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Effect of Isoniazid Preventive Therapy on Tuberculosis Prevalence among HIV Patients Attending Bahati Comprehensive Care Centre, Nairobi, Kenya

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Abstract

Introduction: Worldwide tuberculosis was top ten cause of death alongside, Human Immunodeficiency Virus (HIV) in 2018; 10.0 million people became ill with tuberculosis with 1.2 million deaths occurring among HIV negative people while an additional 251,000 were HIV positive. Isoniazid preventive therapy (IPT), intensified case finding, and infection control have been widely recommended to reduce the burden of TB in people living with Human Immunodeficiency Virus (PLHIV). IPT works synergistically but independently of antiretroviral therapy (ART) to reduce the morbidity, mortality and incidence of tuberculosis among PLHIV, but its uptake has been slow in most developing countries.

Objective: This study sought to find the effect of isoniazid preventive therapy on prevalence of tuberculosis among HIV patients attending Bahati comprehensive care centre.

Materials and Methods: A retrospective cohort study was conducted over a seven month period among consented 346 people living with Human Immunodeficiency Virus (HIV) residing in Makadara Nairobi County, attending Bahati comprehensive care centre with signs and symptoms of TB. Sampled sputa from the participants were analyzed for detection of *Mycobacterium tuberculosis* by GeneXpert MTB/RIF assay and culture by BACTEC MGIT 960. Socio demographic and laboratory data was collected and the data was analyzed using SPSS version 20.0.

Results: Of the three hundred and forty six sputa sampled and analyzed, 10(6.5%) and 67(35.1%) IPT and non-IPT patients had *Mycobacterium tuberculosis* detected respectively; P=0.001. On the other hand 57(18.2%) and 20(60.6%) new and retreatment patients had *Mycobacterium tuberculosis* detected respectively.

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Conclusion: Isoniazid preventive therapy is protective towards progressing to active tuberculosis disease and symptomatic previously treated Tuberculosis (TB) patients are more likely to have confirmed TB disease. There was no significant association between prevalence of tuberculosis, age and gender of the patients

Introduction

Mycobacterium Tuberculosis (*MTB*) is the causative agent of tuberculosis, which still remains a leading cause of mortality and morbidity globally [1]. Worldwide tuberculosis was top ten cause of death alongside Human Immunodeficiency Virus (HIV) in 2018 [2]. In 2018, 10.0 million people fell ill with tuberculosis; 1.2 million TB deaths were among HIV negative people while an additional 251,000 were among HIV positive people [2]. HIV co-infection has been associated with unusual presentations of TB such as smear negative and abnormal chest radiographs thus causing a diagnostic challenge, poor treatment outcome and subsequent increased mortality [3]. People living with HIV who have TB infection have a 5-10% annual risk of developing TB compared to 5-10% lifetime risk in HIV negative individuals [1]. Isoniazid Preventive Therapy (IPT) together with other interventions such as intensified case finding and infection control has been widely recommended to reduce the burden of TB in people living with HIV (PLHIV) [4].

Isoniazid preventive therapy has proven to be safe with minimal and less frequently reported side effects such as hepatotoxicity and gastrointestinal symptoms, studies have shown that IPT can lower TB incidence among people living with human immunodeficiency virus (PLHIV) by up to 70% if used with or without ART [4]. Taking isoniazid as a preventive measure is a cost effective and simple way that prevents TB if present to become inactive, the drug has been a standard for treatment of tuberculosis and preventive therapy due to its high potency, infrequent toxicity, low cost and non- bulk [4]. Treatment of Latent Tuberculosis Infection (LTBI) prevents its progression to active disease, both in HIV negative population and those infected with HIV [5]. Increasing uptake of isoniazid preventive therapy in HIV positive people prevents deaths and cases caused by tuberculosis [6]. Uptake of IPT has been relatively slow in most developing countries; it works synergistically with and independently of antiretroviral therapy (ART) to reduce tuberculosis morbidity, mortality and incidence among PLHIV [7,8].

Isoniazid preventive therapy involves provision of isoniazid tablets to those who meet the eligibility criteria [8]. The recommended dose is 10mg/Kg daily for children and up to 300mg/day for adults [8]. To end the global TB epidemic, it entails addressing the significant reservoir of TB infection, especially in PLHIV who have the highest risk of progression to TB disease [8]. Emphasis on TB prevention not only spares individuals the burden of TB associated morbidity and mortality but it also reduces the economic impact of the disease on the health system as a whole [9]. Isoniazid preventive therapy is protective towards progressing to active tuberculosis disease and retreatment tuberculosis patients are more prone to TB disease [1]. Although IPT is crucial and cost effective component of HIV care for adults and children and has been strongly recommended as an international standard of care for over a decade, it has remained highly underutilized [10]. Regular screening for TB disease among PLHIV is a standard of care and a critical component of HIV care and treatment because it can be effectively treated especially when diagnosed early, hence therefore finding and treating people with TB disease and thus interrupting further transmission remains a top global healthy priority [8].

