Original Research Article

Utilization of WHO symptom screening Approach by Non-Clinicians in the diagnosis of Tuberculosis among Persons living with HIV attending a treatment facility in southern Nigeria

ABSTRACT

AIMS: THE SCREENING FOR TUBERCULOSIS (TB) AMONG PEOPLE LIVING WITH HIV (PLHIV) ENSURES EARLY DETECTION OF TB, PROMPT INITIATION OF TB TREATMENT AND REDUCTION OF MORTALITY FROM TB AMONG PLHIV.THERE IS A NEED FOR TUBERCULOSIS SCREENING AMONG PLHIV. THIS STUDY AIMED TO ASSESS THE BURDEN OF HOSPITAL PTB INITIALLY IDENTIFIED BY COUGH MONITORS IN THE OUT-PATIENT CLINIC OF PLHIV, THE PREVALENCE AND TYPE OF CONFIRMED PTB AMONG THEM AND THE SENSITIVITY AND SPECIFICITY OF THE FOUR-SYMPTOM TB SCREENING APPROACH.

STUDY DESIGN: A DESCRIPTIVE CROSS SECTIONAL DESIGN WAS USED.

PLACE AND DURATION OF STUDY: THE STUDY WAS CONDUCTED AT THE ANT-RETROVIRAL CLINIC OF A TERTIARY HOSPITAL IN SOUTHERN NIGERIA OVER A 9 MONTHS PERIOD BETWEEN JANUARY TO SEPTEMBER, 2020.

METHODOLOGY: THE MEDICAL RECORDS OF ADULTS DIAGNOSED WITH HIV WHO WERE IDENTIFIED BY NON-CLINICIANS TO HAVE AT LEAST ONE OF THE FOUR SYMPTOMS (COUGH, WEIGHT LOSS, NIGHT SWEAT AND FEVER) PRESCRIBED BY WHO FOR TB SCREENING ON ATTENDANCE AT THE ART CLINIC OF THE UNIVERSITY OF UYO TEACHING HOSPITAL, UYO AKWA IBOM STATE, NIGERIA WERE REVIEWED OVER THE STUDY PERIOD.DATA WERE ANALYZED USING STATA VERSION 13.0 LEVEL OF SIGNIFICANCE WAS SET AT P<.05

RESULTS: SIXTY-NINE (69) OUT OF 529 (13.0%) PATIENTS WHO ATTENDED THE ART CLINIC WERE IDENTIFIED TO HAVE AT LEAST ONE OF THE FOUR SYMPTOMS PRESCRIBED BY THE WHO SYMPTOM APPROACH FOR TB SCREENING. THE MEAN AGE OF RESPONDENTS WAS 40.8±12.3 YEARS. THE COMMON TB SYMPTOMS WERE COUGH (62, 89.9%), FEVER (49, 71.0%), WEIGHT LOSS (40, 58%) AND NIGHT SWEAT (29, 42%). NINE (13.0%) RESPONDENTS WERE CONFIRMED OF PTB FROM GENE XPERT TEST, AND ALL 9 HAD RIFAMPICIN RESISTANCE. THE FOUR–SYMPTOM TB SCREENING TEST HAD A SENSITIVITY OF 11.1%, SPECIFICITY OF 98.3% AND A POSITIVE PREDICTIVE VALUE OF 50%.

CONCLUSION: NINE (13%) PLHIV SCREENED FOR TB BY NON-CLINICIANS USING THE WHO SYMPTOM-BASED APPROACH WERE CONFIRMED OF TB BY GENE-XPERT ASSAY. THEY ALL HAD RIFAMPICIN-RESISTANT PTB. THE APPROACH HAD A LOW SENSITIVITY AND HIGH SPECIFICITY RATE. THERE IS A STRONG NEED FOR THE USE OF NON-CLINICIANS IN ART CLINICS IN ACTIVE CASE FINDING OF TB IN HIV-POSITIVE PATIENTS TO REDUCE THE RISK OF IRIS AMONG.

