PREDICTORS OF POOR TREATMENT OUTCOMES FOR DRUG RESISTANT TUBERCULOSIS IN EASTERN UGANDA:

A retrospective cohort study

Damalie NAMUYODI, BSc HSM, DPPM

BU/GS15/MPH/15

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF MASTER OF PUBLIC HEALTH OF BUSITEMA UNIVERSITY

2017

Table of contents

DECLARATION

I, Namuyodi Damalie Waiswa, declare that this dissertation represents my own work except where due acknowledgement has been made in partial fulfillment for the award of the Master's degree in Public Health of Busitema University, 2017. It has not been previously presented or submitted to this university as a research project or any other institution for partial fulfillment of any qualification.

SIGNATURE..... DATE.....

DISSERTATION APPROVAL

This thesis is submitted as a partial fulfillment for the award of a Master's degree in Public Health from Busitema University with our approval as supervisors.

1. Dr. Jayne Byakika-Tusiime, PhD (University of California Berkeley, USA)

   Head, Department of Public Health

   Senior Lecturer

   Busitema University Faculty of Health Sciences

SIGNATURE .....DATE..... 04/09/2017

2. Dr. Samuel Kasozi, MBchB (MuK), MIPH (University of Queensland, Australia)

   Deputy Chief of Party, TRACK TB

   Management Sciences for Health, Bugolobi, Kampala

SIGNATURE ..... DATE 4th September, 2017

DEDICATION

To my dear husband Stephen Waiswa for the words of encouragement, moral and financial support together with my sons and the church family for standing with me during my studies. This is for you. Thanks for being there for me throughout the entire Master's program.

ACKNOWLEDGEMENT

I hereby express my gratitude to the Almighty God for the good health, opportunity and strength to go through the research process and dissertation report writing, so to HIM I give all the glory.

My thanks go to the RUFORUM Nurturing Grant through the Directorate of Post Graduate Studies, Busitema University for contributing to the funding of this research.

I would like to extend enormous gratitude to my supervisors, Dr Jayne Byakika Tusiime and Dr Samuel Kasozi for their absolute guidance, assistance and encouragement through the ups and downs on the proposal writing, research and dissertation report writing.

I would also like to thank the entire fraternity of the Busitema University Faculty of Health Sciences, and specially the lecturers in the Department of Public Health for their support and encouragement in my pursuit of this course.

In particular, I acknowledge the tremendous contribution of the National Tuberculosis and Leprosy Programme and continuous support towards the DR TB treatment facilities where the data collection was done.

My gratitude goes to the DR TB facility teams, the research assistants for the data collection, and Mr Okello Francis and team for their tireless support during the data analysis.

Special Thanks go to the administration of Mbale Regional Referral Hospital for bearing with me studying as I work and more especially to my TB Unit team for standing with me, bearing with my situation and encouragement.

To all of you, may God bless you abundantly!!

LIST OF TABLES

LIST OF FIGURES

LIST OF ACRONYMS AND ABBREVIATIONS

ART	Antiretroviral therapy
ATT	Anti Tuberculosis Treatment
DM	Diabetes Mellitus
DOT	Directly Observed Therapy
DR-TB	Drug Resistant Tuberculosis
HIV	Human Immuno-deficiency Virus
MDR-TB	Multi-drug Resistant Tuberculosis
MOH	Ministry of Health
MUAC	Mid Upper Arm Circumference
NTLP	National Tuberculosis and Leprosy Program
PMDT	Programmatic Management of Drug Resistance Tuberculosis
RPMT	Regional Performance and Management Team
RR-TB	Rifampicin Resistant Tuberculosis
RRH	Regional Referral Hospital
SDG	Sustainable Development Goal
SLID	Second line Injectable anti TB Drugs
SSA	Sub Saharan Africa
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis

OPERATIONAL DEFINITIONS [1-4]

The following are the operational definitions for RR-TB/MDR-TB/XDR-TB patients treated using second-line TB treatment:-

