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Patient Characteristics Associated with Non-Adherence to Tuberculosis Treatment: A Systematic Review

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Abstract

Background: A high level of adherence to treatment is essential for cure and prevention of tuberculosis (TB) treatment resistance. **Methods:** A Systematic review of 53 studies addressing the patient characteristics associated with TB medication non-adherence was performed. The publications were identified by searching the PubMed, World Health Organization (WHO), and Centers for Disease Control and Prevention (CDC) database, EmBase, Scopus database Arts, Humanities, Social Science database and Google scholar. Only English language publications were eligible. Potentially eligible studies were retrieved and the full articles were assessed. The potentially eligible studies were included if they concerned patients treated for tuberculosis, reported non adherence and reported on potential risk factors associated with non-adherence. **Results:** Factors that were most frequently consistently and statistically significantly related to non-adherence to tuberculosis treatment were: family income, patient movement and changing address or giving wrong address, tuberculosis relapse or multidrug-resistant TB (MDRTB), during intensive phase of treatment, history of default, treatment regimen (long course), response to treatment, homeless, stigma, seeking traditional healers, staff receptiveness, lack of directly observed therapy short course (DOTS), poor knowledge or lack of health education, side effects of drugs, feeling better, alcohol intake and lack of family and social support. **Conclusions:** Non-adherence to tuberculosis treatment was influenced by several factors.

Keywords

Tuberculosis, Non-Adherence, Adherence, Defaulter, Compliance

1. Introduction

Tuberculosis (TB) is among the top ten causes of global mortality [1] [2] [3] [4]. It is estimated that approximately one-third of the world's population (approximately two billion people) is infected with tuberculosis bacillus [5] [6] [7]. In 2015, globally 10.4 million new cases of TB and 1.8 million deaths from TB occurred, of which 1.4 million among HIV-negative people and 0.4 million deaths were in HIV-positive people and thus officially classified as HIV deaths in the International Statistical Classification of Diseases [8] [9] [10]. Approximately 80% of TB cases are found in 22 countries; the highest incidence rates being found in Africa and South-East Asia [11].

TB has a high morbidity and mortality rate despite its status as a treatable disease [12] [13]. A high level of adherence to treatment is essential for cure and to avoid development of resistance [14] [15]. Thus, completion of antituberculosis treatment is the foremost priority of tuberculosis (TB) control programs. Treatment that is taken irregular, interrupted for two months or longer or is incomplete increases the risk of treatment failure, relapse of disease, acquisition of drug-resistant TB, death, and prolonged infectiousness [16]-[21]. In turn, treatment failure and relapse can increase transmission of TB. Poor adherence to treatment is common despite various interventions aimed at improving treatment completion [22]. Non-adherence to TB medication is a major barrier to its local and global control and worsen the treatment outcome. In addition, defaulting increases the risk of drug resistance, relapse and death, and may prolong infectiousness. The objective of this systematic review was to identify the patient characteristics that are consistently associated with TB medication non-adherence. This knowledge could be helpful for health care providers and health policy makers to improve treatment adherence. The patient characteristics that we studied were: socio-demographic factors; disease related factors; treatment and services related factors; behavioral factors and social factors.

2. Methods

This systematic review was conducted to answer the question: which patient characteristics are consistently and statistically significantly associated with TB treatment non-adherence. The study reviewed publications found on risk factors associated with defaulting tuberculosis treatment that were published in English between 1990 to 2017. The publications were identified by searching the PubMed database, WHO database, and CDC database, EmBase, Scopus database, Arts, humanities, Social Science database and google scholar. Using the key words "tuberculosis", "mycobacterium tuberculosis", "adherence", "non adherence", "defaulting", "risk factors", "compliance", "determinant factors", "outcome of tuberculosis treatment", "predictors", "leading", "impact", "noncompliance", "Anti tuberculosis treatment", and "anti tuberculosis therapy". Because of resource limitations, papers published in other languages were not considered. Additional reports were identified by manually reviewing the references of the studies found.

The potentially eligible studies were included if the following criteria were all met: it concerned patients treated for tuberculosis (see definition below), it reported on adherence and non adherence, it reported on potential risk factors associated with adherence and non adherence, if the type of study is observation (cohort, case-control, cross-sectional), RCT and community survey, if it is a quantitative study or combined quantitative and qualitative, and if there is association (p value, odds ratio or relative risk and 95% confidence interval, or p value, odds ratio or relative risk, or p value). The papers were excluded if they did not meet the above criteria, and if only an abstract was available. Selected articles were reviewed for information on the country of study, sample size, population source, type of the study, the statistical association, and risk factors e.g. age, sex, and other associated factors.