Materials and methods

Study design

This was a retrospective cohort study design conducted in Makadara sub-county, Nairobi, Kenya. Eligible HIV positive participants (with or without use of IPT) were recruited through cluster random sampling, only those who gave consent were enrolled in the study.

Inclusion and exclusion criteria

Patients who were HIV positive, on care, above 15 years, with signs and symptoms of tuberculosis, at one year post IPT, were included in the study upon consent. While patients with IPT and age records not clear, unable to consent, with other samples other than sputum were excluded from the study.

Sputum collection

Good quality spot and morning sputum samples were collected in 50ml sterile conical tubes; the samples were processed according to the standard operating procedures for GeneXpert MTB/RIF assay and culture using BACTEC MGIT 960 machine.

Laboratory methods

Identification of *mycobacterium tuberculosis*

Good quality sputa [11] and the reagent buffer were mixed according to the standard operating procedure and loaded into the Xpert MTB/RIF assay cartridge and test started on Xpert MTB/RIF assay machine platform[3]. The assay has internal quality controls which serve to verify that lysis of *Mycobacterium tuberculosis* has occurred, sample preparation is adequate and detect any inhibitor of polymerase chain reaction; this is accomplished by the sample processing control (SPC) [3]. Sample processing control must be positive when the result reads *Mycobacterium tuberculosis* not detected, while it can be negative or positive when the result is *Mycobacterium tuberculosis* detected. The system undertakes to measure fluorescence signal, rehydrating the beads and checking stability of the probe and dye. This is accomplished by the probe check control [3]. Upon completion of the test, results were either of the following; *Mycobacterium tuberculosis* not detected, *Mycobacterium tuberculosis* detected very Low, Low, Medium or High. In this case the rifampicin resistance can be either detected or not detected. The test results can also be in form of error or invalid, in this case the test must be repeated [3].

Culture of *mycobacterium tuberculosis*

Sputa were subjected to culture for the presence of *Mycobacterium tuberculosis* (*MTB*) on non-radiometric method Mycobacterium Growth Indicator Tube (MGIT) BACTEC 960. This was done according to manufacturer recommendations. Decontamination of the sputa was done using sodium hydroxide solution (40% w/v) combined with 2.9% sodium citrate solution and N-acetyl-L-cystein powder [12,17]. Sterile phosphate buffer was added and the organisms concentrated by centrifugation at 3,000 rpm for 15 minutes. The supernatant was decanted and the sediment suspended with phosphate buffer and inoculated in liquid MGIT media and incubated along with negative control (un-inoculated MGIT media) and positive control (H37Rv ATCC 27294) [12]. The inoculated MGIT tubes were incubated in the

BACTEC MGIT 960 machine at 37 °C until the instrument flagged them positive. After a maximum of six weeks, the instrument flagged the tubes negative only if there was no growth at 37 °C [13]. Isolates from MGIT 960 were subjected to confirmative identification of MTB using BD MGIT TBc. Positive culture for MTB confirmed diagnosis of active disease [13,14].

Quality control

Un-inoculated Mycobacteria growth indicator tube (MGIT) (negative control), and H37Rv ATCC, 27294(positive control) were processed and included during the run. Purity of bacterial suspensions used was checked by culture on blood agar [15,16].

Statistical analysis

Data was entered and analyzed by SPSS version 20.0 statistical software. Pearson's Chi-square test was applied to determine the differences in proportion for both groups in IPT status, type of patient and gender against the detection of *MTB*. Pearson's Chi-square test was applied to determine the differences in proportion for both groups in IPT status, type of patients and demographics against TB. These results were presented by appropriate tabulations based on the determined variables, odds ratio (OR) with 95% confidence interval (CI) and the corresponding P- values. The threshold for statistical significance was set at P≤ 0.05.