Term	Operational definition
Mono-resistance	Resistance to one first-line anti-TB drug only.
Poly-resistance	Resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.
Multidrug resistance (MDR)	Resistance to at least both isoniazid and rifampicin.
Extensive drug resistance (XDR)	Resistance to any fluoroquinolone and to at least one of three injectable second-line drugs (Amikacin, Capreomycin, or Kanamycin), in addition to Rifampicin and Isoniazid (multi-drug resistance).
Rifampicin resistance (RR-TB)	Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs; included any resistance to rifampicin in the form of mono-resistance, poly-resistance, MDR, or XDR.
Pre-XDR	A patient was diagnosed as MDR-TB with a DST result showing resistance to a fluoroquinolone (FLQ) or any of the Injectable Second Line Drugs (SLDs).
Cured	A patient who completes treatment without evidence of failure and remains consistently culture-negative with three or more consecutive cultures taken at least 30 days apart after the intensive phase.
Treatment completed	A patient who completes treatment without evidence of failure but has no record that three or more consecutive negative cultures taken at least 30 days apart after the intensive phase.
Lost to follow-up (LTF)	A patient whose treatment was interrupted for 2 consecutive months or more without medical reason.
Died	A patient who dies for any reason during the course of treatment.
Successful treatment	The sum of pulmonary TB patients with bacteriologically confirmed TB at the beginning of treatment who successfully completed treatment, whether with bacteriological evidence of success ("cured") or without ("treatment completed").
Treatment failure	When treatment is stopped (at any time) or need for permanent regimen change of at least two anti-TB drugs (in continuation phase) because of lack of culture conversion within 6 months on intensive phase, or bacteriological reversion in the continuation phase after culture conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable or due to drugs adverse drug reactions (ADRs).

Not evaluated	A patient for whom no treatment outcome is assigned and treatment outcome is unknown.
Sputum smear conversion:	Defined as the first two consecutive negative sputum smears in patients who were smear-positive at diagnosis.
Time to culture conversion	Defined as time from treatment start to the date of the first of two consecutive negative cultures whose sputum samples were collected 30 days apart.
Culture reversion (to positive)	When, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. Culture reversion is only is only considered when it occurs in the continuation phase.
Treatment initiation facility	Both inpatient and ambulatory care facilities that initiate and offer "start-to-finish" case management oversight for DR-TB in the region.
Follow up facility	Any public or private health facility identified and accepted to offer DOT to patients on DR TB treatment after being enrolled into care at an initiation facility.
Cohort:	A group of TB cases registered and monitored over a specific period of time, most commonly in the same calendar year; January to December-referred to as an annual cohort.

ABSTRACT

Background

The outcome of treatment in drug resistant tuberculosis (DR-TB) patients is often poor, but predictors of poor treatment outcome have remained obscure. Uganda is one of the 30 high TB/HIV burden countries in the world. The Uganda multidrug resistant tuberculosis (MDR-TB) treatment success rate dropped from 82% among patients enrolled into care in 2012 to 74% among the 2013 cohort and the mortality rate increased from 11% in the 2012 cohort to 18% in the 2013 cohort. I assessed treatment outcomes and predictors of poor treatment outcome among DR-TB patients in Eastern Uganda in order to identify enabling and disabling factors that would inform MDR TB intervention programs to ensure better treatment outcomes.

Methods

A retrospective cohort study was conducted using data from four selected DR TB treatment initiation hospitals in Eastern Uganda: Iganga, Mbale, Soroti and Lira. All DR-TB patients who initiated TB treatment between June 2013 and December 2016 were included in the study. Data were abstracted from DR TB register and patients' files using a data abstraction form. Data from the records of 269 DR-TB patients were analyzed using STATA version 14. Univariate, bivariate and multivariable analyses were done. Outcomes were evaluated at 6, 12 and 24 months.

Results

The median age was 37 years, and 62.4% were female. DR-TB/HIV co-infection was at 54.7% (147). Overall, 69% (203) of patients had favorable treatment outcomes. Death, loss to follow up, not evaluated and failure rates among the study participants were 32 (11.9%) of which 50% of the deaths occurred in the first 6 months of treatment, 9 (3.3%), 24 (8.9%) and 1 (0.3%) respectively.

