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Determinants of Multi Drug Resistant Tuberculosis Treatment Outcomes in Four Counties in Kenya between: 2008-2010

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Abstract:
Multi drug resistant (MDRTB) is a major clinical challenge, with World Health Organization (WHO) acknowledging it as a threat to global TB control. The number of MDR TB patients is on the rise globally and in Kenya. Since 2006 until 2011, the country reported 692 newly confirmed MDR-TB and 3 XDR TB cases. MDR TB is associated with high morbidity with longer, expensive and more toxic treatment regimens with resultant low cured rates. This study aims at establishing the determinants of MDRTB treatment outcome.
Methods: This was a case control study. Participants were culture confirmed former MDRTB patients who were started on MDR TB treatment between 1st January 2008 and 31st December 2010. Using the national category IV TB register, all eligible patients enrolled were stratified into two: unfavourable and favourable groups, according to MDRTB treatment outcome. Simple random sampling was used to select cases and controls. Data collection was done using a structured interviewer administered questionnaire. Univariate, bi-variate and multivariate analyses were performed on models of predictors.
Results: The total number of drug resistant TB patients diagnosed in CRL between 2008 and 2010 were 516; 346 (67 %) had favourable treatment outcome, 86 (16.7%) defaulted, 69 (13.4%) died while 15 (2.9%) were transferred out. More males 321(62.2%) were affected with drug resistant TB than females. To establish the determinants of unfavourable treatment outcomes, 49 cases and 98 controls were enrolled into the study. Independent risk factors associated with unfavourable treatment outcome were; having primary or no education [AOR=4.1; 95% CI (1.7-9.8)]; poor housing [AOR=2.6; 95% CI (1.1-6.1)]; and CD4 count less than 200/µl [AOR=14.1; 95% CI (3.8-52.2)]. Taking 30 minutes or less on travelling to, or waiting for treatment less than at facility [AOR=0.32; 95% CI (0.12-0.83)] and availability of DOTs supporter daily [AOR=0.12; 95% CI (0.o2-0.57)] were found to be protective factors.
Conclusion
Unfavourable MDR TB treatment outcome, is cause by socio-demographic, behavioural, and health related factors. The interaction between the healthcare worker, patient and program factors are key in successful MDR TB treatment which should be decentralized

Keywords: *MDR TB, treatment outcome, determinants*

1. Introduction

Tuberculosis (TB) is a chronic human and other animal communicable disease caused by Mycobacterium *tuberculosis* and occasionally by *M.bovis, M.canetti and M.africanam* affecting almost all bodt organs. Tuberculosis is spread through droplet nuclei and is preventable and treatable disease (Mathema *et al.*, 20006; WHO, 2010).

Tuberculosis occurs in every part of the world. In 2011, WHO reported 8.7 million new TB patients and 1.4 million died from TB globally (WHO, 2012), and over 95% of the TB death occurring in low- and middle-income countries. Africa and Asia are the two continents with the highest incidence and death rate of TB per population unit. However, Sub-Saharan Africa carried the greatest proportion of new cases per population with over 270 cases per 100 000 population in 2010 (WHO, 2012). In Kenya the total number of TB cases (all forms of tuberculosis) reported in 2010 were 106,083. Kenya has a large and rising TB disease burden and is ranked 13th among the twenty-two countries that collectively contribute about 80% of the world's TB cases. As in the rest of Sub-Saharan Africa this large increase in TB is attributed primarily to the Human Immunodeficiency Virus (HIV) infection.

TB will still be among the 10 leading causes of global disease burden by the year 2020 (Mathema *et al*., 2006). This might be due to poverty, HIV/AIDS and the emergence and spread of drug resistance strains of TB particularly multi drug resistance (MDR) and extensive drug resistance (XDR) tuberculosis (Mathema *et al.*, 2006). The treatment of patients with MDR- and XDR-TB is complex, toxic and costly and less effective than treatment for other forms of TB. Also, the treatment outcomes of patients with MDR- and XDR-TB are greatly variable according to the different settings and regions of the world (Shean *et al*., .2008). A better understanding of risk factors associated with poor treatment outcomes among MDR- and XDR-TB patients would be useful in providing case management policies. Such data among MDRTB patients in Kenya is lacking.

2. Methodology

2.1. Study Site

The study was conducted in six facilities in four counties of Kenya. The sites are chosen because they were the first sites where MDRTB treatment was initiated in Kenya and with a cohort which had completed MDRTB treatment. These sites were Kenyatta National hospital (KNH) and MSH Belgium (Mathari) hospital in Nairobi County, Moi Teaching and Referral hospital (MTRH) in Uasin Gishu County, Portreitz hospital in Mombasa County, and Nyanza provincial hospital and Homabay district hospital in Kisumu County.

2.2. Study design

This was a case control study. Cases and controls were defined according to the WHO and the International Union Against Tuberculosis and Lung Disease (Union) recommended definitions. Cases were patients with treatment outcome classified as either default, treatment failure or died of any cause while on MDRTB treatment. Controls were patients with treatment outcome classified as either cured or treatment completed. For analysis purposes, cured and completed treatment cases were classified as favorable outcomes, where as death, default and treatment failure, were classified as unfavorable outcomes. All MDRTB patients from the study sites enrolled for treatment between 2008 and 2010 were identified and categorized according to their treatment outcome. Using MDRTB facility register eligible MDRTB patients were traced based on information available at their treatment sites. Structured interviews with former MDR-TB patients were conducted with additional information extracted from the patient's record cards or MDRTB register.

2.3. Study Population

Participants to the study were adult patients who were confirmed by culture as MDRTB patients and who started MDR TB treatment between 1st January 2008 and 31st December 2010.

2.4. Inclusion criteria

MDR TB enrolled for treatment between 1st January 2008 and 31st December 2010 who consented to the study. Patients who were transferred out were excluded from the study

2.5. Sample Size Determination

From studies, previous exposure to anti-TB drugs is a risk factor to treatment outcome. The proportion of cases and controls with previous treatment for TB was 71% and 47.1% respectively (Kliiman *et al*, 2009).

