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# Clinical Risk Factors Associated with HIV-Tuberculosis Co-Infection Among Patients on Antiretroviral Therapy, Bungoma and Webuye County Hospitals (2015), Kenya

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**Abstract:** Tuberculosis (TB) is the leading causes of death among people living with Human Immune Deficiency Virus (HIV) and first presenting sign in majority of people living with HIV. Factors influencing TB among HIV patients on anti retroviral treatment (ART) are not well described in our settings. The study aimed to assess clinical factors influencing occurrence of TB among people living with HIV after ART initiation in Bungoma and Webuye hospitals in Bungoma County. The study population consists of 156 cases and 156 controls. Case control study conducted from January 2017- April 2017 in two public hospitals in Bungoma County. Cases were adult people living with HIV who developed TB after ART initiation and controls were adult people living with HIV who did not develop TB after ART initiation. An interviewer administered structured questionnaire was used to collect information. at 95% CI and variables with p-value of < 0.05 at multivariable logistic regression were considered as significant predictors of the outcome variable. The findings of the study were presented in text and tables. The result of this study shows that after adjusting for potential confounders not being on Isoniazid (adjusted odd ratio [AOR] = 35.97, 95% confidence interval [CI] 13.81, 90.20), , having World Health Organization (WHO) clinical stage III/IV (AOR = 15.53; 95% CI: 7.67, 31.47), having interrupted ART (AOR=2.72; 95%CI: 0.35,21.31), were predictors for increase risk of TB in PLWH after ART initiation. Not smoking (AOR=0.31;95%CI:0.13,0.71) had decreases chances of acquiring TB in PLWH after ART initiation. In this study, increasing coverage of isoniazid preventive therapy reduced risk of TB among HIV patients. Study recommends that all PLWH should be screened for TB, but for patients who have advanced disease condition (WHO clinical stage III/IV) intensified screening is highly recommended during treatment follow up.

**Keywords:** Antiretroviral Therapy, Co-Infection, Clinical Characteristics

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## 1. Introduction

Tuberculosis (TB) is the leading causes of death among people living with Human immune deficiency virus (HIV) which shares about 25% of all causes of the deaths [1]. HIV weakens the immune system and makes them more susceptible for TB infection. On the other hand, TB increases the progression of HIV to acquired immune deficiency syndrome (AIDS) stage [2]. TB is among the first presenting sign in the majority of AIDS patients; it is also the most common presenting illness among people living with HIV,

including those who are taking Antiretroviral Treatment (ART) [3].

In 2014, 9.6 million people had acquired tuberculosis of which 1.2 million people were HIV positive. Out of the global TB-HIV co-infection, 74% (888,000 cases) was from Sub-Saharan Africa [4]. Kenya, a low-middle income country is ranked 15<sup>th</sup> among the 22 TB high burden countries [4]. In Kenya, of all the cases notified for TB, 31% are TB-HIV co-infected [5].

The life time risk of developing active TB in HIV-negative individuals is approximately 10%, while the lifetime risk

approaches 50% among HIV positive [6]. It is estimated that about one-third of people with HIV are also infected with TB [7]. Even though ART is known to decrease incidence of TB, but some studies have reported TB incidence in HIV patients on ART [8-9].

In developing countries incidence of TB occurrence has been associated with factors like socio-economic [10], lifestyle/habits [11], clinical [10-11], laboratory [10] and other co-morbidities, eg, diabetes [12]. Many patients either have a history of TB when they start ART, or they develop TB while receiving ART in the developing world [13]. It has not been well delineated what factors influence the development of TB in patients on ART [14]. In sub-Saharan Africa, the incidence of tuberculosis in adults receiving highly active antiretroviral therapy (HAART) is higher than in HIV negative adults [15]. Studies on risk factors of TB were done in the general population but determinants of active TB among HIV patients are not well described in our settings.

Understanding the Clinical risk factors of active TB over time in patients on ART is crucial for the design of effective preventive strategies. This study aimed to assess Clinical Risk Factors associated with HIV-Tuberculosis Co-Infection among Patients enrolled on Antiretroviral Therapy, Bungoma and Webuye County Hospitals in the year 2015.

## 2. Methodology

### 2.1. Study Setting

This study was conducted in two public hospital found in Bungoma county which is locate about 420 km from Nairobi the capital city of Kenya. The two public health facilities are providing free ART services. Bungoma County is located in the western region of Kenya and is one of the 47 counties in Kenya. It is 2,069 square kilometers and has a population of about 1.6 million, with 52.9% of the population living below the poverty line. Agriculture is the main economic activity [16]. It is divided into 10 sub-counties namely Bumula, Mt Elgon, Kabuchai, Kanduyi, Kimilili, Sirisia, Tongaren, Cheptais, Webuye East and Webuye west.

