Original

Bi-directional Diagnosis of Tuberculosis (TB) Using Xpert® MTB/RIF Ultra and Determine® TB-LAM Ag Testing Methodologies in a Parallel Algorithm: Pathway Towards Identifying the Nigerian Missing TB Cases.

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Abstract

Background: The endemic nature of TB infection in Nigeria requires that the nation's TB diagnostic tools and algorithms be reassessed towards meeting the current global trends in TB case-detection. Also, the incidence and prevalence of both Pulmonary tuberculosis (PTB) and Extra-Pulmonary tuberculosis (EPTB) needs to be well ascertained for Nigeria to know her true TB prevalence.

Methods: 365 presumptive and consenting TB clients participated in this cross-sectional study. Collected sputum and urine samples were tested with Xpert® MTB/RIF ultra and the Determine® TB-LAM Ag®; following standard laboratory operating processes. Obtained data were statistically analyzed using the student's t-test, the Pearson's correlation statistics, and simple percentages with the Excel® Data Analysis ToolPak.

Results: 30.4% (111/365) combined Mtb cases were detected in this study. Using Student's t-test at 95% CL, the obtained p-value (P 0.018104), and a calculated correlation coefficient (r=1) obtained reveals a significantly strong association and a perfect positive correlation between the bi-directional diagnosis of TB using this parallel TB screening methodologies, and an increased *Mtb* cases detection.

Conclusion: In this study, the high sensitivity of the Xpert® MTB/RIF Ultra at detecting PTB and the high specificity of the Determine® TB-LAM Ag® at detecting EPTB has been synergized in a parallel algorithm. It is believed that the application of this testing methodology in a parallel algorithm would help to optimize Mtb cases detection and TB diagnosis in Nigeria.

Keywords: Tuberculosis, Nigeria, Advanced HIV Disease, Lipoarabinomannan, Xpert® MTB/RIF, TB-LAM, Extra-pulmonary TB

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Introduction

Tuberculosis (TB) is a serious infectious disease that affects people all over the world. While most cases (over 80%) occur in low and middle-income countries, TB remains a threat everywhere. [1] [2] According to the World Health Organization (WHO), the South-East Asian Region bore the highest burden of new tuberculosis (TB) cases in 2022, Africa followed closely at 23%, and the Western Pacific region reported 18% of new cases [3]. Individuals most at risk of developing TB are adults in their prime working years. However, people of all ages can be infected. TB is a leading killer of people living with HIV and a major cause of deaths related to antimicrobial resistance. [4] In 2022, 2.5 million people fell ill with TB in the African region, accounting for a quarter of new TB cases worldwide. An estimated 424,000 people died from the disease in the African region (1.267 million globally) in 2022. [3]

It is reported that Nigeria has the highest TB burden in Africa; with the disease killing about 268 people in the country every day. But despite this alarming record, TB cases are still being under-reported, thus, increasing the high risk of transmission.[5] It is estimated that one missed case can transmit TB to 15 people in a year.[5]. According to provisional data, over 361 000 TB cases were reported in Nigeria in 2023, with 9% of these in children. [5]

Studies indicate that the Xpert® Mycobacterium tuberculosis/Rifampicin (Xpert® MTB/RIF) ultra can detect TB in a large number of people that routine testing services cannot detect. [6]. Therefore, new models of care are possible due to this rapid diagnostic technology that returns results within a short period of time. [6] The molecular amplification of the amino acid bases of the Mycobacterium tuberculosis (*Mtb*) bacteria by the Xpert® MTB/RIF ultra makes for its high sensitivity at detecting TB infection; especially in pulmonary specimens. It should however be noted that despite the high sensitivity associated with this molecular TB diagnostic method, a study has suggested that GeneXpert® may not be used as a stand-alone diagnostic tool for Pulmonary TB (PTB) diagnosis. [7].