Using Fleiss formula (Fleiss, 1981), at 95% confidence, 5% absolute precision, a minimum sample size of **147** (49 cases and 98controls) were sampled.

2.6. Sampling Technique

The sample of cases and controls were selected from facility-based cat IV TB registers in the 4 counties. Simple random sampling was used. The number of patients sampled at health facilities was proportional to the clinic enrollment size. In situation where the participant died or defaulted and cannot be traced, data was collected from the DOT supporter or a family member.

2.7. Data collection tools and methods

Data was collected using a standard semi-structured questionnaire. The questionnaires were pre-tested and appropriate modifications made. With assistance of DTLC, trained interviewers were used to trace and conduct interviews from November 2013 to march 2014.Information was collected on basic socio-demographics characteristics, general clinical information and treatment outcome for all the enrolled patients, while additional information on nature of outcomes, was extracted from category IV registers.

2.8. Data Handling and Management

Data were coded during collection and Epi info version 3.5 statistical used for both data entry and analysis. A descriptive analysis was done based on frequency distribution of selected socio-demographic characteristics. Means, standard deviations and quartiles of selected study variables were obtained. The respondents were categorized into those that have un-favourable treatment (cases) and those who had favourable treatment outcome (controls). Crude Odd Ratio (COR), Yates corrected chi square test and Fishers exact test (where the count in some cells of the tables was less than 5) at 95% confidence interval (CI) and alpha level of significance set at 0.05 were used as measures of association in the analysis of factors associated with MDR-TB treatment outcome. An odds ratio (OR) of < 1 was considered protective while odds ratio of > 1 was considered a risk factor. An odds ratio equal to 1 indicated that there was no difference between cases and controls. Confidence interval was used to assess variability of the odds ratio. A 95% confidence interval that included 1 was interpreted to be not significant. Risk factor variables with P<0.05 were considered as having significant association with MDR-TB treatment outcome. Risk factors with P <0.05 in bi-variate analysis were entered into multivariate analysis where Stepwise backward elimination logistic regression was used to come up with the final "Best" model.

2.9. Ethical Considerations

Approval and clearance for this study was received from KEMRI national Scientific and Ethical Review Board, and hospitals administrative authorities, before commencement of the study. Written Informed consent was sought and obtained from the participants before administration of the questionnaires. Participation was voluntary.

3. Findings

3.1. Prevalence of drug resistance

During the study period, which ran from November 2013 to March 2014, scrutiny of national category IV register was done to assess the magnitude of resistance to anti-TB drugs and later use of the same register to select cases and controls. The total number of drug resistant TB patients diagnosed in CRL between 2008 and 2010 were 516. Three hundred and forty six (67 %) had favourable treatment outcome, 86 (16.7%) defaulted, 69 (13.4%) died while 15 (2.9%) were transferred out. Of the 516 patients 474 (92.2%) had MDR TB, 16 (3.1%) mono-resistance, 22 (4.3%) PDR TB, 2 (0.4%) XDR TB and 2 (0.4%) were not indicated. More males 321(62.2%) were affected with drug resistant TB than females.

3.2. Demographic factors

A total of 147 former patients were recruited; 49 cases and 98 controls. Cases had a mean age of 35.2 (SD=10.4) years, a median of 31 (IQR=26.0-37.0) years, while the controls had a mean age of 34.6 (SD=12.6) years and median of 32.0, (IQR=26.0-40.0) years. Majority of the study participants were in the economically productive age group, 21-45 years. More than one-half of the patients 91 (61.9%) were male. The mean age and range were 34.5 and 18-81 years respectively. Middle age group (30-49 years) was a significant risk factor (OR=2.1; CI=1.046-4.224; P=0.019) to un-favourable outcome. Majority were married 80 (54.4%) with those living with family at 52 (35.4%). Of the five facilities used, Blue house was the only privately owned facility while the other five were public. The number of participants were Port Reitz hospital 26 (17.7%), Nyanza PGH 8 (5.4%), MTRH 7 (4.8), HomaBay hospital 21 (14.3%), Blue House dispensary 40 (27.2%) and KNH 45 (30.6 %). Blue house dispensary was the only level two facility used for this study.

3.3. Socio-economic factors

Casual labour 52 (35.4%) was a common mode employment followed closely by self employment 51(34.7 %). Formal employment and no employment contribute 12.9 % and 17% respectively. Casual worker (COR=2.4: P=0.009) and formal employment (COR=0.33; P=0.041) were statistically significant factors. The level of education was predominantly either completed primary 63 (42.9%) or secondary 64 (43.5%). Tertiary level contributed 15 (10.2%) with the remaining having no education. Having primary education (COR=2.4; P=0.007) was a risk factor while secondary (COR=0.05; P=0.031)) level of education was protective factor.

Although there was less risk of unfavorable outcome when the distance travelled by patient was less than 2 km., the reduce risk was not significant (p =0.08). However when the distance travelled was 2.5 km or more, the risk of cases became approximately twice that travelled by controls (AOR=2.05; P <0.046). A similar observation was found in the mode of transport to the treatment site. Travelling using public means (Matatu) to TB treatment facility was a significant risk factor (AOR=3.63; P=0.028). No statistically significant difference was observed in motor cycle, bicycle or walking to facility between cases and controls. Those given transport token showed a non significant increase in risk. Though the longer the waiting time the higher the risk of being a case, the risk was statistically not significant. A significant protective factor was when the time taken to reach the facility was less than 20 minutes

(AOR=0.41; P=0.007). Though stoppage of medication due to lack of food was more common in case than in control group, the association was statistically not significant.