This study was conducted between January 2017, and April 2017.

### 2.2. Participants

The design for this study was unmatched case control, ratio of 1: 1. Cases were TB/HIV co-infected patients whereas controls were non TB infected HIV-positive patients who had already enrolled on ART.

The inclusion criteria for the study were being 15 years and above, TB/HIV co-infected (PTB, EPTB, mixed or disseminated) and on ART for cases and PLHIV with non-TB infected on ART were selected for controls. Those patients who were unable to give consent, transferred to other facilities outside of the study area, and not confirmed as TB were excluded from the study.

To select the study subjects, lists of cases and controls

were prepared using unique identification numbers from records found in ART clinics by computer-generated random numbers. Cases and controls were selected proportional to a number of patients on clinical care in the health facilities during the study period. With the procedure, 156 TB co-infected and 156 non-TB infected HIV positives were selected for cases and controls, respectively.

### 2.3. Measurements

Being tuberculosis co-infected or not co-infected was the dependent variable for the study. The independent variables include socio demographic and economic characteristics (age, sex, income, educational status, and marital status), host and clinical related characteristics (WHO clinical stage, CD4 count, past history of TB, body mass index (BMI), smoking, history of asthma, and diabetic mellitus), and environmental related characteristics (overcrowding, wall and floor type of residential house).

### 2.4. Data Collection

Four trained nurse counselors (2 per each facility) were used to collect data through face to face interview approach. Pretested structured questionnaire was used to collect the data. The interview was made in a separate room to ensure privacy and to facilitate discussions between the interviewer and the respondent. Other clinical characteristics data were retrieved from each patient record. The overall data collection process was supervised by the investigator and co investigator.

### 2.5. Data Analysis

Analysis was made using statistical package for social science (SPSS) version 20.0 software package. Descriptive statistics were used to assess normality, outliers and identify missing values. Bivariate analysis was performed to see the association between the dependent and independent variables. Multivariable logistic regression was done by entering all variables with *P* value less than 0.05 in the bivariate analysis.

### 2.6. Ethical Approval

This study was reviewed and approved by AMREF research and ethics committee (approval number P254-2016). Permission was granted from the county director of health. A verbal consent was obtained from all study participants 18 years and above, for those under 18years consent was obtain from the guardian.

## 3. Study Results

### 3.1. Socio Demographic Characteristics

A total of 312 (156 cases and 156 controls) were selected and interviewed in the study. The response rate was 100%. More than half 192 (53.8%) of them were females. The median age was 37.6 (IQR =8) years. The mean age was 37

(SD10.59). Males were 93 (60%) for cases and women for controls were 109 (70%). The Males cases were 3 time more likely to develop TB [odds ratio (OR) =3.4 95% confidence interval (CI): 2.14, 5.47]] compared to female cases. The Gender was significantly associated with development of TB ( $p < 0.05$ ). The ages between 55 and 64 were 78 % less likely to develop TB than those in age bracket 15-24 (OR =0.129; 95% CI: 0.10, 1.13). Being widower/divorced was three

times more likely to develop TB (OR= 2.03; 95% CI: 0.99, 4.12). Marital status was significantly associated with development of TB ( $p = < 0.001$ ). Those cases with primary and non education level were three times more likely to develop TB compared to those with tertiary education (OR= 3.16; 95%CI: 1.53, 6.45). Level of education was significantly associated with development of TB ( $p = 0.002$ ). (As shown in table 1).

**Table 1.** Socio-demographic characteristics of study participants in factors affecting TB HIV co-infection in Bungoma County, 2015.

	Cases n=156 (%)	Controls n=156 (%)	P value	uOR	95 % CI		AOR	95 % CI	
					Lower	Upper		Lower	Upper
Gender									
Males	93 (59.6.)	47 (30.1)	<0.001	3.42	2.14	5.47	3.33	1.80	6.15
Females	63 (39.4)	109 (69.9)		1					
Age									
15-24	20 (12.8)	12 (8)	0.002	1					
25-34	35 (22)	64 (41)		0.686	0.221	2.134	.313	.129	.762
35-44	57 (37)	42 (27)		0.225	0.085	0.595	1.046	.410	2.669
45-54	27 (17)	31 (20)		0.559	0.213	1.469	.456	.169	1.233
55-64	17 (11)	7 (4)		0.359	0.129	0.995	1.130	.319	4.006
Marital status									
single	28 (18)	22 (14)	<0.001	1					
married	61 (39)	108 (69)		0.444	0.234	0.842	.295	.138	.632
Divorced/ widow	67 (43)	26 (17)		2.025	0.987	4.155	1.194	.496	2.874
Level of education									
Non	11 (7)	8 (5)	0.002	3.067	0.999	9.413	1.761	.494	6.279
Primary	99 (63)	70 (45)		3.155	1.532	6.496	2.664	1.196	5.934
Secondary	33 (21)	49 (31)		1.502	0.682	3.307	1.690	.725	3.937
Tertiary	13 (8)	29 (19)		1			1.000		
Level of income									
Ksh 0- 5000	115 (73)	98 (63)	0.567						
Ksh. 6000-10000	17 (11)	33 (21)							
ksh. 11000-15000	10 (6)	6 (4)							
>15000	14 (9)	16 (10)							

