



Follow-Up of HIV Positive-Sputum Smear Negative Presumptive Tuberculosis Patients in The EAPHLNP Study Site in Kenya

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The East Africa Public Health Laboratory Networking Project (EAPHLNP) is a regional project involving five East African countries, Namely: Burundi, Kenya, Rwanda, Uganda and Tanzania and it is supported by the World Bank.

Summary

INTRODUCTION

Tuberculosis (TB) is a global health problem that causes ill-health among millions of people each year. The most common method for diagnosing TB worldwide was sputum smear microscopy. However the advent of HIV/AIDS has complicated the diagnosis and management of TB with associated emergence of multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB). Studies that evaluate methods for diagnosing TB and follow-up of Presumptive TB patients to verify the presence or absence of active TB are crucial for prompt diagnosis and treatment.

OBJECTIVE

The study aimed to assess adherence to attend follow up clinical and sputum re-examination clinics for symptomatic HIV positive presumptive TB patients initially assumed to be TB negative. To find out at what stage HIV positive smear negative presumptive TB patients would become positive for TB with which diagnostic method within a 6 month follow up.

METHODOLOGY

This was cohort study conducted in nine East African Public Health Laboratory Networking Project study sites in Kenya. Eligible new and previously treated presumptive TB patients i.e. a patient presenting with symptoms and signs suggestive of TB who tested positive for HIV and had sputum smear negative on initial sputum smear examination were enrolled in to the study. Study participants were expected to be followed up for repeat sputum smear examination at 2 weeks, 2, 4, and 6 months.

RESULTS

Out of the 1323 presumptive TB patients enrolled between February 2013 and February 2014, only 201 (15.2%) were eligible for follow up and 164 (81.6%) did not return at 2 weeks for a follow up. Out of the 37 (18.4%) who returned for a follow up at 2 weeks, none was either sputum smear positive or Gene-Xpert positive. Initial sputum samples from all the 201 participants were



subjected to culture. Culture results were available for only 156 patients of whom 15/156, (9.6%) were culture positive. Follow up adherence at 2 weeks was significantly associated with history of previous treatment (p-value = 0.010) but not associated with gender (p-value =0.268).

CONCLUSION

The high level of non-adherence to follow up among HIV positive presumptive TB patients is a cause for concern to the national TB program. We recommend active follow up of this group who has initial sputum smear negative results using the new diagnostic tools that are available and can diagnosis TB early. Future studies should evaluate strategies that should be put in place to ensure enhanced follow up of the presumptive TB patients as part of the protocol.

Key Words: Presumptive tuberculosis, HIV positive smear negative, Follow up

[Afr J Health Sci. 2014; 27(4) Supplement : 482-492] [*Afr. J. Health Sci.* 2019 32(6) : 41 - 46]

Introduction

Tuberculosis (TB) is a sensitive public health problem all over the world. The East African countries namely Kenya, Uganda, Tanzania, Rwanda and Burundi are among the 22 high TB burden countries with the incidence ranging between 157 and 353 per 100,000 population [1].

Kenya reported 89,760 TB cases in 2013 with incidence of 217 cases per 100,000 population of whom 30% were diagnosed as sputum smear negative [2]. Before the advent of HIV/AIDS, the incidence of TB was on the decline globally including Kenya. However, the advent of HIV/AIDS had complicated the diagnosis and management of TB with associated emergence of MDR-TB and XDR-TB.

Tuberculosis is an early opportunistic disease in the course of HIV infection. Unlike most other opportunistic diseases, which usually appear in the late stages of AIDS upon severe immunological impairment, TB can occur anytime during HIV infection [3]. As HIV infection progresses, CD4 *lymphocytes* decline in number and function. The immune system is less able to prevent the growth and local spread of *Mycobacterium tuberculosis*. HIV therefore fuels the TB epidemic by promoting progression of latent *Mycobacterium tuberculosis* infection to active TB disease. Increasing numbers of TB cases in people living with HIV/AIDS poses an increased risk of TB transmission to the general community.

