

2016

# Cough aerosol production in patients with pulmonary tuberculosis with and without HIV infection

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BOSTON UNIVERSITY  
SCHOOL OF PUBLIC HEALTH

Thesis

**COUGH AEROSOL PRODUCTION IN PATIENTS WITH PULMONARY  
TUBERCULOSIS WITH AND WITHOUT HIV INFECTION**

by

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M.B.B.S., University of Khartoum, Sudan, 2000

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2016



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**COUGH AEROSOL PRODUCTION IN PATIENTS WITH PULMONARY  
TUBERCULOSIS WITH AND WITHOUT HIV INFECTION**

**SARA SAYED TALIB OSMAN**

**ABSTRACT**

**Rationale:** Infectivity of patients with pulmonary tuberculosis who are HIV infected is not clear compared to those who are non-HIV infected. There is an association between cough aerosol production and T.B transmission with great variability in the amount of aerosol produced by infected patients; therefore aerosol production can be used as surrogate marker of infectivity

**Objectives:** To evaluate the amount of cough aerosol produced in patients with pulmonary tuberculosis who are HIV infected compared to those who are non-HIV infected; and to evaluate the association between immunosuppression and aerosol production.

**Methods:** Data from two different cohorts with available information on the amount of cough aerosol produced and HIV status were merged to increase validity of the study

**Measurements and main results:** Secondary data analysis performed on the merged data using the amount of mycobacterial tuberculosis colony forming unit produced in cough aerosol by patients with pulmonary tuberculosis as our outcome variable and compared HIV infected patients with non-HIV infected; thereafter in the HIV-subgroup we ran data analysis to evaluate the association between aerosol production and degree T-cell count.

**Conclusion:** HIV infection is associated with decrease aerosol production in patients with pulmonary tuberculosis, other factor included degree of AFB smear the duration on TB treatment before aerosol collection modified this association. In HIV infected person the degree of immunosuppression dose not correlate with the amount of aerosol produced.

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**I: Summary:**

Tuberculosis (TB) remains a global health problem. It is the leading cause of death in people living with HIV. The cycle of the disease begins when a human host inhales aerosols containing viable *Mycobacterium tuberculosis* (MTB). To date, studies looking at the effect of HIV immunosuppression on infectivity of patients with pulmonary TB have produced inconclusive results (1–3). Jones-Lopez et al. (4) have established a strong association between the number of colony forming units (CFU) of MTB in cough-generated aerosol in patients with pulmonary TB and risk of infection in exposed contacts. There have been no studies looking at amount of culturable MTB in cough aerosol of patients co-infected with HIV and TB.

Secondary analysis of currently available data from studies with baseline assessment of cough aerosol cultures of MTB can provide very useful information to assess a potential link between HIV status and TB infectivity. Our objective is therefore to investigate the association between HIV status and the amount of culturable MTB produced in cough aerosol of patients with pulmonary TB as a surrogate marker of infectiousness using available data from two prospective studies (4,5).

**II: Background:**

Tuberculosis remains a global health problem. It is ranked as the second leading cause of death from a single infection after HIV. In its latest global report, the World Health Organization (WHO) estimated over 9.6 million people fell ill with TB in 2014 (6); of those an estimated 12% million were HIV infected. About 1.4 million people died of the

disease in 2014; of those 320,000 were HIV infected. Globally, approximately one third of HIV infected individuals have latent TB infection (LTBI). It is known that patients with HIV are 29.6 times more likely to develop active disease compared to non-HIV infected individuals (6).

Multidrug-resistant (MDR) TB, defined by antituberculous drug resistance to at least isoniazid and rifampicin, is an increasingly important public health and clinical issue, especially in countries with a high burden of HIV. In March 2006, the first data were published on the worldwide occurrence of TB with resistance to second-line drugs (7), termed extensively drug-resistant (XDR) TB and defined as resistance to isoniazid, rifampicin, any fluoroquinolone, and at least one of three injectable second-line drugs. In 2011 WHO published in its MDR-TB & XDR-TB progress report that 69 countries have reported at least one case of XDR-TB (by the end of 2010), and currently there are an estimated 25,000 cases of XDR-TB emerging every year (8). Studies from New York and South Africa have shown increased mortality and shorter median survival among HIV-infected MDR-TB patients compared to those without HIV infection. A report from KwaZulu-Natal Province, South Africa indicated that 52 out of 53 patients with XDR-TB were HIV positive, and had a median survival time of only 16 days from sputum collection, and a 98% mortality rate (7).

It is well known that MTB is transmitted by fine aerosols (i.e. via the airborne route in infectious droplet nuclei < 5 mm in diameter). Recent studies have shown (4,5,9) significant variability in the amount of culturable MTB in cough aerosol of patients with

pulmonary TB, and MTB CFU has been shown to correlate with both tuberculin skin test (TST) and interferon gamma release assay (IGRA) conversion in close contacts of an index case. While sputum acid fast bacilli (AFB) has been the gold standard for predicting infectivity for decades, these findings suggest that the amount of MTB CFU in cough aerosol could be used as a surrogate marker for transmission and infectivity.

There are several reasons why HIV infected patients with pulmonary TB may be less likely to transmit TB infection when compared to HIV-uninfected patients including that HIV infected patients are more likely to be sputum AFB negative, have fewer cavitory lesions, and have a reduced period of infectiousness since they progress from infection to death more quickly.

### **III: Study questions:**

- 1- Is there an association between HIV infection and cough aerosol production in patients who have pulmonary tuberculosis?
  
- 2- Among HIV-infected persons, is there an association between degree of immunosuppression, as measured by CD4 cell count, and cough aerosol production?

### **IV: Study Objectives and Hypotheses:**

#### **Objectives:**

1. Examine the effect of HIV on the amount of MTB CFU produced in cough-generated aerosol of patients with pulmonary TB.

2. Evaluate the association between degree of immunosuppression and aerosol production in HIV-infected patients who are co-infected with pulmonary TB.

**Hypothesis I:**

Individuals with HIV-associated pulmonary TB will produce lower number of MTB CFU in their aerosol compared to HIV-uninfected individuals.

**Hypothesis II:**

HIV-infected patients with CD4  $\geq$ 200 or no AIDS clinical diagnosis will produce higher aerosol CFU compared to those with CD4 < 200 or AIDS clinical diagnosis.

The cut-off of 200 cells was chosen based on CDC definition of AIDS. This category also included all persons with a diagnosis of opportunistic infection or AIDS defining condition.

**V: Methods:**

- ❑ **Study Design:** A cross sectional study analyzed data from two cohorts with available cough aerosol information (N=185); (2002–2004, 2009–2011)
  
- ❑ **Settings/Study population:** Two studies were combined for this secondary data analysis. Our data analysis was restricted to patients with sputum culture positive confirmed pulmonary TB with available cough aerosols data and HIV status information. The two studies used different sputum AFB smear grading; in our secondary analysis we will be using the WHO grading system (0 or Negative, 1+,

2+, 3+, 4+).

- Both studies included patients with pulmonary tuberculosis, attending the Mulago Hospital in Kampala, Uganda
- Both studies included subjects only if their sputum was confirmed to be culture-positive for MTB
- Cough Aerosol Sampling System (CASS) was used to collect, quantify, and size aerosol particles containing culturable MTB produced by voluntary coughing in patients with active pulmonary TB in both cohorts.

□ **Parent studies:**

**Study 1**

A prospective cohort designed to study nosocomial TB transmission and to evaluate the feasibility of collecting cough aerosols in a resource-limited setting in Kampala, Uganda.

- From 11/2002 to 12/2004, consecutive patients with suspected TB attending the National Tuberculosis and Leprosy Program Chemotherapy Centre at Mulago Hospital in Kampala, Uganda were enrolled.
- Subjects were included if their sputum was confirmed to be culture-positive for MTB
- Study excluded patients with medical conditions that could be worsened by cough or if they were too ill to consent, or unable to understand or to comply with the protocol
- Sputum AFB graded using WHO criteria (0 or negative, 1+, 2+, 3+, 4+)

- 112 patients had suspected TB; 101 (90%) had confirmed culture-positive sputum.
- Included patients who were retreatment TB and patients with MDR-TB
- Patients were mainly inpatient, sick, older in age, with higher HIV-infection rate.
- Of the 112 patients with suspected TB enrolled only 92 had all AFB smear, culture and HIV data and included in our final merged data for analysis.

## **Study 2**

A prospective household contact study designed to evaluate the use of cough-generated aerosols of MTB to predict recent transmission within households.

- From 5/2009 to 1/2011, patients with pulmonary TB attending the Mulago Hospital National Tuberculosis and Leprosy Program (NTLP) clinic in Kampala, Uganda, and their household contacts were enrolled.
- Included patients who were 18 years or older, had a new TB episode with at least one sputum specimen that was initially AFB greater than or equal to 1+ with subsequent growth of *M. tuberculosis* in culture and were untreated or had received 5 days or less of TB treatment, this study also included contacts of the index case.
- Study excluded patients with medical conditions that could be worsened by cough or if they were too ill to consent, or unable to understand or to comply with the protocol.
- Sputum AFB was graded using CDC/ATS grading criteria (Negative, Scanty, 1+,

2+, 3+) (Table 1)

- Patients were mainly outpatients, young, healthy with low HIV infection rate.
- This study included 96 index TB cases of those we excluded 3 patients in our final data merged due to missing HIV data.

**Table 1. ATS and IUATLD sputum AFB smear grading**

ATS Classification	IUATLD *	Acid Fast Bacilli
Negative	0 (negative)	0 AFB/100 fields
scanty	1+	1–9 AFB/100 fields
1+	2+	1–9 AFB/10 fields
2+	3+	1–10 AFB/field
3+	4+	>10 AFB/field

\*Classification used in our data analysis

## **VI: CASS Method**

CASS consists of a custom-built stainless steel cylindrical chamber with non-compressible tubing connecting the inlet to a disposable mouthpiece. The chamber holds two Andersen six-stage cascade impactors for viable bioaerosol sampling, each with six plastic Petri plates holding selective 7H11 agar that were loaded in a class II biological safety cabinet.

A vacuum pump connects the air samplers by tubing to fittings that pass through the wall of the chamber. In-line 47-mm filter holders loaded with high-efficiency particle air filters are placed between the chamber and the vacuum pump for biosafety.

