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Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study

Short title: **Tuberculosis treatment default**

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Figures: 3

Online only material: 2 tables

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References: 21

Abstract

Background and purpose: High rates of antituberculosis treatment (ATT) discontinuation have been reported in places in Africa. The aim of this study was to determine the rate, time to- and determinants of antituberculosis treatment default at the Yaounde Jamot's referral tuberculosis diagnosis and treatment centre.

Methods: All patients started on ATT at the centre between January and December 2009 were considered for inclusion on a retrospective basis. Tuberculosis treatment default or ATT discontinuation was defined as any interruption of treatment for at least 2 months, following treatment initiation. Sociodemographic and clinical predictors of treatment discontinuation were investigated with the use of logistic and Cox regressions models.

Results: Of the 1581 tuberculosis patients with treatment outcome known, 335 (21.2%) defaulted from treatment, 86 (5.4%) died and treatment failed in 6 (0.4%). Therefore, treatment was successfully completed in 1154 (73%) patients. Median duration to treatment discontinuation was 90 days (interquartile range: 30-150), and 62% of treatment discontinuation occurred during continuation phase. Treatment on the outpatient basis during intensive phase [odd ratio 1.44 (95% confidence interval: 1.08-1.91)] and non-consenting for HIV screening [1.84 (1.29-2.61)] were the main determinants of defaulting from treatment in multivariable analysis.

Conclusions – The default incidence rate is relatively high in this centre and treatment discontinuation occurs frequently during the continuation phase of the treatment. Actions are needed to improve adherence to treatment when taken on an ambulatory basis, clarify the association between HIV testing and defaulting to ATT, and identify other potential determinants of treatment discontinuation in this setting.

Word count – 250

Key words – tuberculosis, default, antituberculosis, treatment discontinuation, Cameroon

Article focus: What are the rates, time to- and determinants of antituberculosis treatment (ATT) discontinuation in the era of directly observed treatment in sub-Saharan Africa, using the case of Cameroon for illustration?

Key messages: ATT success rates remain non-optimal in sub-Saharan Africa where the highest global incidence rates for tuberculosis are found. Treatment discontinuation is one of the main reasons, but has been less explored in Africa in recent times.

Knowledge of determinants of ATT discontinuation is critical for informing health service and policy solutions needed to improve the outcome of care for tuberculosis and contain the spread of the disease.

Strengths: Large cohort study with up to 1688 participants

Limitations: retrospective study with lack of some information

INTRODUCTION

Tuberculosis is highly endemic in the majority of sub-Saharan African (SSA) countries where highest global annual incidence rates are recorded.[1] The expected therapeutic success target of 85% among newly diagnosed individuals with positive smear is largely unachieved in many settings in SSA.[1] Defaulting from tuberculous treatment is one of the reasons for this non-optimal performance. Tuberculosis treatment default or antituberculosis treatment (ATT) discontinuation is defined as any interruption of ATT for at least 2 months, following treatment initiation.[2,3] Non-adherence to ATT is associated with disease reoccurrence following treatment, increased mortality, maintenance of micro-organisms reservoirs and emergence drug-resistant species of mycobacterium.[4]

The directly observed treatment (DOT) strategy has been recommended by the World Health Organisation (WHO),[5] for improving the outcome of care for tuberculosis. Implementation of the DOT strategy started in Cameroon in the mid 90's and was expanded to the entire country in the years 2000. Despite this, available evidence suggests that ATT discontinuation has remained relatively high.[6] Many factors have been linked with ATT discontinuation in SSA including infrequent bacilloscopic monitoring, transfer of patients across health services units, lack of family support and side effects of medications.[7] In general, studies on the determinants of ATT discontinuation in Africa are mostly out-dated and less reflective of the DOT era, and the few relevant studies are either inconsistent or too heterogeneous to provide reliable conclusions that can inform health service and policy solutions.[7] In addition, none of the relevant study has been conducted in Cameroon.

The aim of the current study was to assess the incidence rate, determinants and time to ATT discontinuation in the real-life settings of a historical diagnosis and treatment centre for tuberculosis in Yaounde, Cameroon.

METHODS

Study setting

The study was conducted in the pneumology service of Yaounde Jamot Hospital (YJH). The YJH serves a referral centre for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas. It is one of the major centres for diagnosis and treatment of tuberculosis (CDT) in Cameroon. The pneumology service of YJH is a 257

bedded service and 11% of all cases of tuberculosis diagnosed in Cameroon in 2009 were managed in this service. Since five years, about 1600 to 1800 patients with tuberculosis are diagnosed and treated by the CDT. The YJH also hosts an approved treatment centre (ATC) that provides care to people living with Human Immunodeficiency Virus (HIV) infection. Patients received at the CDT during January to December 2009 were considered for inclusion in the study. The study was approved by the administrative authorities of the YJH.

Definition and classification of tuberculosis cases

Patients who receive care at the CDT of YJH are consecutively registered as they are started on treatment. For patients with a past exposure to ATT, the approach is nearly similar. Those patients who report back to the centre with active tuberculosis and who have been treated in the past for at least one month are registered again with a new number and started on a standardised re-treatment regimen. The following international definitions are applied: [2, 3, 5] 1) smear-positive pulmonary tuberculosis (SPTB+) - acid-fast bacillary (AFB) found in at least two sputum specimens; 2) smear-negative pulmonary tuberculosis (SPTB-) – persisting negativity on three sputum examinations after ten-day course of non-specific antibiotic treatment in a patient with tuberculosis-like clinical and radiological signs, and in the absence of any obvious cause; 3) extra-pulmonary tuberculosis – tuberculosis involving organs other than the lungs. Patients with past exposure to ATT are usually all smear-positive and are further classified as “relapse” (i.e. reoccurrence of the disease following a successful ATT course), “failure” (i.e. positive smear after five months of ATT) and “treatment after default” (i.e. starting ATT again after two consecutive months of interruption). A “new case” is a patient with tuberculosis who has never been exposed to ATT for more than one month in the past. “Other cases of tuberculosis” referred to patients who cannot fit in one of the categories described above.

Detection and management of HIV infection

At the CDT of the YJH, all patients with tuberculosis are screened for HIV infection free of charge after informed consent has been obtained from the patient or relative for dependant patients. This includes detection of anti-HIV 1 and anti-HIV 2 antibodies in the serum with the use of two rapid tests: Determine® HIV ½(Abbot laboratories, Tokyo, Japan) and Immunocomb® II HIV 1 and 2 Bispot (Organics, Courbevoie, France). A patient is classified as HIV positive when the two tests are positive. For discordant tests, a confirmatory western blot test (New Lav Blot, Sanofi diagnostics-Pasteur) is conducted. All HIV-positive patients

are started on prophylaxis with cotrimoxazole and those with CD4 lymphocytes count <200/mm^3 (or <15% of the total lymphocyte count in those <15 years of age) are started on triple antiretroviral therapy free of charge. Initial antiretroviral regimens are the combinations lamivudine-zidovudine-efavirenz or lamivudine-stavudine-efavirenz.

Tuberculosis treatment

Tuberculosis treatment at the CDT is based on the DOT approach, in accordance with the guidelines of the Cameroon National Programme Against Tuberculosis (NPAT) and the WHO recommendations.[2, 3] Patients are either admitted during the intensive phase (IP) of ATT, or treated as outpatient. Antituberculosis drugs are dispensed free of charge to all patients. Treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid. During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE. During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly drugs collection visits.

Monitoring and outcomes of tuberculosis treatment

During ATT, SPTB+ patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 in case of re-treatment. SPTB- and patients with extra-pulmonary tuberculosis are monitored clinically and/or radiologically at the same frequency. At the end of the treatment, patients are ranked into mutually exclusive categories as:[2] 1) cured – patient with negative smear at the last month of treatment and at least one of the preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with at least two positive smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Data collection

Tuberculosis treatment registers and ATT treatment forms of the YJH's CDT served as basis for data collection for the study. Data were collected on age, sex, residence (urban vs. rural), history of exposure to ATT, localisation of tuberculosis infection, status for HIV infection, CD4 lymphocyte count (in those with HIV infection), intensive ATT setting (hospital vs. ambulatory), outcome of ATT and time to treatment discontinuation. Cured and ATT completion were considered as favourable outcome (successful treatment) while death, default and failure were considered as unfavourable outcome.[8] Patients who died or were transferred during treatment were included only in time-to-event analysis.

