TB by the year 2015. In 2010, 19,337 cases of all forms of TB were reported with an incidence rate of 68.4 per 100,000 people (WHO, 2011). The Human Immunodeficiency Virus (HIV) epidemic is believed to contribute to this inability to reduce TB incidence in Malaysia. The number of TB/HIV co-infection reported nationwide has increased from six (6) to 1630 cases from 1990 to 2011 (Ministry of Health Malaysia, 2012).

The monitoring of the TB treatment outcome is the essential part of TB disease surveillance to ensure that the disease is successfully eliminated. Published studies showed that unsuccessful outcomes due to incomplete treatment are associated with persistent TB transmission in the community, development of resistant strains and mortality (Maruza et al., 2011; Vasankari et al., 2007). This study is aimed at determining TB treatment outcomes and factors associated with unsuccessful outcomes in HIV-infected patients in Malaysia. This information is crucial in developing strategies targeted at this high risk group.

Methods

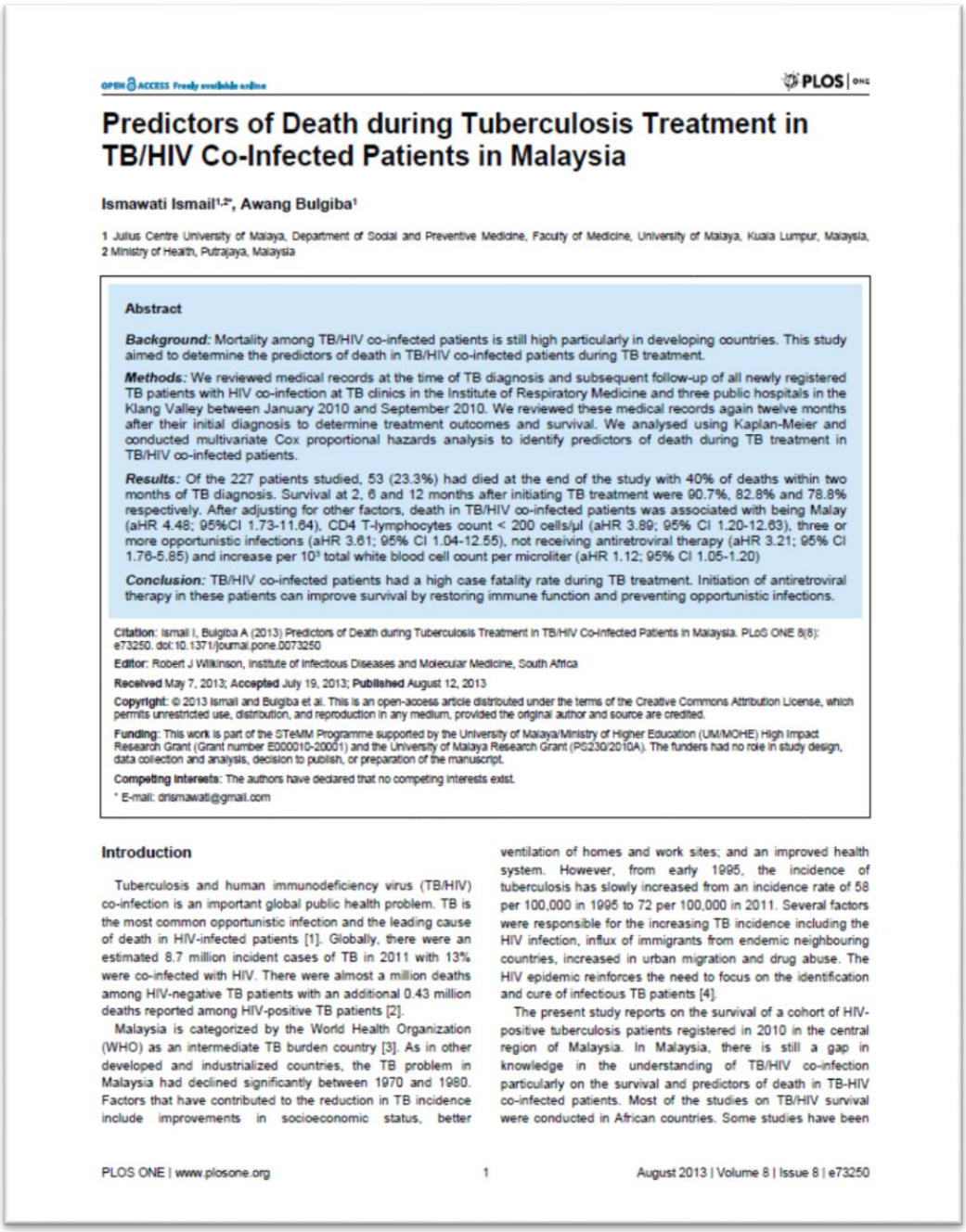
The study was conducted in four public hospitals in the Klang Valley in Malaysia namely the Institute of Respiratory Medicine of Hospital Kuala Lumpur, Sungai Buloh Hospital, Kajang Hospital and the Tuanku Ampuan Rahimah Hospital. Patients who were registered for TB treatment between January 2010 and September 2010; and who were documented to have concomitant HIV infection were included in the study. Detailed socio-demographic, clinical, radiographic, pharmacological information, laboratory results as well as treatment outcome information were obtained from inpatient and outpatient medical records. Information was collected on standardized data collection forms. Patients who were transferred out to other treatment centers or who were still on TB treatment at the end of the study period were excluded because we could not determine their treatment outcomes. Patients who had their TB diagnoses changed because they were later found to have a different diagnosis were also excluded.