Permanent 59 (40.1%), semi-permanent 40 (27.2%) and temporary 48 (32.7%) structure were the categories of houses used. Cases were twice more likely to be living in a temporary (AOR==1.97; P=0.034) structures than controls. A history of the lack of housing (AOR=3.47; P=0.0022), being houseless for more than 2 weeks (AOR=4.42; P=0.0038) and living in either an earth walled house (AOR=2.39; P=0.0076) or earth floored house were risk factors for poor treatment outcome. Though houses roofed using tiles or iron sheet was protective against poor outcome, and those grass-thatched were risk factors, the associations were not significant. Instances of lack of house to live in occurred more frequently during the intensive phase18 (64.3%) and most lasted for a period less than 2 weeks 18 (66.6%). An unexpected finding in the study was observed in the amount of rent paid. When the rent was less than Ksh.2000, the risk of poor treatment outcome was higher (AOR=2.54; P=0.050) though not statistically significant. However, when the rent was higher at Ksh.3000 or more, it became a significant protective factor against poor treatment outcome (AOR=0.441; P=0.013). Most of the patients live in rental houses 101 (68.7%) while others were accommodated 40 (27.2%) or used personal 6(4.1%) houses. All the three variables were not significant (p-values 0.08, 0.161 and 0.35 respectively).

3.4. Behavioural factors associated with treatment outcome of MDRTB

Thirty three (22.4 %) of the MDRTB patients had history of alcohol use with 13 (8.8 %) still using alcohol. Cases were twice more likely to have history of alcohol use than controls (AOR=2.31; P=0.021). However among those who used alcohol majority 18 (54 %) drink 2-3 times weekly and 5(3.4%) drink more than 4 times weekly. There was a positive association between drinking alcohol 2-3 times weekly (AOR=2.53; P=0.042) with un-favourable outcome. Bursaa (traditional brew) 15(46.9%) and beer 10 (31.3%) are the common alcoholic drinks used. Twenty five (17%) had history of cigarette smoking with 20 (80%) smoking more than 4 sticks of cigarette daily. Smoking of more than 3 sticks of cigarette per day (COR=2.25; P=0.050) though risk factor was not statistically significant.

3.5. Health Service and Clinical Related Factors

Patient observations followed DOTS 136 (92.5%) which took place either in facility 110 (75.3%) or the community 26 (17.8%). There was no significant difference on treatment outcome on patients using facility (COR=0.77; P=0.25,) and community (COR=0.87; P=0.39) based DOTS plans. Despite the high level of DOTS program, 20 (13.6 %) reported missing to take MDR TB drugs during the course of treatment. This happened mainly in the first 2 moths 13 (65%) of treatment and for a short period of less than 4 weeks 10 (50%). Having history of missing to take MDRTB drugs was a risk factor (AOR=4.69; P=0.001). Similarly missing to take medication for more than 8 weeks was a strong risk factor (AOR=18.9; P<0.001). DOTs Observation was found to be a protective factor (AOR=0.162; P=0.006) against poor treatment outcome. However, giving a patient specific treatment supporter (AOR=0.544; P=0.103) and nutritional supplementation (AOR=0.926; P=0.407) were not significant protective factors. Occurrence of side effects, 13 (37.1%), lack of food, 5(14.3%), and pill burden 7 (20%) were the major cause of missing medication.

Baseline clinical status was generally poor with a mean weight of 51.4 kg and BMI of 18.5 or less being 49.3% at initiation of treatment. BMI of 18.5 and less (COR=2.30; P=0.011) and body weight of 40 Kgs and less (COR=2.85; P=0.015) were significant risk factors. There was high HIV test uptake 146 (99.9 %) which showed HIV-MDRTB co-infection rate was 25.2% (37) and ART uptake 91.9 % (34). Seventeen (50%) of co-infected patients had been started on ARV before initiation of MDRTB treatment. All HIV positive patients had CD4 count done giving a mean CD4 count of 174. The study found out that HIV positive status (AOR=2.414; P=0.013), CD4 count less than 200 (AOR=11.39; P<0.001) and delay of 8 weeks or more to start MDRTB treatment (AOR=3.80; P<0.001) were found to be risk factors to poor treatment outcomes. However, patients initiated on ART after the commencement of MDR TB treatment (COR=7.8; P= 0.004) and presence of history of chronic illness (AOR=2.48; P=0.015) were found to be significant risk factors.

An important unexpected finding is the fact that the previous type (category) of TB diagnosed were not significant determinants of MDR TB treatment outcomes. Failure after retreatment (COR=0.84; P=0.32), failure after first treatment 37 (COR=0.95; P=0.45) and primary MDR cases (COR=0.70; P=0.31) were not predictors of treatment outcome. There were only 2 XDR TB patients diagnosed and both died.

When factors found significant by bivariate analysis was subjected to multivariate analysis. Using unconditional logistic regression five variables were found to be independently associated with MDR TB treatment outcome in the study. CD4 count less than 200/µl (AOR=14.14; P<0.001) was the strongest risk factor associated with poor MDRTB treatment outcome in Kenya. Other independent risk factors were having none or primary education (AOR=4.10; P<0.01) and poor housing (AOR=2.6; P=0.04). Poor housing combined presence of temporary house, earthten floored and walled houses. Independent protective factors were availability of DOTS daily (AOR=0.12; AOR<0.01) and combine time of less than 30 minutes travelling to treatment site and less than 20 minutes waiting for treatment at the facility(AOR=0.32; P=0.02)

4. Discussion

The present study was designed to identify critical predictors of poor treatment outcomes in patients with MDR TB and XDR TB. In this study, the cure rate was 46.1 %, treatment completion rate 20.9 %, default 86 (16.7%) and death 69 (13.4). Transferred out were excluded. This completion rate is below the WHO target of 75% (WHO global report 2012.). However, this is comparable to the results seen previously in some studies (Kliiman et al., 2009, Kim et al 2001) in South Africa. However, this figure is relatively

lower in comparison to cure rates of about 60% observed in Denver, Netherlands, to over 80% seen in Hong Kong (Törün et al., 2005, Lambregts et al 1998, Narita et al., 2001). Even though treatment strategies were implemented according to WHO recommended MDR-TB treatment guidelines, the differences in social, demographic, economic, behavioral and clinical factors may make the treatment outcomes from different settings to vary considerably. This was the first cohort of MDR TB patients on treatment in Kenya.

