EVALUATION OF MANAGEMENT, TREATMENT OUTCOMES AND HEALTH RELATED QUALITY OF LIFE OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS IN PESHAWAR, PAKISTAN

by

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Dedicated to my beloved parents and wife for their unconditional love and unwavering support

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LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of variance
BMI	Body mass index
BP	Bodily pain
CBC	Complete blood count
CI	Confidence interval
DOTS	Directly observed treatment-short course
DST	Drug susceptibility testing
EMRO	Eastern Mediterranean Region of World Health Organization
EQ-5D	EuroQoL-5D
FACIT	Functional Assessment of Chronic Illness Therapy
GH	General health
GLC	Green Light Committee
GLM	General linear model
HDL	Home DOTS linkage
HRQoL	Health Related Quality of Life
HUI	Health Utility Index
HIV	Human Immunodeficiency Virus
Inh	Isoniazid
KFS	Kidney Function Study

kHZ	Kilo Hertz
LRH	Lady Reading Hospital
MCS	Mental component summary
MDR-TB	Multidrug resistant tuberculosis
MH	Mental health
MID	Minimal important difference
MTB	*Mycobacterium tuberculosis*
NBS	Norm based scoring
NTP	National Tuberculosis Control Program
PCS	Physical component summary
PF	Physical functioning
PMDT	Programmatic management of drug-resistant tuberculosis
QLI	Quality of Life Index
RE	Role-emotional
Rif	Rifampicin
RP	Role-physical
SD	Standard deviation
SF	Social functioning
SF-36	Short Form-36
SLD	Second-line anti-TB drug
SNHL	Sensorineural hearing loss
TB	Tuberculosis
UNICEF	United Nations Children's Emergency Fund

VAS	Visual Analogue Scale
VT	Vitality
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life-BREF
XDR-TB	Extensive drug-resistant TB

PENILAIAN PENGURUSAN, HASIL RAWATAN DAN KUALITI KEHIDUPAN BERKAITAN KESIHATAN DALAM KALANGAN PESAKIT UBAT-UBATAN TUBERKULOSIS DI PESHAWAR, PAKISTAN

ABSTRAK

Secara global, Pakistan merupakan negara yang mempunyai multi-resistan terhadap pelbagai ubat-ubatan tuberkulosis (MDR-TB). Walaupun pengurusan pragmatik multi resistan drug terhadap TB (PMDT) di negara ini dimulakan dalam tahun 2010, namun maklumat berkenaan pengurusan dan hasil rawatan pesakit dari Pakistan MDR-TB masih banyak yang belum diketahui. Untuk tujuan ini, sejumlah 298 pesakit MDR-TB yang dirawat di unit PMDT di Hospital Lady Reading, Peshawar disertakan dalam tinjauan kajian kohort. Pesakit diberi rawatan susulan sehingga hasil rawatan direkodkan. Majoriti pesakit (55.8%) mempunyai tahap resistan terhadap ubat anti-TB pilihan kedua (SLD), dan kebanyakannya dari jenis *fluoroquinolone* (52.7%). Pesakit dengan rawatan TB terdahulu pada sektor campuran swasta dan awam lebih mudah mengalami ketahanan terhadap *fluoroquinolone*. Lebih separuh daripada mereka (53.6%) tiada kultur dalam masa beberapa bulan rawatan. Dalam analisis multivariat, ketahanan terhadap *flouroquinolone* dan penyakit kaviti paru-paru menjadi faktor risiko terjadinya kelewatan konversi kultur yang di lakukan. Kesan buruk dihadapi seramai 70.1% pesakit namun menjurus ke arah modifikasi rejimen rawatan TB sebanyak 18.9%. Pesakit dengan berat badan dasar $\geq$ 40 kg lebih mudah mendapat kesan buruk. Majoriti pesakit (75.1%) mencapai hasil rawatan yang berjaya. Dalam analisis multivariat, pesakit berusia $\geq$40 tahun, berat badan asas <40 kg, mempunyai ketahanan terhadap *fluoroquinolone*, penyakit kaviti paru-paru dan modifikasi regimen akibat kesan buruk menjadi faktor risiko terhadap hasil rawatan yang tidak berjaya.Tambahan pula di

sebalik kesan buruk MDR-TB ke atas Kualiti Kehidupan Berkaitan dengan Kesihatan pesakit serta terdapat banyak kekurangan maklumat yang berkaitan dengan kesan rawatan MDR-TB ke atas HRQoL pesakit. Bagi tujuan ini, seramai 81 pesakit MDR-TB yang layak (boleh membaca, umur $\geq$ 18) telah di pilih menyertai kajian ini. Mereka diminta untuk melengkapkan sendiri soalselidik SF-36v2 pada lawatan permulaan, dan seterusnya, selepas melengkapkan rawatan selama 12 bulan dan pada akhir rawatan. Sejumlah 68 daripada 81 pesakit yang melengkapkan SF-36v2 pada tiga kali pertemuan. Keputusannya menunjukkan rawatan MDR-TB mendapat kesan positif ke atas HRQoL pesakit. Walaubagaimanapun, komponen fizikal pesakit (PCS) dan rumusan komponen tekanan mental (MCS) di dapati berada di bawah norma populasi normal. Jangkamasa keuzuran sebelum diagnosis MDR-TB di lakukan dapat memberi jangkaan perbezaan dalam kedua-dua skor PCS dan MCS, manakala jantina pesakit dapat memberi jangkaan perbezaan dalam MCS. Secara kesimpulannya, resistan yang tinggi terhadap *flouoroquinolone* amatlah membimbangkan sebagaimana yang diperolehi dari kajian ini. Kadar kejayaan rawatan agak menggalakkan namun masih boleh diperbaiki. Walaupun kadar kesan advers terhadap ubat ubatan TB adalah tinggi, namun ianya tidak memberi kesan terhadap hasil rawatan secara negatif. Walaupun pesakit-pesakit HRQoL beransur pulih sepanjang rawatan, namun ianya tidak begitu tinggi berbanding populasi secara umum sehingga ke akhir rawatan lengkap. Faktor risiko penukaran kultur sputum yang tertangguh, kesan buruk, hasil rawatan yang tidak berjaya dan HRQoL yang rendah dapat dikesan sebelum atau pada awal rawatan. Penumpuan yang lebih jitu dan amalan pengurusan rawatan secara klinikal yang lebih baik amatlah diperlukan bagi meningkatkan hasil rawatan dan HRQoL pesakit TB.