Predictors of poor treatment outcomes were negative HIV status (OR 0.39, 95% CI 0.20-0.76), Directly Observed Treatment (DOT) model of care (OR 0.11, 95% CI 0.05-0.23), DOT site (OR 3.8, 95% CI 1.65-8.76) and drug unavailability (OR 2.7, 95% CI 1.20-5.95). The majority of the MDR TB patients (n=193, 71.7 %) had prior exposure to TB treatment, and 66 (25%) of MDR TB patients on treatment had poor outcomes. The community based DOT model of care yielded more treatment success (195/207 (94.2%)) compared to the facility based model (10/207 (4.8%)).

Conclusion

The treatment success of DR TB patients in Eastern Uganda is lower than the global and national targets. This can be majorly attributed to the high death rates. My study shows that being on DOT does not translate to favorable treatment outcomes centrally to what is globally known. The high proportion of unevaluated patients also plays a significant role in the low treatment success rate just as the irregular supply of medicines.

It is recommended that the TB program reviews the DOT model of care and ensure constant drug supply.

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Introduction

Tuberculosis (TB) is a bacterial infection caused by mycobacterium tuberculosis and most often affects the lungs (pulmonary TB) though it could affect other organs (extra-pulmonary TB) [5]. The emergence of resistance to anti-tuberculosis drugs, and particularly multi drug resistance tuberculosis (MDR-TB), has become a major public health problem in many countries and an obstacle to effective global TB control [6, 7]. Globally, the incidence of drug resistance to anti-TB drugs has increased since the first treatment for TB was introduced in 1943. The emergence of MDR-TB followed the widespread use of rifampicin beginning in the 1970s, and led to the need for new regimens using second-line drugs[8].

Drug resistant tuberculosis (DR-TB) is said to occur when TB organisms grow in the presence of one or more anti-TB drugs. MDR-TB is one of the forms of DR-TB that is said to occur when there is resistance to both isoniazid and rifampicin- the two most efficacious drugs in the treatment of TB. The term extensively drug resistant tuberculosis (XDR-TB) describes MDR-TB strains with additional resistance to any fluoroquinolone and at least any of the three injectable second-line drugs (SLIDs) - (Kanamycin, Capreomycin, or Amikacin)[2].

Although its causes are microbial, DR-TB is essentially a man-made problem. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become dominant in a patient infected with TB[8]. Ongoing transmission of established drug resistant strains within a population is also a significant source of new drug-resistant cases, often in populations