4.1. Socio-Demographic Factors

The 2008-2010 cohort of MDR-TB affected mainly the economically active age group: 24-49 years, which was similar to the distribution of sputum smear positive TB cases in Kenya (DLTLD, 2007) and suggests similarities in the epidemiology of MDR and ordinary TB. The distribution of cases and controls across age groups was similar and just like in non resistant forms of TB; men (62.2 %) are more affected with MDR TB than women (37.8%). A study done by Ngungu et al. (2011) in Kenya (ITROMID) found out that a significantly greater number of males were diagnosed with pulmonary TB than females (60.4% and 39.5 % respectively; $P < 0.05$). This compares also with studies in Pakistan (Taha et al., 2009) , where drug resistance was associated with 70.9% males and 29.15% females, and also in Tanzania (Willy et al., 2008) where drug resistance was associated with 68% males and 32% females. Globally a 70% predominance of males over female patients was reported (Uplekar et al., 2001) The World Health Organization reported that 67.2% of the global male population was diagnosed with TB as compared to the female population (WHO 2008) The greater number of males compared to females could be attributed to behavioral factors such as smoking, which is a predisposing factor to TB with more males being smokers than females. Alcohol consumption, malnutrition (Lonnroth et al., 2009) and the delay in seeking medical treatment, especially by men (Rajeswari et al.,2002) are other factors that have been associated with higher numbers of males than females with TB. Despite the pre-dominance of male gender treatment outcomes were similar.

The type of employment could predict treatment outcome. A significantly large proportion of those casually employed, had a higher risk of poor treatment outcomes (COR= 2.4; P=0.009) as compared to formally employed (COR=0.334; P=0.650) who have higher chances of favourable treatment outcomes. This could be attributed to economic challenges faced by patients during the prolong MDR TB treatment. Due to ill health, casual workers loss their employment rendering him/her unable to sustain living costs e.g. transport and food expenses. It's due to this factor that made the DLTLD implement the policy that all the MDRTB patients received transport and nutritional support from TBCARE and GF (DLTLD annual report 2011). The present study confirms poverty significantly increases the risk of poor treatment outcome in MDRTB. This is in line with the results from previous study done in Uzbekistan Central Asia (Epco *et al.*, 2008) where individuals who were pensioners or unemployed had a higher risk for default compared to individuals who were employed by the government.

Receiving formal education has been associated with good health seeking behaviour. In this study having none (COR=8.62; P=0.04) or primary (COR=2.4, P= 0.007) level of formal education was associated with an increase risk of poor treatment outcome. Similarly, secondary education (COR=0.500; P= 0.031) and tertiary (COR=0.124; P=0.025) were protective factors in the bivariate analysis. The results were similar to that of Molly F and others (2008) who found out that low education level, and diagnosis with a psychiatric disorder significantly predicted death. However same study had contradictory finding when it comes to default of treatment.

Living in close proximity to a health facility has been associated with greater access to care and adherence to treatment. In this study, living more than 2.5 kilometers from the TB treatment site was risk factor against MDR-TB treatment outcome (COR= 2.050; P= 0.046) although this did not achieve statistical significance in multivariate analysis. A study in Nigeria (Erhabor et al., 2000) found out that living in close proximity to the chest clinic was associated with improved compliance to anti-tuberculosis drugs while in another study in rural South Africa living far from the hospital was associated with increased risk of death (Barker et al., 2002). Patients who live near the hospital are less likely to fail to collect their drugs or totally abandon their treatment. Similarly a significant protective factor to favourable treatment outcome was the time taken less than 30 minutes (COR= 0.4139; P= 0.007) to reach the TB treating facility. Unlike time of transport, the cost of transport to the treatment centre does not seem to have any effect on compliance to treatment (P=0.21). One possible reason could be that MDR TB patients were giving transport token to and from health facility and some patients were managed at the community level.

4.2. Behavioural Factors

Like other studies, (Corcoran, 1986, Ferrer., *et al* 1991) alcoholism was an important risk factor for poor MDR TB treatment outcome. Univariate analysis demonstrated that a higher likelihood of un-favourable outcome was significantly associated with history of alcohol use (COR=2.31; P= 0.021) and use of alcohol 2-3 times weekly (COR=2.53; P= 0.0417). Improving compliance among alcoholic patients is a challenge and should be addressed by seeking support from families and social organizations. Though the use of more than 4 cigarette per day was a risk factor (COR=2.29; P=0.050), the association was not statistically significant.

Substandard housing conditions—an indicator of poverty—predicted poor treatment outcome. Temporary house (COR=1.9; P=0.034), earthen walls (COR=2.39; P=0.0076) and houses with earthen floors (COR=3.33; P=0.0011) were significant risk factors to poor treatment outcome despite the provision of blanket socioeconomic support to most patients. It is possible that any underlying association between poverty and poor treatment outcome was reduced by aggressive programmatic efforts to alleviate socioeconomic barriers to care. Several descriptive and observational reports have demonstrated that elimination of treatment barriers or provision of incentives improves adherence to long-term therapies (Davidson. *et al.*, 2000.). Elucidating the ways in which poverty impairs a person's ability to complete long-term TB therapy, will permit refinement of interventions to facilitate treatment completion among

the poorest patients. Similarly, patients with history of lack of house during MDR TB treatment (COR=3.47; P= 0.0022) and having nowhere to live in for more than 2 weeks were significant predictors of poor treatment outcomes.