A single-stage impactor loaded with the same 7H11 agar was used to sample ambient

room air. One settle plate of the same agar was placed inside the chamber and one in the study room to sample large aerosol particles. A timer connected to the vacuum pump was set for 5 minutes.

Subjects were instructed to cough into the CASS mouth- piece as much and as frequently as was comfortable for two 5-minute sessions separated by a rest of approximately 5 minutes. No sputum induction was used.

After collection, the aerosol samplers were removed and transported to the laboratory, where they were unloaded in the biological safety cabinet. Plates were incubated at 37<sup>0</sup>C.

Cultures were read at 1 week to detect any rapidly growing contaminants and then at 3, 6, and 9 weeks to record CFU of *M. tuberculosis*

Cut off of >10 CFU will be used in the analysis to evaluate for risk factors association between MTB aerosol production. This cut off was used based on studies showing an association between high MTB aerosol (CFU>10) and TST in close contacts (11).

## **VII: Statistical Methods**

Data has been collected using Microsoft Office Access 2011 and Microsoft Excel. Data was analyzed using Statistical Analysis Software (SAS) version 9.4.

Data is being presented graphically using boxplots for continuous data and frequency histogram for categorical data.

The primary outcome of interest was log CFU in cough aerosol was measured as a continuous variable (Figure 1), the primary predictor of interest was HIV status in the whole sample and CD4 cell count in HIV infected subset of patients; both were dichotomized.

Demographic characteristics of the two cohorts were compared reporting on mean, standard deviation, median and interquartile range [IQR] for continuous variables and frequency and percent for categorical variables. Variables were compared between the two cohort for statistically significant difference at the level of 0.05.

First, we ran a crude analysis to evaluate the relation between the exposure (HIV status in index TB cases) and the outcome of interest (number of CFU of MTB in cough-generated aerosols) at the univariate level. We also examined the association with other factors (Epidemiological, historical risk factors for TB) and amount of aerosol CFU all at the univariate level using a simple logistic regression reporting the regression coefficient for each variable, t-test along with the P-value associated with it.

We then used a multiple logistic regression model to fit all variables that may be associated with aerosol production based on the results of the univariate analysis and literature review for historical variables that have been associated with increased risk of transmission of the infection. In order to evaluate for potential confounding we examined the effect of each variable in the crude estimate of association between the main predictor of interest and our outcome, comparing the adjusted estimate of association. If the adjusted estimate differs from the crude by more than 10%, we then retained that variable

for inclusion in our final multivariable model. After having evaluated all potential confounders in this fashion, we built a comprehensive multivariable model.

Also, we also examined effect modification through stratified analyses and by including interaction terms in our analytic models. Potential effect modifiers were identified on a prior basis based on biologic or clinical theory or evidence from the literature. We will present and report on all the interactions. Results will be presented using unadjusted and adjusted regression coefficient with the associated P-value and T-value where applicable.

### **Outcome and Measurements**

*Demographic*

- Age
- Sex

*Clinical*

- BMI
- HIV status
- TB status
- Duration of TB symptoms
- Days on TB treatment before enrollment
- Chest Imaging

*Laboratory*

- CD4 cell count
- Sputum AFB & culture (MGIT)
- Days to culture positivity
- Aerosol's Colony Forming Units (7H10 Middlebrook agar)

### **VIII: Results:**

Our secondary data analysis included a total of 185 patients; data were generated by combining data from two different prospective studies of patients with sputum culture positive confirmed pulmonary tuberculosis.

Table 2 shows the basic demographic characteristics of our study subjects stratified by cohort data indicating variables that are significantly different between the two cohorts at the level of 0.05.

On comparing demographic characteristics between the two studies we found while participants in the first study were older than those in the second cohort, this was not significant. However, there were more males in the first study compared to the second study. HIV infection status was significantly different between the two cohorts as well as TB-Status, with more retreatment cases coming from the first cohort, the first cohort were on TB treatment for significantly longer duration compared to the second cohort.

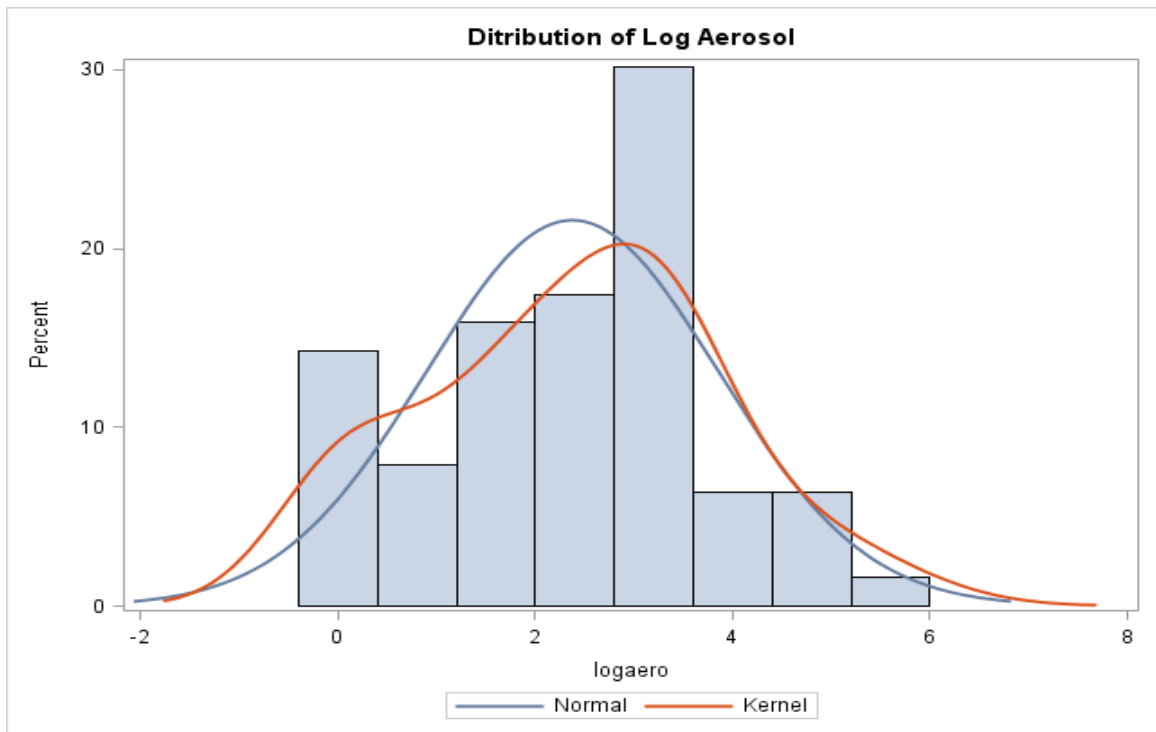
Participants in the first study also had significantly lower BMI compared to the second cohort; however disease severity as measured by extent of lung disease and presence of cavitation did not differ between the two cohorts. Figure 1 shows the normal histogram for the distribution of Log Aerosol for the merged data.

**Table 2. Basic characteristics of study subjects**

<b>Variable</b>	<b>Cohort 1</b>	<b>Cohort 2</b>	<b>Total</b>
<b>Median [IQR]</b>	<b>(2002–2004)</b>	<b>(2009–2011)</b>	<b>N= 185</b>
<b>Frequency (%)</b>	<b>N= 92</b>	<b>N= 93</b>	
<b><i>Demographic</i></b>			
Age	30 [28, 38]	29 [24, 40]	30 [25, 39]
Sex*			
Male	62 (67)	47 (51)	109 (59)
Female	30 (33)	46 (49)	76 (41)
BMI*	17 [16, 19]	19 [18, 21]	18 [17, 20]
HIV*			
Positive	56 (61)	21 (23)	77 (42)
Negative	36 (39)	72 (77)	108 (58)
CD4			
Absolute	121 [33, 281]	264.5 [142, 320]	140 [44, 312]
CD4*			
≥200	18 (32)	7 (33)	25 (32)
<200	36 (64)	3 (14)	39 (51)
Missing	2 (4)	11 (53)	13 (17)
<b><i>Clinical</i></b>			
TB Status*			
New	23 (25)	93 (100)	116 (63)
Retreatment	69 (75)	0 (0)	69 (37)
Duration of TB symptoms in weeks	12 [7, 20]	12 [8, 16]	12 [8, 18]
Duration of TB treatment*	4 [3, 6]	1 [1, 2]	3 [2, 5]
Aerosol CFU*			
Median [IQR]	0 [0, 1]	0 [0, 10]	0 [0, 4]
Mean (sd)	3.91 (10.16)	16.4 (49.5)	10.19 (36.24)
Range	0–59	0–378	0–378
<b><i>CXR findings</i></b>			
Cavitary Disease			
Present	53 (58)	60 (65)	113 (65)
Absent	34 (37)	28 (30)	50 (29)
Missing	5 (5)	5 (5)	10 (6)
Extent of disease on CXR	74 (80)	80 (86)	154 (88)
Far advanced	13 (14)	8 (9)	21 (12)
Other	5 (6)	5 (5)	10 (6)
Missing			
<b><i>Sputum and Culture data</i></b>			
Sputum Smear*			
Positive	77 (84)	92 (99)	169 (91)
Negative	15 (16)	1 (1)	16 (9)

Variable	Cohort 1 (2002–2004)	Cohort 2 (2009–2011)	Total N= 185
Median [IQR]			
Frequency (%)	N= 92	N= 93	
<b>AFB Smear*</b>			
0(Negative)	15 (16)	0 (0)	15 (8)
1+	6 (7)	1 (1)	7 (4)
2+	10 (11)	13 (14)	23 (12)
3+	24 (26)	13 (14)	37 (20)
4+	37 (40)	66 (71)	103 (6)
Days to positive cx*	8 [4, 13]	6 [4, 8]	6 [4, 10]
<b>Sputum Culture</b>			
0	12 (16)	4 (4)	16 (9)
<20	0 (0)	1 (1)	1 (1)
20–100	4 (4)	4 (4)	8 (4)
100–200	2 (2)	3 (3)	5 (3)
>200	72 (78)	81 (87)	153 (83)

\*Variables that are significantly different between the two cohorts at p=0.05



**Figure 1. Normal histograms of Log Aerosol**

**Results – Objective 1: The effect of HIV infection on MTB CFU on cough aerosol of co-infected patients**

On a univariate analysis to examine the association between our predictor variables and log aerosol using a simple linear regression; we found that HIV status and AFB smear grade were both significantly associated with aerosol production at the level of significance of 0.05, but no other factors were found to be associated with aerosol production (Table 3, Figures 2 & 3)