For purpose of data review simple definition were used according to those of the World Health organization publication (WHO, 2013) [23] [24].

A case of tuberculosis was defined as a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a clinician.

A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (WRD) (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB. Extrapulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Potentially eligible studies were excluded if they did not report on potential risk factors associated with adherence and non adherence, if no full articles available or if the review. Potentially eligible studies were retrieved and the full articles were assessed. Results are reported according to the PRISMA guidelines for systematic reviews [25].

Data was extracted by A.A.Ali. For the purpose of data extraction a simple definition for treatment adherence and nonadherence was used according to that of the World Health organization publication (WHO, 2002) [22] [26]. Non-adherence (or Defaulter): A patient whose treatment was interrupted for 2 or more consecutive months.

The following five categories of risk factors for TB treatment non-adherence were considered:

1) Sociodemogaphic factors including: age, sex, ethnicity, marital status, educational level, occupation, employment status, family income, nationality, and residential locality, religion, patients moving or changing address, family size and house size [11] [27]-[40].

2) Disease related factors including: type of tuberculosis (first time to develop tuberculosis, relapse, multi-drug resistant tuberculosis), sputum smear result, severity of disease, and site of tuberculosis [41]-[51].

3) The treatment and services related factors including: treatment regimen, time of defaulting, directly observation therapy short course (DOTS), drugs availability, drug cost, response to treatment, side effects of drugs, distance of residence from treatment center, waiting time, travelling time, travelling cost, satisfaction with treatment and services, staff receptiveness towards the patients, history of default, treatment (in patient or out-patient), type of clinic (governmental or private), hospital referral, and difficulties facing tracing system for defaults [31] [42] [52]-[61].

4) Selected behavioral factors including: smoking, alcohol intake, IVDU and HIV status, homelessness, prison and immigrant [19] [45] [62] [63] [64] [65] [66].

5) other factors influencing defaulting including; presence or absence of social support such as family support, health education and patient knowledge, stigma, chronic diseases, traditional treatment, feeling better, and need incentive [13] [67]-[76].

When possible we extracted odds ratios (ORs), relative risks (RRs), and their 95% confidence interval. Otherwise the direction of the association and statistical significance was used. The relationship was considered consistent if the variable was reported in 3 studies or more to be statistically significantly related with non-adherence to tuberculosis treatment and more often statistically significantly related to non-adherence than none related. Ethics approval was not required for this systematic review.

3. Results

The database searching resulted in a total of 2131 identified citations. About 981 records remained after removal of duplication. Out of these 894 were excluded because they did not focus on the TB treatment and risk factors. Of the 87 abstracts that were potentially eligible, 34 were excluded after the review of the full paper or abstract (see **Figure 1**). Hence 53 eligible articles were finally included.

