

## Assessment of adherence to tuberculosis drug regimen

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### ABSTRACT

**Background and the purpose of the study:** Tuberculosis is curable if patients take sufficient uninterrupted therapy. Most experts acknowledge importance of patient adherence in efforts to control of the disease. This cross-sectional study was designed to evaluate the rate of compliance to anti-tuberculosis regimens by means of urine tests in newly diagnosed tuberculosis patients.

**Method:** Investigation was carried out in Tehran University of Medical Sciences Teaching Hospitals, Tehran, IRAN. Fifty patients completed the study. The patients' urine samples were obtained at 0, 1, 2, 4 and 6 months of the study. Simple chemical methods were used to detect Isoniazid, Rifampin, and pyrazinamide, the three main drugs in tuberculosis treatment regimens. Urine tests at months of 0 and 1 of the study were considered as control tests.

**Results:** After the first month, the patients' compliance was about 96%. At months of second, fourth and sixth, the whole adherence rates were 56 %, 76% and 81% respectively.

**Conclusion:** About 30% of patients were non-compliant with treatment regimen which was more frequent than presumed; therefore detection of non-adherent patients is an essential subject in developing countries.

**Keywords:** Adherence, Tuberculosis, Urine test

### INTRODUCTION

Tuberculosis (TB) is a curable infectious disease if patients take sufficient uninterrupted therapy. Ensuring the regular intake of drugs to achieve a cure is as important as the diagnosis of tuberculosis (1, 2). Effective treatment of tuberculosis requires at least six months treatment with combination of drugs. To improve treatment adherence and cure rates, direct observed therapy is recommended for the treatment of pulmonary tuberculosis (3). It is therefore essential to identify rate of adherence to anti-TB medications so that patients at risk for non-compliance may be identified where adherence promoting interventions can be developed.

### MATERIAL AND METHODS

This prospectively cross-sectional study was designed to evaluate the rate of compliance to anti-TB drugs by means of chemical urine tests, in newly diagnosed pulmonary tuberculosis patients admitted at teaching hospitals affiliated to Tehran University of Medical Sciences, Tehran, IRAN. Fifty-five patients with smear-positive pulmonary tuberculosis who received Isoniazid (INH), Rifampin (RIF) and Pyrazinamide (PZA) in their treatment regimens entered this study. Patients

with HIV infection, hematuria, anuria, changing drug regimen during the study, using of drugs that interfere with the chemical urine tests (e.g. phenazopyridine, triamterene, furazolidone) were excluded from the study. The study was approved by Tehran University of Medical Sciences Research Ethics Board and all participants signed informed consent forms.

Patients' compliance to treatment regimens was assessed by detection of anti-TB drugs or their metabolites in the urine. Duration of treatment regimen for tuberculosis was 6 months, consisting of initial phase of two months treatment with INH+ RIF+ PZA+ ethambutol (EMB) /streptomycin followed by four months treatment with INH and RIF.

Urine samples were collected from patients 3 hours after drug ingestion at 0, 1, 2, 4 and 6 months of the study. In this investigation, time 0 indicates the time that patients were diagnosed for pulmonary tuberculosis for the first time and before the initiation of anti-tuberculosis drug regimen. Urine tests at time 0 was considered as negative control test (no change in urine color after addition of reagents).

During the first month of anti-TB therapy, all patients received their medications under

observation (at hospital or home), so urine tests at this time was considered as positive control tests. Patients received their drugs at home (without observation) during months two to six of the treatment period. Urine tests at second, fourth and sixth months of treatment were collected to evaluate patient adherence to therapy. Patients were not informed about the purpose of urine tests in order to avoid ingestion of medications only before the appointment.

Arkansas method was used to detect INH in the urine. In this method, two drops of a 500µg/mL potassium cyanide solution, two drops of 1400µg/mL chloramin-T solution and a few crystals (about 100mg) of barbituric acid were added to four drops of urine sample. A urine color change to dark blue after 10 seconds of gentle agitation was considered as positive reaction (4). To detect RIF in urine sample, one milliliter of n-butanol was added to five milliliters of urine sample. A change of color to pink or cherry-red showed the presence of RIF in the urine. To assess the presence of PZA in the urine, an equal portions of 2% solution of sodium nitroprusside and 2 N solution of sodium hydroxide (8g/dL) were mixed and one drop of the resulting solution was added to three drops of urine in a porcelain plate. The plate was gently shaken for 3 minutes. A color change to orange was interpreted as positive reaction for PZA (5, 6).

The level of compliance was classified as excellent (no negative urine test), good (just one negative urine test) and poor (negative urine test at all times) of months 2, 4 and 6 for any drugs that were used during this period (7).

## RESULTS

Fifty-five adult subjects (18-65 years old) entered the study of which five were excluded due to travel to other cities during the study. Fifty subjects (27 males and 23 females) with the mean age of 38±12 years old completed the study.