Statistical methods

Data analysis used SPSS® v.12.0.1 for Windows® (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count (proportions), means (standard deviation, SD) or median (interquartile range, IQR). Group comparisons used chi square of Fisher exact test for qualitative variables, and Student t-test or Mann-Whitney U test for quantitative variables. Logistic regression models were used to investigate potential determinants of ATT discontinuation before and after adjustment for confounders. To assess potential influence of those patients excluded as well as time to treatment discontinuation on effect estimates, secondary analyses were conducted with the used of survival methods. In this approaches, Cox proportional hazard regression models were used to relate baseline characteristics with treatment discontinuation during follow-up. Exploratory analyses were adjusted for age and sex; then all significant predictors identified were entered into the same multivariable model adjusted for sex and age. All Cox models were stratified by type of patients (i.e. new patient, retreatment) to account for differences in the duration of treatment. Kaplan-Meier estimator was also used to depict the probability of treatment discontinuation across strata of significant predictors and group comparisons made with the use of the log-rank test. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

Study population and ATT discontinuation rate

During the study period, 1688 patients with tuberculosis were registered at the CDT. Their

demographic and clinical profile, and outcomes are summarised in Table 1. Of these participants, 199 (11.8%) were excluded from the main analysis for transferred or discharged against medical advice during treatment (104 patients), treatment failure (6 patients), deaths (86) and other forms of tuberculosis (3 patients). Of the 1489 eligible patients included in the final analysis, 1154 had successful ATT and 335 (21.2%) were lost to follow-up (Figure 1).

Table 1: Demographic, clinical characteristics and outcomes of patients with tuberculosis at the Yaounde Jamot Hospital in 2009

Characteristics	Sub-category	n=1688 (%)
Age, years	<15	38 (2.3)
	15-59	1556 (92.1)
	> 60	94 (5.6)
	Median (IQR)	32 (25-42)
Sex	Men	954 (56.5)
	Women	734 (43.5)
Residence	Urban	1423/1662 (85.6)
	Rural	239/1662 (14.6)
Place of screening	This centre	1626 (96.3)
	Elsewhere	62 (3.7)
Hospitalisation	Yes	1098 (65)
	No	590 (35)
Clinical form of TB	Smear positive pulmonary TB	1231 (73)
	Smear negative pulmonary TB	168 (10)
	Extra-pulmonary	289 (17)
Type of TB	New case	1543 (91.4)
	Re-traitement cases	142 (8.4)
	Other cases	3 (0.2)
HIV serology	Negative	942 (55.8)
	Positive	505 (29.9)
	Not done	241 (14.3)
Outcome	Cure	275 (16.3)
	Treatment completed	880 (52.1)
	Failure	6 (0.4)
	Death	86 (5.1)
	Transfer-out	104 (6.2)
	Defaulter	337 (20)

IQR, inter quartile range ; TB, tuberculosis ; HIV, Human Immunodeficiency Virus

Of those included in the main analysis, 844 (56.7%) were women, and the median age (IQR) was 32 years (24-42). Fifty-seven (3.8%) had been referred from another CDT; 1099 (73.8%) had PTB+, 138 (9.3%) PTB- and 252 (16.9%) extra-pulmonary tuberculosis; 1358 (91.2%) were new cases, and HIV test was positive in 425 (32.8%) out of the 1296 patients in whom such test was performed.

Time to tuberculosis treatment discontinuation

ATT interruption in 209 patients (62.4%) occurred during continuation phase of treatment (Figure 2) and the median (IQR) duration to ATT discontinuation was 90 days (30-150). ATT discontinuation was more likely to occur during continuation phase in those hospitalised during intensive phase than in those treated as outpatients [133 (74.7%) vs. 76 (48.8%), p<0.0001].

Determinants of treatment discontinuation

In univariable analysis (Table 2), outpatient ATT (odd ratio: 1.78; 95% confidence interval: 1.38-2.29), SPTB- (1.68; 1.12-2.52) and non-availability of HIV test results (2.44; 1.71-3.46) were related to tuberculosis treatment default. In multivariable analysis (Table 3), outpatient ATT (1.44; 1.08-1.91) and non-availability of HIV test results (1.84; 1.29-2.61) were the main determinants of ATT discontinuation.

In secondary analysis, Cox regression models were used to examine predictors of treatment default using the observed follow-up duration for all participants in the overall cohort. The same predictors emerged in sex- and age adjusted models, multivariable model as determinants of treatment discontinuation, although there were differences in magnitudes of the effect size (Online appendix Table 1 and 2). The probability of treatment discontinuation according to setting for intensive treatment and whether HIV test was done is depicted in Figure 3.

Table 2: Demographic and clinical characteristics of patients with tuberculosis according to the outcome of treatment (success vs. treatment default) (n=1489)

Characteristics	Categories	Defaulter n=335(%)	Success n=1154 (%)	Crude odds ratio (95% CI)	P
Sex	Men	195 (58.2)	649 (56.2)	1.08 (0.84-1.40)	0.522
	Women	140 (41.8)	505 (43.8)		
Age, years	≤ 32	169 (50.4)	613 (53.1)	0.90 (0.70-1.15)	0.389
	> 32	166 (49.6)	541 (46.9)		
Residence	Urban	282/329 (85.7)	994/1138 (87.3)	0.87 (0.60-1.26)	0.439
	Rural	47/329 (14.3)	144/1138 (12.7)		
Place of Screening	This centre	318 (94.9)	1114 (96.5)	0.67 (0.36-1.25)	0.177
	Elsewhere	17 (5.1)	40 (3.5)		
Setting of intensive ATT	Outpatient	157 (46.9)	383 (33.2)	1.78 (1.38-2.29)	<0.0001
	Hospitalisation	178 (53.1)	771 (66.8)		
Clinical form of TB	Positive smear	239 (71.3)	860 (74.5)	Reference	
	Negative smear	44 (13.1)	94 (8.1)	1.68 (1.12-2.52)	0.008
	Extrapulmonary	52 (15.5)	200 (17.3)	0.94 (0.66-1.33)	0.699
Type of TB	New cases	299 (89.3)	1059 (91.8)	0.75 (0.49-1.14)	0.153
	Re-treatment	36 (10.7)	95 (8.2)		
HIV serology	Negative	168 (50.1)	703 (60.9)	Reference	
	Positive	96 (28.7)	329 (28.5)	1.22 (0.91-1.64)	0.166
	Not done	71 (21.2)	122 (10.6)	2 .44(1.71-3.46)	<0.0001
Sputum Smear conversion*	Yes	781/858 (91)	173/183 (94.5)	0.59 (0.28-1.20)	0.119
	No	77/858(9)	10(5.5)		

* At the end of intensive phase (applicable only to patients with smear positive tuberculosis)

TB, tuberculosis; ATT, antituberculosis treatment; CI, confidence interval; HIV, Human Immunodeficiency Virus

Table 3: Multivariable adjusted predictors of antituberculosis treatment default

Characteristics	β coefficient	Odds ratio	95% CI	P
Outpatient intensive phase	0.37	1.44	1.68-1.91	0.012
Screened elsewhere	0.095	1.10	0.60-2.01	0.757
Smear negative pulmonary TB	-0.40	0.67	0.41-1.09	0.105
Re-treatment cases	0.40	1.49	0.98-2.25	0.059
Unknown status for HIV	0.61	1.84	1.29-2.61	0.001