### 3.2. Clinical Factors Associated

The study performed a Bivariate and Multivariable logistic regression analysis on various clinical factors. The result indicates those cases in WHO clinical stage iii and iv were 15 times more likely to develop TB compared to those in stage i & ii % (OR= 15.63;95%CI:8.99-27.16). The results showed that WHO clinical stage was significantly associated with development of TB ( $p = < 0.001$ ). The results indicate that CD4 cell of below 500 was 12 times more likely to develop TB compared to those with CD4 500 and above (OR= 12.14; 95%CI: 5.03, 29.33). The results indicate that CD4 was significantly associated with development of TB ( $p < 0.001$ ). The result showed that body mass index (BMI) less than 18.5 was six times more likely to develop TB compared to those with BMI 18.5 and above (OR=6.32; 95%CI: 3.78, 10.58). The results indicate that BMI was not significantly associated with development of TB ( $p = 0.212$ ). The results indicate that cases who had interrupted ART were five times more likely to develop TB compared to those who did not interrupt the ART (OR=5.57;95%CI:3.14,9.9), interruption of ART was significantly associated with development of TB ( $p = < 0.001$ ). The results showed those who were taking alcohol were 11 times more likely to develop TB compared to those not taking alcohol (OR=11.16; 95%CI:6.36,19.62), alcohol was

significantly associated with development of TB. The results showed that those who had never smoked had 83% not likely to develop TB compared to the past or currently smokers (OR=0.17; 95%CI: 0.10, 0.28), Smoking was significantly associated with development of TB ( $p = < 0.001$ ). The results indicated that those cases who were not on IPT were twenty times more likely to develop TB compared to those who were not on IPT (OR=20.94; 95% CI:11.55,37.97), IPT was significantly associated with development of TB ( $p = < 0.001$ ). The results indicated that history of contact of TB was 10 times more likely to develop TB compared to those without the history of TB contact (OR=10.19;95%CI:5.32,19.49), history of contact of TB was significantly associated with development of TB ( $p = < 0.001$ ). (As shown in table 2).

## 4. Discussion

The study assessed the socio demographic risk factors for developing Tuberculosis after highly active anti retro viral treatment initiation the results indicated that several socio demographic factors influence the development of TB after HAART.

The finding of the study showed that males were mostly affected by TB, this is similar to the study done in Russia and Kenya which showed that males are affected more with TB

than females [17-18]. Study done in Mombasa contradicts with this finding which showed that females were more affected with TB than males [19]. This can be attributed to

social factors since men have more social contact thus expose to contagious diseases like TB.

**Table 2.** Clinical characteristics of study participants in factors affecting TB HIV co-infection in Bungoma County, 2015.

	Cases n=156 (%)	Controls n=156 (n)	p value	uOR	95 % CI		AOR	95%CI	
					Lower	Upper		Lower	Upper
WHO stage									
i&ii	31 (20)	124 (79)	<.001	1 REF					
iii&iv	125 (80)	32 (21)		15.63	8.99	27.16	15.53	7.67	31.45
CD4 cell count									
<500	150 (96)	105 (67)	<.001	12.14	5.03	29.33	9.88	3.68	26.50
500+	6 (4)	51 (33)		1REF					
Body mass index									
<18.5	108 (69)	35 (22)	0.212	6.32	3.78	10.58	7.24	3.83	13.66
18.5+	48 (31)	120 (77)		1REF			1		
Interrupted ARV									
Yes	88 (56)	19 (12)	<.001	5.572	3.136	9.9	2.72	0.347	21.308
No	68 (44)	137 (88)		1REF			1		
Alcohol									
Yes	99 (63)	21 (13)	<.001	11.165	6.355	19.616	8.62	3.37	21.99
No	57 (37)	134 (86)		1REF			1		
Smoking status									
Never	57 (37)	121 (78)	<.001	0.17	0.10	0.28	0.31	0.13	0.71
Smoker	98 (63)	35 (23)		1REF			1		
History of Asthma									
Yes	8 (5)	2 (1)	0.054	4.162	0.87	19.923			
No	148 (95)	154 (99)		1REF					
Isonazid preventive therapy									
Yes	20 (13)	118 (76)	<.001	1REF			1		
No	136 (87)	38 (24)		20.937	11.546	37.966	35.29	13.81	90.20
History of TB contact									
Yes	81 (48)	13 (8)	<.001	10.185	5.323	19.488	6.43	2.93	14.10
No	75 (52)	143 (92)		1REF			1		

The study showed that age was not associated with development of TB, this finding are similar to study done in Ethiopia which showed that age was not a risk factor for development of TB [20]. This finding contradicts with study done in Mombasa, Kenya and Gambia that showed that most of the patients affected were between the age of 25 and 49 [17, 18, 21]. This can be attributed to the fact that most of people affected by HIV are in the reproductive age group thus no difference between the TB co-infected and those not co-infected.