Keywords: [TUBERCULOSIS SCREENING, NON-CLINICIANS,PLHIV,UYO,}

INTRODUCTION

Tuberculosis is a leading cause of mortality among persons living with Human Immunodeficiency Virus (HIV), especially in the African and Asian regions, which together account for 75% of tuberculosis (TB) cases associated with HIV infection globally.[1] In many African countries, HIV infection, has been associated with above two-thirds of identified active tuberculosis cases.[2]Nigeria has been ranked sixth among the 30 high-burden TB countries of the world. She is also one of the high burden countries with TB/HIV co-infection and multidrug-resistant TB (MDR-TB).[3]Nigeria also has an adult HIV prevalence of 1.4%, and Akwa Ibom state in southern Nigeria has the highest prevalence in the country of 5.5%.[4]While HIV is known to increase the burden of PTB, PTB is a leading cause of death among persons living with HIV (PLHIV).[5]This buttresses the need for routine screening for tuberculosis in all PLHIV including newly diagnosed clients.

The World Health Organization, in 2011, recommended that adolescents and adults living with HIV be screened for PTB using a four-symptom-based approach to exclude the presence of current cough, weight loss, fever or night sweat before commencing tuberculosis preventive therapy.[6]A systematic review and meta-analysis in over 8000 antiretroviral therapy (ART)-naïve persons with HIV revealed a sensitivity and specificity of 78.9% and 49.6% of this approach which informed the WHO recommendation.[7]The presence of any of the symptoms require further review and investigations to exclude active tuberculosis which if untreated in newly enrolled PLHIV on ART, could trigger immune reconstitution inflammatory syndrome (IRIS).[8]Contrariwise, a patient with active tuberculosis that is not screened out and commenced on tuberculosis preventive therapy is at risk of developing drug-resistant tuberculosis.

Further investigation in patients with any of the four symptoms is done using Gene Xpert MTB/RIF assay. The Gene Xpert MTB/RIF assay is rapid and has a better sensitivity than smear microscopy.[9]Unlike smear microscopy, Gene Xpert MTB/RIF assay enables the detection of rifampicin-resistant tuberculosis. Over nine-tenth of cases of rifampicin resistance have been associated with an accompanying isoniazid resistance; hence, rifampicin resistance is used as a surrogate marker for MDR-TB.[10]

The symptom screening approach could be used by lay persons (cough monitors) in active case finding of TB in both community and clinical settings and has been reported to produce rewarding results.[11–14]A study in Kenya reported that 33% of annual hospital TB burden were initially identified by cough monitors from selected outpatient areas,[15] and 4-24% contribution in a similar Nigerian study.[16]

This study aimed to assess the burden of hospital TB initially identified by cough monitors in an out-patient clinic of PLHIV, the type of confirmed TB among them and the sensitivity and specificity of the four-symptom TB screening approach.

2. MATERIAL AND METHODS

2.1: Study site: The study was conducted at the Anti-retroviral therapy (ART) clinic of the University of Uyo Teaching Hospital (UUTH), Uyo, Akwa Ibom state, southern Nigeria. The UUTH is the only federally owned tertiary health facility in Akwa Ibom state, with an estimated 6 million people. It is one of the many HIV comprehensive treatment centres in Akwa Ibom state and a referral centre for primary and secondary health facilities in and out

of the state. The UUTH ART clinic is supported by FHI360 with funding from the United States Agency for International Development (USAID). At the ART clinic, there is screening for opportunistic infections (OIs) including PTB for newly enrolled HIV infected persons. For identification of PTB, clinical screening using the WHO 4 symptom screening approach is carried out. This is mainly done by non-clinicians at the clinic with further investigation by physicians of clients having any positive symptom for PTB using the Gene Xpert MTB/RIF assay technique, chest x-ray and other techniques. Anti-TB medications are commenced by clinicians for HIV patients diagnosed with PTB and Tuberculosis Preventive Therapy (TPT) are administered to those without any of the four TB screening symptoms. Other services offered include provision of ART and follow-up care for PLHIV.

2.2 Study Design: The study used a retrospective descriptive cross-sectional design to review data of PLHIV who were identified to have at least one of the four symptoms (cough, weight loss, night sweats and fever) prescribed by WHO for TB screening on attendance at the adult ART clinic of the University of Uyo teaching hospital over a nine-month period between January to September, 2020.