TB, tuberculosis ; HIV, Human Immunodeficiency Virus ; CI, confidence interval

DISCUSSION

In this study, we have assessed the incidence of ATT discontinuation and predictors of treatment drop-out in a large cohort of patients with tuberculosis treatment in a major referral centre in Cameroon. Treatment success rate was 73% and the cumulative incidence of Treatment discontinuation was 21.2% overall and 21.7% among patients with smear-positive pulmonary tuberculosis. Before the reorganisation of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, ATT discontinuation was 10% higher among new patients with smear positive tuberculosis in the study centre.[9] The currently observed discontinuation rates are twice higher than the expected <10%, a requirement if the 85% ATT success rates prescribed in the millennium development goals are to be achieved.[10] ATT drop-out/discontinuation rate in sub-Saharan Africa ranges from 11.3 in Ethiopia to 29.8% in Zambia.[11,12] Treatment drop-out/discontinuation is a major challenge to programmes against tuberculosis, in the sense that non-adherence to ATT is associated with reoccurrence of the disease, preservation of reservoirs for micro-organism dissemination, emergence of drug resistant species of mycobacterium and increased tuberculosis related deaths.[14]

Two out of three patients who dropped-out in our study did so during the continuation phase of ATT. Predominantly late ATT discontinuation (i.e. after the intensive phase) has also been confirmed in a systematic review.[13] This late discontinuation could partly be explained by the improved condition of the patient following the intensive phase of ATT. It is possible that patients who feel clinically better following this phase are less motivated to continue the treatment as they don't feel the need to do so.[14]

ATT on the outpatient basis during the intensive phase and unknown status for HIV were the main determinant of treatment discontinuation found in our study. This would tend to suggest that direct daily supervision reduces the risk of drop out. This could be explained at least in part by the fact that those who receive ATT as in-patient during intensive phase also receive more education on the disease, the duration and outcome of care and are therefore more motivated to observe the treatment for the required duration. Two studies from Ethiopia and Zambia have reported that poor knowledge of ATT duration among patients was associated with high risk of treatment discontinuation.[11,12] Unlike our results however, another study in Spain found no protective effect of DOT on ATT discontinuation.[15] Patients with unknown status for HIV in our study are more likely to be those who did not consent for the test, since cost is not a constraint for HIV screening in our setting. It is possible that faced with the persisting invitation from healthcare personnel to accept HIV screening, some of the non-consenting patient would prefer to stop the ATT and walk away from the programme. The stigmatisation of people living with HIV is a reason for not-consenting for screening.[16,17] We can also speculate that ATT discontinuation is not the direct consequence of not-consenting for HIV screening, but the latter is just an indicator of the patient subgroup that will adhere less to any medical prescription. The effects of non-consent for HIV screening on ATT discontinuation have not been confirmed by other studies.[7] In agreement with a previous study in Cameroon,[9] and unlike findings from elsewhere,[18] age, gender and living and rural area were not associated with ATT discontinuation in our study.

This study used administrative data routinely collected for the monitoring of the national programme against tuberculosis. Because such data collection is not comprehensive, we were unable to investigate the effects of some potential determinants of ATT discontinuation such as patient's knowledge about tuberculosis, distance from CDT to patient's residence, side effects of ATT and chronic alcohol abuse.[19-21] That no systematic effort was in place to trace patients who dropped out during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between ATT drug collection visit would have been inappropriately classified as drop-out. However, the effects of misclassification if any would need to be very important to invalidate our findings.

In conclusion, ATT discontinuation in this setting is relatively high, and tends to occur more during the continuation phase of the treatment. Patients who receive treatment on the

outpatient basis during the intensive phase and those who do not consent for HIV screening are more likely to be those who will interrupt their ATT. Specific actions targeting these subgroups would likely improve the outcomes of care for tuberculosis in this centre. Prospective studies are needed to investigate other determinants of ATT discontinuation and refine the incidence data based on a more objective ascertainment of the outcomes of care.

Competing interests – None for all authors

Source of funding – None

Authors' contribution – EWPY conceived the study, supervised data collection, co-analysed the data and drafted of the manuscript; APK contributed to study designed, data analysis, drafting and critical revision of the manuscript; CK supervised the data collection and critically revised the manuscript.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	/

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,11
		(*b*) Report category boundaries when continuous variables were categorized	8,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

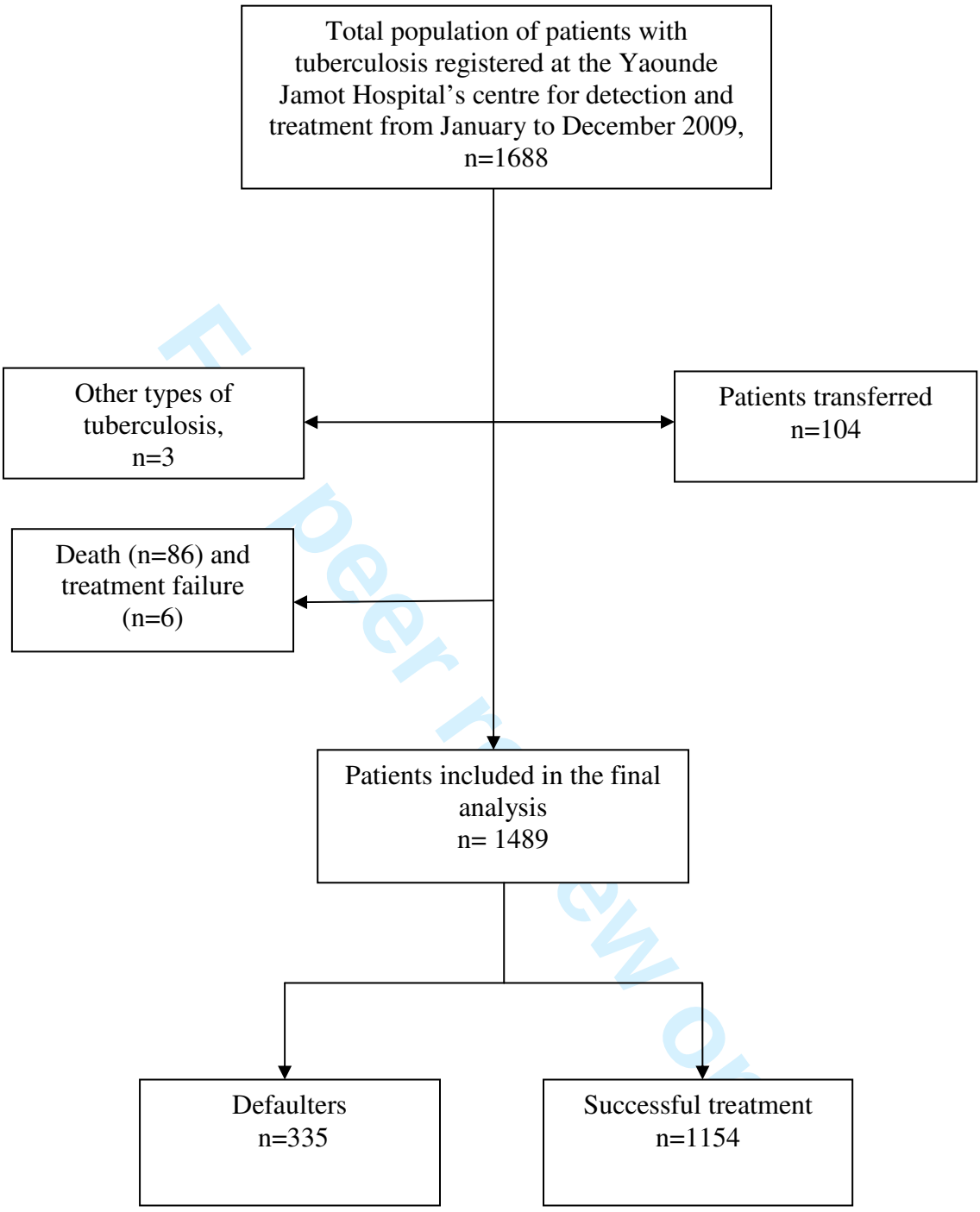

Figure 1 – Flow chart for inclusion of patients who defaulted and those with successful antituberculosis treatment at the Yaounde Jamot Hospital (YJH) in 2009