EVALUATION OF MANAGEMENT, TREATMENT OUTCOMES AND HEALTH RELATED QUALITY OF LIFE OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS IN PESHAWAR, PAKISTAN

ABSTRACT

Globally, Pakistan is a multidrug resistant tuberculosis (MDR-TB) high burden country. Although, programmatic management of drug resistant TB (PMDT) in the country is initiated in 2010, but little is known about the management and treatment outcomes of MDR-TB patients from Pakistan. For this purpose, a total of 298 MDR-TB patients treated at the PMDT unit of Lady Reading Hospital Peshawar were included in an observational cohort study. Patients were followed until a treatment outcome was recorded. The majority of patients (55.8%) were resistant to second line anti-TB drugs (SLD), mainly a *fluoroquinolone* (52.7%). Patients with previous TB treatment at private and public private mix sectors were significantly more likely to be *ofloxacin* resistant. More than half of them (53.6%) achieved sputum culture conversion within first two months of treatment. In multivariate binary logistic regression analysis, resistance to *fluoroquinolone* and cavitary lung disease emerged as risk factors for delayed culture conversion. Adverse events were experienced by 70.1% patients, but led to TB treatment regimen modification for only 18.9%. Patients with baseline body weight $\geq$40 kg were significantly more likely to develop adverse events. The majority of patients (75.1%) achieved successful treatment outcome. In multivariate binary logistic regression analysis, patient's age $\geq$40 years, baseline body weight <40 kg, resistance to *fluoroquinolone*, cavitary lung disease and regimen modification due to adverse events emerged as risk factors for unsuccessful treatment outcomes. Moreover, despite potential detrimental effects of MDR-TB on patients Health Related Quality of Life

(HRQoL), there is lack of information regarding the effects of MDR-TB treatment on patients' HRQoL. For this purpose a total of 81 eligible MDR-TB patients were enrolled at the study site. They were asked to self-complete SF-36v2 questionnaire at the baseline visit, and subsequently, after the completion of 12 months of treatment and at the end of treatment. A total of 68 out of 81 enrolled patients completed SF-36v2 at the three time points. The results revealed that MDR-TB treatment had a positive effect on patients' HRQoL. However, even at the completion of treatment, patients' physical component summary (PCS) and mental component summary (MCS) sores remained well below the general population norms. Length of sickness prior to the diagnosis of MDR-TB was predictive of differences in both PCS and MCS scores, whereas patient's gender was predictive of difference in MCS score. In conclusion, the high prevalence of *fluoroquinolone* resistance observed in the current study was alarming. The rate of successful treatment outcomes was encouraging but still has a room for further improvement. Despite high occurrence, adverse events did not impact treatment outcomes negatively. Patients' HRQoL improved along the course of the treatment, but was inferior to that of general population norms even at the completion of the treatment. Risk factors for delayed sputum culture conversion, occurrence of adverse events, unsuccessful treatment outcomes and poor HRQoL are generally identifiable before or early in the course of treatment. Paying special attention and providing enhanced clinical management to the high risk patients may improve treatment outcomes and HRQoL.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is a highly infectious airborne disease caused by bacillus *Mycobacterium tuberculosis* (MTB). It has affected humanity throughout the known human history, and caused more human deaths than any other infectious disease (Daniel, 2006). Even though, effective treatment strategies are available for TB, it still continues to be a critical health problem worldwide. Latest report of World Health Organization (WHO) estimated that, TB killed about 1.5 million people in 2014 ─ equating to 4109 deaths per day─ and ranked as the leading fatal infectious disease, surpassing human immunodeficiency virus (HIV). In 2014, approximately 9.6 million TB cases occurred globally with an estimated incidence rate of 133 cases per 100,000 population (WHO, 2015).

Since 1990, the TB mortality rate has been declined by 47% (WHO, 2015). In the last 14 years, TB diagnostic and treatment interventions through efficient public health actions have saved an estimated 43.4 million lives globally (WHO, 2015), but unfortunately, the emergence and spread of drug resistant TB pose significant threats to these gains. Resistance to anti-TB drugs has been studied since 1940s (Wolinskye, *et al*., 1948), but multidrug-resistant TB (MDR-TB) defined as "TB caused by the strain of MTB resistant to both *isoniazid* (*Inh*) and *rifampicin* (*Rif*)" came in the clinical literature and practice in early 1990s (Espinal, 2003; Frieden, *et al*., 1995; Kim, *et al*., 2003), and is now reported widely (WHO, 2015). Although, classical MDR-TB cases are curable,

but being resistant to *isoniazid* and *rifampicin*, the two most effective and well tolerated first-line anti-TB drugs, they are treated for prolonged periods with comparatively less potent, more toxic and expensive second-line anti-TB drugs (SLD) (Caminero, 2006; WHO, 2014a). The lack of evidence based recommendations from randomized control trials (Mitnick, *et al*., 2007), insufficient number of experts and diagnostic laboratories (Nathanson, *et al*., 2010), and prolonged therapy with comparatively less effective and potentially toxic regimen of multiple anti-TB drugs make it difficult to produce best possible treatment outcomes in MDR-TB patients (Bloss, *et al*., 2010; Caminero, 2006; Diel, *et al*., 2014; Sagwa, *et al*., 2014). Consequently, in 2014, the global treatment success rate of MDR-TB (50%) was significantly lower than that in drug susceptible TB patients (86%). Moreover, a large proportion of MDR-TB patients (25%) was lost to follow up or had no information about treatment outcomes (WHO, 2015).

Besides poor treatment outcomes, the other major challenge faced during the treatment of MDR-TB is the high incidence and wide spectrum of adverse events (Avong, *et al*., 2015; Bloss, *et al*., 2010; Sagwa, *et al*., 2012; Sturdy, *et al*., 2011; Törün, *et al*., 2005; Wu, *et al*., 2016). These events range from life threatening reactions (renal failure and hypokalemia) and disabling effects (irreversible hearing and vision loss) to non-life-threatening reactions (gastrointestinal disturbances) of negative impact on patients' quality of life (Avong, *et al*., 2015), and may need a temporary or permanent discontiuation of the culprit drug(s) (Bloss, *et al*., 2010; Furin, *et al*., 2001; Hoa, *et al*., 2015; Törün, *et al*., 2005). Adverse events may negatively affect patients' compliance, require hospitalization, and result in increased health care costs, morbidity and mortality (Leimane, *et al*., 2005; Nathanson, *et al*., 2004; Törün, *et al*., 2005).