The Nigerian TB diagnostic algorithm at the moment classifies TB case detection into two: (i) Bacteriological Positive TB Case (*Mycobacterium tuberculosis* (*Mtb*) detected by either Smear microscopy, Culture, Line Probe Assay (LPA), or Molecular techniques) and, (ii) Bacteriological Negative TB Case (Negative tests or the use of strong clinical evidence for TB diagnosis without Laboratory tests).[8]. In Nigeria, TB culture facilities are rare and generally not in use due to the economic costs of this testing method, and the prolonged time lapse before culture results can be obtained with this method also contributes in no small way to its poor utilization. Sputum smears are basically used for client's follow-up after TB treatment initiation, and not for the initial TB diagnosis. In addition, due to economic costs and the lack of technical expertise, LPA is basically employed at TB Reference Laboratories for Quality Control/Assurance (QC/QA) purposes. Thus, emphasis is laid on the use of Molecular diagnostic tools for initial TB detection in Nigeria (basically through the use of the Xpert® MTB/RIF ultra and the TB-LAMP® Loop-Mediated Isothermal Amplification methods). The use of the Xpert® MTB/RIF ultra has fostered the increased diagnosis of PTB and RIF resistance in presumptive TB clients, while not fully detecting *Mtb* in Extra-Pulmonary TB (EPTB) presumptive clients. Thus, EPTB can be present in a client without a pulmonary presentation, and because this TB infection is unrelated to the lungs, there could be no symptoms of coughing or the production of sputum. Sputum samples from EPTB clients may also not yield a positive *Mtb* result. Studies have shown the poor outcomes of *Mtb* case detection in EPTB cases when Xpert® MTB/RIF ultra-assay is applied.[9]

The Nigerian TB diagnostic program has not fully adopted the use of some specific Mtb markers that could be used for the detection of Mtb in specific body fluids. One such Marker, the Lipoarabinomannan (LAM) glycolipid, which is found in the voided urine of *Mtb* infected clients, can help detect EPTB in presumptive TB clients without the use of invasive sampling collection techniques. The only use of the LAM Marker as a tool for TB diagnosis now is seen in the Nigerian HIV Program; and this is solely recommended for use only among HIV positive pediatrics and adolescents.[8] The use of the LAM diagnostic Marker in TB case detection has however been expanded to capture all Advanced HIV Disease (AHD) clients (CD4 <200 cells/mm^3) in the country. There is adequate access to TB diagnosis in Nigeria; the only challenge remains the skewed application of the current TB diagnostic tools and algorithm that does not make for the adequate detection of EPTB. The bi-directional diagnostic methodologies and algorithm employed in this study involves the deployment of two different Laboratory TB diagnostic tools for the detection of *Mtb* in each and every presumptive TB client. Diagnostically identifying

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the missing TB cases in Nigeria will help to reduce the *Mtb* transmission rate among the Nigerian population as affected clients can be adequately placed on requisite TB treatment regimen.

The World Health Organization (WHO) has recommended the use of the Urine TB LF-LAM for active TB infection detection in People Living with HIV (PLWH) on hospital admissions, among outpatient PLWH, and Advanced HIV Disease (AHD) clients.[10] It is imperative to note that studies have also shown that the sensitivity of this test is higher in patients on hospital admissions, those with AHD, and among those with active *Mtb* infection, [11] with a high specificity for *Mtb* detection in HIV negative clients.[12] However, as a simple Point-of-Care (POC) test, Urine TB LF-LAM can help in *Mtb* case detection generally.[12]

This study was primarily conducted as part of the effort/strategy to help Nigeria identify her missing TB cases, while also aiming to help Nigeria establish her true TB prevalence. The main objective of this study is to verify a bi-directional diagnostic methodology and an algorithm than can be used to optimize *Mtb* case detection in Nigeria.

Hypothesis

[a] Null Hypothesis (Ho): The bi-directional diagnosis of TB in presumptive TB clients using Xpert® MTB/RIF Ultra and Determine TB-LAM Ag testing methodologies in a parallel algorithm has no association nor correlation with an increase in *Mtb* cases detection.

[b] Alternative Hypothesis (Ha): The bi-directional diagnosis of TB in presumptive TB clients using Xpert® MTB/RIF Ultra and Determine® TB-LAM Ag testing methodologies in a parallel algorithm has a direct association and correlation with an increase in *Mtb* cases detection.

