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ABSTRACT Defaulting on tuberculosis (TB) treatment remains a challenge to controlling TB. This case-control study aimed to identify determinants of treatment default among TB patients attending treatment clinics in Khartoum State from May to July 2011. Cases were TB patients who defaulted on treatment and controls were those who completed treatment. Of the 2727 TB patients attending the clinics, 328 (14%) had defaulted. Of these, 185 had resumed treatment before data collection and 143 had not and were eligible as cases. Of the 143, 27 could not be traced and 11 declined to participate. Thus, 105 cases and 210 controls were included and interviewed. The variables significantly associated with treatment default were: rural residence (OR: 2.68; 95% CI: 1.51–4.73), not being on a DOTS programme (OR: 2.53; 95% CI:

1.49–4.30), having side-effects from treatment (OR: 1.94; 95% CI: 1.14–3.29), and having a history of TB (relapse, multidrug-resistant TB or treatment failure) (OR: 5.11; 95% CI: 2.69–9.69). Attention should be paid to these groups at risk of defaulting to encourage treatment adherence and continuation.

Facteurs pathologiques et thérapeutiques entraînant un abandon du traitement de la tuberculose dans l'État de Khartoum, Soudan : étude cas-témoin

RÉSUMÉ L'abandon du traitement de la tuberculose (TB) demeure un défi dans la lutte antituberculeuse. La présente étude cas-témoin avait pour objectif d'identifier les déterminants de l'abandon de traitement parmi les patients atteints de tuberculose pris en charge dans des centres de traitement dans l'État de Khartoum entre mai et juillet 2011. Les cas comprenaient des patients atteints de tuberculose et ayant abandonné leur traitement, et les témoins étaient ceux ayant mené leur traitement à terme. Sur les 2727 patients atteints de tuberculose traités dans les centres, 328 (14 %) avaient abandonné le traitement. Sur ce nombre, 185 avaient repris le traitement avant la collecte des données, et 143 étaient restés sans traitement et étaient donc éligibles comme cas. Sur les 143, 27 □ n'ont pu être tracés et 11 ont refusé de participer. Ainsi, 105 cas et 210 témoins ont été inclus et interrogés. Les variables associées de façon significative avec l'abandon de traitement étaient le fait d'habiter en zone rurale (OR = 2,68□ ; IC à 95□ % I 1,51-4,73), la non participation à un programme DOTS (traitement de brève durée sous surveillance directe) (OR = 2,53□ ; IC à 95□ % 1,49-4,30), le développement d'effets secondaires (OR = 1,94□ ; IC à 95□ % 1,14-3,29) et des antécédents de tuberculose □ (rechute, tuberculose multirésistante ou échec du traitement) (OR = 5,11□ ; IC à 95□ % 2,69-9,6). Une attention devrait être accordée à ces groupes à risque d'abandon de façon à encourager l'observance et la poursuite du traitement.

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Introduction

Tuberculosis (TB) has been known for a long time and is still a major public health problem (1). Worldwide TB kills more young and middle-aged adults than any other infectious disease,

although it is a curable and preventable disease (2). The World Health Organization (WHO) estimates that currently about 9.6 million new TB cases occur each year and that about 1.5 million deaths annually are related to TB (3,4).

In 2010, it was estimated that the prevalence of TB cases in Sudan was 209 per 100 000 population with an annual incidence of new cases of 119 per 100 000, resulting in about 37 000 new cases each year in Sudan. Hence, Sudan has about 15% of the TB burden in the WHO Eastern Mediterranean Region and the second highest active TB prevalence of the countries in this region. In addition, the estimated death rate related to TB, including HIV-infected TB patients, was 24 per100 000 per year (5).

Successful treatment of TB involves taking anti-TB drugs for at least 6 months (6,7). The therapeutic regimens given under direct observation short course therapy (DOTS) as recommended by WHO have been shown to be highly effective for both preventing and treating TB (8,9). The health authority of Sudan follows the strategies for TB prevention and treatment recommended by WHO. Despite the efforts that had been made by health authorities, some patients still do not follow their TB treatment and do not complete the intensive stage of treatment. As defined by WHO, patients who fail to collect their TB treatment for 2 consecutive months are reported as defaulters (10). Defaulting on TB medication is a major barrier to its local and global control. In addition, defaulting increases the risk of drug resistance, relapse and death, and may prolong infectiousness (11–15). The TB patient treatment default rate is about 10% in Sudan (5) and 14% in Khartoum State (16). The high rate of default on TB treatment in Khartoum State makes the identification of the risk factors leading to patients to default essential.