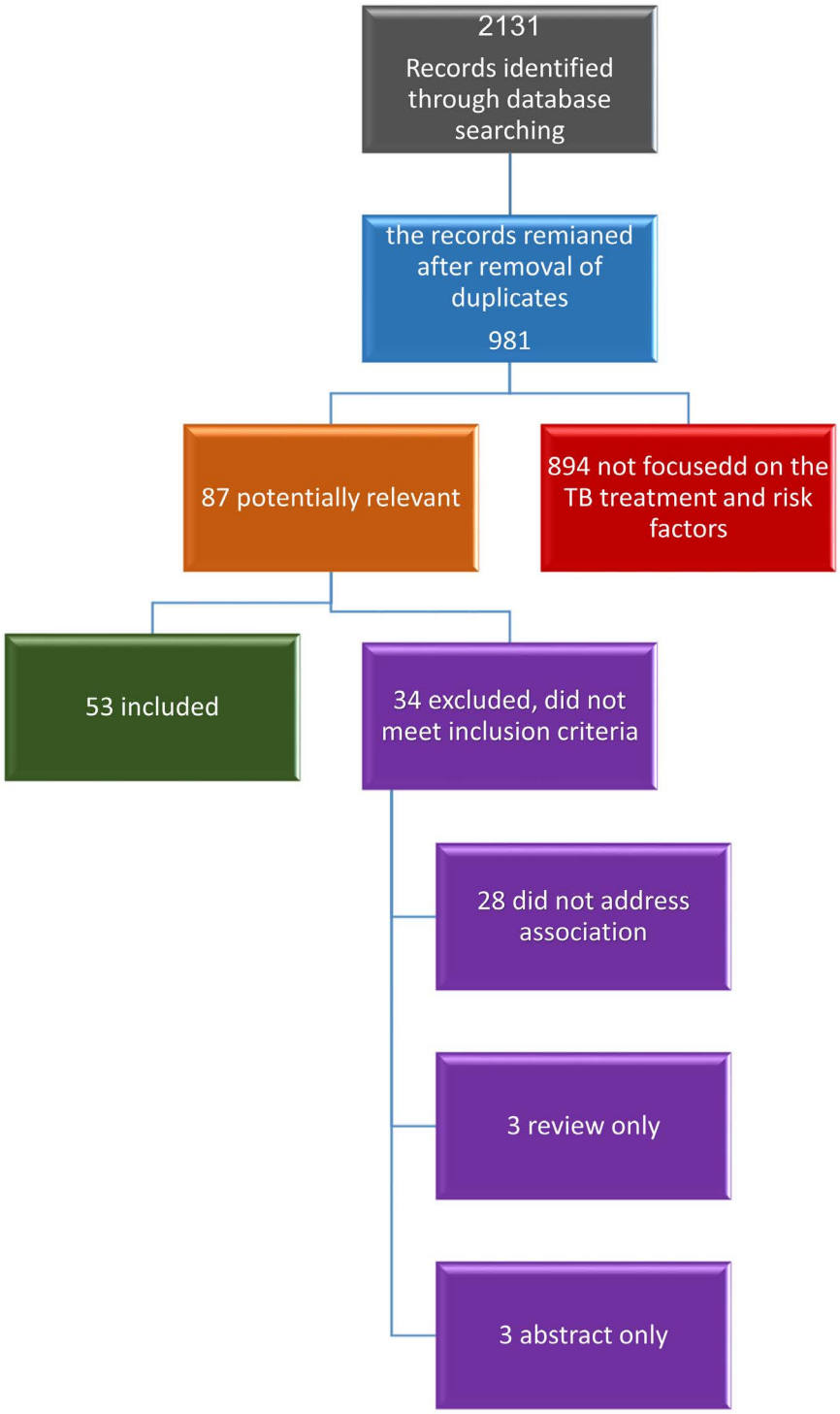

Figure 1. Study flow diagram.

Of these 53 eligible studies, 21 were conducted in Africa, 19 in Asia, five in North America, four in Europe and four in South America.

The study design included 26 cohort studies, 17 case control studies, eight cross-sectional studies, and two surveys. The main characteristics of each study are reported in Table 1.

Table 1. The design of the studies (patient characteristics associated with non-adherence to tuberculosis treatment).

NO	Author	Country and area	N	Default rate	Study type	Population
1	VAN DER Werf T S (1990) [15]	Ghana	569	10	Retrospective cohort study	Sputum-smear positive pulmonary tuberculosis (PTB) patients registered between 1984 and 1987 in a rural ambulatory non-supervised service program in Agogo Hospital in the hills of Ashanti, Ghana
2	Chuah S Y (1991) [17]	Malaysia	227	33	Retrospective cohort study	Tuberculosis patients in Perak started treatment in 1982
3	Menzies R (1993) [18]	Canada	352	16	Retrospective cohort study	Adult Tuberculosis patients treated at the tuberculosis clinic of Montreal Chest Hospital in 1987-1988
4	Me'ndez A P (1997) [66]	USA	184	48	Retrospective cohort study	All patients in New York City with a first-time positive culture for *Mycibacterium tuberculosis* in April 1991 were selected
5	Ngamvithayapong J (1997) [22]	Thailand	412	26	Prospective cohort study	1) blood donors who had indicated a desire to know their HIV test result; 2) persons attending the hospital's anonymous counselling and testing clinic; 3) patients attending the hospital's outpatient clinics for other illnesses but found to be HIV-infected, and 4) female commercial sex workers
6	Jochem K (1997) [24]	Nepal	693	14.8	Prospective cohort study	New cases of Smear positive tuberculosis patients
7	William J (1997) [20]	USA	294	18	Retrospective cohort study	All patients treated with outpatient DOT from 1984 to 1994
8	KATE C (1998) [67]	USA	2576	5.5	Cohort study	Adult patients at least (15 yr of age) reportedas having TB in California during 1993
9	Comolet T M (1998) [27]	Madagascar	149	25.5	Case-control study	Sputum positive tuberculosis patient
10	Tanguis H G (2000) [62]	Spain	2201	13.1	Cohort study	HIV-infected with TB patients between 1987 and 1996
11	Borgdorff M W J (2000) [63]	Netherland	7529	10	Cohort study	Tuberculosis patient in the Netherlands in the period 1993-1997
12	El-Sony A I (2002) [13]	Sudan	1797	16.9	Cross-sectional study	All persons aged 15 - 49 years with respiratory symptoms seen in the general health services from March 1998 to March 2000,from eight states in Sudan
13	Tekle B (2002) [76]	Ethiopia	1367	11.3	A case control study	New tuberculosis patients on DOTS
14	Edginton M E (2002) [29]	South Africa	303	5.6	A descriptive study	TB patients and community members in the rural Tintswalo district of the Northern Province of South Africa registered with tuberculosis in the 18-month period
15	Santha T (2002) [41]	India	676	17	A community survey	All tuberculosis patients registered from May 1999 through April 2000
16	Chan-Yeung M (2003) [53]	China, Hong Kong	5757	8	Nested case-control study	Patients registered for antituberculous drug therapy in 1996 in Hong Kong
17	Sophia V (2003) [54]	India	483	25	Case control study	New and re-treatment smear positive patients followed up till treatment outcome from March to December 1999 and March 1999 to September 2000
18	Robert M (2004) [21]	USA	372	12.6	Prospective cohort study	Culture-positive patients who were reported from 1998-2000
19	Chang K C (2004) [31]	China, Hong Kong	408	8.5	Nested case-control study	All tuberculosis patients registered at the Government chest clinics from 1 January 1999 to 31 March 1999
20	Hill P C (2005) [42]	Gambia	301	25.2	Prospective cohort study	New cases of TB aged > 15 years who started their treatment between 16 October 2002 and 26 November 2003