Diagnosis of pulmonary tuberculosis (PTB) in Kenya relies largely on detection of acid-fast *bacilli* (AFB) by direct microscopic examination of sputum smears. The method is rapid and inexpensive and highly

specific for *Mycobacterium tuberculosis* especially in high TB burden settings.

However, the main limitation is its low and variable sensitivity, exacerbated in high HIV prevalence settings [4]. Due to its low sensitivity, Ziehl Neelsen (ZN) microscopy does not therefore detect all TB cases among presumptive TB patients thus increasing the number of false smear negative cases which subsequently leads to increased TB transmission. However in the previous developments, the use of new TB diagnostic tools namely;

1. Light emitting diodes (LEDs) commonly referred to as Optimized Sputum Smear Microscopy (OSSM).
2. The rapid molecular tests (GeneXpert MTB/RIF) for the diagnosis of TB is increasing.

Therefore there was need to conduct diagnostic evaluations of the new diagnostic tools on important patient outcomes including follow up of particularly HIV positive presumptive TB patients to determine when to diagnosis.

New WHO TB diagnostic algorithm stipulates a further repeat sputum smear examination preceding chest radiography in presumptive TB patients with initial smear negative results and who fail the antibiotic trial of 10-14 days [5]. Although these guidelines have been incorporated in the Kenya National TB program diagnostic algorithms, emphasis was more on follow up smear examinations for patients on treatment to determine patient outcomes but very little attention was given to follow up sputum smear examinations for presumptive TB patients who are classified as TB



negative during the initial assessment. Presumptive TB patients in Kenya have been shown to have a very high prevalence of human immunodeficiency virus (HIV) infection, of between 49% and 63% [6, 7].

In Kenya the TB/HIV co-infection rate stood at 38% (MOH, 2012). A study from Malawi among presumptive TB patients with high HIV prevalence rates found that 20% (16/79) of presumptive TB patients with negative sputum smears and normal Chest X-ray (CXR) were culture positive for *M. tuberculosis*, while 13 out of 41 culture-negative patients who were alive developed X-ray diagnosed TB within 3 months [8].

Smear-negative presumptive TB patients who have not been diagnosed with TB were ill individuals who received very little attention compared to those with a confirmed diagnosis. Follow-up of presumptive TB patients is therefore essential in order to confirm the initial discharge diagnosis of either —confirmed TB or —not-TB. The present study aimed to assess adherence to attend follow up clinical and sputum re-examination clinics for symptomatic HIV positive presumptive TB patients initially assumed to be TB negative.

Methodology

Study sites

The study was part of an ongoing larger operational research aimed at evaluating the impact of new TB diagnostics on patient health outcomes in

