

# Determinants of Persistent Sputum Smear Positivity after Intensive Phase Chemotherapy among Patients with Tuberculosis at Rhodes Chest Clinic, Nairobi, Kenya

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# Abstract

The prevalence of TB in sub-Sahara Africa has been reported as 511 per 100,000 populations and a mortality of 74 per 100,000 in year 2009. In the same period, incidence was estimated at 350 cases per 100,000. In this regard, the health system requires strengthening to respond to the rising cases of infection, drug resistance and quality of life lost while continuing to seek interventions that improve adherence to medication and case detection among those infected. Methods: This study sought to determine factors that are associated with sputum positivity after intensive phase of chemotherapy in people with tuberculosis. It was a retrospective case-control study conducted in Rhodes chest clinic, a City Council health unit in Nairobi that specializes in treatment of chest infections. The participants were sampled from clinic attendants who had completed two months of intensive phase TB chemotherapy and met inclusion criteria. Results: Seventy participants of whom 25 (36%) were sputum positive at the end of two (2) months intensive phase were included in the study. Skipping medication doses was significantly associated with sputum positivity (p = 0.01). Patients who were sputum positive at the end of the two-month period were more likely to have taken longer time before seeking treatment compared to those who were sputum negative by median (IQR) 8 (3 - 12) and 4 (3 - 8) weeks respectively although this difference was not significant (p = 0.09). Patients who had not disclosed their infection status had a two-fold possibility of

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remaining sputum positive at the end of intensive phase. Conclusion: Early diagnosis and treatment of TB, and adherence to medication were important factors that affect sputum conversion during intensive phase of TB treatment. Therefore, public health practitioners should advise patients to seek prompt diagnosis and treatment of signs and symptoms of tuberculosis.

## **Keywords**

Tuberculosis Treatment in Kenya, Intensive Phase, Persistent Sputum Positivity, TB Drug Resistance, Adherence to TB Medication

## **1. Introduction**

Tuberculosis (TB) is one of the most ancient diseases but remains a substantial public health. Kenya is ranked 13 among 22 high burden countries that collectively contributed about 80% of world T.B cases [1] [2]. In year 2008, a total of 110,251 cases of T.B were reported to the Division of Leprosy, Tuberculosis and Lung Diseases DLTLD, representing T.B notification rate of 288 per 100,000 population [3]. New cases of TB in year 2007 according to WHO (World Health Organization) were 132,000 thus an incidence rate of 142 cases per 100,000 population.

Although tuberculosis is a curable disease, it is highly infectious and if untreated, each person with active T.B will infect on average 10 to 15 persons in a year [4]. The success of tuberculosis treatment lies in the consistent administration, adherence and completion of treatment. The goal of treatment must therefore be to achieve optimum desirable cure rate. Despite T.B medication in Kenya being free with the hope of achieving high coverage of persons on medication, the cure rate is about 85% and there is therefore need to examine factors contributing to treatment outcomes so as to improve cure rates and therefore reducing disease burden of morbidity, mortality, relapse, infectiousness, and drug resistance. The first line treatment regimen in Kenya as provided by Division of Leprosy, Tuberculosis and Lung Diseases (DLTLD) entails fixed dose combination (FDC) of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) (Table 1).

Some of the factors identified as influencing treatment completion, in a study in Mbagathi Hospital, include, not having enough pills to last until the next available day after a missed appointment date occasioned by delays due to work or family reasons, lack of money for transport and losing pills as some of the main reason to non adherence [5] [6]. The same study, however, observed high treatment adherence to tuberculosis treatment.

This study sought to outline factors that are associated persistent sputum positivity after intensive phase of TB treatment among patients on medication in Rhodes Chest Clinic with the aim of improving clinical outcomes through identification of key factors that promote persistence of sputum positivity and therefore help care providers and policy makers in designing appropriate TB management and monitoring interventions. The findings will also help clinicians optimize sputum conversion and thus improve care outcomes during and after intensive phase of treatment of tuberculosis.

### 2. Methods

### 2.1. Study Design

This was a case control design with cases being patients with positive sputum results after intensive phase of treatment while controls were patients with sputum smears negative results after intensive phase of treatment.