During the first month, tests for all drugs were positive in the urine samples of 48 (96%) of subjects and at the second month overall compliance was 56%.

Seventy six percent of patients were adherence at month of six and at the end of treatment the compliance was 81%. Patient's compliance for each drug separately at different times of study is shown in table 1.

The changes in compliance between months 2, 4 and 6 were statistically significant ( $p=0.03$ ).

Most of patients claimed that never missed medications when they were questioned, although this was not confirmed by urine tests.

Compliance of females to treatment regimen was 60.5% at the second month, 81% at the fourth

month and 87.5% at the sixth month that was significantly ( $p= 0.01$ ) higher than those of men (47.1%, 59% and 76.6% at the months of 2, 4 and 6 of the study respectively).

Patients were classified to three groups according to their ages to less than 25 years old, 25-35 and more than 35 years old. The most adherent patients were found in the group of 25-35 years old (66% at the month of 2, 85% at the month of 4 and 94% at the month of 6) and the least adherent ones were present in the group over 35 years (52.7%, 62% and 69% at months of 2, 4 and 6 respectively).

Based on the classification of compliance that has been mentioned in the method section, 45 % of the patients showed excellent, 25% showed good and 30% showed poor compliance respectively.

About 50% of patients showed at-least one adverse drug reaction. The most prevalent reactions were nausea (65%), vomiting (44%), anorexia (33%), abdominal pain (26%), rash (4%), headache (20%), insomnia (7%), confusion (15%), and hepatotoxicity (8%).

## DISCUSSION

Patient noncompliance is a major encountered problem in the control of tuberculosis and prevention of drug resistance to mycobacteria. About 50% of patients fail to follow treatment regimen as prescribed (8). Some TB experts have reported that the range of medication non-adherence are 20 to 100 percent (9). The major causes of non-adherence to anti-TB drugs include multiple medications, unpleasant side effects and long duration of treatment. Center for Diseases Control (CDC) has set forth adherence score of 90% as a national goal (10). Use of urine tests for detection of anti-TB drugs has been found as a quick, simple and inexpensive means for measurement of adherence to treatment (5, 7).

In this study, 35 (70%) of patients took all recommended drugs over the period of the treatment that was significantly lower than the cut off point recommended by CDC. Medication compliance rate in our patients were comparable with the findings of some studies (11, 12) but lower than some other studies (6, 13, 14).

The difference in the rate of patients' compliance between different studies may be due to cultural and socioeconomic characteristics of studied population and the method for evaluation of compliance. In some studies questionnaire-based interview was used for assessment of patient's compliance and in other ones only one or two drugs were assessed.

Although in one study more adherence to anti-TB drugs in men have been reported (15), in this study, a higher rate of compliance was observed

**Table 1.** patient's compliance for each drug separately at different times of study

Time (month)	Drug	Population	Positive urine test	Negative urine test	Compliance (%)
0	INH	50	-	50	-
	PIF	50	-	50	-
	PZA	50	-	50	-
1	INH	50	50	0	100
	RIF	50	48	2	96
	PZA	50	48	2	96
2	INH	50	29	21	58
	RIF	50	29	21	58
	PZA	10	27	23	54
4	INH	50	39	11	78
	RIF	50	37	13	74
	PZA	-	—	—	-
6	INH	50	41	9	82
	RIF	50	40	10	81
	PZA	-	-	-	-

INH: Isoniazid; RIF: Rifampin; PZA: Pyrazinamide; Population: Number of patients at each time of study

Positive Urine test: Present of drug in urine sample of patients

Negative Urine sample: Absent of drug in urine sample of patient

among females than males. The finding is in concordance with the results of other reports (12, 16). The differences in the drug compliance between two sexes may be explained by their lifestyles. Most of women which participated in this study were housewives; however, men were at work.

TB is more prevalent in 25-35 years old population in Iran (17) than other age groups. Although some investigations (10) showed no significant association between adherence score and age, in this study the most adherent patients were found of 25-35 years old.

Non-adherent patient are required longer treatment duration for smear conversion (18). In this study, sputum smear of ten subjects (20%) didn't change from positive to negative after the first two months of treatment and initial regimen was continued for 3 months. Eight of them were among poor compliant subjects at the second month.

Of our patients, 6 (22%) of males and 4 (17%) of females needed prolongation of initial phase of study for sputum conversion ( $P=0.04$ ), but in another study (15) not significant sex differences in treatment outcome were found.

Increase in patients' compliance during the course of treatment may be explained by patient education at the time of diagnosis and through the period of treatment and warnings about the consequence of uncontrolled disease. Also the number of drugs of the patients decreased during the course of treatment.

Finally, it should be declared that non-adherence to tuberculosis treatment was more frequent than presumed; therefore detection of non-adherent patients is an essential topic in developing countries.

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