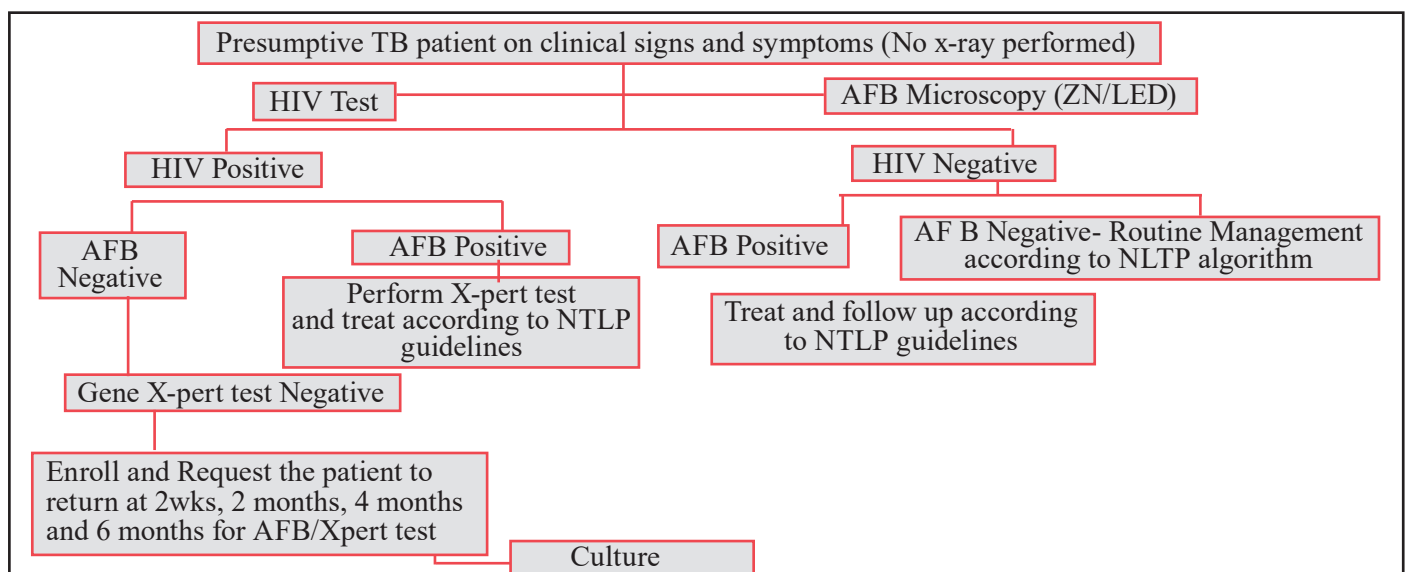
Kenya being conducted in 9 health facilities in Kenya under the auspices of the East Africa Public Health Laboratory Networking (EAPHLN) project.

Study Population and Enrollment

All presumptive TB patients both new and previously treated presenting to study sites between February 2013 and February 2014 were enrolled. At the study sites the clinicians interviewed and registered presumptive TB patients. Triaging of presumptive TB patients was emphasized to ensure only eligible participants were recruited. All eligible participants provided written informed consent by signature or fingerprint before enrollment into the study. Selection of presumptive TB patients followed by clinical examination was done in accordance with National TB program routine procedures/guidelines.

A structured clinical form was used to capture data including TB symptoms which included cough for 2 or more weeks, hemoptysis, breathlessness, chest pain, fever, night sweats, fatigue, weight loss and loss of appetite. All the presumptive TB patients who had initial sputum smear negative results were given appropriate antibiotics to treat possible chest infection and those eligible for study requested to come back after two weeks for follow up. Chest X-ray aspect was not addressed in this study as some of the study sites did not have X-ray facilities. The study was based on symptom screening of all HIV positive smear negative patients after the initial TB investigation as shown in *Figure 1*.

Figure 1: Algorithm of Presumptive TB patient's recruitment and follow-up



Follow Up Procedures

All smear-negative HIV positive participants were asked to come back for re assessment for TB and sputum examination at 2 weeks, 2, 4, and 6 months in accordance with the study protocol. During follow-up assessments, participants underwent repeat examination for signs and symptoms. They submitted further samples for sputum smear microscopy and Xpert at study sites after which samples were transported to KEMRI Mycobacteriology Research Laboratory in Nairobi for culture. Participants were not facilitated for return fare.

Data Collection and Analysis

Data was collected using a questionnaire, clinical form and a laboratory form for each suspect enrolled. The clinician at the TB clinic administered the questionnaire and completed the clinical form for each participant. The suspect was then referred to the laboratory for sputum examination. Initially during the analysis of initial sputum specimen, at the laboratory, participants' details including name, age, sex, date of specimen collection, smear results, physical address and mobile phone number were recorded in the laboratory study register.

After clinical examination participants whose HIV status was unknown were referred for Provider Initiated Testing and Counseling (PITC) and HIV test done according to the Kenya HIV/AIDS programme guidelines.