Methodology

***Study Design*:** This is a randomized cross-sectional study involving the use of sputum and urine samples collected from 365 TB presumptive clients. The study took place from March to August 2024

***Setting*:** This study took place across the three geo-political zones of Plateau State, North-Central Nigeria. The study proposal, a simple data collection tool, and consent form were designed, and Ethical Approval for this study was gotten from the Plateau State Specialist Hospital (PSSH) Research and Ethics Committee (Ref No.: PSSH/ADM/ETH.CO/2024/042). The study proposal, data collection tool and the consent form were further reviewed and approved by the Plateau State Ministry of Health (MoH) (Ref No.: MoH/MIS/202. Vol. T/X).

***Participants*:** Only randomly presenting presumptive TB clients who were referred to the Directly Observed Therapy (DOT) clinics for TB screening were recruited in this study. Considering the ethical ramifications involved in the inclusion of minors in medical research, we have deliberately excluded all minors from this study.
Variables: In order to ensure the confidentiality of each participant, no name of clients was used in the data collection tool. Basic biodata including gender, age, educational status, place of residence, HIV status, and occupation were collected.

***Data Sources/Measurement*:** All data in this study was collected using the designed and duly approved data collection tool that was specifically structured for this study. Randomly presenting participants who consented were asked to produce sputum samples into sterile wide-mouthed sputum containers; same clients also produced mid-stream urine samples into sterile universal containers, simultaneously. The sputum samples were aseptically processed and assayed for Mtb and Rifampicin (RIF) resistance detection using the Xpert® MTB/RIF Ultra cartridge on the GeneXpert machine. The urine samples were tested for the presence of Mtb LAM glycolipid using the lateral flow Determine® TB-LAM Ag testing kit.
***Bias*:** to avoid sampling bias in this study, only randomly presenting presumptive TB clients were recruited in this study.

***Study Size*:** After pulling the total number of study participants from all relevant studies relating to this subject in Nigeria till date and using the online Creative Research Systems® [29] sample size calculator at 99% Confidence Level (CL) with a 1% Confidence Interval (CI), a total number of 365 participants was calculated.
Statistical Methods: Obtained data were statistically analyzed using the student's t-test, the Pearson's correlation analysis, and simple descriptive statistics with the Excel® Data Analysis ToolPak. All variables of interest were fully collected in this study; however, analysis of data was restricted to the variables that are most relevant in the interpretation of our hypothesis.

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Results

Analysis of obtained data indicates that 182 (49.9%) of the participants were males, while 183 (50.1%) were females respectively. Among the males, 31% (57/182) had TB infection, while 30% (54/183) among the female participants had TB infection. Among the entire study population, 70 (19%) were PLWH; while 295 (81%) were individuals who are HIV-Negative. In addition, 31(8.4%) of the *Mtb* cases were detected by the Xpert® MTB/RIF ultra diagnostic method, while 80 (22%) of the Mtb cases were detected by the Determine® TB-LAM Ag diagnostic method.

Table 1: Summary Table of Findings.

Male	Female	HIV Positive	HIV Negative	Total MTB/RIF Ultra (Mtb Detected)	Total LAM (Mtb Detected)	TB-RIF Ag Positive	Mtb Co-detection by both Methods
182	183	70	295	31	80	1	8
49.9%	50.1%	19%	81%	8.4%	22%	0.3%	2%

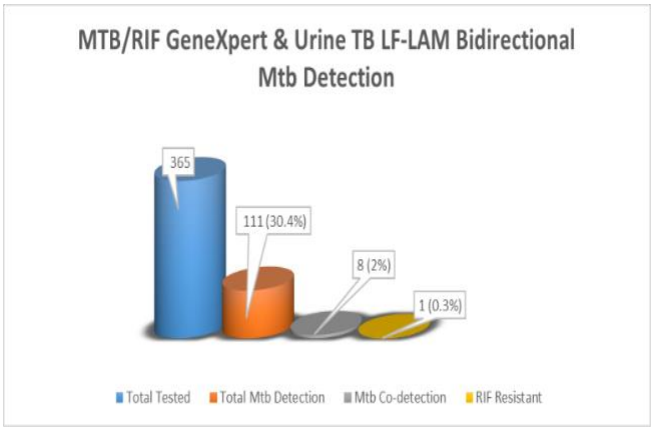

Figure 1: Xpert® MTB/RIF Ultra & Determine® TB-LAM Ag Bi-directional Mtb Case Detection.