Health Related Quality of Life (HRQoL) defined as "the extent to which patient's subjective perception of physical, mental and social wellbeing is affected on a day to day basis by a disease and its treatment(s)" (Leidy, *et al*., 1999) is an important patient reported outcome. It quantifies that how the disease and its treatment affect the lives of the patients, and aims to measure the quality rather than only the quantity of health (Guo, 2010). Multidrug-resistant tuberculosis being a contagious, chronic and debilitating disease of prolonged chemotherapy with potentially toxic drugs, results in high incidence of adverse events and long term physiological, socio-economic and psychological effects (Booker, 1996; Furin, *et al*., 2014; Isaakidis, *et al*., 2013). All these factors can adversely affect the HRQoL of MDR-TB patients (Al-Qahtani, *et al*., 2014; Kittikraisak, *et al*., 2012; Morris, *et al*., 2013; Sharma, *et al*., 2014).

Pakistan is an MDR-TB 5th high burden country (WHO, 2015). Programmatic management of drug resistant TB (PMDT) in the country is initiated in 2010, and in 2013, there were 18 functional PMDT units throughout the country (NTP, 2013a), but little is known about the management and treatment outcomes of MDR-TB patients from Pakistan, particularly after the implementation of PMDT in the country. Moreover, despite a chronic contagious disease of prolonged chemotherapy with potentially toxic SLD, and negative impact on patients physical, mental, social and economic wellbeing, evaluating the effects of MDR-TB treatment on patients HRQoL has remained a neglected area. Therefore, the current study focused on evaluating the management, treatment outcomes and effects of MDR-TB treatment on patients HRQoL at a PMDT unit in Pakistan.

1.2 Origin of drug-resistant tuberculosis

Resistance to anti-TB drug is not a new phenomenon. It appeared soon after the discovery of anti-TB drugs (Crofton & Mitchison, 1948). All chemotherapeutic agents used to treat bacterial infections tend to produce resistant strains. The resistance may be primary or secondary. Primary drug resistance refers to the "drug resistance in a patient who has not received the drug before" (Telenti & Iseman, 2000). During rapid multiplication of bacilli, resistant mutants emerge irrespective of the administration of any particular agent (Zhang & Yew, 2009). It is believed that primary drug resistance is induced by the transference of non-chromosomal heritable genes called "episomes". If an episome containing resistant cell comes in direct contact with a susceptible cell, episome leaves the resistant cell and invade the susceptible one (Cohen, *et al*., 1972). Secondary drug resistance also known as acquired drug resistance refers to the "resistance developed during the course of antimicrobial therapy" (Telenti & Iseman, 2000). In acquired drug resistance, bacteria develop resistance to particular drugs to which they were sensitive at the start of the treatment (Telenti & Iseman, 2000).

1.3 Mechanism of development of drug resistance in *Mycobacterium tuberculosis*

Antimicrobials agents used to treat infections have the ability to actively inhibit or kill microorganisms. The interruption or disturbance of one or more steps necessary for antimicrobial action results in the emergence of antimicrobial resistance. Because of base changes caused by exogenous agents, deoxyribonucleic acid (DNA) polymerase errors; deletion, insertion and duplication, random spontaneous mutations continuously occur at a low frequency in all bacterial population (Drake, 1999). Some of these mutations may confer resistance to a particular antimicrobial agent by several mechanisms. These mechanisms include the production of proteins that modify the

binding site for antimicrobial, enzymes that destroy it, and proteins that reduce its permeability and change of the metabolic pathway of antimicrobial within the bacteria so, that its efficacy is reduced (Dever & Dermody, 1991; Hawkey, 2000). The biological consequence of mutation determines the degree of resistance conferred by chromosomal mutation. With less common single large step mutations, the drug target is altered such that it becomes completely unable to bind the drug. In such case, the resistant mutant is capable to survive and grow, and eventually becomes the predominant or only strain of the population (Drlica, 2003). In the more common multiple step pattern of resistance, the drug target is altered in such a way that despite having some residual affinity, it is unable to bind the drug that efficiently. In such cases, higher concentrations of drug would be required for producing antimicrobial effect (Drlica, 2003). Once a slightly resistant strain has been produced, consequent mutational events confer additional degree of resistance to the strain and make it highly resistant (Long, 2000; Telenti & Iseman, 2000; Zhang & Yew, 2009).

Unlike other bacteria, where drug resistance is caused by horizontal transfer of mobile genetic elements such as plasmids, integrons or transposons; drug resistance in MTB is mediated mainly through spontaneous chromosomal mutations at a frequency ranging from10^{-6}-10^{-8} mycobacterial replications (David, 1970; Kochi, *et al*., 1993; Telenti & Iseman, 2000). As chromosomal mutations are unlinked and spontaneous, shift from an *isoniazid* susceptible MTB to a population with 1% resistance would take 5,000 to 10,000 years (David & Newman, 1971), suggesting that mycobacterial resistance in the presence of three effective anti-TB drugs is high unlikely. However, the suboptimal treatment regimen, mono-therapy, irregular intake of drugs, low drug penetration due to empyema, solid caseous material and extensive cavitation impose

artificial selection power in bacteria (Zhang and Yew, 2009). Under such selective pressure, the drug susceptible strains are killed and the genetic mutants being naturally resistant to the given antibiotic flourish, resulting in the conversion of drug susceptible TB to a mono-resistant one (Mitchison, 1954). Upon exposure to a second course of therapy with yet another anti-TB drug, genetic mutants being naturally resistant to the given drug emerge as dominant strains, generating poly-resistant strains including MDR-TB strains (Rattan, *et al*., 1998; Zhang & Yew, 2009). Concepts of development of drug resistant TB are given in Fig 1.1 (Zhang & Yew, 2009).