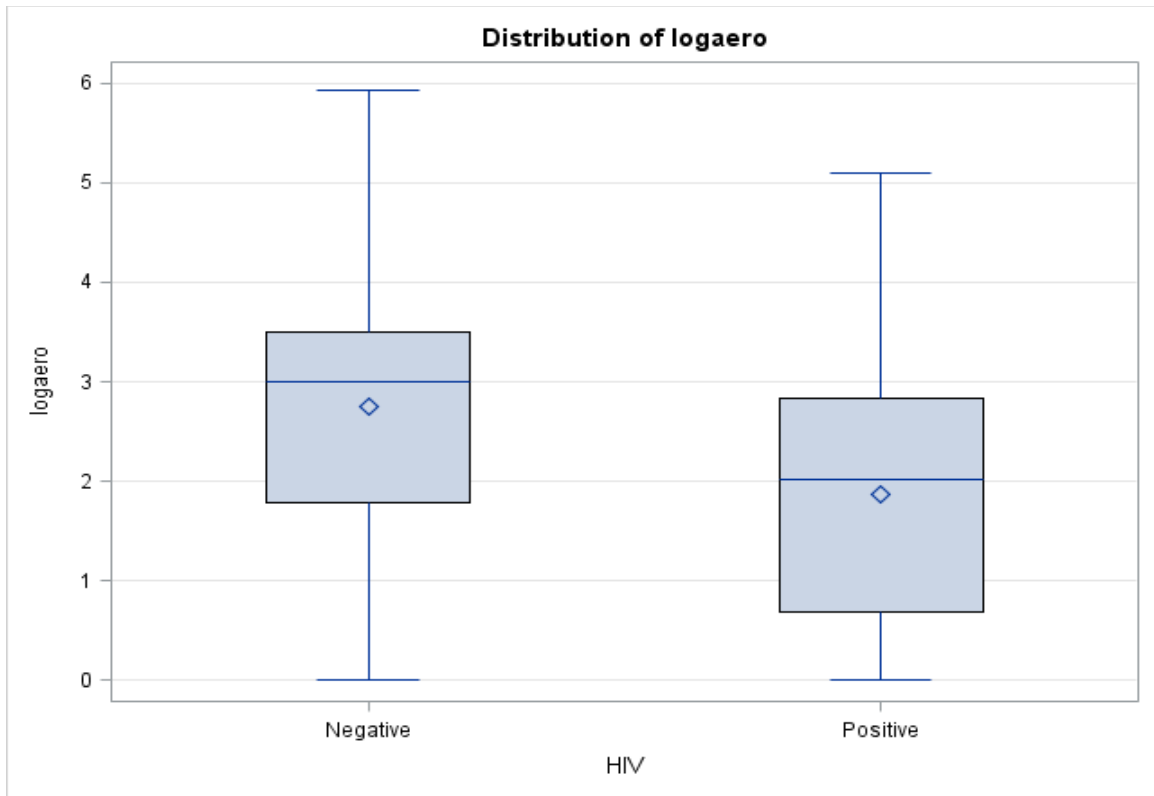
We then started building our final model to include all predictors of aerosol production and examine for presence of confounders and effect modifiers; we first chose variables to be tested for inclusion in our final model (Table 3), variables were chosen based on their effect on the aerosol production at the univariate level, we also tested for epidemiologically important variables and variables from literature review has been historically associated with TB transmission; we used a 10% change in the adjusted regression coefficient of HIV from the crude regression coefficient as our criterion to retain the variable in our final model; testing one variable at a time and calculating percent change in the crude regression coefficient using the formula  $\% \text{ Change} = \frac{\beta_{\text{crude}} - \beta_{\text{adjusted}}}{\beta_{\text{adjusted}}}$  (Tables A1–A8 in addendum), we retained in our final model those variables that changed the crude association between HIV status and aerosol production by 10% or more. Our final model included HIV status, Duration on TB treatment, and AFB Smear Grade (Table 4); AFB smear grading decreased the regression coefficient of HIV status by 21% (adjusted regression coefficient=0.7338 down from 0.9795) but HIV status remained significantly associated with aerosol production (P=0.048), when we

added duration on TB treatment to the model after retaining AFB smear grading the regression coefficient of HIV increased by 14%(regression coefficient= 1.033, P=0.084) Although the P-Value for the effect of HIV on aerosol production is not statistically significant in our final model this can be explained by that duration of TB treatment before aerosol collection is an effect modifier as its known from previous studies that TB treatment reverse AFB smear positivity and decrease aerosol production (11)When testing for interaction between HIV infection and duration on TB treatment we found none between the two variables that affect the regression coefficient significantly (not reported), we also found no interaction between AFB smear grading and duration on TB treatment, this indicates that duration on TB treatment is not a confounder and is an effect modifier.

**Table 3: The univariate analysis for variables associated with aerosol production**

Variable	Regression Coefficient	t test	P-value
Age	-0.0015	-0.09	0.932
Sex		-	0.860
Male	ref.	-0.18	
Female	-0.0679		
BMI	0.1075	1.57	0.122
HIV		-	0.018*
Positive	ref.	2.42	
Negative	0.8843		
TB Status		-	0.610
New	ref.	0.45	
Retreatment	0.1925		
Cavitary lung disease			0.909
Absent	ref.	-	
Present	-0.0451	-0.11	
Log Days to culture positivity	-0.3912	-1.40	0.167
Log Duration of TB symptoms	0.0613	0.22	0.828
Duration on TB treatment	0.0289	1.37	1.80
AFB smear grade			
0/1+/2+	ref.	-	-
3+	-0.1182	-0.17	0.869
4+	1.0892	2.11	0.038*
Cohort data		-0.19	0.853
Cohort 1	-0.0741		
Cohort 2	ref.		

\* P-value significant at the level of 0.05



**Figure 2: The association between HIV and aerosol production**

**Table 4. The final models for factors associated with aerosol production**

Independent Variable	Regression Coefficient	t- test	P-value
HIV		1.79	0.084
Negative	1.033		
Positive	ref.		
Sputum Smear Grade			
3+	0.567	0.70	0.491
4+	1.027	1.69	0.103
0/1+/2+	ref.		
Days on TB treatment	0.267	1.32	0.198

**Results – Objective 2: The correlation between degree of immunosuppression and aerosol production in HIV co-infected patients**

We subset our data set to include HIV infected individuals only (N=64) to examine the effect of degree of immunosuppression on aerosol production. Table A9 (addendum) shows the basic demographic information of these participants. There were more males who were HIV-infected than females. The median CD4 count was 140 with an IQR of 44 & 312.

On this subset of data, we found that log aerosol is normally distributed which allows for analyzing the outcome as a continuous variable (Figure A 11 addendum). However, CD4 count was not normally distributed so will be dichotomized using a cut off 200, which aligns with the CDC definition of AIDS (Figure A12 addendum).

In a univariate analysis we found that TB treatment status and AFB smear grade was associated with aerosol production in HIV infected patients (Table A10 addendum) while the degree of immunosuppression measured by CD4 count was not associated with aerosol production (Table A10 addendum & Figure 3).

Given that regression coefficient for the association between CD4 cell count and log aerosol production was small and to avoid overestimation of the effect of a variable (adjusted regression coefficient) on the relationship between CD4 count and log aerosol production; we first ranked all variables based on their absolute effect on the regression coefficient of CD4 cell count (Table A11 addendum).

We then started building our final model including variables for analysis based on their

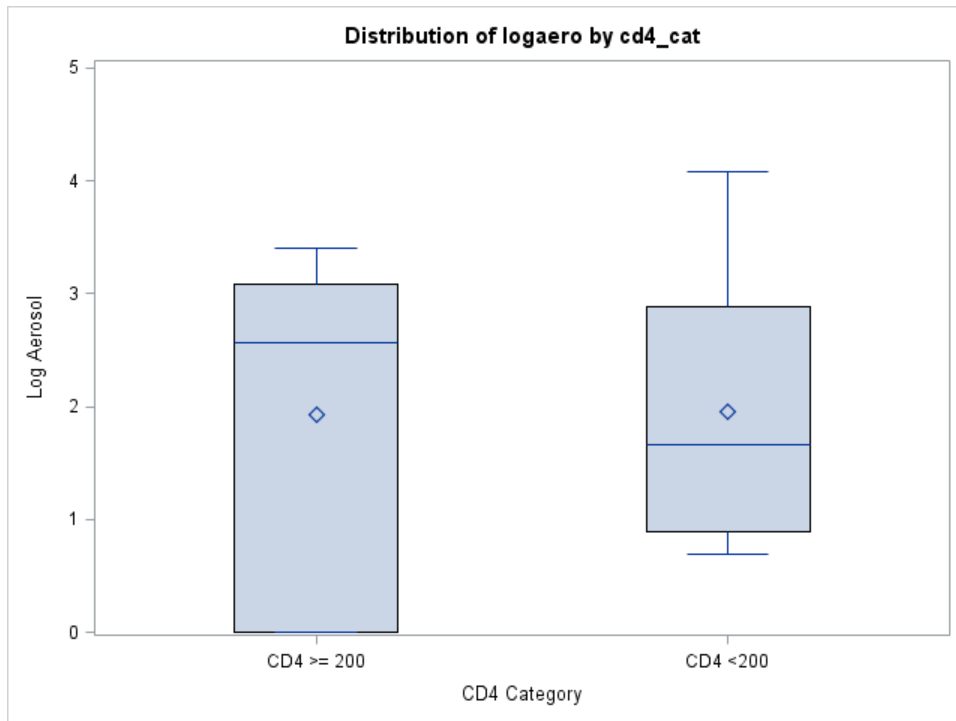
ranking. Variables were retained in our final model based on the 10% rule of change in the crude measure of association between our main predictor (CD4 count) and our outcome of interest; Log aerosol production (Tables A12–A18 addendum); we also forced variables that were significant at the univariate level in our final model (Table A19 addendum).