TB treatment outcomes were assessed twelve months after the initiation of TB treatment. Outcomes were classified according to WHO recommendations—cure, treatment completed, treatment failure, died or defaulted. We categorized the final TB treatment into successful and unsuccessful outcomes. A successful outcome includes TB/HIV infected patients who were cured or completed TB

* Corresponding author at: Julius Centre University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya 50603 Kuala Lumpur, Malaysia.
E-mail address: drismawati@gmail.com (I. Ismail).

0091-7435/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ypmed.2012.12.023

2) Ismail I, Bulgiba A (2013) Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS ONE 8(8): e73250. doi:10.1371/journal.pone.0073250.



OPEN ACCESS Freely available online

PLOS ONE

Predictors of Death during Tuberculosis Treatment in TB/HIV Co-Infected Patients in Malaysia

Ismawati Ismail[1,2]*, Awang Bulgiba[1]

1 Julius Centre University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, 2 Ministry of Health, Putrajaya, Malaysia

Abstract

Background: Mortality among TB/HIV co-infected patients is still high particularly in developing countries. This study aimed to determine the predictors of death in TB/HIV co-infected patients during TB treatment.

Methods: We reviewed medical records at the time of TB diagnosis and subsequent follow-up of all newly registered TB patients with HIV co-infection at TB clinics in the Institute of Respiratory Medicine and three public hospitals in the Klang Valley between January 2010 and September 2010. We reviewed these medical records again twelve months after their initial diagnosis to determine treatment outcomes and survival. We analysed using Kaplan-Meier and conducted multivariate Cox proportional hazards analysis to identify predictors of death during TB treatment in TB/HIV co-infected patients.

Results: Of the 227 patients studied, 53 (23.3%) had died at the end of the study with 40% of deaths within two months of TB diagnosis. Survival at 2, 6 and 12 months after initiating TB treatment were 90.7%, 82.8% and 78.8% respectively. After adjusting for other factors, death in TB/HIV co-infected patients was associated with being Malay (aHR 4.48; 95%CI 1.73-11.64), CD4 T-lymphocytes count < 200 cells/µl (aHR 3.89; 95% CI 1.20-12.63), three or more opportunistic infections (aHR 3.61; 95% CI 1.04-12.55), not receiving antiretroviral therapy (aHR 3.21; 95% CI 1.76-5.85) and increase per 10^3 total white blood cell count per microliter (aHR 1.12; 95% CI 1.05-1.20)

Conclusion: TB/HIV co-infected patients had a high case fatality rate during TB treatment. Initiation of antiretroviral therapy in these patients can improve survival by restoring immune function and preventing opportunistic infections.