REFERENCES

1. Ministry of Health, U., *The Uganda National Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*, N.T.a.L. Program, Editor 2016.
2. World Health Organization, W., *Definitions and reporting framework for tuberculosis*. 2013: p. 40.
3. World Health Organization, ed. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*. 2014: Geneva, Switzerland.
4. World Health Organization, W., *WHO treatment guidelines for drug-resistant tuberculosis*. 2016 update.
5. James J. Champoux, F.C.N., W. Lawrence Drew, James J. Plorde,, *Sherris Medical Microbiolgy An Introduction to Infectious Diseases*. 4TH ed. 2004: McGraw-Hill, Medical Publishing Division.
6. Ducati, R.G., et al., *The resumption of consumption : a review on tuberculosis*. Memórias do Instituto Oswaldo Cruz, 2006. **101**: p. 697-714.
7. Matteelli, A., et al., *Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control*. Expert Rev Anti Infect Ther, 2007. **5**(5): p. 857-71.
8. Colijn, C., et al., *Spontaneous Emergence of Multiple Drug Resistance in Tuberculosis before and during Therapy*. PLoS ONE, 2011. **6**(3): p. e18327.
9. World Health Organization, W., *Guidelines for the programmatic management of drug-resistant tuberculosis*. 2011 update.
10. Lim, S.S., et al., *A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010*. The lancet, 2013. **380**(9859): p. 2224-2260.
11. World Health Organization, W., *Global Tuberculosis Report*. 2015.
12. Lukoye, D., et al., *Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis*. BMC Public Health, 2015. **15**: p. 291.
13. Cohen, T., et al., *On the spread and control of MDR-TB epidemics: an examination of trends in anti-tuberculosis drug resistance surveillance data*. Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy, 2014. **17**(0): p. 105-123.
14. Prasad, R., N. Gupta, and M. Singh, *Multidrug resistant tuberculosis: trends and control*. Indian J Chest Dis Allied Sci, 2014. **56**(4): p. 237-46.
15. World Health Organization, W., *Global Tuberculosis Report*, 2016: Geneva, Switzerland.
16. National Tuberculosis and Leprosy Control Programme, N., *Report on the Population-based Survey of Prevalence of Tuberculosis Disease in Uganda: 2014-15.*, 2015.
17. programme, N.T.a.L., *Uganda NTLP report*, 2015.
18. Lukoye, D., et al., *Anti-Tuberculosis Drug Resistance among New and Previously Treated Sputum Smear-Positive Tuberculosis Patients in Uganda: Results of the First National Survey*. PLoS ONE, 2013. **8**(8): p. e70763.
19. MInistry of Health, U., *Revised National Strategic Plan 2015/16 - 2019/20*, National Tuberculosis and Leprosy Control Programme, Editor 2017.
20. WHO, *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 GLOBAL REPORT ON SURVEILLANCE AND RESPONSE*, 2010.
21. Pinto, L. and D. Menzies, *Treatment of drug-resistant tuberculosis*. Infect Drug Resist, 2011. **4**: p. 129-35.
22. Kliiman, K. and A. Altraja, *Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB*. European Respiratory Journal, 2009. **33**(5): p. 1085-1094.
23. (WHO), W.H.O., *Tuberculosis Facts*. 2015.

24. Loddenkemper, R.L., R); Sagebiel, D (Sagebiel, D); Brendel, A (Brendel, A), *Strategies against multidrug-resistant tuberculosis.* EUROPEAN RESPIRATORY JOURNAL, 2002. **20** (36): p. 66S-77S.
25. Chan, E.D. and M.D. Iseman, *Multidrug-resistant and extensively drug-resistant tuberculosis: a review.* Curr Opin Infect Dis, 2008. **21**(6): p. 587-95.
26. Espinal, M.A., et al., *Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries.* JAMA, 2000. **283**(19): p. 2537-45.
27. Sharma, S.K., et al., *Prevalence of multidrug-resistant tuberculosis among newly diagnosed cases of sputum-positive pulmonary tuberculosis.* The Indian Journal of Medical Research, 2011. **133**(3): p. 308-311.
28. World Health Organization, *Monitor and evaluate MDR-TB case detection and treatment. Module G: Management of Drug-Resistant Tuberculosis Training for Health Facility Staff, Draft training module.* 2009, Geneva, Switzerland.
29. Basit, A., et al., *Predictors of Two Months Culture Conversion in Multidrug-Resistant Tuberculosis: Findings from a Retrospective Cohort Study.* PLOS ONE, 2014. **9**(4): p. e93206.
30. Yew, W.W., et al., *Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens.* Chest, 2000. **117**(3): p. 744-51.
31. Lukoye, D., et al., *Variation and risk factors of drug resistant tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis.* BMC Public Health, 2015. **15**(1): p. 291.
32. Andrews, J.R., et al., *Predictors of Multidrug- and Extensively Drug-Resistant Tuberculosis in a High HIV Prevalence Community.* PLOS ONE, 2011. **5**(12): p. e15735.
33. Kiwanuka, S., et al., *Access to and utilisation of health services for the poor in Uganda: a systematic review of available evidence.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 2008. **102**(11): p. 1067-1074.
34. Chung-Delgado, K., et al., *Mortality among MDR-TB Cases: Comparison with Drug-Susceptible Tuberculosis and Associated Factors.* PLoS ONE, 2015. **10**(3): p. e0119332.
35. Pooran, A., et al., *What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa?* PLOS ONE, 2013. **8**(1): p. e54587.
36. Patel, S.V., et al., *Treatment outcome among cases of multidrug-resistant tuberculosis (MDR TB) in Western India: A prospective study.* J Infect Public Health, 2016. **9**(4): p. 478-84.
37. Meressa, D., et al., *Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study.* Thorax, 2015.
38. Muñoz-Torrico, M., et al., *Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data.* Revista Portuguesa de Pneumologia (English Edition), 2017. **23**(1): p. 27-30.
39. Rifat, M., et al., *Development of multidrug resistant tuberculosis in Bangladesh: a case-control study on risk factors.* PLoS One, 2014. **9**(8): p. e105214.
40. Sharma, S.K., et al., *Prevalence of multidrug-resistant tuberculosis among Category II pulmonary tuberculosis patients.* The Indian Journal of Medical Research, 2011. **133**(3): p. 312-315.
41. He, X.-c., et al., *Epidemiological Trends of Drug-Resistant Tuberculosis in China From 2007 to 2014: A Retrospective Study.* Medicine, 2016. **95**(15): p. e3336.
42. Tang, S., et al., *Risk Factors for Poor Treatment Outcomes in Patients with MDR-TB and XDR-TB in China: Retrospective Multi-Center Investigation.* PLOS ONE, 2013. **8**(12): p. e82943.
43. Ahmad, N., et al., *Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance.* Int J Tuberc Lung Dis, 2015. **19**(9): p. 1109-14, i-ii.
44. van der Walt, M., J. Lancaster, and K. Shean, *Tuberculosis Case Fatality and Other Causes of Death among Multidrug-Resistant Tuberculosis Patients in a High HIV Prevalence Setting, 2000-2008, South Africa.* PLoS One, 2016. **11**(3): p. e0144249.