2.3 Data Collection and Analysis: Socio-demographic features such as age, gender, level of education, WHO clinical staging, history of TB, presence of any of the symptoms using the four-symptom approach were obtained from the folders of patients. Results of Gene Xpert tests for MTB/RIF assay to confirm tuberculosis infection and the presence or absence of rifampicin resistance from sputum samples of PLHIV having any of the symptoms (presumed TB patients) were also obtained from the patients' records. Anti-tuberculosis treatment was commenced for all patients confirmed to have PTB. Antiretroviral therapy was commenced after patients had been on anti-tuberculosis drugs for 2 weeks. Rifampicin resistance was classified as high-level resistance (Isoniazid resistance with inhA and KAT G mutation), moderate level resistance (isoniazid resistance with KatGmutation) and low-level resistance (isoniazid resistance with inhA mutation.[17]

Data was analysed using Stata version 13.0. Categorical variables were summarized using frequencies and percentages. Chi square test was used to determine any association between categorical variables at a P-value <0.05.

3. RESULTS AND DISCUSSION

Sixty-nine (69) out of the 529 (13.0%) PLHIV who attended the clinic over the review period and were identified to have at least one of the symptoms were recruited. The mean (SD) age of respondents was 40.8(12.3) years. Majority of the respondents were females (47, 68.1%). About half of the respondents (35, 50.7%) attained secondary education. More than half of respondents were artisans (56, 81.2%), and in WHO clinical stage 1(50, 72.5%). Only one respondent (1.4%) had a past history of TB. (see Table 1).

Table 1: Socio-demographic and clinical characteristics of Respondents (n=69)

Variables	Frequency	Percent
Age		
Less than 41	41	59.4
41 and above	28	40.6
Mean ±Standard deviation	40.8 +/-12.3	
Sex		
Male	22	31.9
Female	47	68.1
Education Level		
Primary	20	29.0
Secondary	35	50.7
Tertiary	14	20.3
Occupation		
Civil servants	4	5.8
Artisans	56	81.2
Student	9	13.0
Unemployed	1	1.4
WHO clinical staging		
1	50	72.5
2	7	10.1
3	11	15.9
4	1	1.5
Ever Had TB before		
Yes	1	1.4
No	68	98.6

The two most common symptoms of TB manifested by respondents were cough (62, 89.9%) and fever (49, 71.0%) (Table 2)

Table 2: Common PTB symptoms among Respondents

Variables	Frequency	Percentage
Cough		
Yes	62	89.9
No	7	10.1
Fever		
Yes	49	71.0
No	20	29.0
Weight loss		
Yes	40	58.0
No	29	42.0
Night sweats		
Yes	29	42.0
No	40	58.0

Nine out of 69 (13.0% 95%CI: 6.8-23.6%) respondents were confirmed to have PTB from Gene Xpert MTB/RIF test, and all nine had rifampicin resistance with an equal proportion having high and moderate level of resistance to rifampicin (44.4% each) (Table 3)

Table 3: TB Results of Respondents using Gene Xpert MTB/RIF Test

Variables	Frequency	Percentage (95%CI)
Xpert Results		
Positive	9	13.0 (6.8-23.6%)
Negative	60	87.0 (76.5-93.2%)
Rif Resistance test (n=9)		
Mild	1	11.1
Medium	4	44.4
High	4	44.4

Rif=Rifampicin CI=Confidence interval

The respondents confirmed for TB using Gene xpert test had cough (88.9%) fever and weight loss (77.8% each) as their major symptoms. Five (55.6%) were in WHO clinical HIV staging 1 and none were in stage 4. (Table 4)

Table 4: Clinical characteristics of Respondents with Positive Gene xpert test Results

Variables	Frequency	Percentage
Cough		
Yes	8	88.9
No	1	11.1
Fever		
Yes	7	77.8
No	2	22.2
Weight loss		
Yes	7	77.8
No	2	22.2
Night sweats		
Yes	5	55.6
No	4	44.4
WHO clinical staging		
1	5	55.6
2	1	11.1
3	3	33.3
4	0	0.0

The sensitivity of the four-symptom TB screening test was 11.1%, with a specificity of 98.3% and a positive predictive value of 50%.(Table 5)

Table 5: Accuracy and clinical relevance of screening tool in diagnosing tuberculosis

Characteristics	Percentage (%)	95% Confidence Interval
Prevalence	13.0	5.1 – 21.0
Sensitivity	11.1	3.7 – 18.5
Specificity	98.3	95.3 – 101.4
Positive predictive value	50.0	38.2 – 61.8
Negative predictive value	88.1	80.4 – 95.7