Continued

21	Pandit N S K (2006) [70]	India	274	6.2	Cross sectional study	All the patients who registered for DOT treatment during last quarter (Oct-Nov-Dec) 2002, in Anand district, state Gujarat, India
22	Daniel O J (2006) [64]	Nigeria	774	23	Retrospective cohort study	Adult Tuberculosis patients age 15 years and above registered for anti-TB treatment DOTS between January 1997-December 2003 , Sagamu, Nigeria
23	Estifanos B S (2007) [32]	Ethiopia	404	20	Prospective cohort study	Smear-positive tuberculosis patients in Hossana Hospital
24	Gelmanova I Y (2007) [43]	Russia	237	8.8	Retrospective cohort study	Detected, smear and/or culture-positive adult TB patients initiating therapy in a DOTS programme in Tomsk between 1 January and 31 December 2001
25	Fahrettin T (2008) [44]	Turkey	586	5.1	Retrospective cohort study	Adult pulmonary tuberculosis patient age more than 15 years in Istanbul Eyup tuberculosis Dispensary between year 1999-2004
26	Franke M F (2008) [50]	Peru	671	10	Retrospective cohort	Patients with multi drug resistant TB disease
27	Kapella B K (2009) [71]	Thailand	995	40	Cohort study	Registered TB treatment (non Thai) from 1 October 2004 to 31 September 2006.
28	Xu L (2010) [33]	China	501	9	A patient-based study survey	Rural smear-positive pulmonary TB patients registered with the county TB dispensaries at study sites who completed treatment during the period October 2006 to September 2007.
29	Kliiman K (2010) [65]	Estonia	1107	9.4	A retrospective cohort study	patients with culture-confirmed pulmonary TB who started treatment during 2003-2005
30	Samuel A B (2010) [72]	Ghana	165	55.7	Cross-sectional study	TB patients who had registered in New Juaben District from January 2003 to December 2005 (TB Registry) and had fully completed their treatment during the time of the study
31	Muture B N (2011) [45]	Kenya	1978	16.7	A Case-Control study	TB patients (adults and children) registered during the period January 2005 to March 2007
32	Kelly E D (2011) [51]	Morocco	291	13	A retrospective cohort study	Patients with smear- or culture-positive pulmonary tuberculosis
33	Finlay A (2012) [46]	South Africa	3165	12	retrospective case control study	Adult persons ≥ 18 years old enrolled in treatment under DOTS at public health facilities in South Africa between January 1 and December 31, 2002
34	Culqui D R (2012) [56]	Peru	789	5	An unmatched-case-control study	Patients diagnosed with tuberculosis from 2004 to 2005 who completed treatment until September 2006 in Peru
35	Garrido M D S (2012) [60]	Brazilia	11,321	10	Case control study	TB patients from 2005-2010 in the Amazonas State
36	Tamhane A (2012) [75]	India	150	29	Cross-sectional study	Newly diagnosed sputum smear-positive pulmonary tuberculosis (TB) patients
37	Nezenega Z S (2013) [61]	Ethiopia	531	26	Cross sectional study	TB patients on anti TB treatment in 11 public health centers and one hospital of Sidama zone
38	Lalor M K (2013) [49]	Uzbekistan	710	20	A retrospective cohort	Multi and extensively drug-resistant tuberculosis patients who started treatment between 2003 and 2008 and thus had finished approximately 2 years of treatment by the end of 2010
39	Slama K (2013) [39]	Morocco	320	33.8	Case-control study	TB patients (new cases or relapsed) who were enrolled in treatment for TB between 1 January 2009 and 31 December 2010