Our final model included CD4 cell count, age, cavitary lung disease, sex, duration of TB symptoms, TB treatment status, Duration on TB treatment and AFB smear grade. We also ran a separate model that included only our main predictor of interest (CD4 count) and the variables that was significant at the univariate level (AFB smear grade and TB treatment status) (Table 5). The results were not different from the original final model. To examine if there is any masked associated between CD4 count and aerosol production we ran a simple linear regression examining the relation between CD4 count and log aerosol and found no association

**Table 5: The final model for predictors of aerosol production in HIV infected patients**

Independent variable	Regression coefficient	t-test	P-value
CD4 count		-0.23	0.819
≥200	-0.1279		
<200	ref.		
Independent variable	Regression coefficient	t-test	P-value
TB Status *		1.73	0.106
Retreatment	0.9747		
New	ref.		
Smear category *			0.238
0/1+/2+	ref.	-	0.072
3+	1.0685	1.23	
4+	1.4824	1.94	

\*Variables that are associated with aerosol production at p=0.05 in univariate analysis



**Figure 3: Boxplot of aerosols distribution based on CD4 category**

### **Results – Conclusion:**

In our secondary data analysis we found that HIV infection status is associated with the amount of MTB CFU produced in cough aerosol in patients who are co-infected with pulmonary tuberculosis; HIV-uninfected subjects produced more CFU in their cough aerosol compared to HIV infected individuals (regression coefficient= 0.8843,  $t=2.42$ ,  $P=0.018$ ), another factor that is associated with the amount of CFU in aerosol is AFB smear grading; individuals with AFB smear grade 4+ produced more MTB CFU in their cough aerosol compared to those grade 0–2+(regression coefficient= 1.089,  $t=2.11$ ,  $P=0.038$ ). On examining for confounders and the effect modification of other variables on the association between HIV infection status and aerosol production we found that

duration on TB treatment before aerosol collection modified the effect of HIV on the amount of TB CFU on cough aerosol (% change in regression coefficient 12); this effect modification is expected since previous studies have shown strong association between TB treatment and reversal of aerosol production regardless of HIV infection status.

In the HIV infected subset of subjects the degree of immunosuppression as measured by CD4 count and presence of AIDS defining illness was not associated with aerosol production in patients who are co-infected with pulmonary TB.

## **IX: Strengths and Limitations**

### **Weaknesses/Limitations:**

First, this is an observational study and, thus, is susceptible to confounding influences that hinder causal inference. Second, although we found that HIV seropositive individuals who are co-infected pulmonary TB are likely less infective to their close contacts compared to HIV seronegative individuals with pulmonary TB, this study was not designed to directly measure transmission, therefore direct correlation cannot be assumed. However, we think from prior studies that the amount of CFU in cough aerosol could be a good surrogate marker of infectivity. Third, the effect of HIV treatment on the amount of MTB CFU in cough aerosol was not measured and the rate at which patients alter their cough aerosol status or CD4 count in response to start of HIV treatment is unknown.

In our analysis we combined data from two different cohort studies with slightly different inclusion and exclusion criteria for each study and studies conducted at different times

and this may have affected our findings; however there was no correlation between cohort data and cough aerosol production in our analysis

Missing CD4 cell count data in some of the HIV infected subjects may have affected our ability to detect an association between degree of immunosuppression and aerosol production.

**Strengths:**

This secondary data analysis has several notable strengths; To our knowledge, this study is the first to look at the association between HIV-status and the amount of MTB CFU produced on cough aerosol a surrogate marker of infectivity.

By combining two data sets, this is largest study to date with aerosol data available in all subjects, which increased our power to detect differences between HIV-infected and HIV-uninfected patients; this may explain why our findings are different from Fennelly's findings (4)

Both studies were conducted at the same site and data collected included information on similar variables using the same methods for both studies, which increased the internal validity of our study.

Careful consideration of clinical, radiologic and microbiologic confounders with relatively complete data allowed us to control for these.

**X: Importance and Future Directions:**

This study assessed infectious *M. tuberculosis* aerosol produced by HIV-infected individuals as a surrogate marker of infectivity, and the results of our study could help resolve the question of differential infectiousness associated with HIV infection. This is an important question to answer in the era of increased MDR- and XDR-TB where our treatment options are limited.

Since data suggest that only 25–45% of patients with pulmonary TB are infectious (10), improving assessment and identification of infectious individuals could have major implications for infection control, especially in resource-limited areas where TB and HIV are highly endemic; and where HIV complicates these measures (11–13).

The findings from this study could allow for more cost-effective resource allocation and targeted contact tracing and investigations in the community. Most importantly, efficient identification of the most infectious individuals would help break the cycle of transmission and limit incidence of new cases moving us toward the goal of TB elimination and future studies should focus on identification of the most infectious individuals using a CASS technique.

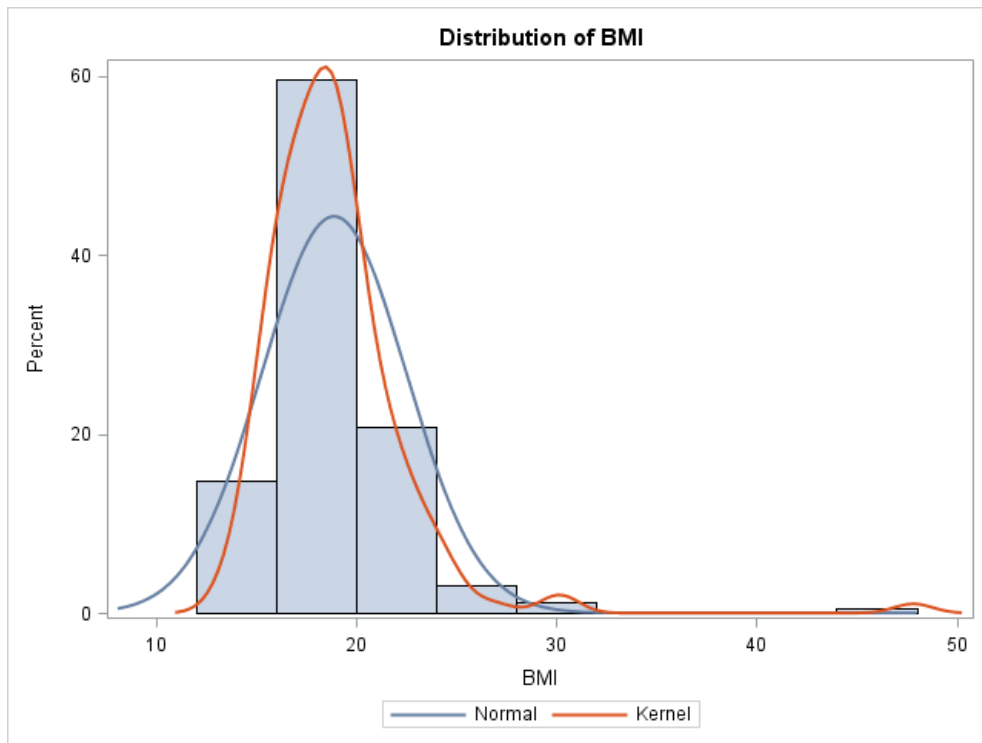
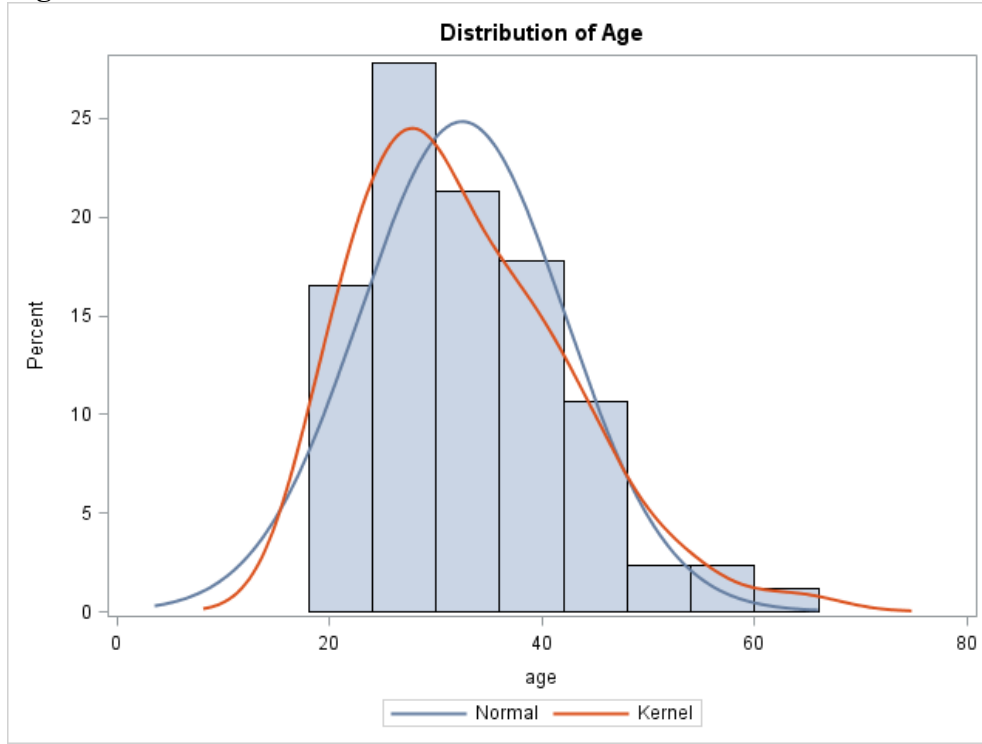
To move this into public health practice we need a more rapid and convenient technique to measure the amount of MTB CFU in cough generated aerosol, and future study should focus on improving aerosol-sampling systems.