4.3. Health care and Clinical related Factors

Many studies (Shin. *et al.*, 2006, Molly et al., Molly. et al., 2008) have shown that poor nutrition state have an effect on treatment outcomes. In this study too, low body weight (less than 40 Kgs) at the initiation of treatment (COR=2.85; P=0.0149) and BMI less 18.5 (COR=2.30; P=0.011 were found to be significantly associated with poor treatment outcome. On the basis of the findings in the study and others, nutritional status is an important predictor of treatment outcomes and long-term survival of patients with MDR-TB. Micronutrient support (e.g., Vitamin A) and/or other interventions to enhance host response could potentially have a role in reducing poor treatment outcomes in severely malnourished patients. The provision of food and transportation incentives as well as increased social support to patients receiving TB treatment is supported by the WHO, (Maher.,et al200) and has been shown to improve outcomes in Russia and elsewhere, particularly through improved adherence to treatment.

This study showed that MDR TB co-infection with HIV increased the risk of poor treatment outcome (COR=2.41; P=0.013) by more than twice in the cases than controls. Such findings are similar to early results of treatment in Lesotho (seung. et al., 2009), where MDR-TB treatment outcomes in HIV-positive patients were likely to be significantly worse compared to HIV-negative patients. These results were also consistent with previous studies showing increased mortality in HIV-positive compared to HIV-negative patients in drug-susceptible TB (Murray et al., 1999, Nunn. et al 1998). A high rate of HIV co-infection is one of the major reasons for the high mortality rate among drug-susceptible TB patients in sub-Saharan Africa (Harries, 2001). Presence of other chronic illness in a patient on MDR TB treatment increases the risk of poor treatment outcome. In this study too, cases were more than twice (COR=2.68; P=0.005) likely to have had concurrent chronic illness than in controls.

We found that low CD4 cell count were the principal risk factors (COR=11.4; p-value<0.001) for poor treatment outcome and confirmed by multivariate analysis. . The low baseline CD4 cell count was strongly associated with poor treatment outcome of MDR-TB patients an association that has been previously demonstrated in patients with susceptible TB/HIV co-infection, (Lawn,et al 2009).

The use and timing of ART was a significant finding in this study. Starting ART treatment after initiation of MDR TB treatment were more likely to have a un-favourable treatment outcome(COR=7.8; P=0.004) when compared to those starting treatment before initiation of MDR TB treatment which reduces the risk of poor treatment outcome. Satti and others (2012) in a study in Lesotho found out that those who were not already on ART had a significantly shorter median time to death. Dheda et al (2010). showed that HIV-positive XDR-TB patients who never received ART had a higher mortality than those who were already on ART. In this cohort in Lesotho, nearly all HIV-positive patients not yet on ART were initiated on ART within several weeks of starting MDR-TB treatment. Nevertheless, the time to death in HIV-positive patients who were not already on ART prior to MDR-TB treatment was significantly shorter compared to HIV-positive patients who were already on ART. This indicated that early initiation of ART is indeed important. However patients who are severely immunosuppressed may take several months to show a benefit from ART. Recent WHO guidelines recommend that ART should be initiated 2–8 weeks after the start of MDR-TB treatment irrespective of CD4 cell count (WHO 2011).

Many national TB control programs worldwide have adopted the DOT strategy for tuberculosis control (Amukoye. 2008). Having a DOT observer daily during TB treatment was protective factor against poor MDR-TB treatment outcome (COR=0.167; P=0.007). Directly observed treatment for tuberculosis has been shown to have higher compliance and cure rate compared to self-administered therapy (Erhabor et al., 2000; Robert et al., 2004). These findings are similar to those in a case control study in Hong Kong (Law et al., 2008). DOT prevents treatment non-compliance since the treatment supervisor ensures that patient actually swallows the right dose of TB medicines, regularly and for the prescribed period. Alongside DOTS, a delay in initiation of MDR TB treatment was found out as a significant factor while assessing treatment outcome. A delay of more than 8 weeks increased the risk of poor treatment outcome to almost fourfold (COR=3.8; P value <0.001). The results show that early identification and treatment of MDR TB may reduce death and treatment failure and thus improve treatment success. This finding is consistent with those of Turett et al. (1995). The delay in initiation of MDRTB treatment results in treatment of patients with chronic disease, progressive parenchymal destruction, higher bacillary loads, and continuing transmission (Park et al 1993).

4.4. Limitations of the Study

This study was limited by several features. Because of the retrospective nature of this study, some data were missing for certain variables. We believe that data were randomly missing, conditional on other covariates. Data were more likely to be missing for patients who defaulted from treatment or died early; however, reasons for missing data were unlikely to be associated with unmeasured variables, because data were collected using forms that were universally required for patients.

Likewise, we were unable to identify individuals with alcohol and/or substance use disorders in a systematic, prospective manner. It is therefore possible that only the most severe cases of alcohol and drug disorders were identified. In addition, there may have been a bias toward documenting alcohol consumption among those individuals who were doing poorly on TB treatment.

Furthermore, the population treated in this cohort may not reflect the overall MDR-TB population in Kenya; these patients represent the earliest cohort to be enrolled in this program and may have different clinical and social characteristics compared with patients who were enrolled later.

In this study it was not possible to establish the cause effect relationship since both exposure and outcome had occurred at the time the study was conducted.

5. Conclusion and Recommendations

Unfavourable MDR TB treatment outcome, recognized as one of the main problems in tuberculosis control is cause by socio-demographic, behavioural, and clinical or health related factors. The interaction between the healthcare worker and the patient is a key factor in successful MDR TB treatment and should be organized in all Counties, in accordance with the country's health system and the patient's social needs. Patient support needs to be tailored in line with the patients' specific characteristics, culture, language level of education and socio-economic environment. The national DOTs protocol needs to be strengthened in all facilities together with management of other co-morbidities.

Systems that provide accessible and affordable MDR TB services for all patients need to be developed and strengthened. MDR TB treatment should be decentralized to all regions so that access barriers to MDR TB treatment are minimized and to reduce the time and distance taken to receive treatment.