Citation: Ismail I, Bulgiba A (2013) Predictors of Death during Tuberculosis Treatment in TB/HIV Co-Infected Patients in Malaysia. PLoS ONE 8(8): e73250. doi:10.1371/journal.pone.0073250

Editor: Robert J Wilkinson, Institute of Infectious Diseases and Molecular Medicine, South Africa

Received May 7, 2013; **Accepted** July 19, 2013; **Published** August 12, 2013

Funding: This work is part of the STeMM Programme supported by the University of Malaya/Ministry of Higher Education (UM/MOHE) High Impact Research Grant (Grant number E000010-20001) and the University of Malaya Research Grant (PG230/2010A). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: drismawati@gmail.com

Introduction

Tuberculosis and human immunodeficiency virus (TB/HIV) co-infection is an important global public health problem. TB is the most common opportunistic infection and the leading cause of death in HIV-infected patients [1]. Globally, there were an estimated 8.7 million incident cases of TB in 2011 with 13% were co-infected with HIV. There were almost a million deaths among HIV-negative TB patients with an additional 0.43 million deaths reported among HIV-positive TB patients [2].

Malaysia is categorized by the World Health Organization (WHO) as an intermediate TB burden country [3]. As in other developed and industrialized countries, the TB problem in Malaysia had declined significantly between 1970 and 1980. Factors that have contributed to the reduction in TB incidence include improvements in socioeconomic status, better ventilation of homes and work sites; and an improved health system. However, from early 1995, the incidence of tuberculosis has slowly increased from an incidence rate of 58 per 100,000 in 1995 to 72 per 100,000 in 2011. Several factors were responsible for the increasing TB incidence including the HIV infection, influx of immigrants from endemic neighbouring countries, increased in urban migration and drug abuse. The HIV epidemic reinforces the need to focus on the identification and cure of infectious TB patients [4].

The present study reports on the survival of a cohort of HIV-positive tuberculosis patients registered in 2010 in the central region of Malaysia. In Malaysia, there is still a gap in knowledge in the understanding of TB/HIV co-infection particularly on the survival and predictors of death in TB-HIV co-infected patients. Most of the studies on TB/HIV survival were conducted in African countries. Some studies have been

Appendix F: Table 2.3

Table 2.3 Critical appraisal of studies on TB treatment outcomes in TB/HIV co-infected patients.

Study	**Broek, 1998**	**Harries, 1998**	**Murray, 1999**	**Mwaugulu, 2004**	**Klautau, 2005**	**Thuy, 2006**	**Quy, 2006**	**Maruza, 2008**	**Kingkaew, 2009**	**Vijay, 2012**	**Girardi, 2012**
DOES THE STUDY ADDRESS A CLEAR QUESTION											
1. Is there a clearly focussed question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Consider											
• Patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
• Disease/Condition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
• Outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ARE THE RESULT VALID											

2. Was a defined, representative sample of patients assembled at a common (usually early) point in the course of the disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the follow-up of these patients sufficiently long and complete?	Yes	Yes	No (Only 6 months)	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear
4. Were objective and unbiased outcome criteria used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was there adjustments for important prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Consider • Was there standardisation for potentially important prognostic factors e.g. age?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
• Were different sub-groups compared?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

• Was there validation in an independent group of patients?	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
6. How likely are the outcome event(s) over a specified period of time	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
7. How precise are the estimates of this likelihood? Consider • Are the results presented with confidence intervals?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
WILL THE RESULTS HELP ME WITH THIS PATIENT?											
8. Were the study patients similar to this patient?	No	No	No	No	No	No	No	No	No	No	No
9. Will the results lead directly to selecting or avoiding a treatment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Are the results useful for reassuring or counselling my patient?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Consider • Will the evidence make a clinically important impact on your conclusions about what to offer or tell this patient?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Scores	15	15	14	15	13	15	15	15	15	14	13

Appendix G: Table 2.5

Table 2.5: Independent factors for TB treatment default.