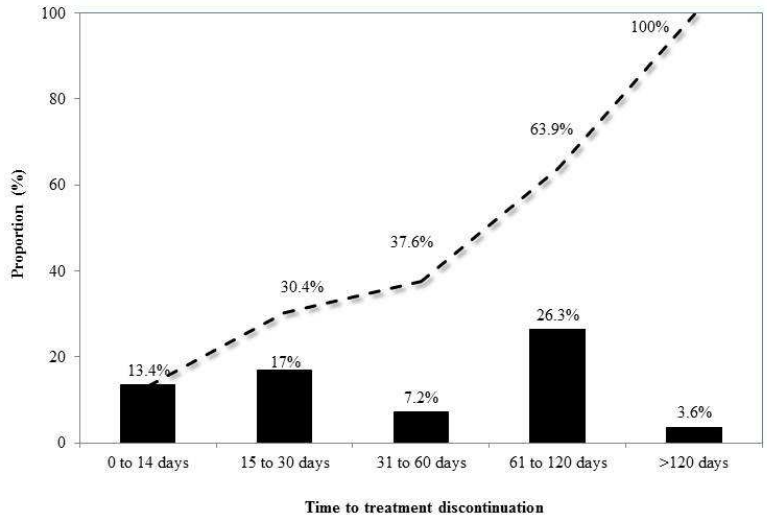

Figure 2 - Time to antituberculosis treatment discontinuation in 335 defaulters at the Yaounde Jamot Hospital in 2009

The vertical bars are proportional to the number of participants who stopped their treatment within the indicated time frame. The doted superimposed curve is for the cumulative number of defaulter across time. Within each time frame, the frame specific proportion of defaulters is shown, together with the cumulative proportion of defaulters up to that time limit.

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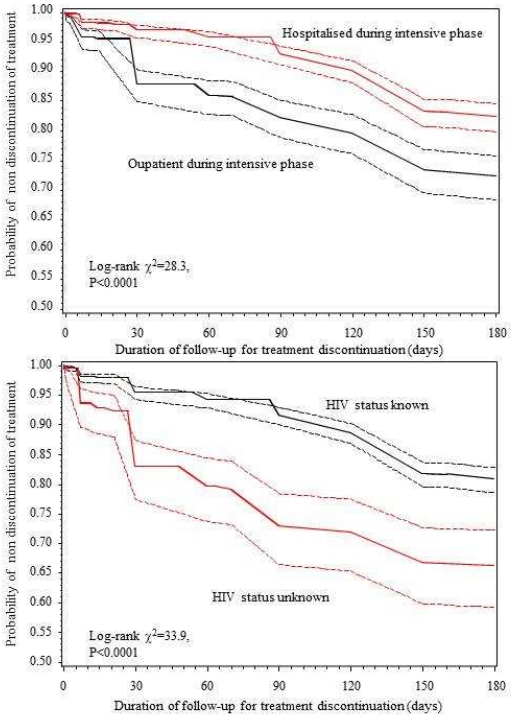

Figure 3 – Kaplan-Meier curves showing the probability of dropping out in subgroups defined by the setting of intensive treatment (upper panel) and knowledge of the status for HIV (lower panel) For each figure panel, the log-rank test results comparing the probability between subgroups are also shown.

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Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study

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Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study

Short title: **Tuberculosis treatment default**

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Abstract

Background and purpose: High rates of antituberculosis treatment discontinuation have been reported in places in Africa. The aim of this study was to determine the rate, time to- and determinants of antituberculosis treatment default at the Yaounde Jamot's referral tuberculosis diagnosis and treatment centre.

Methods: All patients started on antituberculosis treatment at the centre between January and December 2009 were considered for inclusion on a retrospective basis. Tuberculosis treatment default or antituberculosis treatment discontinuation was defined as any interruption of treatment for at least 2 months, following treatment initiation. Sociodemographic and clinical predictors of treatment discontinuation were investigated with the use of Cox regressions models.

Results: Of the 1688 patients treated for tuberculosis in 2009, 337 (20%) defaulted from treatment, 86 (5.1%) died, treatment failed in 6 (0.4%) and 104 (6.2%) were transferred. Therefore, treatment was successfully completed in 1154 (68.4%) patients. Median duration to treatment discontinuation was 90 days (interquartile range: 30-150), and 62% of treatment discontinuation occurred during continuation phase. Hospitalisation during intensive phase [adjusted hazard ratio 0.69 (95% confidence interval: 0.54-0.89)] and non-consenting for HIV screening [1.65 (1.24-2.21)] were the main determinants of defaulting from treatment in multivariable analysis.

Conclusions: The default incidence rate is relatively high in this centre and treatment discontinuation occurs frequently during the continuation phase of the treatment. Actions are needed to improve adherence to treatment when taken on an ambulatory basis, clarify the association between HIV testing and defaulting to antituberculosis treatment, and identify other potential determinants of treatment discontinuation in this setting.

Word count – 251

Key words – tuberculosis, default, antituberculosis, treatment discontinuation, Cameroon

Article focus: What are the rates, time to- and determinants of antituberculosis treatment discontinuation in the era of directly observed treatment in sub-Saharan Africa, using the case of Cameroon for illustration?

Key messages: Antituberculosis treatment success rates remain non-optimal in sub-Saharan Africa where the highest global incidence rates for tuberculosis are found. Treatment discontinuation is one of the main reasons, but has been less explored in Africa in recent times.

Knowledge of determinants of antituberculosis treatment discontinuation is critical for informing health service and policy solutions needed to improve the outcomes of care for tuberculosis and contain the spread of the disease.

Strengths: Large cohort study with up to 1688 participants

Limitations: retrospective study with lack of some information

INTRODUCTION

Tuberculosis is highly endemic in the majority of sub-Saharan African (SSA) countries where highest global annual incidence rates are recorded.[1] The expected therapeutic success target of 85% among newly diagnosed individuals with positive smear is largely unachieved in many settings in SSA.[1] Defaulting from tuberculous treatment is one of the reasons for this non-optimal performance. Tuberculosis treatment default or antituberculosis treatment (ATT) discontinuation is defined as any interruption of antituberculosis treatment for at least 2 months, following treatment initiation.[2,3] Antituberculosis treatment discontinuation is associated with disease reoccurrence following treatment, increased mortality, maintenance of micro-organisms reservoirs and emergence drug-resistant species of mycobacterium.[4]

The directly observed treatment (DOT) strategy has been recommended by the World Health Organisation (WHO),[5] for improving the outcome of care for tuberculosis. Implementation of the DOT strategy started in Cameroon in the mid 90's and was expanded to the entire country in the years 2000. Despite this, available evidence suggests that antituberculosis treatment discontinuation has remained relatively high.[6] Many factors have been linked with antituberculosis treatment discontinuation in SSA including infrequent bacilloscopic monitoring, transfer of patients across health services units, lack of family support, side effects of medications, health care systems factors and patient misinformation.[7-9] In general, studies on the determinants of antituberculosis treatment discontinuation in Africa and in Cameroon are mostly out-dated and less reflective of the DOT and highly active anti-retroviral therapy (HAART) eras, and the few relevant studies are heterogeneous. [7, 8] In addition, none of the relevant study has been conducted in Cameroon after DOT implementation in this country. In this context therefore, updated information are needed on antituberculosis treatment discontinuation and determinants that reflects both the DOT era and recent improvements in the access to HIV testing and treatment, in order to guide further improvement in the outcomes of care for tuberculosis.

The aim of the current study was to assess the incidence rate, determinants and time to antituberculosis treatment discontinuation in the real-life settings of a historical diagnosis and treatment centre for tuberculosis in Yaounde, Cameroon.