Continued

40	Alobu I (2014) [35]	Nigeria	1668	9.9	A retrospective Cohort Study	Adult tuberculosis patients treated during 2011 and 2012 in tow large health facilities in Elbony state
41	Vasudevan K (2014) [59]	India	564	5.9	Retrospective cohort study	TB patients registered at RNTCP in Puducherry, Southern India.
42	Cherkaoui I (2014) [48]	Moroco	277	3	Case-control study	Adult patients with definite or probable pulmonary or extrapulmonary TB who either defaulted from TB treatment (cases) or successfully completed it (controls) were enrolled.
43	Abdelhadi A A (2015) [36]	Sudan	306	11	Case control study	Pulmonary TB patient
44	Lackey B (2015) [38]	Peru	1233	10	A Cohort Study	new adult smear-positive cases of pulmonary TB in a high-Incidence Area of Lima district
45	Roy N (2015) [55]	India	158	15	A case-control study	new sputum-positive (NSP) tuberculosis (TB) patients in Darjeeling District, West Bengal, India from August 2011 to December 2011
46	Basa S (2015) [74]	India	550	7.5	Cross sectional study	TB patients registered under DOTS from January to June 2005 and to study the reasons for default in Mayurbhanj district, Orissa, India
47	Thelma E (2016) [37]	Philippines	273	38	Case-control study	More than 18 years of age with confirmed MDR or rifampin-resistant TB for whom treatment was initiated during July 1-December 31, 2012
48	Saibannavar A (2016) [47]	India	411	6	A retrospective cohort study	TB defaulters patients
49	Ahmed A (2016) [57]	Sudan	315	14	Case control study	Tuberculosis patients registered at tuberculosis centers at all provinces in Khartoum state from May 2010 to May 2011
50	Ahmed O A A (2016) [58]	Sudan	315	14	Case control study	Tuberculosis patients registered at tuberculosis centers at all provinces in Khartoum state from May 2010 to May 2011
51	Kigozi G (2017) [34]	South Africa	110,394	7.2	A retrospective cohort study	Pulmonary TB cases older than 15 years of age with a recorded pre-treatment smear result registered in the ETR.Net electronic register
52	El-Muttalut M (2017) [40]	Sudan	366	16.4	A cross-sectional study	TB patient in Kassala State
53	Hashim E A (2017) [73]	Sudan	160	21.3	Case-control study	Pulmonary tuberculosis treatment Al-muglad rural hospital, Al-Muglad locality, West Kordofan state in Western Sudan

The factors associated with non-adherence to tuberculosis treatment are given in Tables 2(a)-(e). Factors that were most frequently, consistently and statistically significantly related to tuberculosis treatment non-adherence were; low family income reported odds ratio (OR: 1.61 to 11.24), patient moving or giving wrong address reported relative risk (RR: 2.36 to 5.5), tuberculosis relapse or multidrug resistant (MDR) TB (OR 1.61 to 12), intensive phase of treatment (OR: 1.78 to 117.21), history of default (OR 1.09 to 8.2), long course treatment regimen (OR: 1.096 to 6.9), response to treatment (OR: 2.4 to 9.9), side effect of drugs (OR: 1.1 to 13.3), alcohol intake (OR: 1.3 to 4.9) homeless (OR: 2.0 to 3.2),

Table 2. (a) Socio-demographic factors consistently associated with non-adherence; (b) Behavioral factors consistently associated with non-adherence; (c) Treatment and services related factors consistently associated with non-adherence; (d) Disease related factors consistently associated with non-adherence; (e) Other (miscellaneous) factors consistently associated with non-adherence.