Author	Country	Study Design	Study period	N	TB/ TBHIV	Default Rate (%)	Outcome
Vijay S et al., 2003	India	Case-control	1999-2000	483	TB	New (25%), Retreatment (45%)	Male (AOR: 2.49; 95%CI: 1.10-6.18), alcoholism (AOR: 6.38 95%CI: 3.25-12.5)
K.C Chang et al., 2004	Hong Kong	Case Control	1999	408	TB	Not calculated	Current smoking (OR 3.00, 95%CI 1.41–6.39), past TB with default (OR 6.23, 95%CI 1.95–19.91), poor initial adherence (OR 117.21, 95%CI 13.52–1015.92), fair initial adherence (OR 11.02, 95%CI 2.15–56.43), unknown initial adherence (OR 6.59, 95%CI 3.47–12.49), treatment side effects (OR 13.30, 95%CI 3.23–54.79), and subsequent hospitalisation (OR 0.27, 95%CI 0.11–0.67).
P.C Hill et al., 2005	Gambia	Prospective	2002-2003	301	TB	25.2	Uncertain that treatment would work (HR 3.64; 95%CI: 1.42–9.31), those who incurred significant time or money costs travelling to receive treatment (HR 2.67; 95%CI: 1.05–6.81)
P.Mishra et al., 2005	Nepal	Case-control		150	TB		Unemployment (AOR: 9.2; 95%CI: 2.8–29.8), low status occupation (AOR 4.4;

							95%CI:1.5-12.5), low annual income (AOR 5.4, 95%CI: 1.0-30.0), and cost of travel to the TB treatment facility (AOR: 3.0; 95%CI 1.2–7.3)
O.J Daniel et al., 2006	Nigeria	Case-control	1997-2003	774	TB	23	Male (AOR: 1.64; 95%CI: 1.15-2.34)
W.M Jakubowiak et al., 2007	Russia	Case-control	2003	1805	TB	4.6	Unemployment (AOR: 4.44; 95%CI 2.23-8.86), alcohol abuse (AOR: 1.99; 95%CI 1.04-3.81), homelessness (AOR: 3.49; 95%CI 1.25-9.77)
De Albuquerque et al., 2007	Brazil	Prospective	2001-2003	1555	TB	14.8	Age (AOR: 1.89; 95% CI: 1.07-3.34), prior TB treatment (AOR: 2.16; 95% CI: 1.51-3.12), illiteracy (AOR: 1.72; 95% CI:1.17-2.53)
Shargie et al., 2007	Southern Ethiopia	Prospective	2002-2004	404	TB	20.0	Distance from home to treatment centre (AHR: 2.97;), age > 25 years (AHR: 1.71;), necessity to use public transport to get to a treatment centre (AHR: 1.59;)
Epco Hasker et al., 2008	Uzbekistan	Case-control	2005	258	TB	Not applicable	Unemployment (AOR: 2.73; 95%CI: 1.28-5.86), pensioner (AOR: 4.07;95%CI: 1.57-10.52), alcoholism (AOR: 6.01; 95%CI: 1.68-19.47)

Kittikraisak et al., 2009	Thailand	Cohort	2005-2006	554	TB/HIV	11.0	Incarceration history (AOR: 2.0, 95%CI: 1.1-3.7), smoking (AOR 2.3, 1.3-4.1), symptom complaint score > 15 (AOR 3.4, 1.4-8.0)
Amuha et al., 2009	Uganda	Cross-sectional	2008	140	TB/HIV	25.0	On continuing phase of anti TB treatment (AOR = 6.24, 95% CI = 2.41 – 16.15), alcohol consumption (AOR = 3.87, 95% CI = 1.02 – 14.67)
Weiguo Xu et al., 2009	China	Cross-sectional	2006	670	TB	12.2	Illiteracy (AOR:2.42; 95% CI: 1.25-4.67), direct observation by village doctors (AOR: 0.23; 95% CI: 0.11-0.45)
Bernard N Muture et al., 2011	Kenya	Case-control	2006-2008	274	TB	Not applicable	Inadequate knowledge on TB (AOR 8.67; 95% CI 1.47-51.3), herbal medication use (AOR 5.7; 95% CI 1.37-23.7), low income (AOR 5.57, CI 1.07-30.0), alcohol abuse (AOR 4.97; 95% CI 1.56- 15.9), previous default (AOR 2.33; 95% CI 1.16-4.68), co-infection with HIV (AOR 1.56; 95% CI 1.25-1.94) and male gender (AOR 1.43; 95% CI 1.15-1.78)
Elbireer S et al., 2011	Uganda	Case-control	2009	344	TB/HIV	Not applicable	Distance from home to clinic (AOR 2.22; 1.21-4.06), long waiting time at the clinic (AOR 4.18; 2.18-8.02), poor drug availability (AOR 4.75; 2.29-9.84), conduct of staff (AOR 2.72; 1.02-7.25), lack of opportunity to express feeling (AOR 3.47; 1.67-7.21), lack of health education (AOR 5.31; 1.94–14.57);