METHODS

Study setting

The study was conducted in the pneumology service of Yaounde Jamot Hospital (YJH). The Yaounde Jamot Hospital serves a referral centre for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas. It is one of the major centres for diagnosis and treatment of tuberculosis (CDT) in Cameroon. The pneumology service of Yaounde Jamot Hospital is a 257 bedded service and 11% of all cases of tuberculosis diagnosed in Cameroon in 2009 were managed in this service. Since five years, about 1600 to 1800 patients with tuberculosis are diagnosed and treated by the Centre for Diagnosis and Treatment of tuberculosis. The Yaounde Jamot Hospital also hosts an approved treatment centre (ATC) that provides care to people living with Human Immunodeficiency Virus (HIV) infection. Patients received at the Diagnosis and Treatment Centre of tuberculosis during January to December 2009 were considered for inclusion in the study. The study was approved by the administrative authorities of the Yaounde Jamot Hospital.

Definition and classification of tuberculosis cases

Patients who receive care at the Centre for Diagnosis and Treatment of tuberculosis of Yaounde Jamot Hospital are consecutively registered as they are started on treatment. For patients with a past exposure to antituberculosis treatment, the approach is nearly similar. Those patients who report back to the centre with active tuberculosis and who have been treated in the past for at least one month are registered again with a new number and started on a standardised re-treatment regimen. The following international definitions are applied: [2, 3, 5] 1) smear-positive pulmonary tuberculosis (PTB+) - acid-fast bacillary (AFB) found in at least two sputum specimens; 2) smear-negative pulmonary tuberculosis (PTB-) – persisting negativity on three sputum examinations after ten-day course of non-specific antibiotic treatment in a patient with tuberculosis-like clinical and radiological signs, and in the absence of any obvious cause; 3) extra-pulmonary tuberculosis – tuberculosis involving organs other than the lungs. Patients with past exposure to antituberculosis treatment are usually smear-positive [2] and are further classified as “relapse” (i.e. reoccurrence of the disease following a successful antituberculosis treatment course), “failure” (i.e. positive smear after five months of antituberculosis treatment) and “treatment after default” (i.e. starting tuberculosis treatment again after two consecutive months of interruption). A “new case” is a patient with tuberculosis who has never been exposed to antituberculosis treatment for more than one month in the past. “Other cases of tuberculosis” refers to patients who cannot fit in one of the categories described above (i.e. patient relapsing for a second time for tuberculosis,

with involved mycobacterium being sensitive to antituberculosis, and treated for 6 months with standard regimens).

Detection and management of HIV infection

At the Centre for Diagnosis and Treatment of tuberculosis of the Yaounde Jamot Hospital, all patients with tuberculosis are screened for HIV infection free of charge after informed consent has been obtained from the patient or relative for dependant patients. This includes detection of anti-HIV 1 and anti-HIV 2 antibodies in the serum with the use of two rapid tests: Determine® HIV ½(Abbot laboratories, Tokyo, Japan) and Immunocomb® II HIV 1 and 2 Bispot (Organics, Courbevoie, France). A patient is classified as HIV positive when the two tests are positive. For discordant tests, a confirmatory western blot test (New Lav Blot, Sanofi diagnostics-Pasteur) is conducted. All HIV-positive patients are started on prophylaxis with cotrimoxazole and those with CD4 lymphocytes count <200/mm^3 (or <15% of the total lymphocyte count in those <15 years of age) are started on triple antiretroviral therapy free of charge. Initial antiretroviral regimens are the combinations lamivudine-zidovudine-efavirenz or lamivudine-stavudine-efavirenz.

Tuberculosis treatment

Tuberculosis treatment at the Centre for Diagnosis and Treatment of tuberculosis is based on the DOT approach, in accordance with the guidelines of the Cameroon National Programme Against Tuberculosis (NPAT) and the WHO recommendations.[2, 3] Patients are either admitted during the intensive phase (IP) of antituberculosis treatment, or treated as outpatient. Antituberculosis drugs are dispensed free of charge to all patients. Treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid. During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE. During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly drugs collection visits.

Monitoring and outcomes of tuberculosis treatment

During antituberculosis treatment, PTB+ patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 in case of re-treatment. PTB- and patients with extra-pulmonary tuberculosis are monitored clinically and/or radiologically at the same frequency. At the end of the treatment, patients are ranked into mutually exclusive categories as:[2] 1) cured – patient with negative smear at the last month of treatment and at least one of the preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with at least two positive smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Data collection

Tuberculosis treatment registers and antituberculosis treatment forms of the YJH's Centre for Diagnosis and Treatment of tuberculosis served as basis for data collection for the study. Data were collected on age, sex, residence (urban vs. rural), history of exposure to antituberculosis treatment, localisation of tuberculosis infection, status for HIV infection, CD4 lymphocyte count (in those with HIV infection), intensive antituberculosis treatment setting (hospital vs. ambulatory), outcome of tuberculosis treatment and time to treatment discontinuation. Cured and tuberculosis treatment completion were considered as favourable outcome (successful treatment) while death, default and failure were considered as unfavourable outcome.[10]

Statistical methods

Data analysis used SPSS® v.12.0.1 for Windows® (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count (proportions) and median (interquartile range, IQR). Group comparisons used chi square test and equivalents for qualitative variables, and analysis of the variance (ANOVA) and equivalents for quantitative variables. Cox proportional hazard regression models were used to relate baseline characteristics with treatment discontinuation during follow-up. Exploratory analyses were adjusted for age and sex; then all significant predictors identified were entered into the same multivariable model adjusted for sex and age. All Cox models

were stratified by type of patients (i.e. new patient, retreatment) to account for differences in the duration of treatment. Kaplan-Meier estimator was also used to depict the probability of treatment discontinuation across strata of significant predictors and group comparisons made with the use of the log-rank test. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

Study population and antituberculosis treatment discontinuation rate

Between January and December 2009, 1688 patients with tuberculosis were registered at the Centre for Diagnosis and Treatment of tuberculosis. Their demographic, clinical profile and outcomes are summarised in Table 1. They were aged 32 years (interquartile range: 25-42 years) and 954 (56.5%) were men. Clinical forms of tuberculosis were: 1231 (73%) for PTB+, 168 (10%) for PTB- and 289 (17%) for EPTB. The cumulative incidence rate of antituberculosis treatment discontinuation was 20% and the treatment success rate was 68.4%.

Table 1: Characteristics of patients with tuberculosis according to the treatment outcome at the Yaounde Jamot Hospital in 2009

Characteristics	Categories	Total	Outcomes of tuberculosis treatment					
			Treatment success*	Failure	Deaths	Defaulted	Transferred	P-value
N(%)		1688	1155 (68.4)	6 (0.4)	86 (5.1)	337 (20.0)	104 (6.2)	
Age, years	≤15	39 (2.3)	33 (84.6)	0 (0)	0 (0)	5 (12.8)	1 (2.6)	<0.031
	>15-59	1554 (92.1)	1067 (68.7)	5 (0.3)	75 (4.8)	310 (19.9)	97 (6.2)	
	≥ 60	95 (5.6)	55 (57.9)	1 (1.1)	11(11.6)	22 (23.2)	6 (6.3)	
	Median (IQR)	32 (25-42)	32 (24-42)	35 (26-48)	45 (32-54)	32 (25-42)	35.5 (24-42)	<0.001
Men		954 (56.5)	650 (68.1)	4 (0.4)	50 (5.2)	195 (20.4)	55 (5.8)	0.882
Residence	Urban	1423/1662 (85.6)	995 (69.9)	5 (0.4)	72 (5.1)	283 (19.9)	68 (4.8)	<0.001
	Rural	239/1662 (14.4)	144 (60.3)	1 (0.4)	13 (5.4)	47 (19.7)	34 (14.2)	
Place of screening	This centre	1625 (96.3)	1115 (68.6)	6 (0.4)	84 (5.2)	319 (19.6)	101 (6.2)	0.269
	Elsewhere	63 (3.7)	40 (63.5)	0 (0)	2 (3.2)	18 (28.6)	3 (4.8)	
Setting of intensive phase of treatment	Hospitalisation	1098 (65.0)	772 (70.3)	3 (0.3)	69 (6.3)	179 (16.3)	75 (6.8)	<0.001
	Outpatient	590 (35.0)	383 (64.9)	3 (0.5)	17 (2.9)	158 (26.8)	29 (4.9)	
Clinical forms	PTB+	1231 (72.9)	860 (69.9)	6 (0.5)	16 (4.5)	239 (19.4)	70 (5.7)	0.012
	PTB-	168 (10.0)	95 (56.5)	0 (0)	16 (9.5)	45 (26.8)	12 (7.1)	
	ETB	289 (17.1)	200 (69.2)	0 (0)	14 (4.8)	53 (18.3)	22 (7.6)	
Type of patient	New cases	1543 (91.4)	1059 (68.6)	5 (0.3)	81 (5.2)	299 (19.4)	99 (6.4)	0.20
	Retreatment cases	145 (8.6)	96 (66.2)	1 (0.7)	5 (3.4)	38 (26.2)	5 (3.4)	
HIV serology	Not done	241 (14.3)	122 (50.6)	2 (0.8)	20 (8.3)	72 (29.9)	25 (10.4)	<0.001
	Negative	942 (55.8)	703 (74.6)	4 (0.4)	17 (1.8)	166 (18)	50 (5.4)	
	Positive	497/1419 (35)	330 (65.3)	0 (0)	49 (9.7)	97 (19.2)	29 (5.7)	
Sputum smear conversion £	Yes	1378/1471 (93.7)	1072 (77.8)	0 (0)	13 (0.9)	229 (16.6)	64 (4.6)	<0.001
	No	93/1471 (6.3)	82.8)	4 (4.3)	0 (0)	10 (10.8)	2 (2.2)	