(a)

No.	Socio-demographic factors	Factors associated & statistically significant	Factors associated but not statistically significant	Factors not associated
1	Age	15, 32, 34, 71, 35, 34, 36, 47, 74, 48, 49, 60	67, 41, 54, 42, 46, 37, 38, 40	17, 18, 22, 20, 27, 62, 63, 53, 31, 70, 64, 43, 33, 72, 45, 39, 73, 55, 56, 57, 58, 50, 51, 65, 75, 66
2	Gender	15, 17, 22, 27, 41, 53, 54, 64, 72, 45, 34, 47, 74, 56, 51	20, 63, 44, 46, 38, 48, 75	18, 62, 31, 42, 32, 43, 71, 33, 37, 39, 40, 49, 55, 57, 58, 50, 60, 65, 66
3	Ethnicity	47	20, 63, 54, 66	17, 31, 42, 72, 46
4	Marital status	22, 47	45	15, 31, 32, 44, 71, 33, 46, 36, 38, 39, 40, 73, 49, 55, 56, 57, 51, 75
5	Educational level	46, 36, 38, 40, 47, 60	15, 27, 45, 48, 57, 50, 75	22, 41, 54, 70, 32, 44, 33, 72, 39, 55, 56, 65, 66, 76
6	Occupation	17, 47, 48, 57	72	69, 41, 31, 42, 32, 71, 33, 36, 37, 40
7	Employment status	73, 74, 65	48, 75	54, 43, 45, 46, 39, 49, 55, 76
8	Family income	62, 33, 72, 45, 40, 73, 47, 56	54, 39, 48, 66	32, 37, 57, 75, 76
9	Nationality,	63	20, 46	18, 36, 57
10	Residential locality	27, 40, 57, 58, 50, 65	20, 45, 35, 34, 37	17, 63, 31, 32, 71, 48, 60
11	Religion	59		27, 72, 46, 47, 56, 57
12	Patients moving or changing address	67, 27, 54, 71, 45, 46, 73, 57	49, 75	55
13	Family size		48	45, 57, 75
14	House size	50		45, 39, 57

(b)

No.	Behavioral factors	Factors associated & statistically significant	Factors associated but not statistically significant	Factors not associated
1	Smoking	31, 39, 48	41, 37, 38, 55	49, 58, 51, 75
2	Alcohol intake	20, 67, 41, 45, 46, 37, 39, 73, 74, 55, 60, 65	43, 66	27, 62, 31, 49, 58, 51, 65
3	IVDU	67, 43, 38, 56, 50, 66	51	20, 62, 71, 37, 58
4	HIV status	45, 34, 38, 60	67, 62, 31, 64, 66	20, 63, 13, 71, 58
5	Homelessness	20, 67, 62, 63, 66	65	
6	Prison	67, 63, 65	62, 38	49, 38, 71
7	Immigrant	63, 74	22	

(c)

No.	Treatment and services related	Factors associated & statistically significant	Factors associated but not statistically significant	Factors not associated
1	Treatment regimen (long course)	18, 24, 13, 54, 72, 35, 74, 49, 59, 50, 66		17, 67, 71, 47
2	Time of defaulting (intensive phase or continuation phase	17, 18, 53, 54, 31, 42, 64, 45, 36, 59, 61, 76	41, 37, 48	
3	DOTS	15, 62, 21, 70, 53, 33, 35, 74, 48, 60, 66		31
4	Drugs availability	29, 61	72	
5	Drug cost	68, 75		70
6	Response to treatment	24, 20, 29, 54, 42, 43, 66	50	
7	Side effects of drug	29, 31, 70, 43, 72, 37, 74, 48, 55, 56, 76	22, 54, 46, 45	15, 20, 27, 39
8	Distance of residence from treatment center	15, 29, 32, 33, 72, 47, 74,	45, 57	17, 22, 54, 37, 73, 48, 50, 76
9	Waiting time	29, 61	45	70, 46, 58
10	Travelling time	27, 42, 39	37, 57	15, 70, 43, 73, 75
11	Travelling cost	29, 42	32, 57	15, 70
12	Satisfaction with treatment and services	73, 61		58
13	Staff receptiveness	18, 27, 29, 33, 72, 46, 37, 73, 74, 55, 58, 75, 61	45	
14	History of default	18, 41, 53, 54, 31, 45, 46, 70, 71, 72, 73, 76	51	65
15	Treatment (in patient or out-patient)	22, 31		46
16	Type of clinic (governmental or private)		35	
17	Hospital referral	17		
18	Difficulties facing tracing system for defaults	55		
19	Access health-care services within office hours	56		
20	Too many patients when visiting health center	58		
22	Health center appearance	58		76

(d)