Abbreviation of the regimen	2RHZE/4RH	
Phase	Intensive phase	Continuation phase
Duration	Directly Observed Treatment (DOT), for two months	Directly Observed Treatment (DOT), for four months
Drugs Used	Rifampicin (R), Isoniazid (H) Pyrazinamide (Z), Ethambutol (E)	Rifampicin (R) and Isoniazid (H),

Table 1. 1st line treatment regimen for new adult TB patient.

#### 2.2. Study Area

This study was conducted at Rhodes Chest Clinic that provides diagnostic, treatment and monitoring for tuberculosis. The health centre (level III) is in Nairobi, the capital city of Kenya with an estimated population of 3 million residents majority of whom are low income earners. It also serves as a referral for several city council of Nairobi clinics for diagnosis, treatment and monitoring of tuberculosis.

## 2.3. Study Population

The study participants were clinic attendants receiving medication and continued TB treatment and care services, they were sampled from patients on tuberculosis treatment willing and consenting to participate in the study. They were required to have completed 2 months intensive phase of TB treatment. A total of 70 persons were sampled of whom 25 patients (cases) were sputum positive after intensive phase of treatment while 45 patients (controls) were sputum negative after intensive phase of treatment.

#### 2.4. Sample Size and Data Collection

TB medication compliance has been identified as a significant risk factor for persistent sputum positivity after intensive phase [6]. We postulate that among the cases (sputum positive) 40% will be non compliant and that among the controls (sputum negative), 10% will be non compliant. Assuming a power of 80%, alpha of 0.05 and conservative exposure level of 50% for socio demographic and treatment factors with ratio of 1:2 (case: control), we estimated that we would require a sample size of 72 respondents (24 cases and 48 controls). All cases were selected on the basis of their positive sputum microscopy status while controls were selected on condition they had converted to sputum negative after intensive phase. 25 patients on medication for tuberculosis and with positive sputum smear after intensive phase were selected as cases and 45 controls (positive sputum smear after intensive phase) were enlisted in the study. Due to low numbers of the cases, purposive samples were taken while controls were randomly selected. Sputum positive patients were requested to be interviewed even on days that were not their scheduled clinics. The inclusion criteria for cases and controls were: 1) must be an adult (18 years); 2) consenting to taking part in the study; 3) being managed on the recommended 1st line regimen for TB and able to communicate in English or Swahili.

Data collection was through interviewer-administered questionnaires, used to gather information on TB treatment progress while existing patients' records were used to gather information of patients at baseline (at onset of treatment) and sputum results at completion of intensive phase of treatment in addition to clinical outcomes. 3 clinical field assistants, (a clinical officer, a nurse and a records clerk) were recruited and trained on data collection procedures. No pre-scheduled interview appointments were planned and patients presenting as part of routine follow-up visits to the health facilities were requested to participate in the study.

*Analysis*: Data was entered and analysed using SPSS (16 version). Each questionnaire had a unique identifier to allow validation. Descriptive and inferential statistics were calculated for various social demographic characteristics and treatment outcomes. Univariable logistic regression was used to examine the association between the primary outcome (persistent sputum positivity after intensive phase) and all pre-specified covariates. A multivariable predictive model for persistent sputum positivity after intensive phase was then developed. Gender was included as *a priori* independent risk factors for persistent sputum positivity with additional variables identified in univariate analysis as associated with persistent sputum positivity (p < 0.05) added into the model starting with those with the strongest association. Variables were retained in the model if a likelihood ratio test (LRT, p value of <0.05) supported improved model fit. For the univariable and multivariable analyses the odds ratios, accompanying 95% confidence intervals and Wald test p values (two-tailed) are reported.

#### **Ethical Considerations**

Scientific and ethical approval for the study were sought and granted by Kenya Medical Research Institute's (KEMRI). Scientific steering committee (SSC) and Ethical Review Committees (ERC) for research to be conducted.

Participation in this study was voluntary. Consent was sought from all study participants with a signed consent form preceding all interviews, minors and those too sick to participate were excluded from the study. There were no benefits or incentives to the participants. Long-term benefit to society is anticipated as results of this survey may be of medical importance. Confidentiality was guaranteed for all information obtained from study participants.

#### 3. Results

## **3.1. Patient Characteristics**

A total of 70 patients who were on TB treatment were recruited into the study at ratio of 1:2 (cases:controls) with 25 of these being cases (persistent sputum positive results after intensive phase). The sex distribution of the respondents was such that males were over three quarters (77%). In respect to marital status, patients who were married constituted 52% (37) of the patients while 44% (31) and 4% (3) were single and separated respectively.