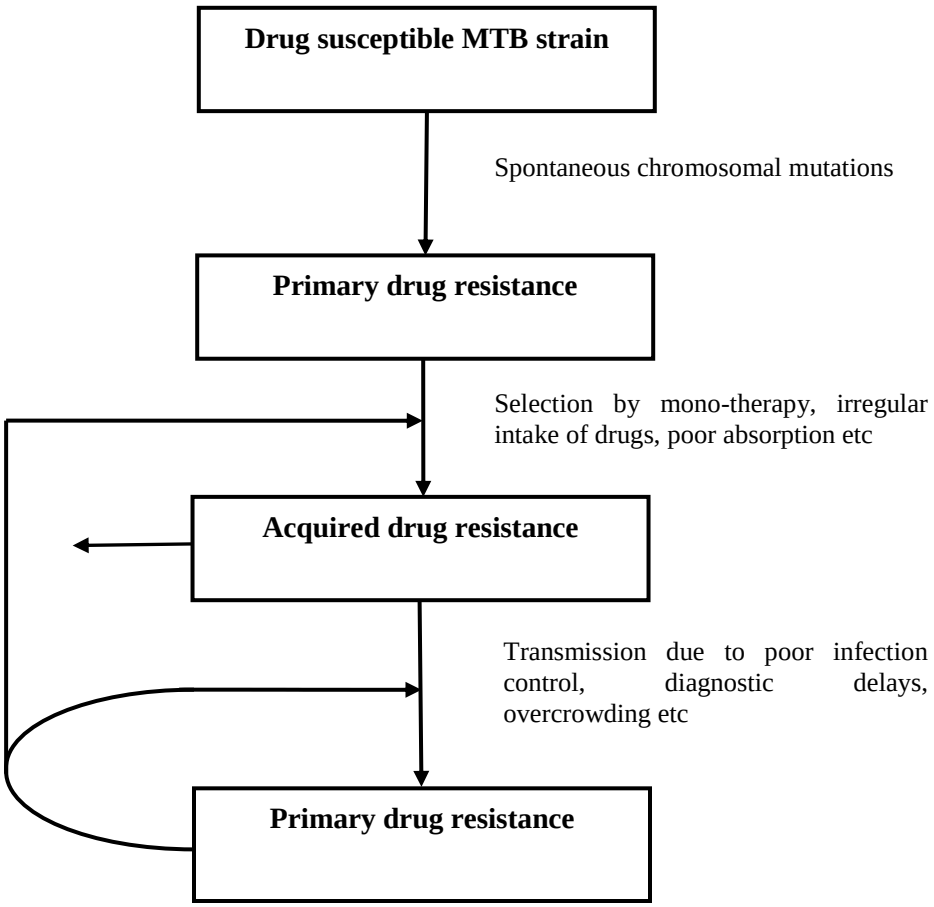

Fig. 1.1 Concepts of development of drug resistant tuberculosis

The emergence and prevalence of drug resistant TB has a strong correlation with the past and present management of TB (Caminero, 2010). It can be avoided by successfully treating the drug susceptible TB. Countries with a high incidence and prevalence of drug resistant TB have a history of poor TB control programs (WHO, 2009). Multiple, and often the combination of various risk factors are responsible for the emergence of drug resistant TB. These factors include i) healthcare related factors like previous faulty TB treatment (Caminero, 2010; Chen, *et al*., 2013; Espinal, *et al*., 2001; Liang, *et al*., 2012), no or poor implementation of DOTS (Aguilar, *et al*., 2005; Chacón, *et al*., 2009), substandard anti-TB preparations (Lambregts-van Weezenbeek & Veen, 1995; Wells, *et al*., 2011), erratic or interrupted supply of drugs (Chen, *et al*., 2013; Lambregts-van Weezenbeek & Veen, 1995), guidelines divergent practices by practitioners (Achanta, *et al*., 2013; He, *et al*., 2011; Shah, *et al*., 2003), patients' non-adherence with anti-TB treatment (Ejaz, *et al*., 2010; Sharma, *et al*., 2003; Volmink & Garner, 2007), and ii) patients related factors like co-infection with HIV (Faustini, *et al*., 2006; Joseph, *et al*., 2006; Pereira, *et al*., 2005), diabetes mellitus (Gomes, *et al*., 2014; Rifat, *et al*., 2014), patients age (Atre, *et al*., 2011; Rifat, *et al*., 2014), gender (Ejaz, *et al*., 2010; Faustini, *et al*., 2006), close contacts with MDR-TB (Martínez, *et al*., 2010; Vella, *et al*., 2011) and residence in overcrowded or congregate settings like refugee camps, prisons (Andrews, *et al*., 2007; Habeenzu, *et al*., 2007) etc.

1.4 Epidemiology of MDR-TB

1.4.1 Global epidemiology of MDR-TB

According to Global Tuberculosis Report 2015, MDR-TB accounts for 5% of all TB cases. It is estimated that in 2014, a total of 480,000 (95% confidence interval [CI]: 360,000-600,000) new MDR-TB cases emerged globally with an estimated proportion

of 3.5% of new cases and 20% of previously treated cases (WHO, 2015). Twenty seven MDR-TB high burden countries accounted for more than half of the estimated MDR-TB cases in 2014. Three countries; India, China and Russian Federation make more than half of the global MDR-TB burden. Among notified pulmonary TB cases, India has the highest estimated MDR-TB cases (71,000) followed by China (52,000) and Russian Federation (39,000). Among new cases, the percentages with MDR-TB were highest in Belarus (34%) followed by Kyrgyzstan (26%) and Kazakhstan (26%). Among retreatment TB cases, the percentages with MDR-TB were highest in the Belarus (69%) followed by Estonia (62%) and Republic of Moldova (62%) (WHO, 2015).

1.4.2 Epidemiology of MDR-TB in Pakistan

Tuberculosis is an endemic and major public health problem in Pakistan (Javaid, 2011; Khan, *et al*., 2000; NTP, 2013b; Vermund, *et al*., 2009). Sadly, despite the critical nature of the problem and high prevalence of TB in the country, it remained a forgotten area in the past. TB control was almost nonexistent in the country until the revival of National TB Control Program (NTP) in 2001 (Vermund *et al*., 2009; Javaid, 2011). First TB survey in Pakistan took place in 1962, the results of which led to the establishment of collaborative efforts for TB control between Ministry of Health Pakistan, WHO and United Nations International Children Emergency Fund (UNICEF) (De Muynck, *et al*., 2001; Javaid, 2011). The said collaboration mainly focused on establishing the specialized TB treatment centers and wards at the district headquarter hospitals (De Muynck *et al*., 2001; Javaid, 2011). Unfortunately, in 1985 UNICEF withdrew its financial support. In order to achieve effective TB control after WHO declaration of TB as a global emergency, Government of Pakistan piloted Directly Observed Treatment- Short course (DOTS) strategy at five sites in 1995, but only one

remained operational. Despite revised TB control policy in 1994 and the drafted national policy and technical guidelines for TB control, in 1998 Pakistan was declared as a country without a proper functional NTP (De Muynck, *et al*., 2001). In 2000, the estimated percentage of case detection rate for new and relapse smear-positive cases–a key indicator of a successful TB control program–was 2.8%, far below the WHO target of $\geq$ 70% (WHO, 2009).

Since the revival of NTP and nationally adopting DOTS in 2001 (NTP, 2013a; Vermund, *et al*., 2009), Pakistan has made enormous progress regarding DOTS coverage, TB case notification and treatment success rates. It took four years to bring DOTS coverage to all public health facilities in the country (Javaid, 2011; NTP, 2013a; Vermund, *et al*., 2009). In Pakistan, 100% population had DOTS coverage in 2005 as compared to only 8% in 1998 (WHO, 2009). Estimate of the case detection rate for new and relapse cases has been increased from 3.9% in 1995 to 62% in 2014 (WHO, 2015). Moreover, TB treatment success rate has been increased from 70% in 800 treated patients in 1995 to 93% in 289,376 treated cases in 2013 in the country (WHO, 2015).