No.	Disease related factors	Factors associated & statistically significant	Factors associated but not statistically significant	Factors not associated
1	Type of tuberculosis - first time to develop - relapse - multi-drug resistant	67, 62, 41, 53, 43, 44, 46, 34, 38, 39, 49, 65, 66		63, 71, 45, 37
2	Severity of disease	22, 51		15, 17, 53, 66

Continued

3	Sputum smear result	18, 24, 35, 50, 51	63, 34	15, 17, 13, 53, 31, 64, 43, 37, 60, 65, 66
4	Site of tuberculosis	35	17, 41, 48, 57	53, 44, 39, 66

(e)

No.	Other factors influencing defaulting	Factors associated & statistically significant	Factors associated but not statistically significant	Factors not associated
1	Social support	29, 72, 37, 74, 48, 57, 58, 76		
2	Health education, counseling and patient knowledge	18, 27, 29, 54, 70, 72, 45, 46, 37, 39, 48, 55, 56, 58, 75, 76	42	36
3	Stigma	22, 29, 70, 72, 46, 36, 73	45, 58	
4	Chronic diseases	53, 60	38, 50	31, 71, 48
5	Traditional treatment	72, 45, 46, 74, 75	41	
6	Feeling better	46, 36, 39, 40, 74, 48		
7	Need incentive	46	37	

stigma (OR: 2.0 to 5.0), seeking traditional healers (OR: 1.9 to 5.7), staff receptiveness (OR: 1.7 to 12.3), lack of DOTS (OR: 1.42 to 2.29), poor knowledge or lack of health education (OR: 1.88 to 8.67), lack family and social support (OR: 2.14 to 3.23) and feeling better (OR: 5.28 to 21.0).

Factors frequently but not consistently related to tuberculosis treatment non-adherence were: male, residential locality, distance to tuberculosis treatment unit, HIV status, IVDU, prison, and smoking.

All studies reported the default rates. The reported default rates ranged between 3% and 55.7%. These default rates varied substantially among the studies as either cumulative or incremental percentages of all patients. Also it varied according to regimen of treatment, age, sex, ethnicity, and residential locality.

All the papers included in the systematic synthesis had reported the number of patients (the sample size) participated in the individual study. The total number of the participant subjects in all articles was 165,842.

Ninety eight percent of the studies included in the systematic review showed a significant effect of the 17 related factors on TB treatment default.

The number of studies showed increased risk of TB treatment default for each of the 17 significant variables varied from 5 to 16 studies: 5/52 for homeless and seeking traditional healers; 6/52 for feeling better; 7/52 for response to treatment and stigma; 8/52 for low family income, patient moving or giving wrong address, and lack of family and social support ; 11/52 for long course treatment regimen, lack of DOTS, and side effects of drugs; 12/52 for intensive phase of treatment and alcohol intake; 13/52 for tuberculosis relapse or multidrug resistant (MDR) TB, staff receptiveness and history of default; and 16/52 for poor knowledge or lack of health education and counseling.

4. Discussion

The results of this systematic review show that family income, moving of patient or giving wrong address, tuberculosis relapse or MDR TB, intensive phase of treatment, history of default, long course treatment regimen, response to treatment, homeless, stigma, seeking traditional healers, staff receptiveness, DOTS, poor knowledge or lack of health education were consistently and statistically significantly related to tuberculosis treatment non-adherence. Surprisingly some frequently cited factors which were traditionally thought to be related to tuberculosis treatment non-adherence appeared to be not consistently associated with non-adherence, these include age, sex, marital status, occupation, employment status, level of education.

The most important methodological aspect of this systematic review that requires explanation is the use of a qualitative approach, *i.e.* counting statistical results of the patient characteristics related to non-adherence to tuberculosis treatment. Ideally, numerical results of individual studies are combined. However, when reviewing eligible studies it was discovered that in most of these primary studies only numerators were given if a factor was statistically significant related to non-adherence. Hence, only including the results of a characteristic if full numerical data was given had the potential to lead to an extreme bias. Since studies dating back to 1990 were included we assumed that it was unlikely to get full responses of all authors. Hence, we resorted to, admittedly a less optimal qualitative approach.

Some other methodological aspects of this systematic review require attention: First of all, we attempted to identify all relevant articles published up to date of this review and found a large number of relevant references. However, due to language restriction and lack of resources we only included articles in the English language. Secondly, data extraction was hampered by unclear methodology and definitions in many relevant studies. In addition, many relevant factors for non-adherence were not taken into account in many studies. Thirdly, the majority of articles included in this study were conducted in developing countries; the findings are therefore most applicable to countries with low resources which carry the greatest burden of TB disease and where urgent interventions are needed to improve adherence to tuberculosis treatment. However, our findings may also be applicable to more developed countries. Fourthly, our review took many types of risk factors (social and biomedical) for non-adherence to Tb treatment into account while many individual articles solely have focused on the factors related to health services provision.