Patients who were in formal employment (salaried positions) constituted the majority 45% (32) with those in informal employment being 28% (20) and the least were the unemployed 27% (19). Majority of the patients 45% (32) had an income of <10000 while the least 7% (5) had an income of >40000, however 15% of the patients did not give their income. More descriptive demographics are Table 2.

#### **3.2. Pre-Medication Factors**

In addition to the socio-demographic factors age, gender, marital status education, occupation and income, the numbers of rooms, no of persons living with per house and duration to seeking treatment were also considered as pre-treatment factors that determined sputum conversion. Of these only duration to seeking treatment was a significant predictor to sputum conversion (Table 2).

Patients who were sputum positive took longer before seeking treatment compared to those who were sputum negative in median weeks (IQR) 8 (3 - 12) and 4 (3 - 8) weeks respectively although not significant (kruskal wallis test p = 0.09). However patients who took too long before seeking treatment were significantly (kruskal wallis test p = 0.01) more likely to miss their medication with those who ever missed medication having a median (IQR) 8 (6 - 12) duration to seeking treatment while those who never missed medication had a duration of 4 (3 - 8) weeks (data not shown).

### **3.3. Medication Factors**

Majority 89% of the respondents never forgot to take their medication with only 3% (2) and 8% (6) forgetting to take their medication sometimes and rarely respectively. Very few patients were rated as being careless about taking their medication with majority 92% reporting never being careless. 89% of the patients were adherent to treatment with less than 1% reporting either missing or sometimes stopping treatment if they felt better. 30% (21) of the patients had missed their medication at some point during treatment. Of those who missed treatment, 62% (13) only missed treatment for one day, 14% (3) missed treatment for two days while 14% (3) missed treatment erratically.

Ever missing medication was significantly associated with persistence of sputum positivity (OR 0.20; 95% CI 0.10 - 0.84; p = 0.023). Although not significant patients who were not offered a HIV test as part of TB care and those who did not disclose their TB status were likely to have an increased odds of sputum positive results by 1.76 (95% CI 0.11 - 29.38; p = 0.694) times and 2.55 (95% CI 0.52 - 12.40; p = 0.247) times respectively. Similarly the need for a treatment supporter was not significant (see Table 3).

#### 3.4. Multivariate Analysis

In the multivariate analysis, two predictive models for sputum positivity after intensive phase were developed: one for the demographic factors and the other for treatment factors. In Model 1 (**Table 4**), gender age and income were identified as the main demographic factors predictive of sputum positivity after intensive phase of treatment (LRT 0.053). Regarding treatment factors, gender, age and ever missing medication (LRT 0.05) predicted sputum positivity as shown in Model 2 in **Table 5**.

## 4. Discussion

The aim of our study was to assess the determinants of persistent sputum smear positivity after intensive phase of chemotherapy. The striking findings from this study were that ever missing drugs was significantly associated with sputum positivity while patients who were sputum positive were likely to have taken longer before seeking

Sputum Positive Negative **Odds Ratio** Upper CI lower CI p Value Age Mean (SD) 37.5(10.8) 1.02 0.97 1.08 0.345 35.2(9.6) Gender male 22(88) 32(71) 1.00 0.08 0.32 1.26 0.103 female 3(12) 13(29) Marital 12(48) 19(42) 1.00 single married 25(56) 0.76 0.28 2.06 0.59 11(44) separated 2(8) 1(2)3.17 0.26 38.84 0.367 Religion Christian 24(96) 44(98) 1.00 others 1(4) 1(2) 1.76 0.11 29.38 0.694 Education 10(40) 14(31) 1.00 primary secondary 11(44) 18(40) 0.78 0.26 2.31 0.651 9(20) 0.42 0.09 1.95 0.271 tertiary 3(12) university 1(4) 4(9) 0.32 0.03 3.27 0.335 Occupation 7(28) 12(27) 1.00 unemployed informal 13(52) 18(40) 1.33 0.42 4.27 0.628 formal 0.57 0.14 2.26 0.425 5(20) 15(33) Income <10000 14(56) 17(38) 1.0010000 - 20000 4(16) 12(27) 0.38 0.10 1.42 0.151 20000 - 30000 1(4) 6(13) 0.19 0.02 1.75 0.143 ≥40000 0.28 0.03 2.82 0.282 1(4)4(9) No of rooms Median (IQR) 1(1 - 2)1(1 - 2) 0.80 0.42 1.53 0.496 No of persons per house Median (IQR) 2(1 - 4)2(1 - 4)0.90 0.71 1.16 0.43 Duration to treatment (weeks) Median (IQR) 8(3-12) 4(3 - 8) 1.09 0.98 1.20 0.101