In a previous paper, we reported on the sociodemographic factors associated with non-adherence to TB treatment (17). In the present paper we identify the disease- and treatment-related determinants of treatment default among TB patients in Khartoum State. This information could help to suggest actions that could lead to a reduction of TB treatment defaulting.

Methods

Study design

This was an observational case–control study. Cases were TB patients who defaulted from treatment and controls were those who completed treatment.

Setting

This study was conducted in Khartoum State. In 1993, the Ministry of Health in Khartoum State established a TB control programme. The decentralized health care system in Khartoum is divided into 7 districts and 19 health areas. Its health facilities include 43 hospitals, 147 health centres, 185 centres run by nongovernmental organizations, 235 dispensaries and 365 primary health care units. TB services are available in 53 of the primary health care centres in Khartoum State and is where TB patients receive their treatment (16). A registered nurse is designated responsible for TB treatment and follow up of continuation of treatment in the primary health care unit. This primary health care unit is the basic unit of management and reporting of the TB programme. Staff at the primary health care unit responsible for TB services include a medical assistant, a laboratory technician and a clerk. The programme provides care through the DOTS strategy as recommended by WHO.

Population

Our cases and controls were drawn from all TB patients attending the 53 treatment clinics in Khartoum State. The inclusion criteria for both cases and controls were: patients over 15 years who were clinically and laboratory diagnosed with TB and registered at the treatment units in Khartoum State. Cases were those patients identified as having defaulted on TB treatment during the data collection period. Following identification of each case (defaulter), without exclusion criteria, the next 2 patients who had completed their treatment without defaulting were included as controls, without exclusion criteria. They were attending the clinics because they had been requested to come for follow up, in the same TB treatment unit or the nearest one in the same area, either to do the final sputum smear or to collect the smear results. Patients were excluded from the study if they were too ill for interview, had a psychiatric illness or had given an incorrect address and could not be traced.

The interview process was done from 1 May 2011 to 15 July 2011, but in order to reach the target defaulted group for the interviews, we used clinic records for the patients registered from May 2010 to May 2011.

TB and treatment definitions

The following definitions were applied. A pulmonary TB patient was one with TB disease involving the lung parenchyma. An extra-pulmonary TB patient was one with TB of organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones and meninges). A patient in whom both pulmonary and extra-pulmonary TB were diagnosed was classified as pulmonary TB (10).

Treatment default was defined as an interruption of TB treatment for 2 or more consecutive months during the intended treatment period. Relapse was defined as a patient previously

treated for TB who has been declared cured or has completed treatment and is diagnosed with bacteriologically positive (smear or culture) TB. Treatment failure was defined as a patient who is sputum smear positive at 5 months or later during treatment. Multidrug resistant (MDR) TB was defined as TB resistance to at least isoniazid and rifampicin. Side-effects of treatment were defined according to a patient's complaint and as identified by doctors and taken from the records (5,18–20).

Drug regimen was defined as a drug or several drugs given in certain doses for a stated duration, as described by the treating doctor according to the national TB control programme. All new TB patients should receive the category 1 (CAT1) regimen for 6 months, which includes rifampicin, isoniazid, pyrazinamide and ethambutol. The category 2 (CAT2) treatment regimen is used for retreatment of TB patients; it lasts for 8 months and includes streptomycin in the first 2 months (5,10,19).

DOTS is directly observed treatment, or watching the patient take his/her medication to ensure medications are taken in the right combination and for the correct duration (10,19).

Data collection

Information on disease-related and treatment-related factors was retrieved from the medical records of the patients. In addition, face-to-face interviews were held, using a structured questionnaire, by trained interviewers to obtain information on the various factors possibly associated with treatment default. The questionnaire was pretested on 35 patients and, based on the results, was used without any major changes. All TB patients who had defaulted prior to the data collection period were identified and their address retrieved from patient records. Then, the interviewers used the following sequence of contact attempts: telephone calls, first to the patient and then to known family members or friends, and then home visits, first to patient and then to known family members or friends. If there was no telephone number on record, home visits were made.

Data on the following variables were collected: sociodemographic characteristics including age, sex, residence (urban/rural); and disease- and treatment-related factors including BCG vaccination status, sputum smear result, treatment regimen, on a DOTS programme or not, chest X-ray, response to treatment, side-effects from treatment, sputum smear after 2 months, previous history of TB (including relapse, treatment failure and MDR-TB), other treatments sought, and other chronic diseases, e.g. diabetes mellitus (1,4,11,16,20–22).