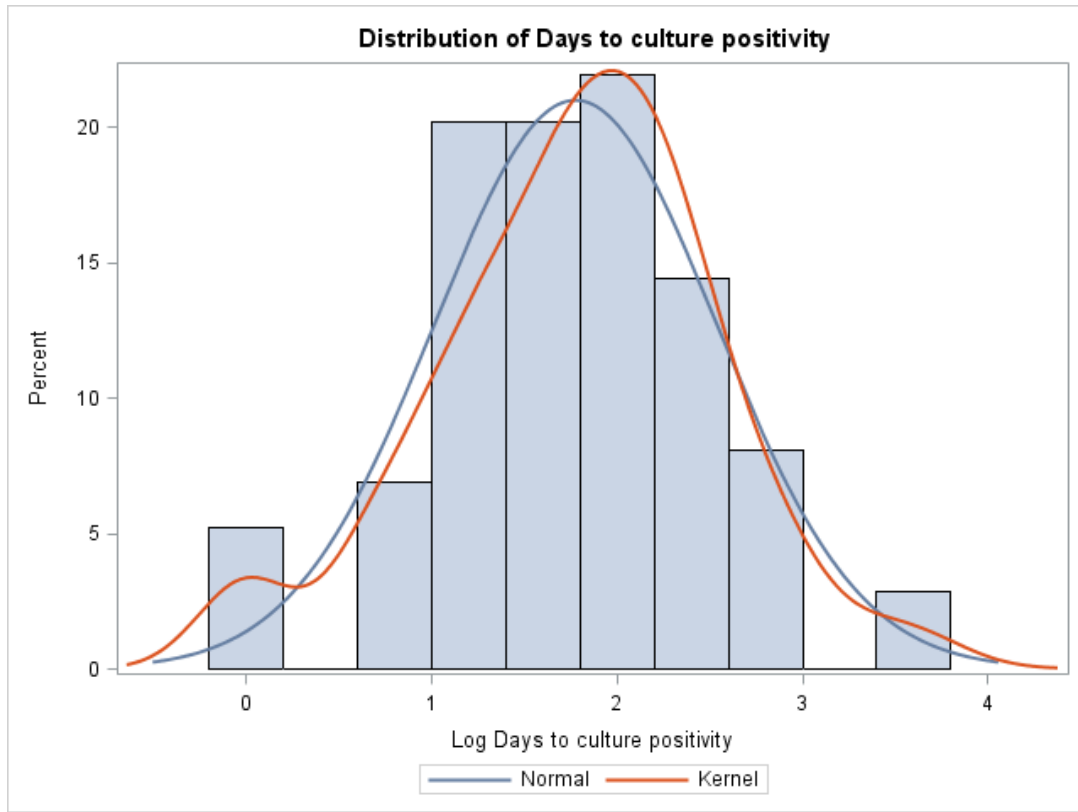
**XI: Role in the study:**

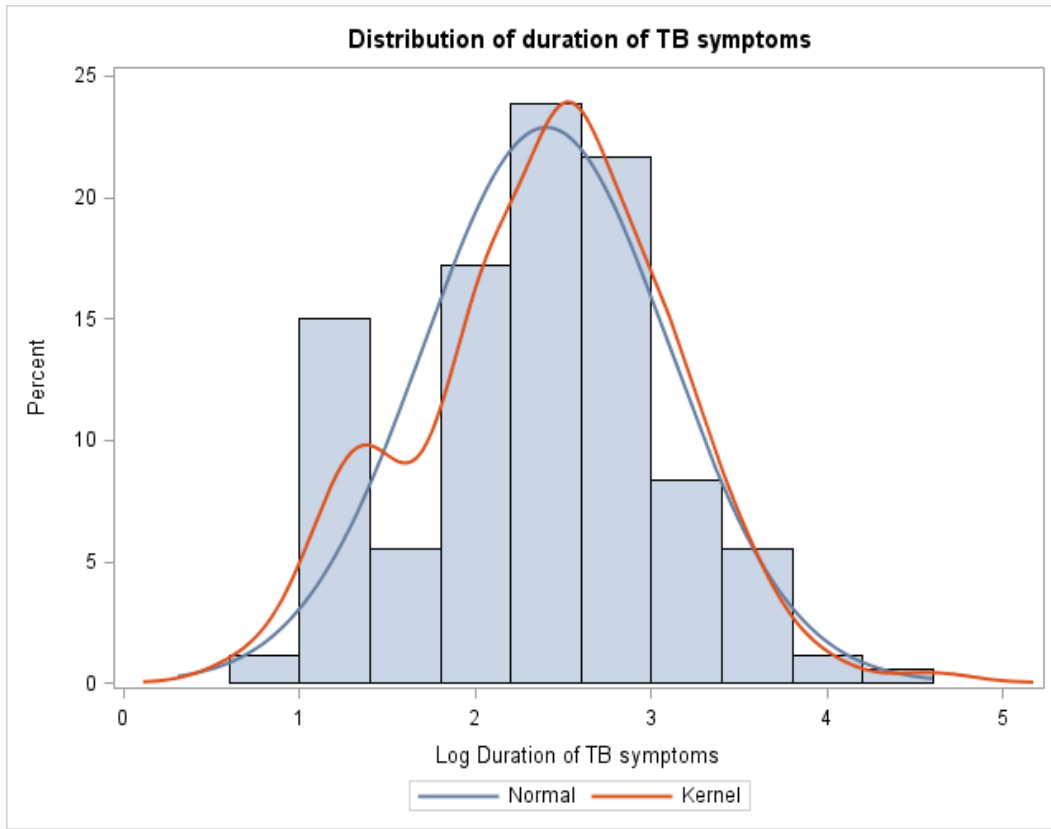
The investigator conducted data management and analysis. I wrote and reported the results of the study in this written thesis. I presented the results orally to the thesis committee.

*Addendum*

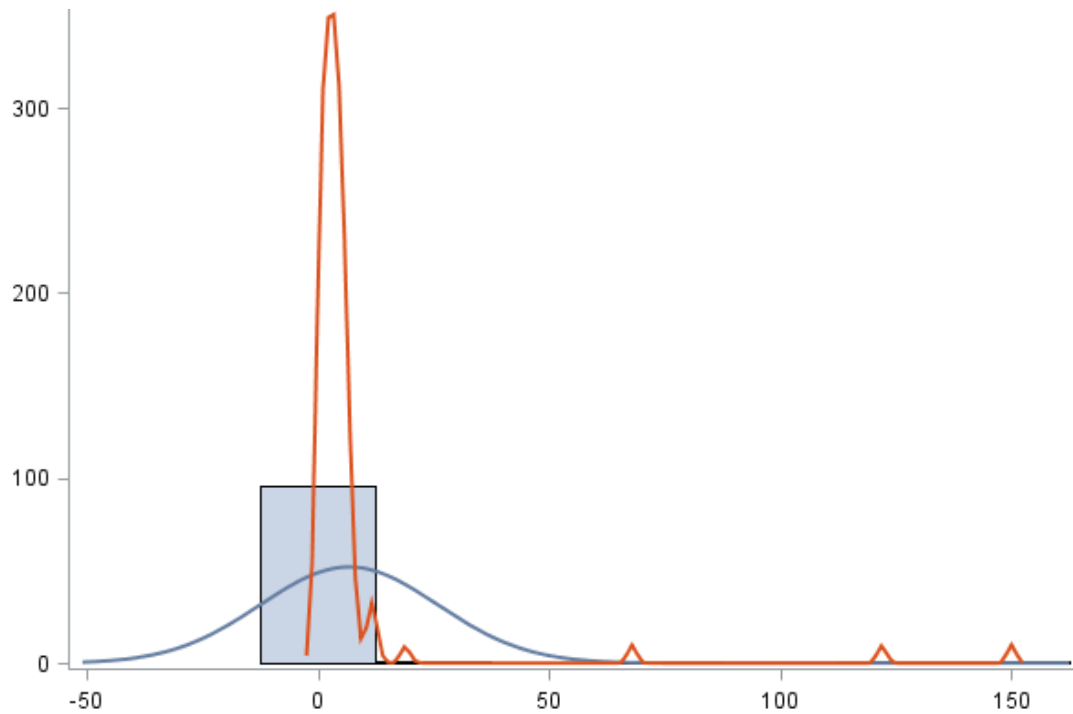
**Figures A1–A5: The distribution of all continuous variables in the data**







**The distribution of duration on TB treatment**



## Results for Objective 1: The effect of HIV infection on MTB CFU on cough aerosol of co-infected patients

### Variables that were be tested for inclusion

- Main predictor of interest
  - HIV
- Epidemiologically significant variables
  - Age
  - Sex
- Historically associated with transmission
  - Cavitory lung disease
  - Duration of TB symptoms
  - AFB smear grading
- Statistically significant variable
  - Any variable was associated with aerosol production in the univariate analysis
- Others
  - Days to culture positivity

### ***Building the Model (Tables A1–10)***

**Table A1. Simple linear regression between outcome and main variable of interest**

Independent Variable	Regression Coefficient	F-Model	t-test	P-value	comment
Intercept	0.9795	5.84	1.61	1.61	
HIV Status			2.42	0.018*	Main variable of interest
Negative	0.8843				
Positive	ref.				

**Table A2. Adding Age to the model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		8.3	2.50	0.015*	Main variable of interest
Negative	0.9628				
Positive	ref.				
Age	0.0126	-	0.67	0.503	Not retained in the model

**Table A3. Adding Sex to the Model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		1.83	2.41	0.019*	Main variable of interest
Negative	0.9005				
Positive	ref.				
Sex	0.0922	-	0.25	0.807	Not retained in the Model
Female	ref.				
Male					

**Table A4. Adding Cavitory Lung Disease to the Model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		-9.2	2.17	0.034*	Main variable of interest
Negative	0.8097				
Positive	ref				
Cavitory disease	-0.0126	-	-0.03	0.974	Not retained in the Model
Present	ref				
Absent					

**Table A5. Adding Days to Culture Positivity to the Model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		-2.4	2.35	0.022*	Main variable of interest
Negative	0.8633				
Positive	ref				
Log DTP	-0.3718	-	-1.38	0.173	Not retained in the Model