3.2: Discussion

The WHO recommended 4-symptom screening tool for TB used by lay persons helped in identifying 13% of the hospital TB burden over a nine-month period. This finding agrees with the 2-24% reported in a previous Nigerian study on the usefulness of lay persons in active case finding of TB in a health facility[16] but lower than reports from a similar study in Kenya with 33%.[15] The small proportion of TB cases identified in this study could be due to our relatively small sample size and the fact that most of our respondents were already on highly Active Anti-retroviral therapy (HAART). The use of this four-symptom screening approach by lay persons (cough monitors or ward cough officers) in active case finding of TB in both community and clinical settings is reported to produce rewarding results.[11–14]

This study identified nine confirmed TB cases, with all being rifampicin resistant. With rifampicin resistance detection from Gene Xpert MTB/RIF assay being a surrogate marker for multi-drug resistant tuberculosis,[10] it is possible that some of the PLHIV being treated for latent tuberculosis with isoniazid may already have had isoniazid resistance given the low sensitivity of the screening tool. The use of urinary lipoarabinomanam for PLHIV with advanced HIV disease (WHO Stage 3,4) has served to increase tuberculosis case detection in that cohort of patients.[18] Tuberculosis can occur at any stage of HIV disease though decline in CD4+ cell count has been associated with increasing incidence of tuberculosis.[19] Interestingly, most of our study subjects in both the suspected tuberculosis and subsequently confirmed tuberculosis cohorts were in WHO clinical stages 1 and 2 where urinary lipoarabinomannan is currently not used. Urinary lipoarabinomannan is a more sensitive test hence its use in HIV stages 3 and 4 because of their very low immunity which stops them from mounting an immune response thus making it more difficult for more conventional test to detect TB in these sub groups. It is therefore possible that as a more sensitive/specific test, it can increase the case detection of TB even in HIV stages 1&2. This emphasizes the need for intense case finding of TB among both Highly Active Antiretroviral therapy HAART-naïve and HAART-experienced patients to prevent the development of rifampicin-resistant TB.

The screening tool had a low sensitivity of 11%, a high specificity (98.3%) and an average positive predictive value. The sensitivity of the symptom screening tool varies in the literature. A study among pregnant women living with HIV in South Africa found a symptom screening sensitivity of 28% from 226 suspected tuberculosis patients.[20] This was attributed to physiological changes in pregnancy that may have masked tuberculosis symptoms. Other studies in South Africa not involving pregnant women had also noted low sensitivity. These studies include a community survey (sensitivity of 33%),[21]and symptom screening of gold miners(sensitivity of 29%).[22] Some other studies reported significantly higher sensitivities including several of the studies in the WHO meta-analyses.[23–26] The heterogeneity in the

sensitivities of the four-part symptom screen has been noted and the reason is still not clear.[20]Studying a mixed cohort of both HAART-naïve and HAART-experienced patients may be responsible for the low sensitivity in our study. In addition, conducting the study during part of the harmarttan season in Nigeria with increased occurrence of cough caused by viral flu (October to February) may contribute to the low sensitivity of this test.[27–29]In addition, these four symptoms are also common to other diseases such as HIV even without TB.

The addition of chest radiograph to the symptom screening has been suggested as a means of increasing the sensitivity.[30]Where feasible, this could come in handy particularly among PLHIV where the annual risk of tuberculosis is 5-15%.[31] Limitations of chest radiograph will be the cost implication and logistic challenges of implementing it as an additional screening tool for all patients.[32]Another approach that has been considered at increasing the sensitivity is the addition of more symptoms to the screening tool. An analysis was done using the 2010 Zambia South Africa Tuberculosis and HIV/AIDS Reduction (ZAMSTAR) survey data.[30] As a screening tool, the use of only cough of ≥2 weeks from the data had a sensitivity of <25% but increased to 38% with the addition of any three of six tuberculosis symptoms (cough <2 weeks, night sweats, weight loss, fever, chest pain and shortness of breath), or 2 or more of cough <2 weeks, night sweats and weight loss. A similar survey in western Kenya had a sensitivity of 41% for cough ≥2 weeks and 82% for any tuberculosis symptom (cough, haemoptysis, fever, night sweats, weight loss, of any duration or severity) among individuals without HIV, and 69% and 96% respectively among PLHIV.[33] There is need to compare the sensitivities from the additional symptoms screening tools with the WHO four-symptom screening rule and not just cough alone, in-order to determine if there will be a significant change in sensitivity. However, from our study, cough of any duration was the most significant symptom, being present in about nine-tenths of the persons that were both suspected and eventually confirmed to have tuberculosis.