Statistical analysis

The sample size was calculated according to Fleiss (1981) (23–25) assuming a two-sided type one error of 0.05, a power of 80% and the ability to detect an odds ratio (OR) of 2.0 with an exposure frequency of 30% in the control group and a ratio of cases to controls of 1:2. This gave a sample size of 105 cases and 210 controls.

Data were reviewed for consistency and completeness. Data analysis was performed in SPSS, version 16. The demographic characteristics of the cases and controls were compared using the chi-squared test for qualitative variables and Student t-test for continuous variables. Univariate and multivariate analyses were done. Descriptive statistics were calculated for the dependent variable (treatment default). Logistic regression analysis was done to calculate the ORs and its 95% confidence intervals (CI). Variables that were related to treatment default with a P-value less than 0.20 were entered in a multivariate model, using a backward selection.

Ethical considerations

Ethical approval was obtained from the ethics committee of the Ministry of Health, Khartoum State. Permission was granted by public committee leaders (senior health officers at the locality: director of health services, health team coordinator and PHC director) in the localities through official letters. Informed verbal consent was obtained from every eligible patient included in the study before the interview. Prior to the interview, all relevant aspects of the study were explained to the participants, including the purpose of the study, interview process and potential benefits. The interviews took place at the TB units in a suitable and separate room. The interviewers introduced themselves to the participants and outlined the scope of the interview and its approximate length at the beginning of each interview. The participants were informed that participation was entirely voluntary, and that privacy and confidentially would be maintained during data processing and reporting. Potential respondents also were informed that they had the right to decline to participate, or to end the interview at any time without jeopardizing their right for care and treatment.

Privacy and confidentially were maintained and the information was used only for this study and will not be used by any other person for any other purposes.

Results

Cases and controls

There were 2 727 TB patients who attended the 53 TB treatment clinics in Khartoum State

during the study period. Out of these, 2 399 patients (86%) had completed their treatment while 328 patients (14%) had interrupted treatment. The 328 patients were divided into 2 categories: 1) 143 who had defaulted and never come back until the time of data collection, who were be eligible to be included as cases; and 2) 185 who had defaulted but were traced and came back to continue treatment before the start of data collection, who were excluded.

Of the 143 eligible cases, 15 had given a wrong address and 12 had moved away from Khartoum State and could not be interviewed. A further 11 patients declined the interview. None of the cases was too ill for interview or had a psychiatric illness. Hence, 105 cases were traced and interviewed. In addition, 210 patients who had completed their treatment were included as controls; none declined to participate.

Demographic characteristics of the cases and controls

The demographic characteristics of the cases and controls are given in Table 1. Among the cases, 70.5% were males compared with 60.9% among the controls. The mean ages and standard deviations (SD) were 32.8 (SD14.4) years for the cases and 34.6 (SD 14.9) years for the controls; 53.3% of the cases and 47.6% of the controls were aged 15 to 30 years. Among the cases, 61.0% were urban residents while 80.5% of the controls were urban residents.

Disease and treatment characteristics of the cases and controls

The disease and treatment characteristics of the cases and controls are given in Table 1 . Cases and controls had a similar BCG vaccination status (61.9% and 53.3% had had the BCG vaccination respectively) and sputum smear results at the beginning of treatment (71.4% and 74.8% were positive respectively) as well as after 2 months (10.5% and 6.1% were positive respectively). However, more cases had a previous history of TB (37.1%), including relapse, failure and MDR-TB, compared with controls (10.0%). Hence, more cases (45.7%) received the CAT2 treatment regimen than controls (22.9%). Fewer cases were on DOTS (36.2%) than the controls (59.5%) and fewer had a good response to treatment (76.2%) compared with controls (88.6%). In addition, more cases (52.4%) developed side-effects from treatment than the controls (31.0%) and more also sought traditional remedies (28.6%) than the controls (12.9%) (Table1).

Risk factors for defaulting

In the univariate analysis the following disease- and treatment-related factors were statistically significant associated with defaulting (P Table 1).

The multiple logistic regression analysis and adjusted ORs (aOR) and 95% CIs are shown in Table 2. The variables that remained in the model were: rural residence (aOR: 2.68; 95% CI: 1.51–4.73), not being on a DOTS programme (aOR: 2.53; 95% CI:1.49–4.30), having side-effects from treatment (aOR: 1.94; 95% CI:1.14–3.29) and previous history of TB (aOR: 5.11; 95% CI: 2.69–9.69) (Table 2).