Data are number (%) unless otherwise indicated; IQT, interquartile range; ETB, extra-pulmonary tuberculosis; PTB+, smear positive pulmonary tuberculosis; PTB-, smear negative pulmonary tuberculosis; *treatment success = cured+completed; £ at the end of intensive phase (applicable only to patients with smear positive tuberculosi

Time to tuberculosis treatment discontinuation

Antituberculosis treatment interruption in 210 patients (62.3%) occurred during continuation phase of treatment (Figure 1) and the median (IQR) duration to tuberculosis treatment discontinuation was 90 days (30-150). Tuberculosis treatment discontinuation was more likely to occur during continuation phase in those hospitalised during intensive phase than in those treated as outpatients [134 (74.9%) vs. 77 (48.7%), p<0.0001].

Determinants of treatment discontinuation

The probability of treatment discontinuation according to setting for intensive treatment and whether HIV test was done is depicted in Figure 2. At each time point during follow-up the probability of treatment discontinuation was always lower in patients hospitalized during intensive treatment phase than in those treated as outpatients during intensive phase. Similarly, discontinuation probability was always lower in patients with known status for HIV infection than in those with unknown status.

Cox regression models were used to examine predictors of treatment discontinuation using the observed follow-up duration for all participants in the overall cohort. In models adjusted for age and sex, hospitalisation during intensive phase reduced the risk of treatment discontinuation [hazard ratio (HR) 0.58, 95% confidence interval (95% CI): 0.46-0.72], while having PTB- [1.59 (1.15-2.21)] or unknown status for HIV infection [1.28 (1.17-1.41)] significantly increased the risk of treatment discontinuation. With further adjustment for those variables that were significant in basic models, ambulatory treatment during intensive phase and unknown status for HIV infection were the main determinants of antituberculosis treatment discontinuation (Table 2).

Table 2: Hazard ratio (HR) and 95% confidence interval (95% CI) for predictors of antituberculosis treatment discontinuation from Cox regression analysis

Characteristics	Basic models		Final models	
	HR (95% CI)	p	HR (95%CI)	p
Age (per year)	1.01 (1.00-1.01)	0.121	1.01 (1.00-1.01)	0.133
Sex (women vs. men)	0.96 (0.77-1.20)	0.723	0.99(0.79-1.23)	0.922
Hospitalised intensive phase	0.58 (0.46-0.72)	<0.0001	0.69 (0.54-0.89)	0.004
Residence (urban vs. rural)	0.92(0.67-1.26)	0.596	/	/
Clinical form of tuberculosis				
Positive smear (Reference)	1.00 (reference)		1.00 (reference)	
Negative smear	1.59(1.15-2.21)	0.005	1.25 (0.89-1.76)	0.192
Extra-pulmonary	0.99(0.73-1.34)	0.948	0.96(0.71-1.30)	0.780
Unknown status for HIV	1.28 (1.17-1.41)	<0.0001	1.65 (1.24-2.21)	0.0007

HIV, Human Immunodeficiency Virus; Basic models are adjusted for age and sex; and final models further adjust for all significant predictors in basic models. All Cox models are stratified by type of patients (i.e. new patient, retreatment) to account for difference in the duration of treatment.

DISCUSSION

In this study, we have assessed the incidence of antituberculosis treatment discontinuation and predictors of treatment discontinuation in a large cohort of patients treated for tuberculosis in a major referral centre in Cameroon. Treatment success rate was 68.4% and the cumulative incidence of treatment discontinuation was 20% overall and 19.4% among patients with smear-positive pulmonary tuberculosis. Discontinuation was most likely to occur during continuation phase of treatment and mostly among those treated as outpatients during intensive phase and patients with unknown status for HIV infection.

Treatment discontinuation in our study was based on the World Health Organisation's definition, which refers to a defaulter as a patient who's treatment has been discontinued for at least two consecutive months.[2] Compared with other few studies from Africa that have used similar definition, discontinuation rate in our cohort was similar to that reported by Shargie and co-workers in South Ethiopia, [11] lower that the rate found by Kaona and his colleagues in Zambia,[12] and higher than the rate by Tekle et al in Arsi in Ethiopia.[13] The above studies however differs from our study in a number of respects. The largest of those studies had 20% fewer patients than our cohort,[13] while the two others had less than ¼ the number of participants in our sample. [11, 12]. Furthermore, the two studies in Ethiopia involved only rural participants, with one based only on patients with smear-positive tuberculosis,[12], while the study in Zambia was based on a cross-sectional sample of urban dwellers.[13] In general, it has been recognised that using a stricter definition for treatment discontinuation results in much higher rates than when using the World Health Organisation's definition.[7]

Before the reorganisation of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, antituberculosis treatment discontinuation rate was 31.7% among adults with PTB+ in the Yaounde Jamot Hospital.[14] Our study would tend to suggest that implementation of the DOT strategy has positively impacted on antituberculosis treatment discontinuation, with a 12% drop, although much efforts are still needed to bring the rate below 10%. The currently observed discontinuation rates are twice higher than the expected <10%, a requirement if the 85% antituberculosis treatment success rates prescribed in the millennium development goals are to be achieved.[15] Treatment discontinuation is a major challenge to programmes against tuberculosis, in the sense that non-adherence to antituberculosis treatment is associated with reoccurrence of the disease, preservation of reservoirs for micro-organism dissemination, emergence of drug resistant species of mycobacterium and increased tuberculosis related deaths.[16]

Two out of three patients who defaulted to treatment in our study did so during the continuation phase of tuberculosis treatment. Predominantly late antituberculosis treatment discontinuation (i.e. after the intensive phase) has also been confirmed in a systematic review.[17] This late discontinuation could partly be explained by the improved condition of the patient following the intensive phase of antituberculosis treatment. It is possible that patients who feel clinically better following this phase are less motivated to continue the treatment as they don't feel the need to do so.[16]

Tuberculosis treatment on the outpatient basis during the intensive phase and unknown status for HIV were the main determinants of treatment discontinuation found in our study. This would tend to suggest that direct daily supervision reduces the risk of drop out. This could be explained at least in part by the fact that those who receive antituberculosis treatment as in-patient during intensive phase also receive more education on the disease, the duration and outcome of care and are therefore more motivated to observe the treatment for the required duration. Two studies from Ethiopia and Zambia have reported that poor knowledge of antituberculosis treatment duration among patients was associated with high risk of treatment discontinuation.[12,13] Unlike our results however, another study in Spain found no protective effect of DOT on antituberculosis treatment discontinuation.[18] Patients with unknown status for HIV in our study are more likely to be those who did not consent for the test, since cost is not a constraint for HIV screening in our setting. It is possible that faced with the persisting invitation from healthcare personnel to accept HIV screening, some of the non-consenting patient would prefer to stop the antituberculosis treatment and walk away from the programme. The stigmatisation of people living with HIV is a reason for not-consenting for screening.[19,20] We can also speculate that antituberculosis treatment discontinuation is not the direct consequence of not-consenting for HIV screening, but the latter is just an indicator of the profile of those patients who will adhere less to any medical prescription. The effects of non-consenting for HIV screening on antituberculosis treatment discontinuation have not been investigated by other studies.[7] In agreement with a previous study in Cameroon,[14] and unlike findings from elsewhere,[11] age, gender and living and rural area were not associated with antituberculosis treatment discontinuation in our study.