Despite remarkable progress regarding DOTS coverage, TB case notification and treatment success rate in the last decade, Pakistan still ranks 6th among the 22 TB high burden countries. According to WHO latest report, Pakistan accounts for 68% of TB burden in Eastern Mediterranean Region of WHO (EMRO) with estimated incidence of 500,000 (95% CI: 370,000-650,000) and prevalence of 630,000 (95% CI: 530,000-740,000) (WHO, 2015). Similar to other developing countries, people aged $\geq$ 15 years were the most affected group in Pakistan. In 2014, the estimated deaths attributed to TB in the country were 48,000 with a mortality rate of 26 per 100,000 population (WHO, 2015).

Unfortunately, in the last 25 years, consistent increase in the incidence of drug resistant TB including MDR-TB has been observed in the country (WHO, 2014b; Hasan, *et al*., 2009). As in the early 2000, the management of drug resistant TB was not included in NTP; there was a scarcity of data regarding the prevalence of drug resistant TB in the country. Previously conducted studies which evaluated drug resistance trends in MTB isolates from all over the country have reported a significant increase in prevalence of MDR-TB in the country (5.5% in 1990, 33.1% in 2007 and 34.1% in 2009) (Hasan, *et al*., 2009; Jabeen, *et al*., 2011). However, the results of these studies should be interpreted with the notable limitation of passive case finding designs, where majority of the cases referred from all over the country were either treatment failures or complicated cases.

With the adoption PMDT in 2010 and improved efficiency of NTP, the notification of MDR-TB cases in Pakistan has been increased. In comparison to the 40 notified cases among the estimated 8290 cases in 2008, a total of 3243 MDR-TB/*rifampicin* resistant TB cases of the estimated 12000 cases have been notified in 2014 (WHO, 2015; WHO, 2008a). Due to the lack of surveillance system to monitor drug resistance in the country, the most recent data available on drug resistant TB from Pakistan is the trend data generated through special survey conducted from 2010-2013. In 2014, a total of 316,577 TB cases were notified in the country including 3,243 cases of MDR-TB (WHO, 2015). In terms of MDR-TB burden, Pakistan ranks MDR-TB 5th high burden country globally and harbors the largest population of MDR-TB patients in EMRO. According to WHO latest report, it is estimated that in 2014, a total of 12,000 (95%CI: 8,800-15,000) MDR-TB cases emerged in Pakistan with an estimated proportion of 3.7% of new cases and 18% of previously treated cases (WHO, 2015).

Despite reported TB treatment success rate of 91% with 72% cure rate in the country (NTP, 2013a), such a high prevalence of MDR-TB with relatively low primary drug resistance, raises the possibility that a significant proportion of TB patients receiving treatment in private sector are not included within the DOTS program (Hasan, *et al*., 2009). Notified TB cases in Pakistan from 2008-2014 have been given in Table 1.1.

Table 1.1 Notified tuberculosis cases in Pakistan (2008-2014)

	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
All TB cases (notified)	245635	316864	269290	270394	273097	298446	316577
New Cases	240695	301867	255329	255094	261380	282607	300350
Relapse + Retreatment cases	4940	14997	13691	15300	11717	15839	16227
Estimated MDR-TB among notified pulmonary TB	8290	9800	9700	-	11000	13000	12000
Notified MDR-TB Cases	40	49	444	344	1602	2596	3243

TB, tuberculosis; MDR, multidrug resistant; (WHO reports 2009- 2015)

1.5 Management of MDR-TB in Pakistan

After implementation of PMDT strategy in June 2010, MDR-TB in Pakistan is treated under a uniform protocol guided by national guidelines for PMDT (NTP, 2012). These guidelines were drafted in 2008 and updated in 2012. Table 1.2 provides details about anti-TB drugs used for the treatment of drug resistant TB in Pakistan.

Table 1.2 Details of most commonly anti-TB drugs used for the management of MDR-TB in Pakistan

Group	Drug name (abbreviation)	Recommended dose		Common adverse effects
		Daily dose (mg/kg body weight)	Maximum dose (mg)	
Group 1. First-line oral agents	Ethambutol (Emb)	25	1600-2000	Visual impairment
	Pyrazinamide (Pza)	30-40	2000-2500	GI disturbance, photo-sensitization, jaundice, hepatitis, arthralgia
Group 2. Injectable anti-TB drugs	Kanamycin (Km)	15-20	1000	Ototoxicity, nephrotoxicity
	Amikacin (Amk)	15-20	1000	
	Capreomycin (Cm)	15-20	1000	
Group 3. Fluoroquinolones	Levofloxacin (Lfx)	7.5-10	750-1000	GI disturbances, insomnia, headache, thrush, anxiety, allergic reactions, tremors
	Moxifloxacin (Mfx)	7.5-10	400	
Group 4. Oral bacteriostatic SLD	Ethionamide (Eto)	15-20	750-1000	GI disturbances, metallic taste, Salivation. hepatitis, peripheral neuropathy
	Prothionamide (Pto)	15-20	750-1000	
	Cycloserine (Cs)	15-20	750-1000	Dizziness, headache, depression, memory loss, psychosis
	Para-aminosalicylic acid (PAS)	150	8-12 gm	GI disturbances, drug fever, cutaneous reactions
Group 5. Anti-TB drugs with limited data on efficacy	Amoxicillin/Clavulanate (Amx/Clv)	Dosages for drug resistant TB not well defined. Normal adult dose is 875/125 mg twice daily or 500/125 mg three times a day		GI disturbances, cutaneous reactions, headache
	Clarithromycin (Clr)	Usual adult dose is 50 mg twice daily		

GI, gastro-intestinal; SLD, second-line anti-TB drugs

According to national guidelines, presumed MDR-TB patients referred to a PMDT unit should be initially evaluated for the presence of AFB and *rifampicin* resistance by using smear microscopy and rapid drug susceptibility testing (DST). For rapid DST, GeneXpert MTB/RIF (*Mycobacterium tuberculosis*/*rifampicin*) assay which is a nucleic acid amplification assay should be used. This test concurrently detects MTB and resistance to *rifampicin* in less than 2 hours.

Upon positive sputum smear microscopy and *rifampicin* resistance, patient should be enrolled for MDR-TB treatment with empirical treatment regimen, and the specimen sample should be sent to a reference laboratory for culture and DST against both first and SLD. Upon reception of DST results, patients should be switched from empirical regimen to DST based individualized regimen.

National guidelines have outlined the following general principles for MDR-TB treatment: i) treat the patients with at-least four likely effective SLD plus *pyrazinamide* ii) avoid drugs for which resistance crosses over iii) eliminate the drug not safe for the patient iv) remain ready to prevent, observe and manage adverse effects for each selected drug.