Results

Prevalence of Tuberculosis (TB) in relation to Isoniazid Preventive Therapy (IPT) and patient treatment status

Of the 346 sputum samples subjected to Xpert MTB/RIF assay analysis, 10(6.5%) and 67(35.1%) had *Mycobacterium tuberculosis(MTB)* detected in IPT and non-IPT patients respectively, (OR 7.835[95% C.I =3.866-15.878]; P=0.0001) (Table 1), on the other hand new and retreatment patients recorded 57(18.2%) and 20(60.6%) detection of *MTB* respectively,(OR 0.145[95% C.I=0.068-0.308]; P=0.0001) (Table 1). This indicated a significant association between the IPT status of the patient and *MTB* detection; the non-IPT arm of patients was more prone to TB, than the IPT arm. On the other hand there was a significant association between *MTB* detection and patient treatment status; retreatment TB patients were more prone to TB disease than the new patients. Further findings revealed that detection of TB was high among the males of age category (20-39), 27(14.1%) from the Non- IPT arm, in the same age category females documented 16(8.4%) TB cases (Table 2). There was no significant association between prevalence of TB and the age or gender of the patients. Study findings also revealed that 145(93.5%) and 124(64.9%) samples were negative for *MTB* among IPT and Non-IPT patients while 256(81.8%) and 13(39.4%) samples were negative among new and retreatment patients.

Table 1: *Mycobacterium tuberculosis* results from Xpert MTB/RIF Assay among study patients

Variables	Total (N)	MTB Detected n (%)	MTB Not Detected n (%)	OR (95% CI)	P Value
IPT Status					
IPT Patients	155	10 (6.5)	145 (93.5)	7.835 (3.866-15.878)	**0.0001**
Non-IPT Patients	191	67 (35.1)	124 (64.9)		
Patient Treatment Status					
New Patients	313	57 (18.2)	256 (81.8)	0.145 (0.068-0.308)	**0.0001**
RT Patients	33	20 (60.6)	13 (39.4)		
Gender					
Female	153	30 (19.6)	123 (80.4)	0.758 (0.452-1.271)	0.293
Male	193	47 (24.4)	146 (75.6)		
Age(Years)					
< 20	34	4 (11.8)	30 (88.2)		
20 – 39	191	47 (24.6)	144 (75.4)	0.791 (0.62-2.333)	0.624
40 – 59	103	23 (22.3)	80 (77.7)	0.613 (0.423-3.899)	0.454
60 +	18	3 (16.7)	15 (83.3)	0.696 (0.332-0.78)	0.591

MTB: Mycobacterium Tuberculosis; RT: Retreatment; IPT: Isoniazid Preventive Therapy; OR: Odds Ratio; CI: Confidence Interval

Table 2: Xpert MTB/RIF Assay Results in relation to IPT status, Gender and Age

				MTB DETECTION		Total
IPT Status	Gender			MTB DETECTED	MTB NOT DETECTED	
IPT Patients	Male	Age (Years)	60+	1(0.6%)	4 (2.6%)	5
			40 – 59	2(1.3%)	19 (12.3%)	21
			20 – 39	3(1.9%)	43 (27.7%)	46
			< 20	0(0%)	8 (5.2%)	8
		Sub-Total		**6(3.9%)**	**74 (47.7%)**	**80**
	Female	Age (Years)	60+	1(0.6%)	4 (2.6%)	5
			40 – 59	1(0.6%)	22 (14.2%)	23
			20 – 39	1(0.6%)	33 (21.3%)	34
			< 20	1(0.6%)	12 (7.7%)	13
		Sub-Total		**4(2.6%)**	**71 (45.8%)**	**75**
	Total	Age (Years)	60+	2(1.3%)	8 (5.2%)	10
			40 – 59	3(1.9%)	41 (26.5%)	44
			20 – 39	4(2.6%)	76(49%)	80
			< 20	1(0.6%)	20(12.9%)	21
		Total		**10(6.5%)**	**145 (93.5%)**	**155**
Non IPT patients	Male	Age (Years)	60+	1(0.5%)	3 (1.6%)	4
			40 – 59	12(6.3%)	31 (16.2%)	43
			20 – 39	27(14.1%)	35 (18.3%)	62
			< 20	1(0.5%)	3 (1.6%)	4
		Sub-Total		**41(21.5%)**	**72 (37.7%)**	**113**
	Female	Age (Years)	60+	0(0%)	4 (2.1%)	4
			40 – 59	8(4.2%)	8(4.2%)	16
			20 – 39	16(8.4%)	33 (17.3%)	49
			< 20	2(1%)	7 (3.7%)	9
		Sub-Total		**26(13.6%)**	**52 (27.2%)**	**78**
	Total	Age (Years)	60+	1(0.5%)	7(3.7%)	8
			40 – 59	20(10.5%)	39 (20.4%)	59
			20 – 39	43(22.5%)	68 (35.6%)	111
			< 20	3(1.6%)	10 5.2%)	13
		Total		**67(35.1%)**	**124 (64.9%)**	**191**
Total				**77**	**269**	**346**