5.1. Competing interests

The authors declare no competing interest. The funders (CDC) had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

5.2. Authors' contributions

All the authors listed in this article made contributions during the design of the study, data collection and interpretation, provided critique for intellectual content and gave final approval of the version submitted. **.**

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6. References

1. Mukherjee Joia S, Michael L Rich MD, Adrienne R, Felix Alcántara Virú MDc, Sonya S Shin MD , Jennifer J Furin MD, Mercedes C Becerra Donna J Barry NP Jim Yong Kim MD, Paul Farmer MD, Mary C Smith Fawzi ScD, Kwonjune J Seung MD; Programmes and principles in treatment of multidrug-resistant tuberculosis
2. Epco Hasker, Maksad Khodjikhanov, Shakhnoz Usarova, Umid Asamidinov,Umida Yuldashova, Marieke J van der Werf, Gulnoz Uzakova and Jaap Veen(2008): Default from tuberculosis treatment in Tashkent, Uzbekistan; Who are these defaulters and why do they default?
3. Morisky, D. E., Nyamathi, A., Sneed, C. D. &, Liu, K. Y. (1998). Health education improves tuberculosis control in county health clinics. International Conference on Emerging Infectious Diseases. NLM Gatew. 8.11
4. Erhabor, G. E., Aghanw, H. S., Yusuph, M., Adebayo, R. A., Arogundade, F. A. & Omidiora, A. (2000). Factors influencing compliance in patients with tuberculosis on directly observed therapy at Ile-Ife, Nigeria. East Afr Med J 77(5), 235-239.
5. Barker, R. D., Nthangeni, M. E. & Millard, F. C. (2002). Is the distance a patient lives from hospital a risk factor for death from tuberculosis in rural South Africa? Int J Tuberc Lung Dis 6(2). 98-103.
6. Corcoran R (1986): Compliance with chemotherapy for tuberculosis. Irish Med J; 79: 87–90.
7. Ferrer X, Kirschbaum A, Toro J, et al. 1991): Compliance with chemotherapy for tuberculosis in adults in Santiago, Chile. Bol Oficina Sanit Panam; 111: 423–431.
8. Davidson H, Schluger NW, Feldman PH, et a (2000). The effects of increasing incentives on adherence to tuberculosis directly observed therapy. Int J Tuberc Lung Dis; 4:860–5.
9. Shin, A. D. Pasechnikov, I. Y. Gelmanova, G. G. Peremitin,¶ A. K. Strelis,Y. G. Andreev, V. T. Golubchikova,¶ T. P. Tonkel, G. V. Yanova, M. Nikiforov, A. Yedilbayev,‡J. S. Mukherjee, J. J. Furin,*†‡ D. J. Barry,* P. E. Farmer,*†‡ M. L. Rich,*‡ S. Keshavjee (2006): Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia; int j tuberc lung dis 10(4):402–408
10. Maher D, Gupta R, Uplekar M, Dye C, Raviglione M (2000). Directly observed therapy and treatment adherence. Lancet; 356: 1031–1032
11. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P (1999) Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. Am J Respir Crit Care Med 159: 733–740.
12. Nunn P, Brindle R, Carpenter L, Odhiambo J, Wasunna K. (1992) Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality. Am Rev Respir Dis 146: 849–854.