45. Manda, S.O.M., et al., *Risk of Death among HIV Co-Infected Multidrug Resistant Tuberculosis Patients, Compared To Mortality in the General Population of South Africa.* Journal of AIDS & clinical research, 2013. **Suppl 3:** p. 7.
46. Gandhi, N.R., et al., *Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study.* J Acquir Immune Defic Syndr, 2009. **50.**
47. Mohd Shariff, N., S.A. Shah, and F. Kamaludin, *Predictors of death among drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: A retrospective cohort study from 2009 to 2013.* J Glob Antimicrob Resist, 2016. **6:** p. 102-7.
48. Mabunda, T.E., N.J. Ramalivhana, and Y.M. Dambisya, *Mortality associated with tuberculosis/HIV co-infection among patients on TB treatment in the Limpopo province, South Africa.* African Health Sciences, 2014. **14**(4): p. 849-854.
49. Kibret, K.T., et al., *Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies.* Infectious Diseases of Poverty, 2017. **6**: p. 7.
50. Egbewale, B.E., et al., *Tuberculosis treatment outcomes in State Hospital, Osogbo, southwestern Nigeria: a four year review.* Niger J Med, 2007. **16**(2): p. 148-55.
51. Udwadia, Z.F. and L.M. Pinto, *Review series: the politics of TB: the politics, economics and impact of directly observed treatment (DOT) in India.* Chron Respir Dis, 2007. **4**(2): p. 101-6.
52. Anuwatnonthakate, A., et al., *Directly Observed Therapy and Improved Tuberculosis Treatment Outcomes in Thailand.* PLoS ONE, 2008. **3**(8): p. e3089.
53. Kaplan, R., et al., *An integrated community TB-HIV adherence model provides an alternative to DOT for tuberculosis patients in Cape Town.* Int J Tuberc Lung Dis, 2016. **20**(9): p. 1185-91.
54. Udwadia, Z.F. and L.M. Pinto, *REVIEW SERIES: The Politics of TB: The politics, economics and impact of directly observed treatment (DOT) in India.* Chronic Respiratory Disease, 2007. 4(2): p. 101-106.
55. V. K. Dhingra, S.R., Anshu Mittal and M. Hanif, *Outcome of Multi-Drug Resistant Tuberculosis cases treated by individualized regimens at a tertiary level clinic.* Indian Journal of Tuberculosis, 2007.
56. Horter, S., et al., *"Home is where the patient is": a qualitative analysis of a patient-centred model of care for multi-drug resistant tuberculosis.* BMC Health Serv Res, 2014. **14**: p. 81.
57. Mhimbira, F., et al., *Home-Based and Facility-Based Directly Observed Therapy of Tuberculosis Treatment under Programmatic Conditions in Urban Tanzania.* PLOS ONE, 2016. **11**(8): p. e0161171.
58. Uganda Bureau of Statistics (UBOS), *National Population and Housing Census 2014 - Main Report*, 2016: Kampala, Uganda.
59. Mpagama, S.G., et al., *Diagnosis and Interim Treatment Outcomes from the First Cohort of Multidrug-Resistant Tuberculosis Patients in Tanzania.* PLoS ONE, 2013. **8**(5): p. e62034.
60. Ejaz, M., et al., *Prevalence of multi-drug resistant tuberculosis in Karachi, Pakistan: identification of at risk groups.* Trans R Soc Trop Med Hyg, 2010. **104**(8): p. 511-7.
61. Lomtadze, N., et al., *Prevalence and Risk Factors for Multidrug-Resistant Tuberculosis in Republic of Georgia: A Population Based Study.* The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 2009. **13**(1): p. 68-73.
62. Onifade, D.A., et al., *Gender-related factors influencing tuberculosis control in shantytowns: a qualitative study.* BMC Public Health, 2010. **10**(1): p. 381.
63. Miller, C.R., et al., *Sex disparities in tuberculosis suspect evaluation: a cross-sectional analysis in rural Uganda.* The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 2013. **17**(4): p. 480-485.