Table 2: Data Analysis Table

Variables	Fields	*Mtb* Detected	*Mtb* Undetected	Pearson's Correlation Coefficient (r)	Student's t-test (p-value)
TB Screening Methodologies	Xpert® MTB/RIF Ultra	31	334	1	0.018104
	Urine TB-LAM Ag	81	284		
Gender	Male	57	125	0.99726	0.00122
	Female	54	129		
HIV Status	HIV Positive	23	47	1	0.494731
	HIV Negative	88	207		

The Pearson's correlation coefficient and the student's t-test statistical methods were used to test for both relationship and association between the two TB screening methods employed in this study and *Mtb* case detection. Upon critical analysis, the student's t-test at 95% CL, and at a 0.05% margin of error yields a calculated p-value of 0.018104 (P 0.018104). The calculated correlation coefficient (r) using Pearson's correlation statistics was 1 (r=1). These outcomes show that there is a perfect positive correlation between Xpert® MTB/RIF Ultra and Determine® TB-LAM Ag bi-directional TB diagnostic methodologies and an increase in *Mtb* cases detection among the study participants. The obtained p-value of 0.018104 (P 0.018104) also reveals a significant association between the bi-directional diagnosis of TB cases using this parallel algorithm and an increase in *Mtb* cases detection. Thus, at 95% CL, we reject the null hypothesis (H_o) while we accept the alternative hypothesis (H_a) which states that "The bi-directional diagnosis of TB in presumptive TB clients using Xpert® MTB/RIF Ultra and Determine® TB-LAM Ag kit in a parallel algorithm has a direct association and correlation with an increase in *Mtb* cases detection".

A further analysis on the role of gender in Mtb transmission and infection yields a correlation coefficient (r) value of 0.99726 (r=0.99726). The student's t-test analysis for gender role in TB transmission yields a p-value of 0.00122 (P 0.00122) respectively. These results clearly indicate that there is a perfect positive correlation between gender and *Mtb* infection. Also, with a p-value of 0.00122 (P 0.00122),

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there is a significant association between gender and *Mtb* infection; with the male gender more prone to contracting *Mtb* infection. These findings are in agreement with similar findings from several studies which strongly associate higher rates of TB with the male gender. [13,14,15].

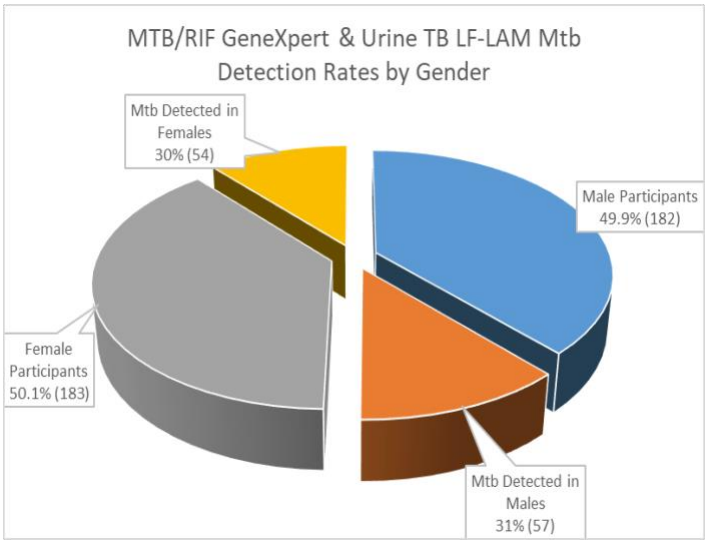

Figure 2: Xpert® MTB/RIF Ultra & Determine® TB-LAM Ag *Mtb* Case Detection Rates by Gender.

Additional analysis of the association and correlation between HIV status and *Mtb* detection yields a correlation coefficient value of 1 (r=1), and the student's t-test analysis yields a p-value of 0.494731 (P 0.494731) respectively. These results clearly indicate that while *Mtb* detection in PLWH and the HIV negative population could occur with an equal margin of possibility or probability (P 0.49 ≈ 50%) using this *Mtb* detection algorithm, there is however a perfect positive correlation between HIV and *Mtb* infection; thus, the higher the rate of HIV infection, the higher the chances of *Mtb* detection. Hence, the diagnosis of TB with these bi-directional methodologies and algorithm has an equal probability in *Mtb* case detection between these two population groups (HIV positive and HIV negative populations).

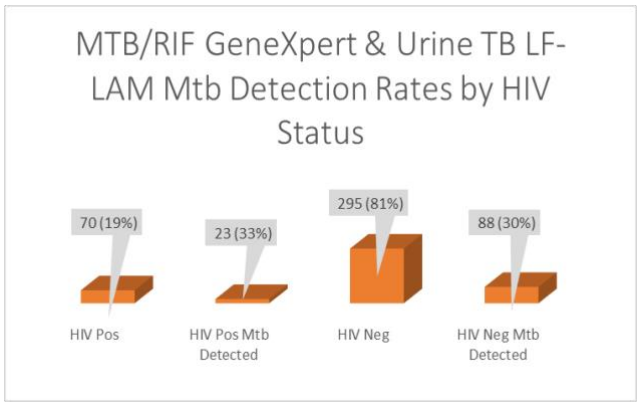

Figure 3: Xpert® MTB/RIF Ultra & Determine® TB-LAM Ag Mtb Case Detection Rates by HIV Status.

Discussion

This study which was conducted with the intent to establishing a new TB diagnostic model or algorithm that could help in the detection of all forms of TB infections in Nigeria; either Pulmonary TB (PTB) or Extra-Pulmonary TB (EPTB), has helped to reveal the gross inadequacies in the Nigerian TB diagnosis methodologies and algorithm. This study has shown that a large number of EPTB clients are left undiagnosed in Nigeria, thus, giving room to increasing morbidity and mortality among presumptive TB clients. The failure of the current national TB diagnostic algorithm and methodologies has also prevented the possibilities of establishing the true prevalence of TB in Nigeria.

Statistical analysis of data obtained in this study shows that there is a direct association (P 0.018104) and a perfect positive correlation (r=1) between the bi-directional diagnosis of TB using Xpert® MTB/RIF Ultra and the Determine® TB-LAM Ag testing methodologies in a parallel algorithm, and an increase in *Mtb* cases detection. Our study further shows that there is a direct association (P 0.00122) and a perfect positive correlation (r=0.99726) between gender and *Mtb* case detection, with the male gender more prone to TB infection.[13,14,15] This study also reveals a perfect positive correlation (r=1) between increasing Mtb cases detection in PLWH and the use of this bi-directional TB diagnostic methodologies and algorithm. The p-value of 0.49 (P 0.494731) obtained after further statistical analysis using the student's t-test clearly shows that there

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is an equal (50%) probability of this bi-directional TB diagnostic algorithm to detect *Mtb* in PLWH and in HIV-negative populations. Thus, while the Determine® TB-LAM Ag has very high specificity for EPTB detection in PLWH and in HIV negative clients, [16,17,18] the Xpert® MTB/RIF Ultra is highly sensitive at detecting PTB in the same population groups [19], [20], [21], [22]. Hence, the combined application of these two diagnostic methodologies in a bi-directional and parallel algorithm could help to optimize *Mtb* case detection in PLWH, and among the general HIV-Negative population respectively. Among the 365 clients who participated in this study, the Xpert® MTB/RIF Ultra detected 8.4% of the *Mtb* cases, while the Determine® TB-LAM Ag detected 22% of the *Mtb* cases. The combined case detection rate in this study was 30.4%, which clearly shows the efficacy of this combined TB diagnostic algorithm.