 Table 2. Descriptive and univariate logistic regression analysis for the association of pre-treatment factors between sputum results and covariates.

 Table 3. Descriptive and univariate logistic regression analysis for the association of treatment related factors between sputum results and covariates.

	Spu	ıtum				
	Positive	Negative	Odds Ratio	Upper CI	Lower CI	p Value
Ever missed medication						
yes	12(48)	9(20)	1.00			
no	13(52)	36(80)	0.29	0.10	0.84	0.023
Reason missed medication						
side effect	3(12)	2(4)	1.00			
forgot	7(28)	4(9)	1.17	0.13	10.22	0.889
Require a treatment suppo	orter					
yes	18(72)	32(71)	1.00			
no	3(12)	8(18)	0.89	0.23	3.37	0.862
Don't know	4(16)	5(11)	1.42	0.34	5.98	0.631
Requested HIV test as TB	care					
yes	24(96)	44(98)	1.00			
no	1(4)	1(2)	1.76	0.11	29.38	0.694
Ever disclose TB status						
yes	21(84)	42(93)	1.00			
no	4(16)	3(7)	2.55	0.52	12.40	0.247

 Table 4. Multivariate model for demographic factors that predict sputum positivity.

		Odds Ratio	Upper CI	Lower CI	p Value	LRT
Gender						0.053
	Male	1.00				
	Female	0.14	0.01	1.29	0.083	
Age in years		1.04	0.97	1.11	0.271	
Income						
	<10,000	1.00				
	10,000 - 20,000	0.19	0.04	0.86	0.032	
	20,000 - 30,000	0.16	0.02	1.61	0.119	
	<40,000	0.18	0.01	2.18	0.176	

Table 5. Multivariate model for Treatment factors that predict sputum positivity.

		Odds Ratio	Upper CI	Lower CI	p Value	LRT
Gender						0.05
	Male	(base)				
	Female	0.20	0.02	1.81	0.152	
Age in years		1.03	0.97	1.09	0.357	
Ever missed medication						
	Yes	(base)				
	No	0.30	0.09	1.06	0.061	

treatment when compared to those who were sputum negative which is consistent with findings from other studies.

## 4.1. Pre-Treatment Factors Affecting Sputum Conversion

Considerations of patient's socio-demographic and treatment-related factors have been found to be significant determinants of tuberculosis treatment outcome. In this study, there is a suggestive trend for a decrease in the risk of sputum positivity with increase in education level although this association was not significant. However, these results compare with those from Panambuco, Brazil by Magda and colleagues [7] which highlighted that complete or incomplete secondary or university education was associated with a lower risk of defaulting from TB treatment. It is believed that a low level of education hinders perception of the seriousness of the disease and causes difficulties in understanding medical guidelines. Further, the more one is educated the higher the chance of conceptualizing the danger of non adherence and the importance of treatment compliance.

Although TB medication is free, other indirect costs associated with TB infection like lost income, transport, food costs due to the extra nutritional requirements among others may hinder treatment uptake and adherence. This could therefore explain the decreased risk of sputum positivity associated with medication adherence among individuals in formal employment and those having an income of greater than ksh 10,000 (ksh 85 = 1 USD).

The decrease in the risk of being sputum positive after intensive phase for every increase in one room in the house may allude to the assumption that with congestion, there are chances of re-infection with the mycobacterium if the patient is living in enclosed environment where they may have infected other people living with them.

#### **4.2. Treatment Factors**

#### 4.2.1. HIV Testing and TB Status Disclosure

Not disclosing TB status had a two fold increase in risk of sputum positivity while not being offered HIV services alongside TB treatment increased risk of sputum positivity. Which highlight the possibility of reinforcing messages that are given during counseling on importance of treatment and adherence which are common in both HIV and TB. This finding highlights the fears that people have regarding disclosure of the illnesses and hence the need for disclose to a suitable person who could provide the role of a treatment supporter actively or passively. It also shows that stigma and discrimination may be related to tuberculosis.