							not knowing that TB can be cured (AOR 44.11; 13.66–142.41); length of TB treatment (AOR 10.77; 5.18–22.41), side effects of treatment (AOR 5.53; 2.25–13.61)
Maruza M et al., 2011	Brazil	Prospective	2007-2009	273	TB/HIV	21.7	Male (AOR: 2.28; 95%CI: 1.06-4.94), smoking (AOR: 2.62; 95%CI: 1.31-5.26), CD4<200 cells/mm (AOR: 2.93; 95%CI: 1.56-5.23), age over 29 (AOR: 0.50; 95%CI: 0.25-0.99), complete or incomplete secondary or university education (AOR: 0.33; 95%CI: 0.15-0.71), HAART use (AOR: 0.12; 95%CI: 0.05-0.33)
M da silva Garrido, et al. 2012	Brazil	Case-control	2005-2010	11,312	TB	Not applicable	Previous default (AOR 3.20; p<0.001), HIV positivity (AOR 1.62; p<0.001), alcoholism (AOR 1.51; p<0.001), low education level (AOR 1.35; p<0.001) and other co-morbidities (AOR 1.31; p = 0.05). Older patients (AOR 0.98; p = 0.001), DOT (AOR 0.72; p<0.01).
Naidoo et al., 2013	South Africa	Cross-sectional	NA	3107	TB	26.1	Poverty, one or more co-morbidity, high risk for alcohol mis-use, partner who is HIV-positive, tobacco use.

Appendix H: WHO Clinical Staging

Source: (WHO, 2007)

Primary HIV Infection

Asymptomatic

Acute retroviral syndrome

Clinical Stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical Stage 2

Moderate unexplained weight loss (<10% of presumed or measured body weight)

Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)

Herpes zoster

Angular cheilitis

Recurrent oral ulceration

Papular pruritic eruptions

Seborrheic dermatitis

Fungal nail infections

Clinical Stage 3

Unexplained severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhea for >1 month

Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant)

Persistent oral candidiasis (thrush)

Oral hairy leukoplakia

Pulmonary tuberculosis (current)

Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)

Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis

Unexplained anemia (hemoglobin <8 g/dL)

Neutropenia (neutrophils <500 cells/μL)

Chronic thrombocytopenia (platelets <50,000 cells/μL)

Clinical Stage 4

HIV wasting syndrome, as defined by the CDC (see Table 3, above)

Pneumocystis pneumonia

Recurrent severe bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)

Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)

Extrapulmonary tuberculosis

Kaposi sarcoma

Cytomegalovirus infection (retinitis or infection of other organs)

Central nervous system toxoplasmosis

HIV encephalopathy

Cryptococcosis, extrapulmonary (including meningitis)

Disseminated nontuberculosis *Mycobacteria* infection

Progressive multifocal leukoencephalopathy

Candida of the trachea, bronchi, or lungs

Chronic cryptosporidiosis (with diarrhea)

Chronic isosporiasis

Disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis)

Recurrent nontyphoidal *Salmonella* bacteremia

Lymphoma (cerebral or B-cell non-Hodgkin)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy

Symptomatic HIV-associated cardiomyopathy

Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis