

Intensified or Routine Case Finding for Pulmonary Tuberculosis among HIV-Infected Patients: Which is Better?

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Abstract

Background: Intensified strategy includes special attention to the symptoms such as cough (more than two weeks), fever (more than three weeks), night sweats (more than three weeks), and weight loss (more than 3 kg per month). If any of the above symptoms was positive, in suspected individuals for TB, more assessment should be done. The aim of this study was to compare between intensified and routine case finding for a better case selection method for diagnosis of pulmonary tuberculosis among HIV-Infected Persons.

Methods: The sample size was calculated 237 patients (474 for the two groups). In the current study, the patients were divided randomly into two groups: A) intensified case finding group and B) routine case finding group. Considering the sputum culture as the gold standard, we calculated the sensitivity and specificity, Positive predictive value (PPV), Negative predictive value (NPV) for fever, weight loss, coughing more than two week, night sweats, and PPD test.

Result: A total of eight positive cases of tuberculosis were detected in the intensified while four were found in the routine case finding group. Sensitivity, specificity, PPV, and NPV for cough in diagnosis of TB were 25%, 87%, 6%, and 97%, respectively. For weight loss, they were 62.5%, 83%, 10.8%, and 98.5% respectively while these amounts were, 7%, 85%, 97.6, 37.5 for night sweats. For fever, they were, 25%, 92.9%, 10.5%, and 97% respectively, and for PPD they were 87.5%, 40%, 4.6%, and 98.9%, respectively.

Conclusion: Key symptom screening, such as cough, fever, weight loss and night sweats, has an important role in detecting TB among HIV-infected patients.

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Introduction

Co-infection of HIV/TB is increasing worldwide¹ and epidemic of HIV has had a huge impact on the prevalence of TB.^{2,3} Approximately a half million of TB cases diagnosed annually are attributed to HIV infection.^{4,5} The risk of death in HIV positive patients who were

also infected by TB is high; TB is the cause of 14-45% of deaths in HIV positive patients.⁵⁻⁹ Mycobacterium tuberculosis and HIV are the two major causes of adults' death among infectious diseases,¹⁰⁻¹² and co-infection of HIV/TB has imposed a great burden on the health systems.¹³ The World Health Organization information, implies that the percentage of HIV associated TB is

increasing dramatically,¹⁴⁻¹⁶ and 85% of TB cases in HIV positive patients are among the new cases.¹⁷ In Iran, like other developing countries, the prevalence of HIV is rising.^{18,19} Diagnosis of TB in HIV patients accounts for a fundamental and problematic challenge for the health systems,²⁰ and diagnosis delay has a great impact on the mortality rate.²¹ Studies have shown that in HIV positive patients, only 45% of TB cases can be diagnosed properly.^{22,23} The key strategies of the WHO for reducing the burden of HIV/TB co infection is implementing intensified case finding for diagnosis of TB in HIV positive individuals.²⁴ This method has two main objectives, including reduction of TB transmission, mortality, and morbidity by early diagnosis.²² Intensified strategy includes special attention to the symptoms such as cough (more than two weeks), fever (more than three weeks), night sweats (more than three weeks), and weight loss (more than 3 kg per month). If any of the above symptoms was positive, suspected individuals of TB should undergo more assessment.²⁵

Methods

This study was designed to compare two methods of case finding of pulmonary TB in HIV positive patients referring to behavioral diseases consultation center in Shiraz, Iran, in 2013.

Sample Size

Required samples for the study were calculated according to the differences between two ratios formula ($\alpha=0/05, 1-\beta=0/80$) 237 patients (474 for two groups); regarding the probability of loss, this number rose to 500 patients. The patients were selected using simple random sampling method from the patients' list and enrolled in two groups (RCF and ICF case finding for TB).

Inclusion and Exclusion Criteria

The study population included patients diagnosed with HIV and referred to behavioral disorders consulting center of Shiraz University of Medical Sciences; they agreed to participate in the study. Those who were unable or unwilling to complete the full diagnostic evaluation, pregnant women, imprisoned persons, those taking medications with antimycobacterial activity within the previous 2 weeks, and patients currently receiving anti-TB treatment were excluded.

Data Collection

A trained physician conducted a standardized symptom screening and physical examination in a private consultation room, within the clinic. The patients were asked about the presence and duration of their cough, hemoptysis, fever, weight loss, night

sweats, shortness of breath, chest pain, diarrhea, appetite loss, and fatigue and result of PPD Test. Additional data were collected on basic demographics and risk factors for TB. A special checklist was designed for data collection. If one was positive in each of the above-mentioned signs or positive PPD result (its adequate to be positive in just one sign), he or she entered the ICF group. Otherwise, he or she entered the RCF group for TB case finding.

Implementation of the Study and Laboratory Methods

Taking screening test depended on symptoms, such as fever, weight loss, coughing more than two weeks and night sweats. If these signs were positive, the patients entered the next stage of the study and were evaluated by other tests, such as CXR, AFB, and sputum cultures. So, considering sputum culture as a GOLD STANDARD, we calculated the sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) of the four above mentioned tests. In the current study, the patients were divided into two groups of intensified case finding group (Figure 1), and routine case finding group (Figure 2). In the ICF method, the patients were evaluated by physician for such signs as fever, weight loss, coughing for more than two weeks, and night sweats. Furthermore, tests such as sputum culture, AFB, CXR were also performed for the patients who had these symptoms. Based on the above criteria, if one patient in the intervention group was negative, he/she was treated according to the routine manual, so that AFB test was carried out three times, and due to two or three times of positive result, the patient was considered as positive tuberculosis; otherwise, we referred to the CXR results. On the other hand, in the case of positive test results CXR consistent with TB, the patients were considered as positive cases of TB. If all three tests were negative but CXR was consistent with TB, a panel of experts determined the presence or absence of tuberculosis. Then, sputum culture was taken once if the result was positive and at least one positive AFB result was obtained and the patient was considered positive for tuberculosis. However, the patient was considered as a pulmonary positive smear TB case with positive sputum smear test and two negative AFB results. If the sputum smear test was positive and the three AFB results were negative, the patient was considered TB smear negative. Some patients in the intensified case finding group had not any of the four listed symptoms for screening, so such patients were treated in accordance with the routine program the same as patients who had a negative PPD test result. PPD was the first test in the routine case finding group and if it was positive, the patient was followed by some clinical assessments, CXR result, existing series of clinical symptoms, and positive AFB test. Finally, the patients were placed in the active

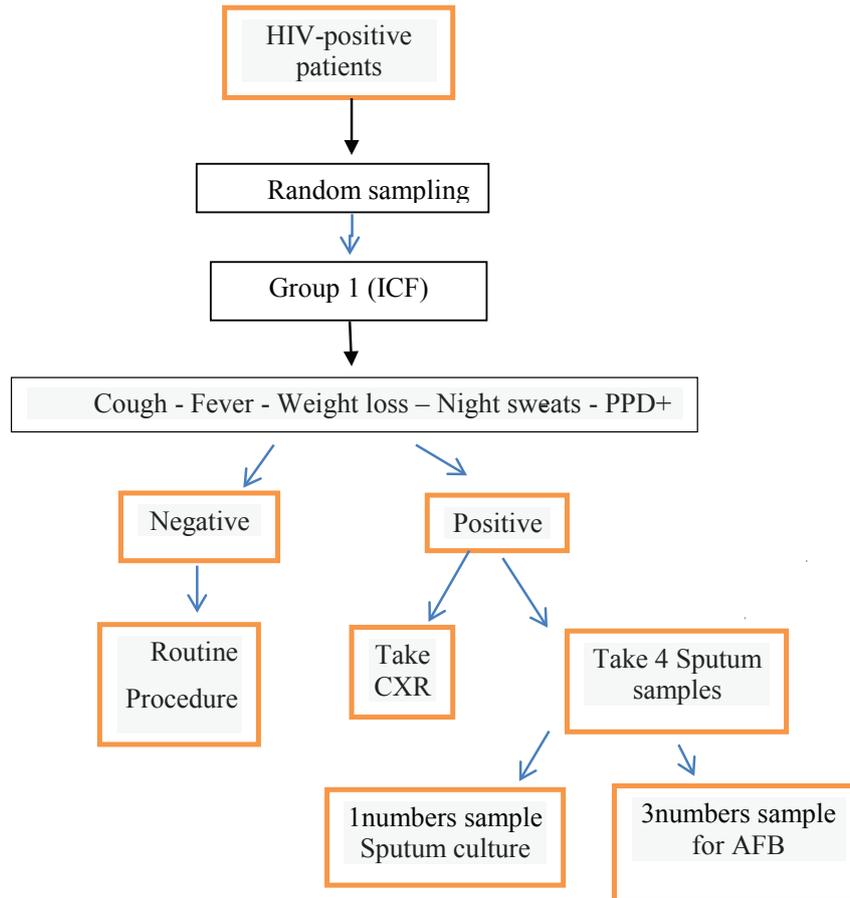


Figure 1: Intensified strategy includes special attention to such symptoms as cough (more than two weeks), fever (more than three weeks), night sweats (more than three weeks), and weight loss (more than 3 kg per month)²²

tuberculosis group. And in case of negative sputum test results, the patients were classified as latent TB. However, the patients with negative PPD results were evaluated in terms of the history of recent contact with TB patients and the number of the CD4. The previous steps were repeated if the PPD result was negative and the patient had a history of recent contact with active tuberculosis patients. However, after reviewing the results of clinical examination, CXR results, and a series of clinical symptoms and positive AFB sputum smear result, the patient was considered as active tuberculosis. Besides, regarding no prior history of contact with positive TB patients, CD4 result determined the diagnosis. In CD4 results was over 200, there was no need for prophylaxis and the annually repetition of the skin test was recommended. Moreover, if the CD4 count was less than 200, repeated skin test after initiation of antiretroviral therapy and increased CD4 count over 200 was recommended.

Statistical Methods

We used simple proportions for all analyses of sensitivity, specificity, and predictive value. For categorical variables, we compared proportions, and used χ^2 test, Fisher's exact test; OR was computed

according to the formula below:

$$\text{Odds ratio} = OR = \frac{a/b}{c/d} = \frac{a \times d}{b \times c}$$

All data were analyzed by the team of investigators using Statistical Package for Social Sciences (SPSS) software, version 19.0.

Ethical Considerations

The Shiraz University of Medical Sciences ethics committee reviewed and approved the protocol.

Results

500 patients were enrolled in the study and divided into two groups of 250: routine case finding and intensified case finding groups. The two groups were comparable in terms of characteristics such as age, sex, marital status, stages of disease, treatment with ART, and CD4 count, as shown in Table 1.

A total of eight positive cases of tuberculosis were detected in the intensified case finding group vs. four in the routine case finding group. Thus, the number of cases in the intensified case finding

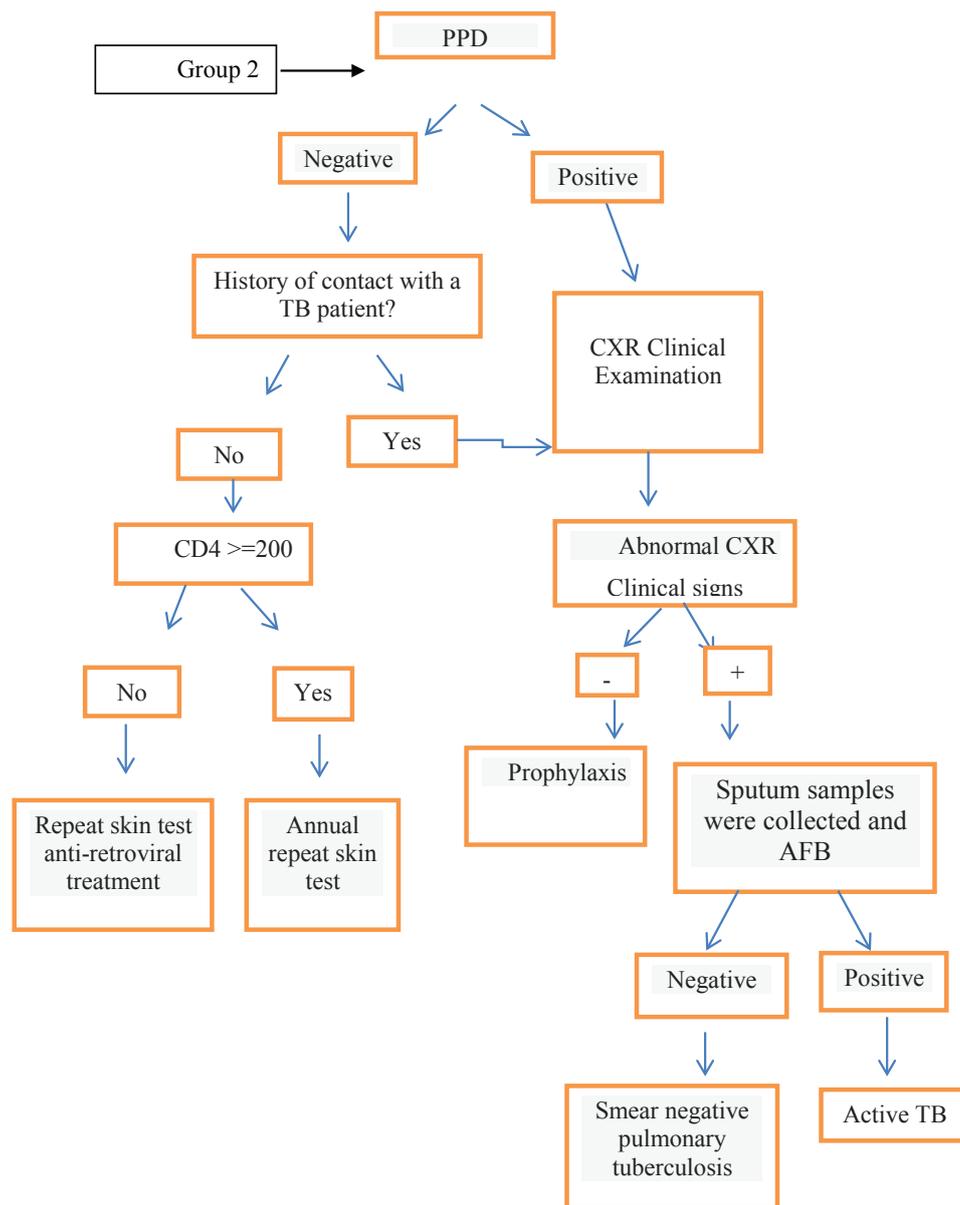


Figure 2: Routine case finding methods that are routinely carried out annually²⁶

group were doubled. (an increase of 100 percent) The number of detected cases according to some important characteristics of both groups is listed in Table 2.

Comparison of indexes of four listed symptoms in the intensified case finding method is explained in Table 3.

In addition, each of these four main symptoms in TB, TB cases in intensified case finding group was compared and the results are shown in Table 4.

Discussion

Compared with the routine case finding method, the number of patients diagnosed in the intensified case finding method was doubled (8 vs. 4). Despite its

clinical significance, this difference was not statistically significant (statistical significance measures how likely any surface differences in the outcome between treatment and control or case and control groups are real and not due to chance or random error and clinical significance measures how large the differences in treatment effects are in clinical practice). Overall, diagnosis of TB in HIV positive patients is difficult and the predominant form of the disease presents as pulmonary forms. Perhaps, this is one of the most obstacles in progress of diagnosis of pulmonary tuberculosis; the process of TB diagnosis requires using more expensive and sophisticated methods. Many similar studies have been done all around the world using intensified case finding method. We found that routinely available TB screening tests have limited sensitivity for detecting active TB disease among HIV-infected persons and intensified case

Table 1: Comparison of important characteristics of the two study groups

Variable	Total n (%)	ICF ⁽¹⁾ n (%)	RCF ⁽²⁾ n (%)	P value ⁽³⁾
Sex				
Male	327 (65.4%)	157 (62.8%)	170 (68.0%)	0.22
Female	173 (34.6%)	93 (37.2%)	80 (32.0%)	
Age				
15<	1 (0.02%)	0 (0.0%)	1 (0.4%)	0.25
15-25	13 (2.6%)	8 (3.2%)	5 (2.0%)	
26-45	363 (72.6%)	174 (69.6%)	189 (75.6%)	
46-65	123 (24.6%)	68 (27.2%)	55 (22.0%)	
cd4 Enumeration				
200>	194 (38.8%)	94 (37.6%)	100 (40.0%)	0.41
200-350	175 (35.0%)	96 (38.4%)	79 (31.6%)	
350-500	57 (11.4%)	27 (10.8%)	30 (12.0%)	
500>	74 (14.8%)	33 (13.2%)	41 (16.4%)	
Marital Status				
Single	135 (27.0%)	67 (26.8%)	68 (27.2%)	0.73
Married	225 (45.0%)	108 (43.2%)	117 (46.8%)	
Divorced	91 (18.2%)	50 (20.0%)	41 (16.4%)	
Husband's death	49 (9.8%)	25 (10.0%)	24 (9.6%)	
ART treatment				
Yes	272 (54.4%)	135 (54.0%)	137 (54.8%)	0.85
No	228 (45.6%)	115 (46.0%)	113 (45.2%)	
Stage of disease				
Clinical	115 (46.0%)	52 (20.8%)	63 (25.2%)	0.28
Non-clinical	385 (54.0%)	198 (79.2%)	187 (74.8%)	