Discussion

In our study, the overall prevalence of TB treatment default among the patients who attended TB treatment clinics during the study period was 14%, which is similar to that reported in other studies conducted in Khartoum State (5,16). A high default rate on TB treatment has also been reported in other developing countries in Africa and Asia, e.g. 22.88% in Ethiopia and 10.33% in India (26,27).

Our study showed that DOTS reduced default rates as those not on a DOTS programme had 2.5-times higher odds of default. This agrees with the results of previous studies conducted in both developed and developing countries (20,22,28–30).

Rural residence was strongly associated with TB default which concurs with the findings of other studies in Ethiopia (31), and South Africa (32). TB treatment default was also strongly associated with having side-effects from the TB medication and having a history of TB (relapse, failure and MDR-TB), which concurs with other studies (6,11,33–36). However, our findings are in contrast to those reported from Malaysia where residence, medicine side-effects and history of TB were not associated with TB treatment default (20). Furthermore, in contrast to the findings of our study, a study in Estonia found that urban residence was positively associated with TB default (37).

The findings of our study might help doctors and policy-makers in Khartoum State and other developing countries in planning and policy development to strengthen TB control programmes in general. Although we highlight the relation between disease and treatment-related factors and defaulting TB treatment, further exploration of precipitating factors for defaulting are needed.

To combat the TB spread in communities, WHO launched the DOTS strategy in 1993. Since that time, DOTS implementation has achieved good results by increasing patient compliance with treatment and decreasing treatment interruption in communities of both low and high socioeconomic status (28,29). The Ministry of Health in Khartoum State adopted a DOTS

strategy when it was recommended by the WHO in 1993 (5). To make the access of TB services available, the Ministry of Health set up more than 50 TB units (microscopic and treatment centres) distributed all over the State, according to geography and population density (16). Despite these efforts, TB treatment default remains high.

In view of our findings, in order to reduce TB treatment default further, attention should be paid to more adequate follow-up of patients, treatment of their side-effects, increasing the number of health units that use DOTS and tracing defaulters, particularly among rural patients who may face barriers to continuing treatment, and among those with a history of TB (those who have relapsed, experienced treatment failure and those with MDR-TB). An objective of the TB control programme in Khartoum State is to provide tracing teams for defaulters in all TB units, which are responsible for contacting defaulting patients, encouraging them to come back to continue their treatment and visiting them at their home if they do not reply so as to identify the barriers and advise them on how to overcome them when they first start to default. The fact that this does not appear to be happening, at least up to our study period, may indicate that the programme and its allocated resources need to be reassessed. The introduction of a revised retrieval system in Saudi Arabia significantly improved the retrieval of non-attenders and reduced the dropout rate (38).

In terms of the generalizability of our findings, some methodological aspects of our study need to be considered. First, our study was conducted in Khartoum State, which is the most populated state in Sudan. Its population may represent the whole country as most of the inhabitants come from various parts of Sudan. In addition, the TB patients included in this study were selected from all TB treatment units in the State. Thus, our findings can be generalized to the total TB population in the State and also Sudan as well as to communities with similar settings. Second, recall bias was minimized by using a standardized questionnaire during the interview and by cross-checking patients' responses for each study variable against their medical records. Third, the reliability of the information gathered from each patient could not be counter-checked but questions about sensitive issues were carefully handled to maximize the accuracy of the responses obtained. Fourth, possible confounders were taken into consideration in the design (by restricting the diagnosis criteria) and in the analysis by using logistic regression analysis. Lastly, the major problem we faced during the study was how to reach the defaulting patients (cases). This problem was tackled in 3 steps. First, the patient medical records were traced and identified and all contact information was reviewed. Then, study personnel first tried to telephone the patient and, failing that, to telephone known family members or friends. If telephone contact failed or if there was no telephone number on record, home visits were made, first to the patient and then to known family members or friends. Interestingly, we found that many of the defaulting patients did not have access to any phone (mobile or landline), a risk factor not previously described or evaluated in our study. The interviewers made an average of 3 attempts to contact each defaulter before recording a defaulter was a non-respondent. Due to the number of eligible cases who could not be traced and interviewed (27 of 143), generalizing the findings to the whole population of patients with

TB should be done with caution.

In conclusion, our study shows that living in a rural area, not being on a DOTS programme, developing side-effects to treatment and having a history of TB (relapse, MDR-TB or treatment failure) increased the likelihood of defaulting on treatment. These findings may help guide improvement in the current TB treatment delivery in Sudan and similar developing countries.

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