**Table A6. Adding Duration of TB symptoms**

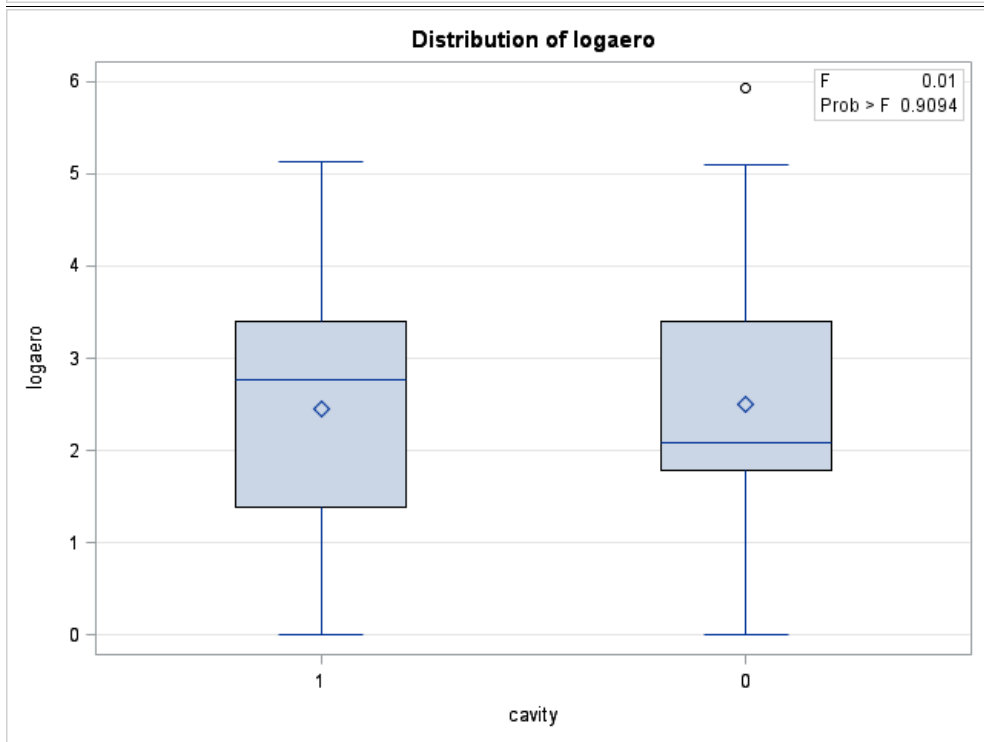
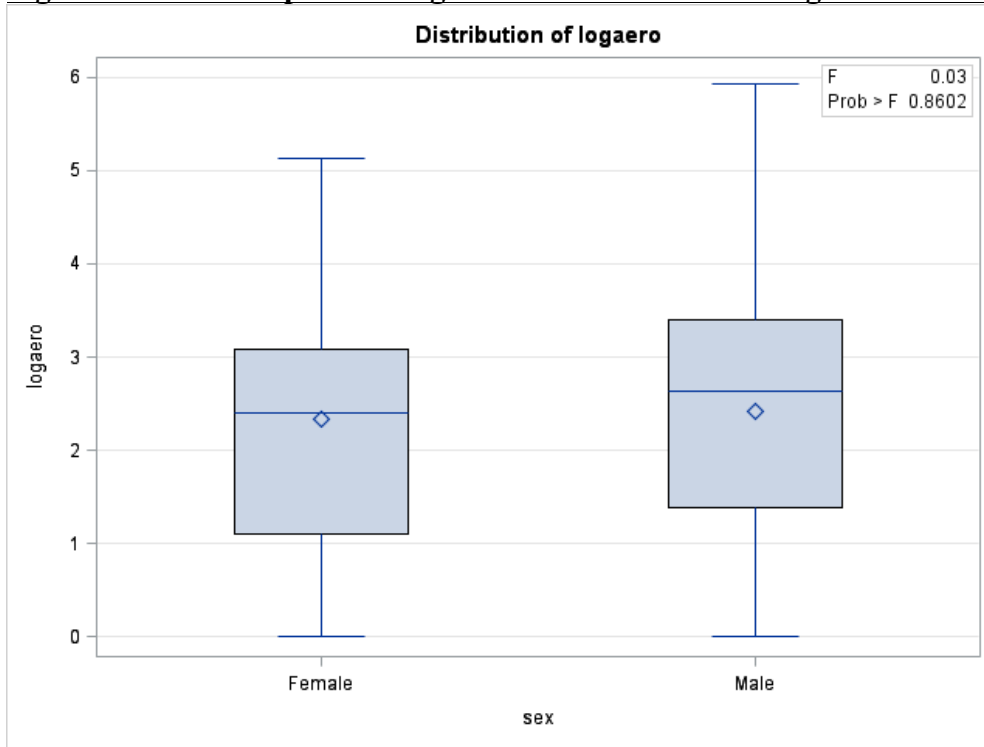
Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		8.1	2.65	0.010*	Main variable of interest
Negative	0.9626				
Positive	ref				
Log Duration of symptoms	-0.1397	-	-0.05	0.959	Not retained in the Model

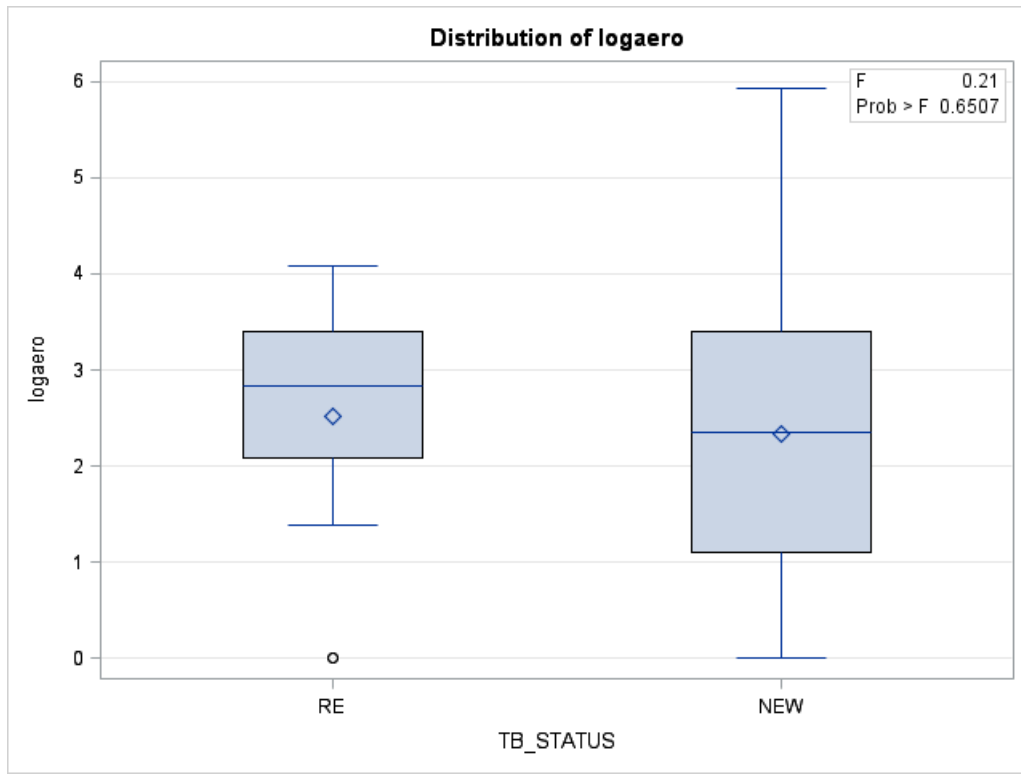
**Table A7. Adding AFB Smear Grading to the final model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		-20.5	2.02	0.048*	Main variable of interest
Negative	0.7338				
Positive	ref				
AFB smear grade	ref	-	-	-	Given % change of ~21% which is more than 10% we will retain AFB smear grade in our final Model
0/1+/2+	0.0798		0.11	0.910	
3+	1.0285		2.04	0.046*	
4+					
4+					

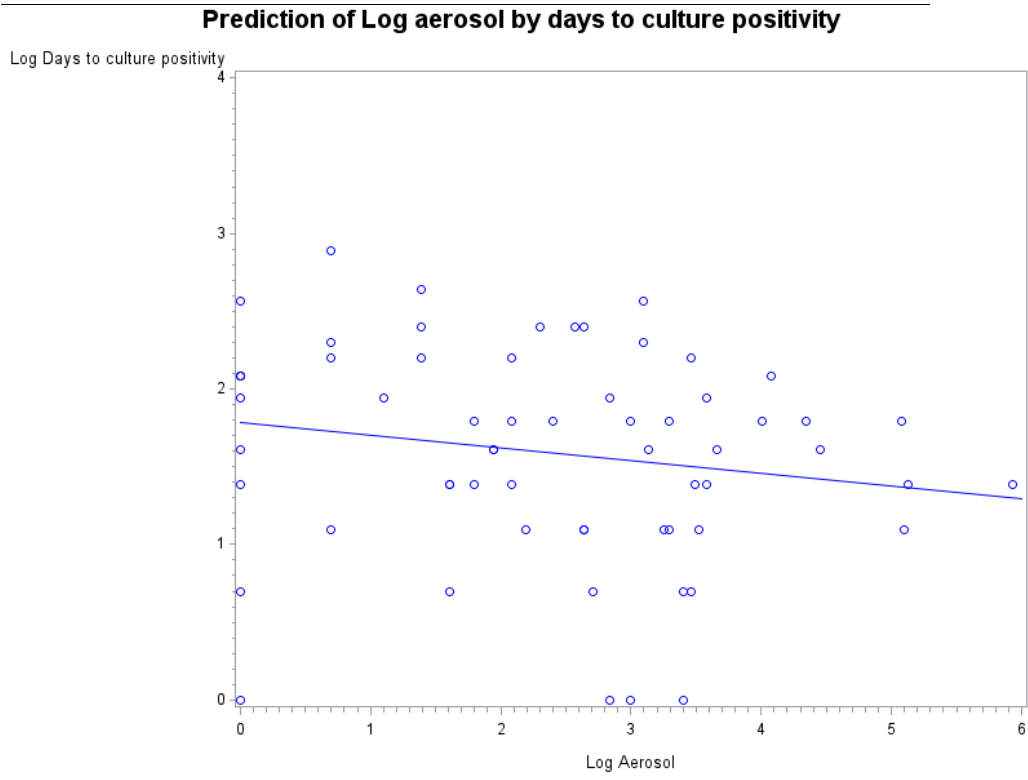
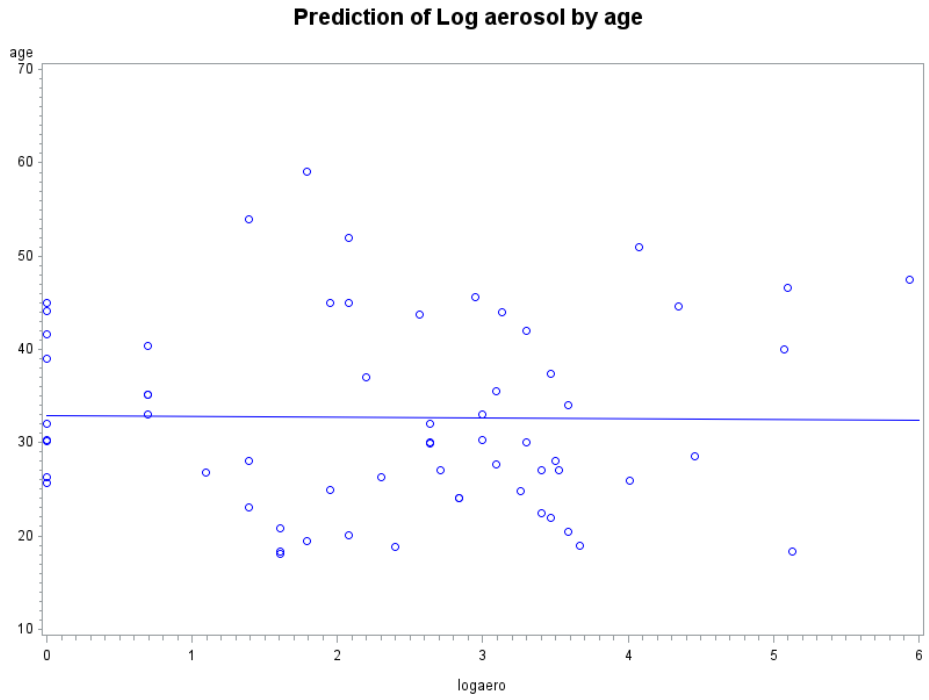
**Table A8. Adding Duration on TB treatment to the model**