13. Harries AD, Hargreaves NJ, Gausi F, Kwanjana JH, Salaniponi FM (2001: High early death rate in tuberculosis patients in Malawi. Int J Tuberc Lung Dis 5: 1000–005.
14. Lawn SD, Little F, Bekker LG,(2009). Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. Aids. 2009; 23:335–42. [PMC free article] [PubMed].
15. Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, et al. (2012): Outcomes of Multidrug-Resistant Tuberculosis Treatment with Early Initiation of Antiretroviral Therapy for HIV Co-Infected Patients in Lesotho. PLoS ONE 7(10): e46943. doi:10.1371/journal.pone.0046943
16. Turett GS, Telzak EE, Torian LV, Blum S, Alland D, Weisfuse I, (1995). Improved outcomes for patients with multidrug-resistant tuberculosis. Clin Infect Dis. 21:1238–44.
17. Park MM, Davis AL, Schluger NW, Cohen H, Rom WN (1993). Outcome of MDR-TB patients, 1983–1993. Prolonged survival with appropriate therapy. Am J Respir Crit Care Med.; 153:317–24.
18. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, et al. (2010) Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet 375: 1798–1807. doi: 10.1016/s0140-6736(10)60492-8
19. Amukoye. (2008). Multi drug resistant tuberculosis: A challenge in the management of tuberculosis. Afr J Health Sci. 15. 6-13.
20. Gandhi NR, Andrews.JR, Brust. JCM, Montreuil R, Weissman1D, Heo M, AP Moll, Friedland GH, and Shah NS (2012): Risk Factors for Mortality among MDR- and XDR-TB Patients in a High HIV-Prevalence Setting; Int J Tuberc Lung Dis. 2012 January ; 16(1): 90–97. doi:10.5588/ijtld.11.0153.
21. Kim HJ, Hong YP, Kim SJ, Lew WJ, Lee EG (2001). Ambulatory treatment of multidrug-resistant pulmonary tuberculosis Patients at a chest clinic. Int J Tuberc Lung Dis 1; 51129–1136.
22. Lambregts-van Weezenbeek, C. S. B., H. M. Jansen, N. J. D. Nagelkerke, B. van Klingeren, and J. Veen (1998). Nationwide surveillance of drug-resistant tuberculosis in The Netherlands: rates, risk factors and treatment outcome Int J Tuberc Lung Dis; 2: 288-295.
23. Narita M, Alonso P, Lauzardo M, Hollender ES, Pitchenik AE, Ashkin D (2001). Treatment experience of multi-drug resistant tuberculosis in Florida, 1994-1997. Chest; 120: 343-348.
24. World Health Organization (WHO 2012). Global tuberculosis report 2012. Geneva: WHO: Available from: http://apps.who.int/ iris/bitstream/10665/75938/1/9789241564502
25. Taha N, Hamed A, Qurechi JA, Ahmad B, Abraham S (2009) Rifampicin resistance profile of Mycobacterium tuberculosis isolated from human patients. Proc Pakistan Acad Sc 46: 131-136
26. World Health Organization (2011) Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: WHO.
27. Willy U, Fernand M, Eduardo V, Gernard M, Candida M, Ronald B, Elma S, Wafaie F (2008) Primary antimicrobial resistance among Mycobacterium tuberculosis isolates from HIV seropositive and HIV seronegative patients in Dar es Salaam Tanzania. BMC (Research Notes) 1: 58.
28. Uplekar MW, Rangan S, Weiss MG, Ogden J, Borgdorff MW (2001) Attention to gender issues in tuberculosis control. Int J Tuberc Lung Dis 5: 220-224.
29. Erhabor, G. E., Aghanw, H. S., Yusuph, M., Adebayo, R. A., Arogundade, F. A. & omidiora, A. (2000). Factors influencing compliance in patients with tuberculosis on directly observed therapy at Ile-Ife, Nigeria. East Afr Med J 77(5), 235-239.
30. Law, W. S., Yew, W. W., Chiu Leung, C., Kam, K. M., Tam, C. M., Chan, C. K. & Leung, C. C.,(2008): Risk factors for multidrug resistant tuberculosis in Hong Kong. Int J. Tuberc Lung Dis 12 (9).1065-1070.
31. Robert, M. J., Christopher B. S., Gonzalez, L. C., Kawamura, M., Osmond, D. H. & Daley, C. L. (2004). TB Treatment Outcomes Directly Observed Therapy Compared with self administered Therapy. Am J Respi crit Care Med 170.561-566.
32. Lonnroth K, Juramillo E, Williams B, Dye C, Raviglione M (2009) Drivers of tuberculosis epidemics. The role of risk factors and social determinants. Social science and medicine 68(: 2240-2246. Available http://www.sciencedirect.com/science/article/pii/SO2777953609002111. Accessed 8 November 2011.
33. Rajeswari R, Chandrasekaran V, Suhedev M, Sivasubramaniam S, Sudha G, Rehu G (2002) Factors associated with patient and health system delays in diagnosis of tuberculosis in South India. Int J Tub Lung Dis 6: 789-795.
34. Perpetual Wangui Ndung'u, Samuel Kariuki, Zipporah Ng'ang'a, Gunturu Revathi (2011):
35. Resistance patterns of Mycobacterium tuberculosis isolates from pulmonary tuberculosis patients in Nairobi. J Infect Dev Ctries 2012; 6(1):33-39

Treatment Outcome	Frequency	% frequency
Cured	238	46.1
Treatment Completed	108	20.9
Defaulted	86	16.7
Died	69	13.4
Transferred out	15	2.9
Total	516	100

Table 1: Treatment outcomes of MDR TB patients: 2008-2010
Source: DLTLD category IV Register

variable	Cases N=49	Controls N=98	OR	CI	P-value
	Gender				
Male	30 (61.2)	61 (62.2)	0.958	0.473-1.9381	0.4512
Female	19 (33.9)	37 (66.1)	1.044	0.516-2.116	0.4512
	Education				
none	4	1	8.62	0.941-79.36	0.04
primary	28	35	2.4	1.911-4.84	.007
secondary	16	48	0.50	0.2467-1.034	0.031
Tertiary	1	14	0.124	0.0159-.98	0.025
	occupation				
None	7	18	0.7407	0.286-1.914	0.221
Casual	24	28	2.4	1.178-4.887	0.009
Self employed	15	36	0.7598	0.364-1.581	0.2
Formal employment	3	16	0.3342	0.092-1.208	0.041
	weight				
<40 Kgs	12	10	2.8541	1.131-7.182	0.0149
	BMI				
<18.5	31	42	2.2963	1.13-4.648	0.011

Table 2: Demographic characteristics of MDR-TB cases and controls, Kenya: 2008-2010