64. Trajman, A., et al., *Impact on Patients' Treatment Outcomes of XpertMTB/RIF Implementation for the Diagnosis of Tuberculosis: Follow-Up of a Stepped-Wedge Randomized Clinical Trial.* PLoS ONE, 2015. **10**(4): p. e0123252.
65. Oladimeji, O., et al., *Intensive-phase treatment outcomes among hospitalized multidrug-resistant tuberculosis patients: results from a nationwide cohort in Nigeria.* PLoS One, 2014. **9**(4): p. e94393.
66. Umanah, T., et al., *Treatment outcomes in multidrug resistant tuberculosis-human immunodeficiency virus Co-infected patients on anti-retroviral therapy at Sizwe Tropical Disease Hospital Johannesburg, South Africa.* BMC Infect Dis, 2015. **15**: p. 478.
67. Isaakidis, P., et al., *Poor outcomes in a cohort of HIV-infected adolescents undergoing treatment for multidrug-resistant tuberculosis in Mumbai, India.* PLoS One, 2013. **8**(7): p. e68869.
68. Deivanayagam, C.N., et al., *Prevalence of acquired MDR-TB and HIV co-infection.* Indian J Chest Dis Allied Sci, 2002. **44**(4): p. 237-42.
69. Harris, R.C., et al., *The effect of early versus late treatment initiation after diagnosis on the outcomes of patients treated for multidrug-resistant tuberculosis: a systematic review.* BMC Infectious Diseases, 2016. **16**: p. 193.
70. Kenyon, C., et al., *THE RISKS OF CONCURRENT TREATMENT WITH TENOFOVIR AND AMINOGLYCOSIDES IN PATIENTS WITH HIV-ASSOCIATED TUBERCULOSIS.* Southern African Journal of HIV medicine, 2011. **12**(1): p. 43-45.
71. Tierney, D.B., et al., *Time to Culture Conversion and Regimen Composition in Multidrug-Resistant Tuberculosis Treatment.* PLOS ONE, 2014. **9**(9): p. e108035.
72. Jain, K., et al., *Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis.* Journal of Pharmacology and Pharmacotherapeutics, 2014. **5**(2): p. 145-149.
73. World Health Organization, W., *Global Strategy and Targets for Tuberculosis Prevention, Care and Control After 2015.*, 2014.
74. Bassat, Q., et al., *Development of a post-mortem procedure to reduce the uncertainty regarding causes of death in developing countries.* The Lancet Global Health. **1**(3): p. e125-e126.