Another study register was maintained at the clinic at each study site with information of participant study code, name, age, sex, date of assessment, HIV

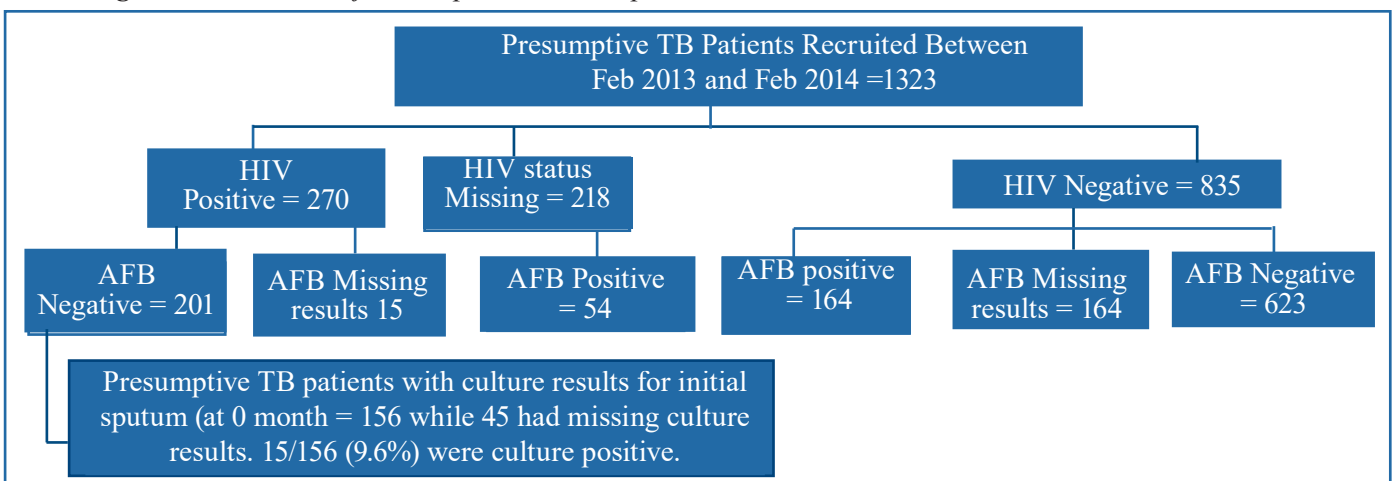
test date and result, date of sputum sample, collection, and date samples were transported for culture. Data was analyzed by the SPSS and baseline characteristics of participants expressed as proportions and compared with adherence to follow up.

Results

Between February 2013 and February 2014 a total of 1323 presumptive TB patients with symptoms suggestive of TB were enrolled for study. The HIV prevalence was 24.4% among the study participants. The total presumptive TB patients who were HIV positive and negative on smear microscopy and therefore eligible for follow up were 201 of whom 57% (113/199) were females and 86/199(43%) were males while two participants had missing data on gender.

We found only 37/201 (18%) had attended the scheduled 2 week follow up while there was no data available on patient follow up at 2, 4 and 6 months. Out of the 37 participants who had returned at 2 weeks for follow up, 18 were females and 19 male. Seven out of 37 participants who returned for follow up, had a history of the previous treatment recorded of whom 6 had been treated while only 1 was a new TB suspect. Follow up adherence at 2 weeks was significantly associated with history of the previous treatment (p-value = 0.010) but not gender (p-value =0.268). From the 37 presumptive TB patients who returned at 2 weeks none was diagnosed with active TB by sputum smear microscopy or GeneX-pert at the study site. However the 156 out of the 201 participants with available culture results of initial sputum, 15 (9.6 %) were culture positive. There was a higher proportion of culture positivity among presumptive TB patients who did not return for repeat

Figure 2: Flowchart of TB Suspects Follow Up





sputum re-examination at 2 weeks (10.4%) than those who returned during the follow up (6.5%), though the difference was not significant (OR = 1.67; 95% CI : 0.36-7.88)

Discussion

According to our knowledge, this is the first time to document this kind of study of presumptive TB patients follow up in Kenya. Twenty four (24%) percent HIV prevalence among presumptive TB patients tested was almost four times higher than that of the general population which was 5.6% [9]. These findings indicate that individuals who are HIV positive and have signs and symptoms suggestive of TB are at high risk of developing TB.