This study used administrative data routinely collected for the monitoring of the national programme against tuberculosis. Because such data collection is not comprehensive, we were unable to investigate the effects of some potential determinants of antituberculosis treatment discontinuation such as patient's knowledge about tuberculosis, distance from Centre for Diagnosis and Treatment of tuberculosis to patient's residence, side effects of antituberculosis treatment and chronic alcohol abuse.[8, 9, 21-23] That no systematic effort was in place to trace patients who interrupted their treatment during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between drugs collection visit would have been inappropriately classified as defaulters, particularly among HIV infected patients [24-26]. Our

study also has major strengths including the large population and inclusion of common forms of tuberculosis in this setting. Unlike recent studies on this topic in Africa, assessment of predictors of treatment discontinuation used robust methods to account both for the observed time to treatment discontinuation as well as differences in the duration of treatment for various forms of tuberculosis.[7] Those studies have either been based in patients with HIV and tuberculosis, or lacked information on status for HIV. Accordingly, none has investigated the effects of HIV testing on the outcome of care for tuberculosis; what our study has successfully done.

In conclusion, antituberculosis treatment discontinuation in this setting is relatively high, and tends to occur more during the continuation phase of the treatment. Patients who receive treatment on the outpatient basis during the intensive phase and those who do not consent for HIV screening are more likely to be those who will interrupt their antituberculosis treatment. Specific actions targeting these subgroups would likely improve the outcomes of care for tuberculosis in this centre. That patients treated entirely on ambulatory basis were less like to achieve good outcomes of care as compared to those hospitalised during intensive treatment phase, together with much higher discontinuation rates in the same setting in the pre-DOT era, all suggest that DOT strategy is associated with improved outcomes of care for tuberculosis in this setting. Prospective studies are needed to investigate other determinants of antituberculosis treatment discontinuation and refine the incidence data based on a more objective ascertainment of the outcomes of care.

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Source of funding – None

Authors' contribution – EWPY conceived the study, supervised data collection, co-analysed the data and drafted of the manuscript; APK contributed to study designed, data analysis, drafting and critical revision of the manuscript; CK supervised the data collection and critically revised the manuscript.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	5,7
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	7,8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	/

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10,11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

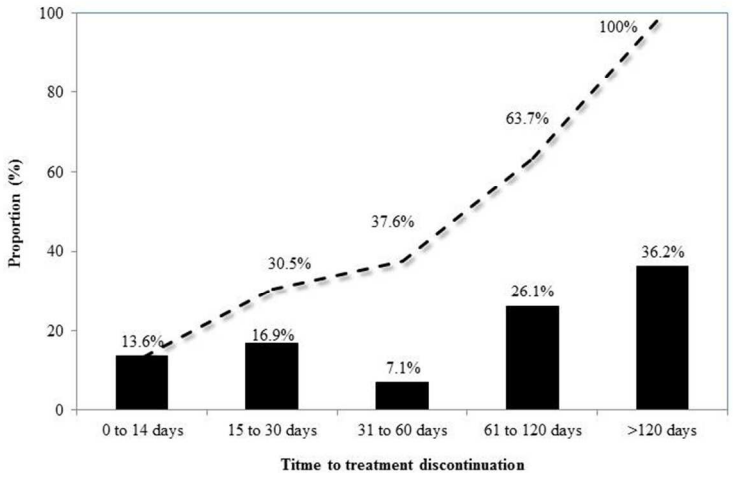

Figure 1 - Time to antituberculosis treatment discontinuation in 337 defaulters at the Yaounde Jamot Hospital in 2009

The vertical bars are proportional to the number of participants who stopped their treatment within the indicated time frame. The doted superimposed curve is for the cumulative number of defaulter across time. Within each time frame, the frame specific proportion of defaulters is shown, together with the cumulative proportion of defaulters up to that time limit.

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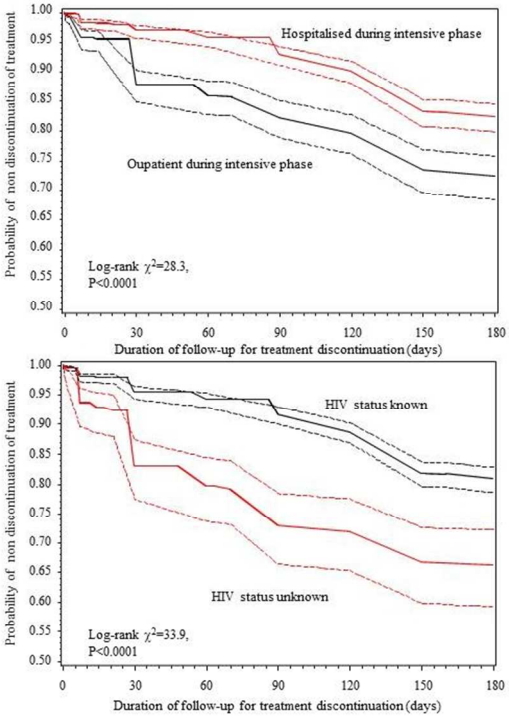

Figure 2 – Kaplan-Meier curves showing the probability of dropping out in subgroups defined by the setting of intensive treatment (upper panel) and knowledge of the status for HIV (lower panel)
For each figure panel, the log-rank test results comparing the probability between subgroups are also shown.

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Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study

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Incidence, time and determinants of tuberculosis treatment default in Yaounde, Cameroon: a retrospective hospital register-based cohort study

Short title: **Tuberculosis treatment default**

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Figures: 2

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Abstract

Objectives: High rates of antituberculosis treatment discontinuation have been reported in places in Africa. The aim of this study was to determine the rate, time to- and determinants of antituberculosis treatment default in Yaounde.

Design: This was a retrospective cohort study based on hospital registers. Tuberculosis treatment default or antituberculosis treatment discontinuation was defined as any interruption of treatment for at least 2 months, following treatment initiation. Sociodemographic and clinical predictors of treatment discontinuation were investigated with the use of Cox regressions models.

Setting: This study was carried out to the Yaounde Jamot's referral tuberculosis diagnosis and treatment centre. The Yaounde Jamot Hospital serves a referral centre for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas.

Participants: All (1688) patients started on antituberculosis treatment at the centre between January and December 2009.

Outcome measures: Antituberculosis treatment default, time to treatment default.

Results: Of the 1688 patients included, 337 (20%) defaulted from treatment, 86 (5.1%) died, treatment failed in 6 (0.4%) and 104 (6.2%) were transferred. Therefore, treatment was successfully completed in 1154 (68.4%) patients. Median duration to treatment discontinuation was 90 days (interquartile range: 30-150), and 62% of treatment discontinuation occurred during continuation phase. Hospitalisation during intensive phase [adjusted hazard ratio 0.69 (95% confidence interval: 0.54-0.89)] and non-consenting for HIV screening [1.65 (1.24-2.21)] were the main determinants of defaulting from treatment in multivariable analysis.