The cost effectiveness and ease of deployment of the four symptom tool, justifies its use by non-clinicians for the screening of TB until a more sensitive screening tool is discovered. Cost-effectiveness and ease of deployment by laypersons in individuals irrespective of their HIV status, must be taken into consideration in the development of new highly sensitive TB screening tools to ensure improved TB case detections in both the community and hospital settings. High school graduates trained in the symptomatic recognition of tuberculosis suspects and assisted sputum production in a Kenyan referral hospital contributed to the detection of 33% of the referral hospital's annual tuberculosis case burden.[15]The use of laypersons in community settings through household surveys also showed rewarding results in improving active tuberculosis case detection.[11–14]

The major strength of our study is the demonstration of the effectiveness of the use of symptom-based screening tool in increasing drug-resistant tuberculosis detection when combined with Gene Xpert MTB/RIF assay. A limitation of our study was the small sample size of the tuberculosis suspects recruited over a 9-month period from a single site. In addition, the review period covered the COVID-19 pandemic where attendances at health facilities were reduced. There is therefore a need for a multi-centre study in Nigeria with accompanying larger number of participants to make the findings more generalizable. Furthermore, the screening tool relied on the symptom-complex of cough, fever, night sweat and weight loss, thus increasing the possibility of missed opportunities for patients with extrapulmonary tuberculosis or pulmonary tuberculosis patients who had difficulty producing sputum.

4. CONCLUSION

In conclusion, the WHO four-symptom screening though having a low sensitivity in tuberculosis case detection, can serve as a means of identifying drug-resistant tuberculosis patients in combination with Gene Xpert MTB/RIF assay. There is need for the development of more sensitive and cost effective screening techniques that can be deployed by individuals without specialized trainings in-order to address tuberculosis in PLHIV in resource-constrained settings.

ETHICAL APPROVAL

Ethical approval was obtained from the institutional health research ethical committee of the University of Uyo Teaching Hospital.

REFERENCES

1. García JI, Mambuque E, Nguenha D, Vilanculo F, Sacoor C, Sequera VG, et al. Mortality and risk of tuberculosis among people living with HIV in whom TB was initially ruled out. Sci Rep. 2020;10(1):1–11.

2. Swindells S, Komarow L, Tripathy S, Cain KP, MacGregor RR, Achkar JM, et al. Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. Int J Tuberc Lung Dis. 2013;17(4):532–9.

3. Global Tuberculosis Report 2021. Geneva: World Health Organization; 2021.

4. Federal Ministry of Health (Nigeria). Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) 2018: Technical Report. Abuja, Nigeria.; 2019.

5. Usmonov I, Shukurov U. Features of the Clinical Course , the State of Diagnosis and Treatment of HIV-Associated Pulmonary Tuberculosis in Modern Conditions: Literature Review. Ann Rom Soc Cell Biol. 2021;25(4):1809–28.

6. WHO. Tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011.

7. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. PLOS Med. 2011;8(1):e1000391.

8. Walker NF, Stek C, Wasserman S, Wilkinson RJ, Meintjes G. The tuberculosis-associated immune reconstitution inflammatory syndrome: recent advances in clinical and pathogenesis research. Curr Opin HIV AIDS. 2018;13(6):512–21.

9. Mbu ET, Sauter F, Zoufaly A, De C Bronsvoort BM, Morgan KL, Noeske J, et al. Tuberculosis in people newly diagnosed with HIV at a large HIV care and treatment center in Northwest Cameroon: Burden, comparative screening and diagnostic yields, and patient outcomes. PLoS One. 2018;13(6):e0199634.

10. Raoot A, Dev G. Evaluate “Rifampicin Resistance” as Surrogate Marker for Rapid Detection of MDR-TB Using Real-Time PCR Directly on FNAC Samples of Tuberculous Lymphadenitis. Br J Med Med Res. 2015;9(5):1–8.

11. Shargie EB, Mørkve O, Lindtjørn B. Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: community randomized trial. Bull World Health Organ. 2006;84(2):112–9.

12. Xiong CF, Fang Y, Zhou LP, Zhang XF, Ye JJ, Li GM, et al. Increasing TB case detection through intensive referral of TB suspects by village doctors to county TB dispensaries. Int J Tuberc Lung Dis. 2007;11(9):1004–7.