Independent Variable	Regression Coefficient	% Change	t-test	P-value	Comment
HIV Status		14%	1.79	0.084	Main variable of interest
Negative	1.033				
Positive	ref.				
AFB smear grade		-	0.70	0.491	Retain in the final model
0/1+/2+	0.567		1.69	0.103	
3+	1.027				
4+	ref.				
Duration on TB treatment	0.267	-	1.32	0.198	Retain in the final model

**Figures A6–A8: Boxplots of Log Aerosol in relation to categorical variables**



**Figures A9–A10: The relation between Log Aerosol and continuous variables**

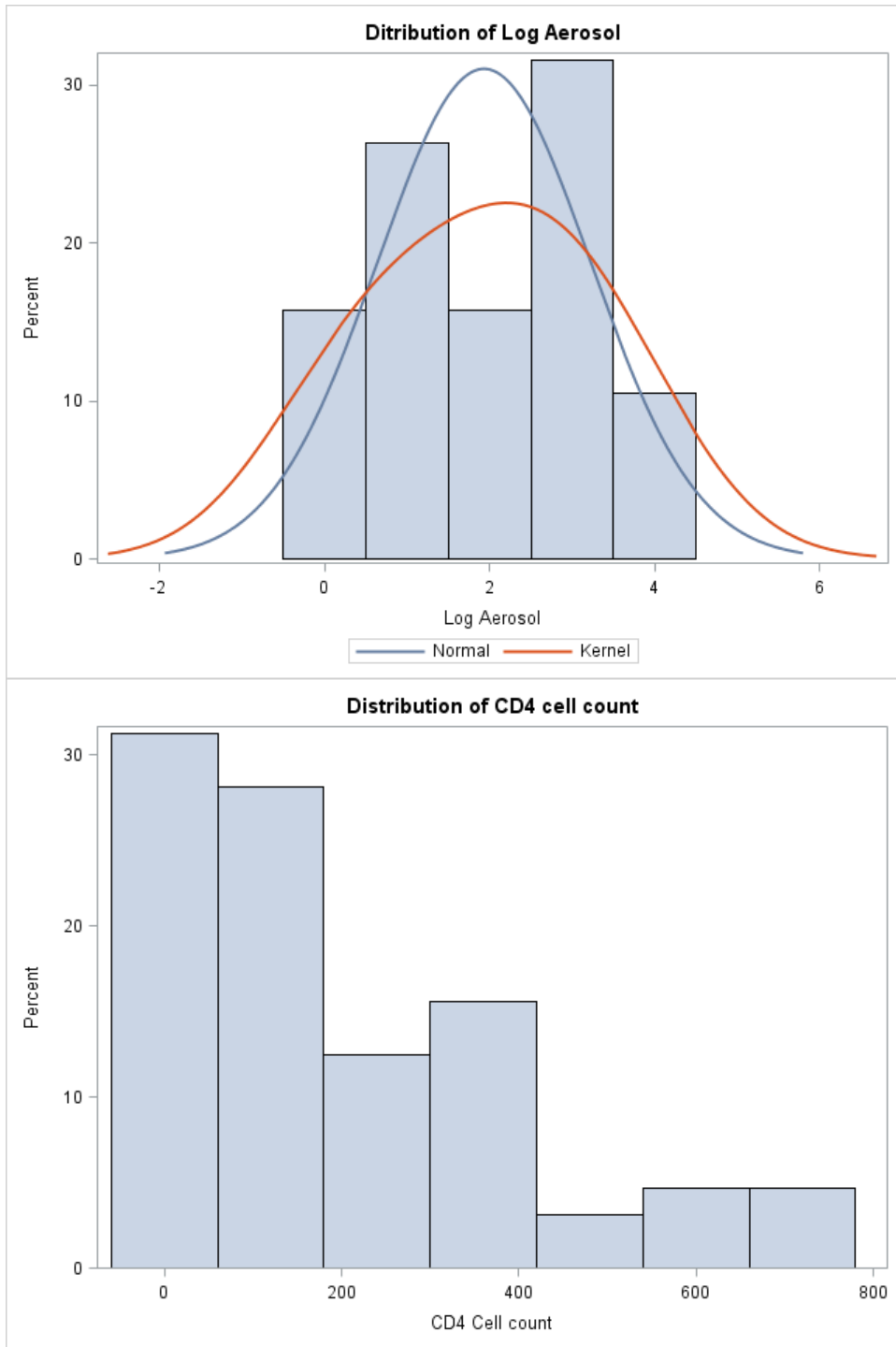


**Objective 2: The correlation between degree of immunosuppression and aerosol production in HIV co-infected patients**

**Table A9. Basic demographic characteristics of HIV infected**

Variable N= 64	Median [IQR] Frequency (%)
Age	35 [30, 40]
Sex	
Male	37 (58)
Female	27 (42)
CD4	
≥200	25 (39)
<200	39 (61)
CD4	
Absolute	140 [44, 312]
Percent	9 [4, 17]
TB Status	
New	26 (41)
Re-infected	38 (59)
Cohort data	
Cohort 1	54 (84)
Cohort 2	10 (42)
Variable N= 64	Median [IQR] Frequency (%)
Sputum Smear	
Positive	54 (84)
Negative	10 (16)
Smear Grade	
0	10 (16)
1+	3 (5)
2+	6 (9)
3+	18 (28)
4+	27 (42)
Duration of TB treatment	3 [2, 5]
Days to positive culture	2 [1, 3]
Sputum Culture	
0	10 (16)
<20	0 (0)
20–100	4 (6)
100–200	3 (5)
>200	47 (73)
Cavitary lung disease	
Present	29 (45)
Absent	33 (52)
Missing	2 (3)

**Figures A11–A12: The distribution of variables amongst HIV-infected individuals**



**Table A10. The univariate analysis of variables and association with aerosol production**

Variable	Regression Coefficient	t test	P-value
CD4		-0.06	0.955
<200	-0.035		
≥200	ref.		
Age	-0.004	-0.10	0.921
Sex			0.302
Female	0.634	1.06	
Male	-	-	
TB Status*			0.033*
Retreatment	1.232	2.32	
New	ref.	-	
Cavitary lung disease			0.408
Present	-0.529	-0.85	
Absent	ref.	-	
Log Days to culture positivity	-0.048	-0.13	0.812
Duration of TB symptoms	0.651	1.42	0.173
AFB smear grade*	ref.	-	0.317
0/1+/2+	0.879	1.03	0.035*
3+	1.752	2.31	
4+			
Cohort data	1.019	1.68	0.110
Cohort 1	ref.		
Cohort 2			
TBDUR	0.0299	1.50	0.154

**Tables: Building the Model****Table A11. Ranking of variables based on their absolute effect on  $\beta$  CD4**

Variable	$\beta$ CD4 before adjustment (ref. CD4<200)	$\beta$ CD4 after adjustment (ref. CD4<200)
<b>1. Duration of TB symptoms</b>	<b>-0.0353</b>	<b>0.3582</b>
<b>2. Cavitary lung disease</b>	-	0.3508
<b>3. TB treatment duration</b>	-	0.3143
<b>4. Sex</b>	-	0.2149
<b>5. TB status</b>	-	0.0208
<b>6. Cohort data</b>	-	0.0818
<b>7. Sputum AFB smear</b>	-	-0.1166
<b>8. Duration to positive culture</b>	-	<b>-0.0699</b>
<b>9. Age</b>	-	-0.0325

**Table A12. Main variable of interest**

Independent variable	Regression coefficient	t-test	P-value	Comment
CD4 count		-0.06	0.955	Main predictor of interest
≥200	-0.0353			
<200	ref.			

**Table A13. Adding Duration of TB Symptoms**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		110	0.55	0.589	Main predictor of interest
≥200	0.3582				
<200	ref.				
Log duration of TB symptoms	0.7648	-	1.5	0.154	Retain in the model

**Table A14. Adding Cavitory Lung Disease**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count	0.4235	15	0.63	0.541	Main predictor of interest
≥200	ref.				
<200					
Log duration of TB symptoms	0.2849	-	0.42	0.678	Retain in the model
Cavitory lung disease	-0.5202	-	-0.69	0.499	Retain in the model
Present					
Absent	ref.				

**Table A15. Adding Sex to the model**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		12	0.69	0.504	Main predictor of interest
≥200	0.4831				
<200	ref.				
Log duration of TB symptoms	0.1154	-	0.15	0.881	Retain in the model
Cavitary lung disease	-0.4919	-	-0.64	0.535	Retain in the model
Present	ref.				
Absent					
Sex		-	0.54	0.598	Retain in the model
Female	0.4113				
Male	ref.				

**Table A16. Adding Age to the model**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		14	0.78	0.453	Main predictor of interest
≥200	0.5618				
<200	ref.				
Log duration of TB symptoms	0.0209	-	0.03	0.979	Retain in the model
Cavitary lung disease		-	-0.89	0.393	Retain in the model
Present	-0.7825				
Absent	ref.				
Sex		-	0.45	0.659	Retain in the model
Female	0.3527				
Male	ref.				
Age	-0.0302	-	-0.72	0.484	Retain in the model

**Table A17. Adding TB Status to the model**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		-22	0.67	0.515	Main predictor of interest
≥200	0.4598				
<200	ref.				
Log duration of TB symptoms	0.0826	-	0.11	0.912	Retain in the model
Cavitary lung disease		-	-0.53	0.608	Retain in the model
Present	-0.4518				
Absent	ref.				
Sex		-	0.60	0.558	Retain in the model
Female	0.4443				
Male	ref.				
Age	0.0059	-	0.13	0.898	Retain in the model
TB Status		-	-1.16	0.135	Retain in the model
Retreatment	-1.1253				
New	ref.				