#### 4.2.2. Adherence to Medication

A great challenge to a tuberculosis control programme is ensuring that TB patients seek diagnosis in a timely manner and, once diagnosed, adhere to treatment. Central to this inquiry was the assessment of adherence to treatment medication using Morisky adherence scale [8]. Missing drugs was significantly associated with sputum positivity. Those who poorly complied with medication had an increased risk of sputum positivity *i.e.* rarely/sometimes careless about drugs, forgot or even stopped medication. These finding may be explained on the basis of low or suboptimal levels to suppress multiplication of the mycobacterium tuberculosis. Several studies have been undertaken on the relationship between adherence to medication and persistent sputum positivity [9]-[11].

#### 4.2.3. Time to Diagnosis and Initiation of Treatment

Time from onset of symptoms to diagnosis and initiation of tuberculosis chemotherapy has in this study been found to be significant to persistence in sputum positivity after intensive phase. The longer one takes to have a diagnosis and initiate treatment, the higher the chance of sputum positivity after completion of intensive phase. A study in Gambia reported the median delay from onset of symptoms to commencement of treatment was 8 weeks (range 4 - 12) in the urban area which compares with the similar median of 8 weeks and IQR of 3 to 12 week reported in this study [12]. The study in Gambia however did not establish a relationship between duration of delay to treatment and cure rate, but longer delay did increase the risk of death [12]. Banu and colleagues in India [13] indicated that pulmonary cavitation is associated with persistent sputum positivity after intensive phase chemotherapy. Though this study did not seek to establish the extent of the disease by the time of initiation of medication, it is possible that delayed diagnosis and treatment initiation leads to adverse effect to the

lung tissue.

These findings are consistent with those from another recent study in South Africa by Calver *et al.* [10] which showed that diagnosis delay and inappropriate therapy facilitate disease transmission and drug-resistance. This finding therefore calls for implementation of rapid diagnostics and enhanced active screening strategies, for all with coughs for other signs and symptoms of tuberculosis. All persons with unexplained weight loss, unexplained persistent cough for more than 2 weeks, and unexplained night sweats should be investigated for tuberculosis.

#### 4.2.4. Time to Diagnosis and Missing Medication

In this study, it was further established that patients who took long (median time of 8 weeks) to seek diagnosis and treatment had higher likelihood of missing medication during treatment. It is possible that the delay in seeking treatment may be characterized by denial that may spill over to the treatment phase. This calls for adherence counseling and for close monitoring of this category of patients by health care providers.

#### 4.2.5. Limitations of the Study

Despite these positive findings these results should be interpreted in the light of the following drawbacks. Firstly, we did not take into account results of culture and there is a possibility that some of the bacilli detected in the sputum were dead, however the action on whether to institute additional period for intensive phase are based on sputum microscopy findings in developing world. Secondly, we did not attempt to have sputum samples reread to validate the findings, however the laboratory in which these investigations were carried out are accredited. Other general limitations are the draw backs associated with this type of study such as recall bias. Despite the above mentioned limitations the following strengths reinforce our arguments. There was a deliberate effort to ensure construct validity at design level of the questionnaire and further external validity of the study finding.

## **5.** Conclusion

Treatment adherence to TB medication is associated with desirable treatment outcome while sub-optimal cure rates pose a risk in the increase in the multi drug resistant strains which have recently been reported to be on the rise in Kenya. Therefore to guard against expensive to treat form of drug resistant TB, success with first line treatment must be optimized. An early reliable indicator of treatment outcome is sputum smear status. Further, more research is required to explore how adherence to treatment and time to diagnosis overly affects TB treatment outcomes.

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## **Contributions**

The idea for the study and its design were conceived David Maingi (DM), with advice from Mutugi Marion (MM), Wanzala Peter (WP), Mutai James (MJ), Mwaniki Peter (MP). DM was responsible for data collection, and data entry. DM, MM, WP PM MJ MP were responsible for data analyses and DM prepared the initial draft manuscript. All authors reviewed the draft manuscript and provided input to and approval for the final version of the report.

## **Conflict of Interest Statement**

There are no conflicts of interest.

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