13. Yimer S, Holm-Hansen C, Yimaldu T, Bjune G. Evaluating an active case-finding strategy to identify smear-positive tuberculosis in rural Ethiopia. Int J Tuberc Lung Dis. 2009;13(11):1399–404.

14. Sekandi JN, Neuhauser D, Smyth K, Whalen CC. Active case finding of undetected tuberculosis among chronic coughers in a slum setting in Kampala, Uganda. Int J Tuberc Lung Dis. 2009 Apr;13(4):508–13.

15. Burmen BK, Mogunde J, Malika T. The Use of Laypersons to Support Tuberculosis Screening at a Kenyan Referral Hospital. Int J Prev Med. 2018;9:44.

16. Adejumo AO, Azuogu B, Okorie O, Lawal OM, Onazi OJ, Gidado M, et al. Community referral for presumptive TB in Nigeria : a comparison of four models of active case finding. BMC Public Health. 2016;16:177.

17. National Guidelines for the Management of TB/HIV Coinfection in Nigeria. 3rd ed. Federal Ministry of Health, Department of Public Health; 2021.

18. Huerga H, Mathabire Rucker SC, Cossa L, Bastard M, Amoros I, Manhiça I, et al. Diagnostic value of the urine lipoarabinomannan assay in HIV-positive, ambulatory patients with CD4 below 200 cells/μl in 2 low-resource settings: A prospective observational study. PLOS Med. 2019;16(4):e1002792.

19. Jaryal A, Raina R, Sarkar M, Sharma A. Manifestations of tuberculosis in HIV/AIDS patients and its relationship with CD4 count. Lung India. 2011;28(4):263–6.

20. Hoffmann CJ, Variava E, Rakgokong M, Masonoke K, Van Der Watt M. High Prevalence of Pulmonary Tuberculosis but Low Sensitivity of Symptom Screening among HIV-Infected Pregnant Women in South Africa. PLoS One. 2013;8(4):e62211.

21. Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed Tuberculosis in a Community with High HIV Prevalence: Implications for Tuberculosis Control. Am J Respir Crit Care Med. 2007;175(1):87–93.

22. Lewis JJ, Charalambous S, Day JH, Fielding KL, Grant AD, Hayes RJ, et al. HIV Infection Does Not Affect Active Case Finding of Tuberculosis in South African Gold Miners. Am J Respir Crit Care Med. 2009;180(12):1271–8.

23. Corbett EL, Zezai A, Cheung YB, Bandason T, Dauya E, Munyati SS, et al. Provider-initiated symptom screening for tuberculosis in Zimbabwe: diagnostic value and the effect of HIV status. Bull World Health Organ. 2010;88(1):13–21.

24. Lawn SD, Edwards DJ, Kranzer K, Vogt M, Bekker LG, Wood R. Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. AIDS. 2009;23(14):1875–80.

25. Chheng P, Tamhane A, Natpratan C, Tan V, Lay V, Sar B, et al. Pulmonary tuberculosis among patients visiting a voluntary confidential counseling and testing center, Cambodia. Int J Tuberc Lung Dis. 2008 Mar;12(3 SUPPL. 1):54–62.

26. Cain KP, McCarthy KD, Heilig CM, Monkongdee P, Tasaneeyapan T, Kanara N, et al. An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV. N Engl J Med. 2010;362(8):707–16.

27. David-West TS, Cooke AR. Laboratory and clinical investigation of the 1974 influenza epidemic in Nigeria. Bull World Health Organ. 1974;51(1):103–5.

28. Adefolalu DO. On bioclimatological aspects of Harmattan dust haze in Nigeria. Arch Meteorol Geophys Bioclimatol Ser B. 1984;33(4):387–404.

29. Bannor TT, Ogunsan EA. Harmattan—A predisposing factor in the spread of viral diseases in domestic animals. Trop Anim Health Prod. 1988;20(4):211.

30. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: Individual participant data meta-analysis of observational studies. PLoS Med. 2011;8(1):e1000391.

31. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012;8(2):e1002464.

32. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. Lancet HIV. 2018;5(9):e515–23.

33. van't Hoog AH, Meme HK, Laserson KF, Agaya JA, Muchiri BG, Githui WA, et al. Screening Strategies for Tuberculosis Prevalence Surveys: The Value of Chest Radiography and Symptoms. PLoS One. 2012;7(7):e38691.