According to national guidelines, following drugs should be included for devising a DST based individualized treatment regimen:

a) any available first line oral anti-TB drug

b) an injectable SLD

c) a *fluoroquinolone*

d) two or more second line oral bacteriostatic SLD until the goal of four likely effective SLD is achieved

e) if four likely effective anti-TB drugs from Group 2-4 are not possible, consider the addition of Group 5 drugs.

Because of higher incidence of ototoxicity and resistance against *streptomycin* in patients with drug resistant TB, *streptomycin* should not be the part of MDR-TB treatment regimen even if DST suggests susceptibility. National TB control program supports individualized treatment regimen if DST to first-line and SLD is available. Otherwise, treatment in a presumed MDR-TB patient should be initiated with an empirical regimen based on patient's history of TB treatment.

National guidelines have outlined the following general principles for initiating treatment in a presumed MDR-TB patient:

i) Treatment in patients with no history of previous use of SLD should be initiated with:

A*mikacin/kanamycin/capreomycin + levofloxacin + ethionamide + cycloserine + pyrazinamide*

ii) Treatment in patients with a documented history of previous use of *fluoroquinolones* should be initiated with:

Amikacin/kanamycin/capreomycin + levofloxacin + ethionamide + cycloserine + para-amino salicylic acid + pyrazinamide

iii) Treatment in patients with documented history of previous use of injectable SLD should be initiated with:

Capreomycin + levofloxacin + ethionamide + cycloserine + para-amino salicylic acid+ pyrazinamide

MDR-TB treatment is divided into two phases; the intensive phase and the continuation phase. The time the patient is on injectable SLD is referred to as the intensive phase. The duration of intensive phase is guided mainly by sputum culture

conversion defined as “two consecutive negative sputum cultures taken at least 30 days apart following an initial positive culture” (Holtz, *et al*., 2006) and should be continued for at least eight months with a minimum of six months after sputum culture conversion. However, other clinical indicators like weight gain, resolution or improvement of respiratory symptoms and/or pulmonary lesions can also be taken in consideration while deciding about the duration intensive phase. During continuation phase, only the injectable SLD is discontinued and the patient continues to take the same oral drugs which he/she was using at the end of intensive phase. A new MDR-TB patient should be treated for a minimum of 20 months, at-least 18 months past culture conversion (NTP, 2012).

1.6 Treatment outcomes of MDR-TB patients

In 2014, among 1.5 million TB related deaths worldwide, 0.19 million were attributed to MDR-TB (WHO, 2015). As MDR-TB patients are resistant to *isoniazid* and *rifampicin*, they are treated with SLD for a prolonged period of $\geq$20 months. The comparatively less effective and potentially more toxic nature of SLD make it difficult to achieve the desired treatment success rate in MDR-TB treatment (Caminero, 2006; Sharma & Mohan, 2004). This is very obvious from the recently reported significantly lower global treatment success rate in MDR-TB (50%) as compared to treatment success rate in drug susceptible TB (86%). In 2014, only 43 out 127 countries and territories that reported treatment outcomes for 2012 cohort of MDR-TB patients achieved the WHO target treatment success rate (>75%) (WHO, 2015). In a recently published study, Falzon *et al*., (2015) reported that the median treatment success rate among 30,021 MDR-TB patients from 25 countries was 53% (IQR 40-70%), and in comparison to 87% of drug susceptible TB patients only half of MDR-TB patients completed treatment.

The lower treatment success rate among MDR-TB patients is corroborated by the findings of the published systematic reviews. In a systematic review of 64 cohorts of MDR-TB patients, Akcakir (2011) reported a pooled treatment success rate of 50% (95% CI 46-59%). Treatment for > 20 months, individualized treatment regimen, use of > 3 likely effective drugs and use of *fluoroquinolones* or use of SLD in general were predictors of successful treatment outcomes. The study reported that, mortality rate was significantly high in patients co-infected with HIV and those who were on $\leq$ 3 likely effective drugs, whereas the use of SLD was significantly associated with high default rate.

In a systematic review which included MDR-TB patients of 31 programs from 21 countries, Johnston *et al*., (2009) have reported a pooled treatment success rate of 62% [95% CI: 57-67]. The authors reported that male gender, low body mass index (BMI), alcohol abuse, resistance to *fluoroquinolones*, smear positive status at the diagnostic visit and presence of and extensive drug resistance (XDR) pattern were the risk factors for unsuccessful treatment outcomes. Patients with no history of previous TB treatment, and those who received *fluoroquinolones* and surgical intervention were more likely to develop successful treatment outcomes.

Orenstein and colleagues (2009) in a systematic review of 33 studies from 20 countries, reported a similar percentage (62%, 95%CI: 58-67%) of favorable treatment outcomes in MDR-TB patients. However, they observed an improved pooled treatment success rate (69%) for those studies in which the patients received the combination of treatment for more than 18 months and DOT throughout the treatment duration.

Ahuja *et al*., (2012) conducted a meta-analysis of an individual patient data of 9,153 pulmonary MDR-TB patients. Among the studied patients, only 54% achieved

successful treatment outcomes. The multivariate analysis revealed the use of later generation *fluoroquinolones*, *ofloxacin* and *thioamides*, and receiving 4≥ likely effective drugs in the intensive phase of treatment as predictors of successful treatment outcomes.

In order to effectively manage and achieve best possible treatment outcomes in drug resistant TB, the WHO and its partner agencies devised and launched DOTS-Plus strategy in 1998 (Bastian, *et al*., 2000; Farmer & Kim, 1998). Basic principles of this strategy are: i) sustained political commitment ii) precise and timely diagnosis of drug resistant TB through quality assured culture and DST iii) uninterrupted supply and appropriate use of quality assured first-line and SLD iv) DOT and v) standardized recording and reporting system.

Later on, to ensure the effective implementation of DOTS-Plus strategy and devise "Models of Good Practice" for MDR-TB treatment, the WHO along with its international partners established a committee known as the "Green Light Committee" (GLC) (Cobelens, *et al*., 2008; Gupta, *et al*., 2002). This committee provides technical support for implementing the DOTS-Plus protocol and makes it sure that standards are met before initiating DOTS-Plus program at any site. Furthermore, GLC by linking up with drug manufacturers also facilitates the continuous supply of quality assured SLD at concessional prices (Cobelens *et al*., 2008). On the basis of experience from successful implementation of DOTS-Plus projects at five resource poor settings and achieving promising results of MDR-TB treatment success rate of 59-83% (Nathanson, *et al*., 2006), WHO devised and issued guidelines for what is now called PMDT (WHO, 2008b). Updated guidelines and a companion handbook to the WHO guidelines for PMDT have been issued in 2011 and 2014 respectively (WHO, 2011b; WHO, 2014). DOTS-Plus strategy (Bastian, *et al*., 2000; Farmer & Kim, 1998) has been proven

feasible, cost effective and having a greater impact on reducing mortality in MDR-TB patients particularly in high burden areas and resource poor settings (Sterling *et al*., 2003; Tupasi, *et al*., 2006). Table 1.3 presents the treatment success rates of MDR-TB patients treated under DOTS-plus or PMDT strategy.