1. Intensified case finding; 2. Routine case finding; 3. Chi-square test

Table 2: Comparison of two methods of detecting some important characteristics

Variable	Total n (%)	ICF ⁽¹⁾ n (%)	RCF ⁽²⁾ n (%)
Sex			
Male	8 (66.6%)	2 (50.0%)	6 (75.0%)
Female	4 (33.3%)	2 (50.0%)	2 (25.0%)
Age			
26-45	7 (58.3%)	2 (50.0%)	5 (62.5%)
46-65	5 (41.7%)	2 (50.0%)	3 (37.5%)
cd4 Enumeration			
200>	3 (25.00%)	2 (50.0%)	1 (12.5%)
200-350	7 (58.3%)	2 (50.0%)	5 (62.5%)
350-500	1 (8.3%)	0 (0.0%)	1 (12.5%)
500>	1 (8.3%)	0 (0.0%)	1 (12.5%)
Marital Status			
Single	4 (33.3%)	1 (25.0%)	3 (37.5%)
Married	4 (33.3%)	1 (25.0%)	3 (37.5%)
Divorced	2 (16.6%)	0 (0.0%)	2 (25.0%)
Husband's death	2 (16.6%)	2 (50.0%)	0 (0.0%)
ART treatment			
yes	5 (41.6%)	3 (75.0%)	2 (33.3%)
no	7 (58.4%)	1 (25.0%)	6 (66.7%)
Stage of disease			
clinical	7 (58.4%)	3 (75.0%)	4 (50.0%)
Non-clinical	5 (41.6%)	1 (25.0%)	4 (50.0%)

1. Intensified case finding; 2. Routine case finding

finding is an effective method for detecting active TB disease among HIV-infected persons. This finding was confirmed in Elden's and Taye's studies.^{27,28} In Elden's study and Herman's study,²⁹ most of the detected cases were female, but in our study the largest numbers of

detected cases were male patients.²⁷ In Dhungana's study, the results were similar to our study while the highest range of detected cases was in the age of 21-40.³⁰ So, in another study by Sarita Shah in Ethiopia, among 433 HIV positive patients, 32 cases were TB positive, while

Table 3: Comparison of indexes of four listed symptoms in the intensified case finding method

Sign	Number	TB cases N=8	Not TB cases N=242	Sensitivity	Specificity	PPV ⁽¹⁾	NPV ⁽²⁾
Cough	33	2	31	25.0%	87.0%	6.0%	97.0%
Weight loss	46	5	41	62.5%	83.0%	10.8%	98.5%
Night sweats	39	3	36	37.5%	85.0%	7.7%	97.6%
Fever	19	2	17	25.0%	92.9%	10.5%	97.0%
PPD+	152	7	145	87.5%	40.0%	4.6%	98.9%

1. Positive predictive value; 2. Negative predictive value

Table 4: Comparison of patient and non-patient groups in terms of four symptoms

Sign	Total	TB CASES	NON TB CASES	PV	OR (95%CI)
Cough	33	2	31	0.28	2.69 (0.43-11.74)
Weight loss	46	5	41	0.00	8.10 (1.8-35.54)
Night sweats	39	3	36	0.11	3.43 (0.78-15)
Fever	19	2	17	0.11	4.40 (0.82-23.54)

the results were negative in 406 patients. However, in our study 250 HIV positive patients were enrolled and 8 patients were diagnosed as TB positive cases. Thus, negative diagnosis was made for 242 patients.²² So, comparison of the two studies showed that the highest sensitivity belonged to weight loss so that it may have an important role in diagnosing the disease, and it seems that the most significant symptom was fever. It means that the probability of being healthy among patients who have no sign of fever is very high. In Sarita Shah's study, the highest PPV was associated with fever but in the current study weight loss had the highest PPV. Both studies were also the same in terms of PPV and NPV. In Kevin's study, the highest PPV was associated with fever and highest NPV was associated with fever and weight loss.³¹

Conclusion

Diagnosis of tuberculosis in HIV patients in comparison with normal individuals seems difficult; symptoms such as cough for more than two weeks, fever, night sweats and weight loss which play important roles in detecting the disease should be considered. They also prevent diagnosed TB with costly diagnosis programs. This fact was shown in our study as well as other studies such as Sarita's study. Symptoms such as weight loss, fever, night sweats and cough have a proper sensitivity and a significant impact on the diagnosis of TB in HIV positive cases. In addition, assessment of classical symptoms such as cough, fever, weight loss and night sweats has an important role in detecting TB disease among HIV-infected persons.

Existing Problems in the Study

Some patients were reluctant to continue the test due to financial problems and we were forced to substitute other patients (approximately about 20-50 patients).

Conflict of Interest: None declared.

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