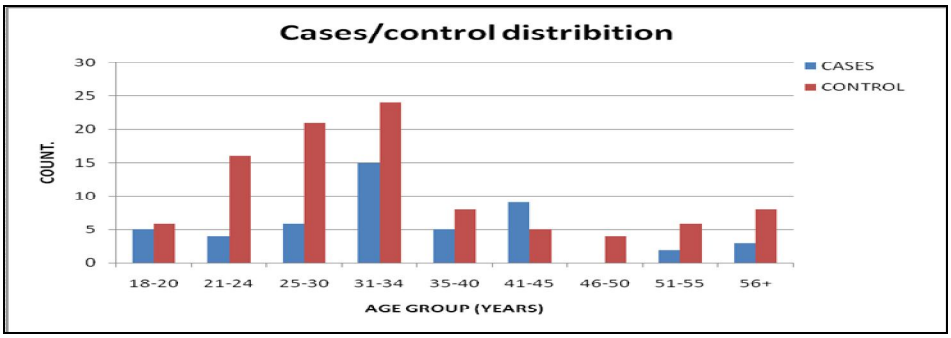

Figure 1: Age Group Distribution of Cases and Controls Kenya 2008-2010

variable	Cases n (%)	Controls n (%)	OR	95 %CI Lower-Upper	P-value
Living with					
alone	11 (22.4)	38 (77.6)	1.4836	0.6286-3.50	0.188
Family	14 (28.6)	35 (71.4)	0.6316	0.3010-1.32	0.11
Friend	3 (6.1)	46 (93.9)	0.5739	0.2425-1.86	0.219
Parent/guardian	7 (14.3)	42 (85.7)	1.00	0.3752-2.66	0.499
Relative	14(28.6)	35 (71.4)	1.56	0.7074-3.44	0.14
Alcohol					
History of use (yes)	16 (32.7)	33 (67.3)	2.3102	1.044-5.108	0.021
Never used alcohol	33 (67.3)	16 (33.3)	0.4329	0.196-0.955	0.021
2-3 times weekly	9 (18.4)	40 (81.6)	2.5313	0.910-7.039	0.0417
Cigarette					
History of use(yes)	11 (22.4)	38 (77.6)	1.7368	0.722-4.178	0.114
Cigarette sticks>4	10 (20.4)	39 (79.6)	2.2564	0.869-5.858	0.050
House ownership					
Accommodated	17 (34.7)	23 (23.5)	1.73	0.817-3.672	0.08
Personal	1 (2.0)	5 (5.1)	0.39	0.044-3.41	0.35
Rental	31 (63.3)	70 (71.4)	0.69	0.330-1.43	0.161
Type of house					
Permanent	11 (22.4)	38 (77.4)	0.3015	0.138-0.657	0.0014
Semi-permanent	17 (34.7)	32 (65.3)	1.7323	0.8173-3.67	0.079
Temporary	21 (42.9)	28 (57.1)	1.9722	0.962-4.046	0.034
No housing period					
Yes	16 (32.7)	33 (67.3)	3.4747	1.486-8.124	0.0022
Duration- no house					
>2 weeks	6 (12.2)	43 (87.8)	4.4186	1.053-18.50	0.038
wall made of					
bricks	8 (16.3)	41 (83.7)	1.3984	0.530-3.685	0.251
earth	29 (59.2)	20 (40.8)	2.3905	1.179-4.819	0.0076
stones	3 (6.1)	46 (93.9)	0.1745	0.031-0.371	0.00008
wooden	9 (18.4)	40 (81.6)	1.6125	0.628-4.136	0.166
roof made of					
Grass-thatched	17(34.70	32 (65.3)	1.5513	0.737-3.261	0.127
Iron sheets	30 (61.2)	19 (38.8)	0.8388	0.411-1.705	0.314
tiled	2 (4.1)	47 (95.9)	0.7915	0.148-4.233	0.571
floor made of					
cemented	19 (38.8)	30 (61.2)	0.4011	0.198-0.811	0.0056
earthen	21(42.9)	28 (57.1)	3.3333	1.554-7.146	0.0011
tiled	3 (6.1)	46 (93.9)	0.5739	0.150-2.189	0.3125
wooden	6 (12.2)	43 (87.8))	1.2279	0.418-3.600	0.3521
rental charges					
<Ksh 2000	8 (16.3)	41 (83.7)	2.5366	0.862-7.464	0.050
>Ksh 3000	15 (30.6)	34 (69.4)	0.4412	0.213-0.911	0.013

Table 3: Social- behavioural factors related to MDR treatment outcome 2008-2010

VARIABLE	control n (%)	CONTROL n (%)	COR	95 % CI	P-VALUE
Dots location					
Community based	8 (16.3)	18 (18.4)	0.867	0.348-2.16	0.39
Facility based	35 (71.4)	75 (76.5)	0.767	0.353-1.66	0.253
None	5 (10.2)	3 (3.1)	3.60	0.83-15.73	0.089
Dots availability					
Daily (Yes)	41 (83.7)	95 (96.9)	0.1618	0.041-6.41	<0.007
Given specific Supporter (yes)	39 (79.6)	86 (87.8)	0.5442	0.217-1.36	0.1034
Missed treatment due to Facility- closed	9 (18.4)	13 (13.3)	1.4712	0.581-3.72	0.231
Counsel on TB Treatment (yes)	42 (85.7)	79 (80.6)	1.443	0.562-3.71	0.231
Type of TB					
FFT	12 (24.5)	25 (25.5)	0.9470	0.428-2.09	0.451
FRT	28 (57.1)	60 (61.2)	0.8444	0.421-1.69	0.318
NEW	4 (8.2)	11 (11.2)	0.7030	0.212-2.33	0.296
CHRONIC ILLNESS					
Yes	16 (32.7)	16 (16.3)	2.48	1.114-5.54	0.015
HIV status					
HIV positive	18(36.7)	19 (19.4)	2.4143	1.121-5.19	0.013
DRUG RESISTANCE					
Ethambutol (yes)	12 (24.5)	32 (32.7)	0.6689	0.308-1.45	0.158
Pyrazinamide (yes)	4 (8.2)	10 (10.2)	0.7822	0.232-2.63	0.472
Drug missing phase					
<1st 2 weeks	8(72.7)	5 (83.3)	0.533	0.043-6.65	0.555
> 8 weeks	5 (38.5)	1 (5.1)	3.750	0.342-41.1	0.277
To start treatment					
≤4 weeks	5(10.2)	6 (6.1)	1.742	0.504-6.02	0.282
> 8 weeks	18 (36.7)	13 (13.3)	3.796	1.666-8.65	< 0.001

Table 4: Clinical and health related factors related to MDR treatment outcome 2008-2010

Term	Odds Ratio	95% lower	C.I. upper	Coefficient	S. E.	Z-Statistic	P-Value
AVAILABILITY(DOTs)DAILY (Yes/No)	0.1208	0.0256	0.5700	-2.1139	0.7917	-2.6700	0.0076
CD4 <200/$_{ul}$ (Yes/No)	14.1378	3.8327	52.1503	2.6489	0.6660	3.9774	0.0001
EDUCATION LOWER (Prim. or none) (Yes/No)	4.0991	1.7086	9.8341	1.4108	0.4465	3.1598	0.0016
POOR_HOUSING- (temporary/earthen wall/floor) (Yes/No)	2.5552	1.0646	6.1328	0.9381	0.4467	2.1001	0.0357
TIME taken to get treatment (Yes/No)	0.3169	0.1208	0.8309	-1.1492	0.4919	-2.3365	0.0195

Table 5: Final "Best Fit" model of unconditional logistic regression on determinants of MDR-TB treatment outcome in Kenya: 2008-2010