Overall we trust that the factors identified as consistently related to TB treatment non-adherence are of truly associated with non-adherence. For the potential risk factors for non-adherence that were not consistently associated a numerical approach in large data set of new studies might still show an association. However, it is likely that these associations are of little importance.

Exploration of the factors associated with non-adherence to tuberculosis treatment deserves some attention. Some of these factors identified can be changed and

solved. These include factors associated with patient behavior: moving of patient or giving wrong address, homeless, stigma and seeking traditional healers, and factors related to treatment services: not on DOTS, long course treatment regimen, staff receptiveness and poor knowledge or lack of health education. Other factors related to non-adherence are difficult to change as they are not of patients or the treating physician control. Most of these factors are related to the treatment and the system of services provision and include: low family income, tuberculosis relapse or MDR TB, intensive phase of treatment, history of default and response to treatment. Hence, the presence of these factors might guide to the targeting of extra attempts to stimulate treatment adherence.

The doctor-patient-relationship offers good environment for communication giving patients comfort in expressing the obstacles they face during treatment course. This enables treating doctors and health worker staff to analyze patients' problems and provide advice, counseling and health education regarding type of disease, side effect of drug, duration of treatment, implementation of DOT short course program. Moreover, it will enable health care workers to be more flexible with patients in giving them choices and options that maintain their autonomy in treatment compliance and to overcome obstacles related to health services provision.

The doctors and health worker staff receptiveness and their effort in counseling and health education provision increases awareness of patients and their families and the whole community about Tuberculosis. The social support positively affects the patients' knowledge to counteract the feeling of guilt and shame (stigma). This will be reflected on patients' compliance with tuberculosis medication instead of seeking traditional medicine. Patients' compliance assists the tuberculosis control program to achieve high cure rates and decrease the MDR prevalence in the community.

This synthesis suggests that governmental and nongovernmental organizations need to give more attention to support poor patients financially and offer accommodation for the homeless. Another cost effective suggestion is to consider even distribution of health services to improve its availability, accessibility and affordability to all tuberculosis patients. This, combined with good referral system from health unit to hospital, will result in reduction of the cost of travelling, waiting time at tuberculosis clinic, and patient movement. Besides, good counseling to patients would encourage them to give their correct address and to report any change of address to health worker staffs and therefore improve adherence to tuberculosis treatment.

The review findings are important for the policy makers, medical practitioners, health worker staff and researchers to study the patient context as a whole (social, behavioral factors, believes and knowledge) and not to ignore their experience and opinion in treatment course. This will make the health care consumer share the responsibility of the treatment process and will combat non-adherence. Moreover, it helps in creating good relationship between the patients, health care providers and the whole community. This new approach in thinking will im-

prove tuberculosis treatment adherence and will reinforce the surveillance system of tuberculosis control program at state, national and international levels.

In addition to the findings of this systematic review we believe that further studies are needed to be conducted to deeply understand different aspects of tuberculosis disease and its treatment (social and biomedical) aspects which is a complex process. These studies should include the experience of policy makers, the health personnel working in the field, nongovernmental organizations, patient support groups and the community leaders. Moreover, the patients' knowledge about tuberculosis for example, patient satisfaction with health services provision and staff receptiveness. This will substantially help the health care system planners in developing good future strategy to improve treatment adherence among tuberculosis patients.

5. Conclusions

Non-adherence to tuberculosis treatment is a complex dynamic process, which was influenced by multiple factors. Identifying and understanding the nature of these factors facilitates development of appropriate and effective intervention plans.

The relationship between the identifiable variables and TB treatment default is important for the knowledge of policy makers and clinicians dealing with TB patients. Despite the fact that association of these variables with increased risk of TB treatment default had been reported in many individual studies, it had not received attention in terms of planning, training, guidelines, and research. This systematic review attempts to alter the current situation with the aim to increase knowledge about treatment default and to promote adherence to TB treatment.

The results of our review can help to find out the consistently statistically related factors to TB default treatment and assist the health care system designers, health service providers including clinicians, nurses, counselors, patients, families, and the community leading to high adherence to tuberculosis treatment, reinforcing the surveillance system of tuberculosis control program hence achieving the goal of tuberculosis elimination at state, national and international levels.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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