Among the 70 HIV positive clients in this study, 33% (23) were *Mtb* detected; with the Xpert® MTB/RIF Ultra detecting 9% (2) as *Mtb* positive while the Determine® TB-LAM Ag detected 91% (21) as *Mtb* positive respectively. This outcome gives credence to the reported high specificity and high detection rate of Mtb in PLWH [23],[24],[25]. 81% (295) of the participants were HIV negative, with 30% (88) *Mtb* detection rate among this cohort. Among the 295 HIV negative clients, the Xpert® MTB/RIF Ultra detected 33% (29) as *Mtb* positive while the Determine® TB-LAM Ag detected 67% (59) as *Mtb* positive. This outcome clearly shows that the utility of the Determine® TB-LAM Ag can be fully optimized among the general HIV-Negative presumptive TB population. Thus, its applicability and deployment apply to both the HIV positive and the HIV negative populations. Also of note in this study is the co-detection of *Mtb* by these two testing methods in 2% (8) of the participants. This study outcome also indicates only 0.3% (1) RIF resistant case was detected. In addition, while the Determine® TB-LAM Ag could not detect 94% (29/31) of the Pulmonary Mtb positive cases which were detected by the Xpert® MTB/RIF Ultra assay, the Xpert® MTB/RIF Ultra assay also could not detect 98% (78/80) of the Extra-Pulmonary *Mtb* positive cases which were detected by the Determine® TB-LAM Ag testing. Thus, with a combined *Mtb* case detection of 30.4% among the study population, the bi-directional application and deployment of these two testing methods in a parallel algorithm could help optimize the TB case detection in Nigeria.

Implications of the findings

For Nigeria to be among the committee of nations meeting the global "End TB" target of year 2035 [27],[28] the country needs to forge a new direction through the formulation and implementation of new TB diagnosis and TB case finding policies. At this point in human history, Nigeria can no longer work with an estimated TB prevalence.[26] The ease with which this bi-directional diagnostic algorithm can be employed in the diagnosis of both PTB and EPTB makes for its scalability, user centeredness, and sheer inclusivity. Our hope is that not only Nigeria will employ this new TB diagnostic methodologies and algorithm in *Mtb* case detection, but other countries would also conduct similar studies to ascertain the level of effectiveness of this bi-directional TB diagnostic approach in their respective efforts aimed at ending the global TB epidemic.

Strengths and limitations

This study shows a high prevalence of TB in Nigeria; with many EPTB cases left undiagnosed among the general population due to the nation's current TB diagnosis policies, poorly optimized TB testing methodologies and algorithms. The high sensitivity of the MTB/RIF GeneXpert® Ultra at detecting PTB and the high specificity of Urine TB-LAM® lateral flow antigen testing at detecting EPTB has been synergized in this study; resulting in an increased Mtb cases detection. Due to varied logistics and funding constraints, this study has been limited to Plateau State, North-Central Nigeria. A larger study with representations from all the geo-political zones and states of Nigeria is recommended in order to further appreciate the magnitude and importance of this study.

Conclusion

Tuberculosis can only be eradicated when we know the true prevalence of the TB epidemic in a given society. The endemicity of tuberculosis and its close association with malnutrition, diabetes, and HIV has made it a major public health threat in sub-Saharan Africa (SSA). Nigeria remains the sixth country in the world with the highest TB burden. And in Africa, Nigeria remains the only country with the highest number of undetected and missing TB cases. Recent intensified efforts in TB case-finding at the community level and increasing TB contact-tracing has led to the increased diagnosis of TB cases in Nigeria. However, it is an established fact that Nigeria still works with an estimated TB prevalence which does not give a true reflection of its TB burden. We thus recommend the introduction of a parallel bi-

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directional TB screening approach in Nigeria using MTB/RIF GeneXpert® and the Urine TB-LAM.

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Authors' Contribution:
Adeniyi DS – Concept, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review, guarantor.
Tongvwam PJ – Clinical studies and data acquisition
Okonkwo PC – Clinical studies and data acquisition
Owolagba FE – Manuscript editing, Manuscript review, and Guarantor
Ofuche E – Manuscript editing, Manuscript review, and Guarantor
Onwuatuelo I –Manuscript editing, Manuscript review, and Guarantor
Samuels JO – Manuscript editing, Manuscript review, and Guarantor
Okonkwo P – Manuscript editing, Manuscript review, and Guarantor.

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