In Kenya, the National TB program policy guidelines recommends follow up of all symptomatic presumptive TB patients for re-examination and repeat sputum microscopy. However, adherence to follow up has not been documented. In this study, it was found that 81.6% of the enrolled participants for follow up did not return at 2 weeks for repeat sputum examination. This is likely to contribute to diagnostic delays resulting to continued transmission of TB. The high proportion of non-adherence to follow up among HIV positive Presumptive TB patients observed in this study was, therefore, a cause for concern to the national TB program. History of previous treatment was associated with adherence to first follow up visits at 2 weeks, probably due to prior knowledge on effects of TB.

These observations were in agreement with those of a study conducted in Tanzania to assess the diagnostic performance of the QuantiFERONH-TB Gold In-Tube test in TB suspect children. The study showed that being treated for active TB in the DOTS program and receiving money for bus fare were positive predictors for attending follow-up examinations at 2 months. However non-adherence to follow up at 2 months was 39% [10]. The study also showed that limited financial resources, i.e. lack of money for transportation and poor communication, were related to non-adherence for follow up [10].

In the study, several reasons may have contributed to poor adherence to first and subsequent follow up visits. These include; lack of transport to the clinic, lack of adequate knowledge of TB as a

risk factor, poor communication, social-cultural and domestic factors. A cohort follow-up study done in Guinea Bissau among presumptive TB patients over a 10-month period, 21 out of 343 (6%) were diagnosed with smear negative TB. Eighty nine (42%) of the 212 suspects who were further followed up were still symptomatic and 5 (5.6%) were diagnosed with TB on the basis is of repeated sputum smears and chest X-ray [11]. Smear negative TB especially among HIV positive suspects presents a diagnostic challenge to the clinicians in Kenya despite the fact that the majority of these patients could be diagnosed on a repeat sputum smear examination, which is usually not requested. Another study conducted in New Delhi, India to assess the utility of repeat sputum smear examination in symptomatic initial smear negative presumed TB patients, 272/2195 (12.3%) of those who underwent repeat sputum examination after 2 weeks of antibiotic trial were found to be smear positive [12].

The fact that HIV infection is common among presumptive TB patients requires better identification and systematic follow up after initial examination if found sputum smear negative. It should always be emphasized that the patient should return if symptoms persist. A repeat sputum smear examination gives a chance to detect a “previously missed” sputum positive due to various reasons transport costs and lack of knowledge on TB.

This study demonstrated, for the first time, that there was great loss to follow up of HIV positive, smear negative presumptive TB patients who may convert to TB positive. We conclude that the high proportion of non-adherence to follow up among HIV positive presumptive TB patients observed in this study is a cause for concern to the national TB program. We recommend active follow up for HIV positive presumptive TB patients with initial sputum smear negative results. Since the study is ongoing strategies should be put in place to ensure active follow up of the presumptive TB patients as part of the protocol.

Limitations

We used only sputum smear as the only diagnostic tool, which has low sensitivity, especially among HIV-infected individuals. We were therefore not sure how many of our participants were subsequently diagnosed with active TB using chest x-ray.



The study participants were not facilitated in terms of fare or calling them to return for follow up. We were also not able to systematically collect data for the entire period of 6 months to find out reasons for not returning for follow up.

Acknowledgements

We wish to thank, study sites personnel from Malindi, Lamu, Busia, Kitale, Nyahururu, Wajir, Machakos, Narok and Kisii county hospitals for specimens and data collection, persons with symptoms or signs suggestive of TB who provided informed consent and participated in the study. We thank Center for Respiratory Diseases Research (CRDR) TB laboratory and the

Tuberculosis Central Reference Laboratory staff for performing the routine Mycobacteriology testing. Director Kenya Medical Research Institute (KEMRI) for the support and permission to perform the study.

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