IPT: Isoniazid Preventive Therapy; RIF: Rifampicin; MTB: Mycobacterium Tuberculosis

Discussion

The current study findings indicate that there is significant association between the isoniazid preventive therapy(IPT) status of the patient and likelihood of developing active Tuberculosis disease (TB); the non-IPT arm of patients had a significantly high rate of tuberculosis(TB) cases (35.1%) compared to the IPT arm (6.5%), these study findings confirm with other previous findings that IPT protects against progressing to active TB in the risk populations, among them being people living with HIV. The current study findings were relatively higher than those observed in previous studies in South Africa (15.9%) [18], Zimbabwe (3.0%) [8], Indonesia (Hasan Sadikin hospital) (4.3%) [9] Ethiopia 16.32% [4], (27.8%) [19] (13.4%) [5], (8.8%) [1]. On the other hand the findings were comparable with results from a previous study conducted in Egypt (Al- Hussein university) (36.7 %) [20], but the findings were relatively low than previous study findings in Pakistan 49.46% [21], (98.7) [22].

The difference in the findings can be attributed to low uptake of isoniazid preventive therapy. The study findings further indicated significant difference in the number of TB cases among patient treatment status; retreatment patients had (60.6%) while new patients had (18.2%), there was a significantly high rate of TB cases among the retreatment cases. The current findings confirm with other previous studies that retreatment patients are significantly associated to TB disease. The current study findings are slightly high than those documented in Ethiopia (53.8%) [23], on the other hand these findings are markedly high than previous findings in a study conducted in Benin (6%) [24], this difference may be attributed to lack of patient compliance to TB drugs, treatment interruptions due to either (imprisonment, defaulting) and weak active case finding strategies which allow re-infection of the already cured people, HIV prevalence [23]. Further findings of the current study indicated that a high percentage of male patients of age category 20-39 years had TB (14.1%), further the findings were markedly lower than those recorded in Thailand (43.7%) [25]. On the other hand the study findings were comparable with those recorded in Ethiopia (14.2%) [19].

These finding would be attributed to the fact that in this age category (20-39), people are normally in institutions of learning, which are often crowded increasing transmission of this air borne disease. Also because of peer pressure which is common during this period, engaging in irresponsible behavior like drug abuse coupled with the already depressed immunity due to HIV makes the body vulnerable to TB disease [10]. The health service seeking behavior can also be attributed to the high TB cases in males of this age category (they tend to seek health services only when the condition is serious) and the mobility they exhibit; in African culture males are supposed to fend for the family thus they have to move seeking for menial jobs in the process they are exposed to conditions which predispose them to get TB [26]. 20-39 years is the productive age of an individual, TB disease being chronic will compromise productivity of this population in the sectors they offer their services and thus decrease a country's gross domestic product which eventually will lead to an unstable economy [10]. In institutions of learning students will drop out because of either stigma from friends and the lecturers or the challenges which come along with the long TB treatment duration, this might lead to a country lacking work force because the productive population will lack the necessary skills because of lack of education, worse more because of stigma treatment defaulting is high and this might lead to increased mortality and morbidity [10]. One important limitation of this study is that it involved participants who consented to be part of the study; the non-participants would not be profiled.

Conclusions

IPT protects against development of active Tuberculosis (TB) disease in eligible patients, who harbor latent TB. Retreatment patients were significantly associated with TB because of either lack of adherence to medications during previous TB treatments or interruptions during treatment which lead to lack of treatment completion. Of the patients infected with the disease a high percentage (14.1%) was male of age 20-39 years and those patients from the non-IPT arm.

Recommendation

Call for intensified efforts towards increasing the uptake of isoniazid preventive therapy in patients who are eligible to curb progressing of latent tuberculosis to active disease, especially in vulnerable population like people living with HIV. Active case finding on index cases should be made routine to avoid re-infections for those already cured. In this case there should be a budget for purposes of tracing the contact cases in their homes. Through the ministry of health friendly health education should be put in place, mostly in social gatherings to inform the population on what is TB, how it is spread, prevented, diagnosed, treated and importance of seeking medical attention earlier to avoid complications and further spread of the disease. This should be done in such a way that the target should be males 20-39 years of age.

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