Table 1.3 Treatment outcomes of MDR-TB patients treated under DOTS-Plus strategy

Study	**Country**	**Data Collection**	**Sample size** (*n*)	**Patients enrollment Period**	**Type of regimen**	**HIV Positive** (%)	**Treatment Success** (%)
van der Walt, *et al*.,2016	South Africa	Retrospective	671	2000-2008	STR	59%	65
Akshata & Chakrabarthy, 2016	India	Retrospective	69	2011-2012	STR	4.4	47.8
Kapadia & Tripathi, 2016	India	Retrospective	102	2007-2014	STR	2.9	45.1
Patel, *et al*., 2015	India	Retrospective	145	Feb-Dec 2010	STR	1.3	38.6
Gadallah, *et al*., 2015	Egypt	Prospective	228	2006-2010	ITR	-	69.3
Bastard, *et al*., 2014	Armenia & Georgia	Retrospective	393	2002-2010	ITR	-	56.5
Jain, *et al*., 2014	India	Prospective	130	Jan-Dec 2009	STR	--	45
Rodriguez, *et al*., 2013	Dominican Republic	Retrospective	150	2006-2010	STR[µ]-ITR[£]	--	72
Chan, *et al*., 2013	Taiwan	Retrospective	651	2000-2008	ITR	0.9	69.3
Kurbatova, *et al*., 2012	Russia, Peru, Estonia Latvia, Philippines	Retrospective	1768	2000-2004	ITR	1.6	65.4
Farley, *et al*., 2011	South Africa	Retrospective	757		STR	5	46
Joseph, *et al*., 2011	India	Prospective	37	2006-2007	STR	--	66
Leimane, *et al*., 2010	Latvia	Retrospective	979	2000-2004	ITR	23	69.3
Singla, *et al*., 2009	India	Retrospective	126	2002-2006	STR	--	61
Malla, *et al*., 2009	Nepal	Prospective	175	2005-2006	STR	--	70
Keshavjee, *et al*., 2008	Russia	Retrospective	579	2000-2004	ITR	0.8	66.7
Cox, *et al*., 2007	Uzbekistan	Prospective	87	2003-2005	ITR	--	62
Shin, *et al*., 2006	Russia	Retrospective	244	2000-2002	ITR	--	77
Tupasi, *et al*., 2006	Philippines	Prospective	117	1999-2002	ITR	-	61
Holtz, *et al*., 2006	Latvia	Retrospective	178	Jan-Dec 2001	ITR	--	65
Nathanson, *et al*., 2006	Estonia, Latvia, Russia Peru, Philippines &	Retrospective	1047	1999-2001	ITR	1.7*	69.6
Leimane, *et al*., 2005	Latvia	Retrospective	204	2000-2004	ITR	1.5	66
Leimane, *et al*., 2005	Latvia	Retrospective	204	Jan-Dec 2001	ITR	0.5	66
Van Deun, *et al*., 2004	Bangladesh	Prospective	58	21 months	STR	--	69

DOTS, Directly Observed Treatment Strategy; Feb, February; Dec, December; Jan, January; ITR, individualized treatment regimen; STR, standardized treatment regimen; *HIV testing was not performed in Manila; [µ]n=105; [£]n=45

1.7 Risk factors for unsuccessful treatment outcomes among MDR-TB patients

1.7.1 Previous TB treatment

Previous TB treatment with and without exposure to SLD is not only a risk factor for the emergence of drug resistant TB (Caminero, 2010; Chen, *et al*., 2013; Liang, *et al*., 2012) but is also widely reported as a risk factor for unsuccessful treatment outcomes in MDR-TB patients. Kliiman and Altraja (2009) have reported three times greater risk of unsuccessful treatment outcomes in MDR-TB patients who had a history of previous TB treatment. A study conducted in Turkey has also reported previous exposure to SLD as a predictor of unfavorable outcomes in MDR-TB patients (Tahaoğlu, *et al*., 2001). Similarly, Kurbatova and colleagues (2012) have reported a significantly greater risk of death and treatment failure among MDR-TB patients who had a history of previous use of SLD. On the other hand, absence of previous TB treatment among MDR-TB patients has been reported as a predictor of successful treatment outcome (Johnston, *et al*., 2009; Milanov, *et al*., 2015). Amplification of drug resistance due to faulty TB treatment in the past and patients' poor adherence with therapy could be the possible reason of poor outcomes in MDR-TB patients with a history of previous TB treatment (Kliiman & Altraja, 2009; Kurbatova, *et al*., 2012).

1.7.2 Co-infection with Human Immunodeficiency Virus

HIV reduces immunity, predisposes patients to infections and activates latent one. In 2014, there were an estimated 1.2 million new HIV positive TB cases (12% of all TB cases). Out of 1.5 million deaths from TB, 390,000 deaths were among HIV positive TB patients (WHO, 2015). HIV co-infection in MDR-TB patients significantly increases the risk of unsuccessful outcomes (Burgos, *et al*., 2005; Farley, *et al*., 2011; Flament-Saillour, *et al*., 1999; Kliiman & Altraja, 2009; Kurbatova, *et al*., 2012; Mannheimer, *et*

al., 1997; Uffredi, *et al*., 2007). Concurrent presence of MDR-TB and HIV infection puts the clinicians in multiple challenges. HIV positive patients are more likely to have sputum negative and extra-pulmonary TB (WHO, 2014a; Palacios, *et al*., 2012). Thus, the first challenge the clinician faces is the diagnosis of MDR-TB and evaluation of drug resistance pattern, leading to misdiagnosis or delayed diagnosis. Therefore, treatment of HIV-MDR-TB patients is initiated with empirical rather than DST-based individualized regimen, resulting in high rate of morbidity and mortality (Palacios *et al*., 2012; WHO, 2014). Immunosuppression and overlapping toxicity of Highly Active Anti-retroviral Therapy (HAART) and anti-TB drugs causes a high incidence of adverse effects in HIV co-infected MDR-TB patients (WHO, 2014a; Hoffmann, *et al*., 2007). This makes the treatment of MDR-TB further challenging and can lead to high rate of TB treatment failure (WHO, 2014a; Palacios, *et al*., 2012; Wells, *et al*., 2007). Furthermore, the complex medication schedule is another possible reason for the poor treatment outcomes in this group of patients (Kang, *et al*., 2013). However, there are certain studies which have reported no impact of HIV co-infection on MDR-TB treatment outcomes (Ahuja, *et al*., 2012; Leimane, *et al*., 2005; Marais, *et al*., 2014).