The study showed that marital status was a factor influencing TB, being divorce or widower was associated with development of TB among people living with HIV, this is consistent with study done in Gambia and Guinea Bissau [11, 22], which showed that patients who were divorced/widowed were at great risk of developing TB. This can be due to being married lead to positive psychological and social impacts [23].

The study results showed education level was not a factor associated with development of TB after adjusting for the odd ratio. This contradict with the finding in the study done in Ethiopia and India that showed that those no formal education were more likely to develop TB [24-25] this can be due to high level of patient who at least have primary level in

the study population.

The study showed that income was not associated with development TB. This contradicts with the study done in 134 countries, Nairobi and Nakuru which showed that TB was associated with poverty [26-28]. This can be attributed to the fact that most of the study population was from area where Agriculture is done on large scale; most of the study participants were farmers.

The study assesses the clinical risk factors for developing Tuberculosis after highly active anti-retroviral treatment initiation the results indicated that several factors influence the development of TB after starting on HAART

The study showed that WHO clinical stage iii and iv was associated with development of TB which is similar to the results of a studies done in South Africa and Ethiopia [29-30] that showed that WHO clinical stage iii & iv was associated with development of TB. This can be attributed to reactivation of latent TB due to reduced immunity.

The study results indicates that malnutrition was not associated with development of TB the result contradict with a study done in Uganda and South Africa [31-32] which showed that BMI below 18.5 was associated with development of TB. This can be attributed to the fact that most of HIV patients are put on food supplements and

counseling which tend to improve their nutritional status.

The study results also indicates that past and current smoking was a factor associated with development of TB, the results agrees with the study done in West Africa that showed that smoking was associated with development of TB [11], but it differs with the study done in Gambia [22] which showed that smoking was not associated with the development of TB. The association between smoking and TB has been studied in several systematic reviews [33-38]. Bates and colleagues, shows that relative risk of TB disease and TB death was more among the smokers [36]. This can be attributed to impaired clearance of mucosal secretion, reduced phagocytic ability of alveolar macrophages [39-40] and decrease in the immune response due to the nicotine [40].

The study also showed that alcohol was a factor influencing TB in patients living with HIV, this results is similar in meta analysis that recognize alcohol as a strong risk factor for TB disease [41]. A systematic review of 3 cohort and 18 case control studies concluded that the risk of TB was high in alcoholic. This can be attributed to alteration in the immune system.

Different studies have shown that Isoniazid preventive therapy (IPT) reduces the risk of TB infection in PLWHIV [41-45]. Similarly, in this study, patients who were on IPT were at the lower risk of developing TB and being on isoniazid was protecting against. The study agrees with the study done in Ethiopia with showed that being on IPT was not associated with TB co-infection [25]. This is attributed to the fact that Isoniazid is used in treatment of latent TB thus reduced risk of reactivation of latent TB.

The study showed that low CD4 was associated with the development of TB, this is similar to the results done in study done in Ethiopia and South Africa [25, 46] that showed that those with low CD4 were at a higher the risk of TB during ART, *this can be attributed to the factor of low immunity which predispose one to reactivation of latent TB.*

The study showed that Asthma was not associated with development of TB this is consistency with study done in Gambia which showed that Asthma was not associated with TB [22] but contradicts with study done in West Africa which showed that asthma was protective against TB [47].

The study showed that those patients who had interrupted ART was associated with development of TB this can be due to the factor that when one stop taking the ART the immunity reduces and there is reactivation of latent TB.

## 5. Conclusion and Recommendation

Having poor clinical stage (WHO stage iii & iv) and low CD4 cell count were found to be associated with development of Tuberculosis. All people living with HIV/AIDS should be screened for TB. But, in the presence of the risk factors mentioned in this study, intensified screening is highly recommended during follow up. In addition, increasing coverage of IPT is necessary to reduce the overall risk of TB among HIV. Adherence counseling is important in

order to avoid ART treatment interruption.

## Conflict of Interest

The authors declare that they have no competing interests.

## Authors' Contribution

All authors participated by writing the study protocol, participated collecting data, data analysis, report writing, drafted the paper with subsequent revision and approved the final manuscript

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