**Table A18. Adding Smear Category to the model**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		-313	0.12	0.909	Main predictor of interest
≥200	0.1114				
<200	ref.				
Log duration of TB symptoms	-0.1406	-	-0.16	0.876	Retain in the model
Cavitary lung disease		-	-0.41	0.694	Retain in the model
Present	-0.3780				
Absent	ref.				
Sex		-	0.14	0.889	Retain in the model
Female	0.1326				
Male	ref.				
Age	-0.0048	-	-0.09	0.928	Retain in the model
TB Status		-	-1.08	0.307	Retain in the model
Retreatment	-0.9111				
New	ref.				
Smear category		-	-	0.678	Retain in the model
0/1+/2+	ref.		0.43	0.532	
3+	0.6629		0.65		
4+	1.0765				
5+					

**Table A19. Adding TB Treatment Duration to the model**

Independent variable	Regression coefficient	% change	t-test	P-value	Comment
CD4 count		-313	0.12	0.909	Main predictor of interest
≥200	0.1114				
<200	ref.				
Log duration of TB symptoms	-0.1406	-	-0.16	0.876	Retain in the model
Cavitary lung disease		-	-0.41	0.694	Retain in the model
Present	-0.3780				
Absent	ref.				
Sex		-	0.14	0.889	Retain in the model
Female	0.1326				
Male	ref.				
Age	-0.0048	-	-0.09	0.928	Retain in the model
TB Status		-	-1.08	0.307	Retain in the model
Retreatment	-0.9111				
New	ref.				
Smear category		-	-	0.678	Retain in the model
0/1+/2+	ref.		0.43	0.532	
3+	0.6629		0.65		
4+	1.0765				

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**VITA**

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Year of Birth: 1974

*Country of Citizenship:*

United States of America

*Licensures And Certifications*

- 12/2014 American Board of Internal Medicine – Subspecialty  
in Infectious Diseases
- 11/2011 American Board of Internal Medicine certified
- 05/2011 Massachusetts Full Medical License
- 07/2003 Sudan Medical license

*Clinical work experience:*

- 08/2011-Current Academic Hospitalist  
St. Elizabeth's Medical Center, Steward  
Medical Group  
Boston, MA- USA

Was responsible for patients care including diagnosing, treatment and prescribing medications. Participated in resident teaching and supervised residents and interns. Currently continues to work as per dime with average of 9-10 shifts/month

- 07/2012 -07/2014 Infectious Disease Fellow  
Boston Medical Center, Boston University  
Boston, MA- USA

- 01/2007-04/2007                      General Practitioner  
Arkawet Medical Center  
Khartoum, Sudan.

Responsible for patients care diagnosing a variety of medical conditions and performing simple procedures like Lumbar Punctures and prescribing appropriate medications. Patient's education and preventive care medicine.

*Research work experience:*

- 8/2014 -Present                      Postdoctoral research fellow  
Boston Medical Center, Infectious Disease  
department

Conducting high quality research in HIV associated tuberculosis infection and infectivity of tuberculosis infection. Presentations related to research project.

*Other work experience:*

- 05/2012-0/6/2012                      Maternity leave
- 07/2006 -11/2006                      Observer  
Radiology department, University of Missouri,  
Columbia, MO

*Education & Postdoctoral training*

- 09/2013-05/2016                      Boston University School of Public Health  
Master of Science and research in  
Epidemiology  
Boston, MA- USA
- 09/2013- 07/2015                      CTSI CREST fellowship  
Boston University Clinical and  
Translational Science Institution  
Boston, MA- USA
- 07/2012-06/2014                      Infectious Disease Fellowship  
Boston Medical Center  
Boston, MA- USA

- 07/2008-08/2011 Internal Medicine Residency  
St. Elizabeth's Medical center  
Boston, MA- USA
- 07/2002 - 03/2005 Internal Medicine Internship  
Khartoum Teaching University  
Hospital  
Khartoum, Sudan
- 07/2001-06/2002 Houseman-ship  
Several teaching hospitals  
Khartoum, Sudan
- 03/1994-06/2000 Medical School: MBBS  
University Of Khartoum, Sudan

*Honors and awards*

- 08/2013 T-32 Training grant
- 05/2000 University Of Khartoum, Credit in Surgery
- 05/1998 University Of Khartoum, Credit in Microbiology
- 10/1994 University of Khartoum, Distinction in Botany
- 10/1994 University Of Khartoum, credit in Scientific English

*Professional societies*

- 05/2011-Present AMA Associate Member
- 09/2010-Present IDSA Associate Member
- 08/2010 ACP Associate Member
- 07/2012-07/2014 CIR (Committee of Interns and Residents  
Boston Medical Center
- 10/2008 Resident committee permanent member
- 07/2008 Massachusetts Medical Society
- 07/2003 Sudan Medical council
- 01/2001 Sudanese Physician Association

*Committee services*

- 04/2014:IRB Boston Medical Center

Sat in an IRB as part of IRB-Internship of CREST fellowship.

- *10/2008: Resident committee permanent member*  
St. Elizabeth's medical center  
A committee to negotiate important aspects to improve internal medicine residency and improve resident's education

*Volunteer experience:*

- *07/2000 to 09/2000: Field Health worker*  
Ministry of Health. Khartoum, Sudan.  
Worked in the Polio eradication program conducted by the WHO in countries identified for eradication of polio.
- *05/1999 to 08/1999: Health care provider*  
Department of community medicine, Khartoum University.  
Khartoum, Sudan  
Rural residency program served to provide medical services to the underserved areas in Sudan.
- *1998 to 1999: Student tour group leader*  
Medical school rural trip to Kasala, West Sudan. Provided education to the community on health related subjects including family planning, hand hygiene and food handling.

*3. Teaching Experience*

- *1/2013-4/2013 Boston University school of Medicine medical student teaching*  
Teaching second year students about basic history taking skills and physical examination as part of the medical schools curriculum.
- *2012-2014 Boston Medical Center fellow as a teacher*  
Fellow in service teaching responsibility: Teaching residents, interns and students on the inpatient ID rotation about major infectious disease related to their patients condition, Through review of literature and Power point presentations

- *2010-2011 Resident teacher*  
Part of Tufts Compassionate Care Resident as Teacher Initiative, where residents and interns participate in meetings and patient case presentation and at the end develop a presentation to all attending physicians, residents and nurses about the results of the course. Course took place at St. Elizabeth's medical center.
- *2009 Resident teacher*  
Tufts Medical Interviewing course for first year Medical student teaching them basic patient's interviewing techniques as part of the medical school curriculum.
- *1999-2000 Health Educator. Khartoum, Sudan*  
Numerous lectures for health workers in how to deal with the patients, blood withdrawal techniques and basic clinical skills.
- *1995-2000 Resident teacher*  
Teaching undergraduate students about pathophysiology of diseases, physical examination and basics of management.

### *Research Experience*

#### *Current projects*

- HIV associated TB infection: Examining the effect of HIV-1 infection in culturable mycobacterial aerosol production in patients with pulmonary TB infection in a cohort of patients from Kambala, Uganda.
- Rate of extra-genital chlamydia and GC screening in men who have sex with men in outpatient setting at a tertiary care center and way to improve quality of care. The project is funded by the Boston Department of Public Health.
- Latent Tuberculosis Infection in the elderly; a review article evaluating incidence and prevalence of LTBI in people who are 65 years or older

#### *Prior Research projects*

- 10/2000 - 12/2000 Female circumcision in Sudanese culture  
Researcher assistant, Dr: Mohammed Ali. Funded by the Ministry of health, Khartoum, Sudan
- 01/1999-04/1999 Impact of sexual health on STDs

Researcher assistant, Dr: Kamil Elsaid. Conducted by the University of Khartoum Medical School as part of community health project, Sudan

*Presentations and publications*

-Poster presentation at MMS

11/2010 ACP poster presentation for chapter meeting; Rhinoscleroma A forgotten infection –A Case report. Osman S, Alarcon I, Fliesher J.

-Kelesidis T, Osman S, Tsiodras S. Emphysematous cystitis in the absence of known risk factors: an unusual clinical entity. South Med J. 2009 Sep; 102(9): 942-6.

-Kelesidis T, Osman S, Trayner E, Worthington M, Celli B. Tracheobronchitis caused by MRSA as a cause of chronic wheezing in non-ventilated adult with Tracheomalacia Respiration 2010;80(2):148-56. Epub 2009 Dec 30.

-Kelesidis T, Osman S, Dinerman H. An unusual foreign body as a cause of chronic sinusitis J Med Case Reports. 2010 May 26; 4:157

*Regional Presentations*

*-06/2015 CREST fellows research presentation*

Presented to professors of epidemiology, biostatistician, world known TB epidemiologists, professors of medicine and other research fellows preliminary results of my findings of tuberculosis transmission in HIV infected individuals

*-11/2014:Review over site committee*

Presented to world wide known TB experts from the school of public health, infectious disease department project on the effect of HIV1 infection on TB infectivity.

*-6/2014:Effect of climate change on infectious disease*

Journal club presentation on the state of the art on expected effect of global warming on infectious disease epidemiology and transmission. Mentored by Dr Jean-Van Seventer with a known expertise in the area of climate change. Audience is infectious disease attendings, Pediatrics infectious disease attendings, Internal medicine residents, Infectious disease fellows and BU medical student on ID rotation.

*-10/2013: Malnutrition and role that gut Microbiota.*

A journal club presentation about the role that gut microbiota plays on malnutrition and a place for antibiotics use in malnourished children in Malawi. Audience is infectious disease attendings, Pediatrics ID attendings, GI fellows, ID fellows, ID pharmacists, Medical students and medical residents.

*-10/2013:Empiric treatment for mycobacterial infections in SCT*

Case presentation highlighting the importance of thinking outside the box when treating critically ill patients with recent receipt of stem cell transplant.

*-9/2013:Significance of persistent high levels of serum Cryptococcus antigen*

Case presentations highlighting the significance of high Cryptococcus antigen in non-HIV patients with pulmonary symptoms despite several rounds of appropriate antifungal therapy. Case also underscored the importance of drug levels monitoring and susceptibility testing when feasible.

*Skills*

- Fluent in both English and Arabic.

*References*

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