1.7.3 Resistance to fluoroquinolones

Fluoroquinolones are broad spectrum antibiotics. These agents due their fast bactericidal and sterilizing effects make the backbone of MDR-TB treatment (Falzon, *et al*., 2013; Migliori, *et al*., 2012). The published literature has extensively reported the use of *fluoroquinolones* with susceptibility as a predictor of favorable treatment outcomes in MDR-TB patients (Ahuja, *et al*., 2012; Akcakir, 2011; Anderson, *et al*., 2013; Bastos, *et al*., 2014; Chiang, *et al*., 2006; Kwak, *et al*., 2015). A recently published meta-analysis which analyzed the individual data from 31 cohorts has reported

the in-vitro susceptibility to *fluoroquinolones* as a significant and consistent predictor of successful treatment outcomes in both MDR as well as extensively drug resistant-TB (XDR-TB) patients (Bastos, *et al*., 2014). This association is supported by another meta-analysis which included the individual data of 6724 M/XDR-TB patients from 26 centers (Falzon, *et al*., 2013). On the other hand, various individual studies, meta-analyses and systematic reviews have reported resistance to *fluoroquinolones* as an independent risk factor for unsuccessful treatment outcomes in MDR-TB patients (Johnston, *et al*., 2009; Kliiman & Altraja, 2009; Kurbatova, *et al*., 2012; Leimane, *et al*., 2005; Smith, *et al*., 2015).

1.7.4 Resistance to injectable second-line anti-TB drugs

Injectable SLD (*amikacin, kanamycin* and *capreomycin*) along with *fluoroquinolones* plays a central role in the management of MDR-TB (Bastos, *et al*., 2014; Falzon, *et al*., 2013; WHO, 2014a). In a South Korean cohort, odd of favorable treatment outcomes in MDR-TB patients susceptible to *kanamycin* was greater than those who were susceptible to *fluoroquinolones* (Franke, *et al*., 2008). Sufficient data are available reporting unfavorable treatment outcomes among MDR-TB patients with additional resistance to an injectable SLD. A multi-country study which included MDR-TB patients from Germany, Italy, Estonia and Russian Federation has reported resistance to *capreomycin* as a risk factor for poor treatment outcomes (Migliori, *et al*., 2008). A study recently conducted in Russia has also reported resistance to *capreomycin* as a risk factor for poor treatment outcomes in MDR-TB patients (Smith, *et al*., 2015). These findings have been complemented by a meta-analysis of individual data of 6724 MDR-TB patients from 26 centers, which has reported a high risk of unsuccessful treatment outcomes in MDR-TB patients with additional resistance to an injectable SLD (Falzon,

et al., 2013). A recently conducted meta-analysis of individual data of 8955 MDR-TB patients corroborated the positive association between in-vitro susceptibility to an injectable SLD and higher odds of treatment success (Bastos, *et al*., 2014).

1.7.5 Low body mass index

Being a marker of the severity of a disease and poor nutritional and socioeconomic status, low BMI (<18.5 kg/m^2) at the onset of treatment has widely been reported a risk factor of poor treatment outcomes in both MDR as well as XDR-TB patients. A systematic review of 31 cohorts of MDR-TB patients has reported low BMI as a risk factor for unsuccessful treatment outcomes (Johnston *et al*., 2009). Similar finding has been reported by various individual studies conducted elsewhere (Farley, *et al*., 2011; Holtz, *et al*., 2006; Kurbatova, *et al*., 2012; Leimane, *et al*., 2005; Malla, *et al*., 2009; C. Mitnick, *et al*., 2003; Tang, *et al*., 2013). On the other hand, higher odds of successful treatment outcomes have been reported in MDR and XDR-TB patients with baseline BMI $\geq$ 18.5 Kg/m^2 (Kwon, *et al*., 2008). Studies in which patient's heights was not measured to calculate BMI, patients' lower body weight at base-line visit has been reported as a risk factor for unsuccessful treatment outcomes. An Ethiopian study has reported TB patient's baseline body weight <40 kg as a risk factor of unsuccessful treatment outcomes (Biruk *et al.,* 2016). In a study conducted at PMDT unit Multan, lower body weight (< 40 kg) of MDR- TB patients at baseline visit has been reported a predictor of death. Those with baseline weight < 40 kg were two times more likely to develop death (Javaid *et al.,* 2016). Likewise, in a prospective cohort of MDR-TB patients with high prevalence of HIV, patient's baseline body weight <45 kg was associated significantly with high hazards of death and treatment failure (Farley *et al.,* 2011).

1.7.6 Diabetes mellitus

Diabetes mellitus, in addition to be a risk factor for the development of drug resistant TB (Gomes, *et al*., 2014; Rifat, *et al*., 2014) is also reported as a predictor of unsuccessful outcomes in drug susceptible (Alisjahbana, *et al*., 2007; Dooley, *et al*., 2009; Wang, *et al*., 2009) as well as resistant TB patients (Kang, *et al*., 2013; Tang, *et al*., 2013). Poor sterilizing effects of anti-microbial agents because of high bacterial load, and impaired cell mediated immunity due to alterations in monocyte chemoattraction, type 1 cytokine phenotype and alveolar macrophage activity (Moutschen *et al*., 1991; Restrepo, *et al*., 2008; Yamashiro, *et al*., 2005) are the possible reasons for higher odds of unsuccessful treatment outcomes in diabetic TB patients. Sub-therapeutic serum levels of anti-TB drugs due to malabsorption and altered pharmacokinetics (Kang *et al*., 2012), patients' non-adherence with anti-TB therapy due to complex medication schedules and relatively high incidence of adverse events are the other possible contributing factors for poor treatment outcomes in this group of patients (Kang, *et al*., 2013; Tang, *et al*., 2013).

1.7.7 Lung cavitation

The presence of lung cavities is suggestive of severe and advanced disease. By reducing drug penetration, lung cavities decrease the efficacy of anti-TB drugs and hence increase the likelihood of unfavorable treatment outcomes (Yew, *et al*., 2000). A study from DOTS-Plus projects at five resource poor settings reported that cavitary disease at the baseline visit was an independent predictor of death among MDR-TB patients (Kurbatova, *et al*., 2012). Positive association between lung cavitation and poor treatment outcomes among MDR-TB patients is confirmed by various studies conducted