Conclusions: The default incidence rate is relatively high in this centre and treatment discontinuation occurs frequently during the continuation phase of the treatment. Actions are needed to improve adherence to treatment when taken on an ambulatory basis, clarify the association between HIV testing and defaulting to antituberculosis treatment, and identify other potential determinants of treatment discontinuation in this setting.

Word count – 289

Key words – tuberculosis, default, antituberculosis, treatment discontinuation, Cameroon

Article focus: What are the rates, time to- and determinants of antituberculosis treatment discontinuation in the era of directly observed treatment in sub-Saharan Africa, using the case of Cameroon for illustration?

Key messages: Antituberculosis treatment success rates remain non-optimal in sub-Saharan Africa where the highest global incidence rates for tuberculosis are found. Treatment discontinuation is one of the main reasons, but has been less explored in Africa in recent times.

Knowledge of determinants of antituberculosis treatment discontinuation is critical for informing health service and policy solutions needed to improve the outcomes of care for tuberculosis and contain the spread of the disease.

Strengths: Large cohort study with up to 1688 participants.

Limitations: retrospective study with lack of some key information.

INTRODUCTION

Tuberculosis is highly endemic in the majority of sub-Saharan African (SSA) countries where highest global annual incidence rates are recorded.[1] The expected therapeutic success target of 85% among newly diagnosed individuals with positive smear is largely unachieved in many settings in SSA.[1] Defaulting from tuberculous treatment is one of the reasons for this non-optimal performance. Tuberculosis treatment default or antituberculosis treatment (ATT) discontinuation is defined as any interruption of antituberculosis treatment for at least 2 months, following treatment initiation.[2,3] Antituberculosis treatment discontinuation is associated with disease reoccurrence following treatment, increased mortality, maintenance of micro-organisms reservoirs and emergence drug-resistant species of mycobacterium.[4]

The directly observed treatment (DOT) strategy has been recommended by the World Health Organisation (WHO),[5] for improving the outcome of care for tuberculosis. Implementation of the DOT strategy started in Cameroon in the mid 90's and was expanded to the entire country in the years 2000. Despite this, available evidence suggests that antituberculosis treatment discontinuation has remained relatively high.[6] Many factors have been linked with antituberculosis treatment discontinuation in SSA including infrequent bacilloscopic monitoring, transfer of patients across health services units, lack of family support, side effects of medications, health care systems factors and patient misinformation.[7-9] In general, studies on the determinants of antituberculosis treatment discontinuation in Africa and in Cameroon are mostly out-dated and less reflective of the DOT and highly active anti-retroviral therapy (HAART) eras, and the few relevant studies are heterogeneous. [7, 8] In addition, none of the relevant study has been conducted in Cameroon after DOT implementation in this country. In this context therefore, updated information are needed on antituberculosis treatment discontinuation and determinants that reflects both the DOT era and recent improvements in the access to HIV testing and treatment, in order to guide further improvement in the outcomes of care for tuberculosis.

The aim of the current study was to assess the incidence rate, determinants and time to antituberculosis treatment discontinuation in the real-life settings of a historical diagnosis and treatment centre for tuberculosis in Yaounde, Cameroon.

METHODS

Study setting

The study was conducted in the pneumology service of Yaounde Jamot Hospital (YJH). The Yaounde Jamot Hospital serves a referral centre for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas. It is one of the major centres for diagnosis and treatment of tuberculosis (CDT) in Cameroon. The pneumology service of Yaounde Jamot Hospital is a 257 bedded service and 11% of all cases of tuberculosis diagnosed in Cameroon in 2009 were managed in this service. Since five years, about 1600 to 1800 patients with tuberculosis are diagnosed and treated by the Centre for Diagnosis and Treatment of tuberculosis. The Yaounde Jamot Hospital also hosts an approved treatment centre (ATC) that provides care to people living with Human Immunodeficiency Virus (HIV) infection. Patients received at the Diagnosis and Treatment Centre of tuberculosis during January to December 2009 were considered for inclusion in the study. The study was approved by the administrative authorities of the Yaounde Jamot Hospital.

Definition and classification of tuberculosis cases

Patients who receive care at the Centre for Diagnosis and Treatment of tuberculosis of Yaounde Jamot Hospital are consecutively registered as they are started on treatment. For patients with a past exposure to antituberculosis treatment, the approach is nearly similar. Those patients who report back to the centre with active tuberculosis and who have been treated in the past for at least one month are registered again with a new number and started on a standardised re-treatment regimen. The following international definitions are applied: [2, 3, 5] 1) smear-positive pulmonary tuberculosis (PTB+) - acid-fast bacillary (AFB) found in at least two sputum specimens; 2) smear-negative pulmonary tuberculosis (PTB-) – persisting negativity on three sputum examinations after ten-day course of non-specific antibiotic treatment in a patient with tuberculosis-like clinical and radiological signs, and in the absence of any obvious cause; 3) extra-pulmonary tuberculosis – tuberculosis involving organs other than the lungs. Patients with past exposure to antituberculosis treatment are usually smear-positive [2] and are further classified as “relapse” (i.e. reoccurrence of the disease following a successful antituberculosis treatment course), “failure” (i.e. positive smear after five months of antituberculosis treatment) and “treatment after default” (i.e. starting tuberculosis treatment again after two consecutive months of interruption). A “new case” is a patient with tuberculosis who has never been exposed to antituberculosis treatment for more than one month in the past. “Other cases of tuberculosis” refers to patients who cannot fit in one of the categories described above (i.e. patient relapsing for a second time for tuberculosis,

with involved mycobacterium being sensitive to antituberculosis, and treated for 6 months with standard regimens).

Detection and management of HIV infection

At the Centre for Diagnosis and Treatment of tuberculosis of the Yaounde Jamot Hospital, all patients with tuberculosis are screened for HIV infection free of charge after informed consent has been obtained from the patient or relative for dependant patients. This includes detection of anti-HIV 1 and anti-HIV 2 antibodies in the serum with the use of two rapid tests: Determine® HIV ½(Abbot laboratories, Tokyo, Japan) and Immunocomb® II HIV 1 and 2 Bispot (Organics, Courbevoie, France). A patient is classified as HIV positive when the two tests are positive. For discordant tests, a confirmatory western blot test (New Lav Blot, Sanofi diagnostics-Pasteur) is conducted. All HIV-positive patients are started on prophylaxis with cotrimoxazole and those with CD4 lymphocytes count <200/mm^3 (or <15% of the total lymphocyte count in those <15 years of age) are started on triple antiretroviral therapy free of charge. Initial antiretroviral regimens are the combinations lamivudine-zidovudine-efavirenz or lamivudine-stavudine-efavirenz.

Tuberculosis treatment

Tuberculosis treatment at the Centre for Diagnosis and Treatment of tuberculosis is based on the DOT approach, in accordance with the guidelines of the Cameroon National Programme Against Tuberculosis (NPAT) and the WHO recommendations.[2, 3] Patients are either admitted during the intensive phase (IP) of antituberculosis treatment, or treated as outpatient. Antituberculosis drugs are dispensed free of charge to all patients. Treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid. During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE. During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly drugs collection visits.

Monitoring and outcomes of tuberculosis treatment

During antituberculosis treatment, PTB+ patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 in case of re-treatment. PTB- and patients with extra-pulmonary tuberculosis are monitored clinically and/or radiologically at the same frequency. At the end of the treatment, patients are ranked into mutually exclusive categories as:[2] 1) cured – patient with negative smear at the last month of treatment and at least one of the preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with at least two positive smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Data collection

Tuberculosis treatment registers and antituberculosis treatment forms of the YJH's Centre for Diagnosis and Treatment of tuberculosis served as basis for data collection for the study. Data were collected on age, sex, residence (urban vs. rural), history of exposure to antituberculosis treatment, localisation of tuberculosis infection, status for HIV infection, CD4 lymphocyte count (in those with HIV infection), intensive antituberculosis treatment setting (hospital vs. ambulatory), outcome of tuberculosis treatment and time to treatment discontinuation. Cured and tuberculosis treatment completion were considered as favourable outcome (successful treatment) while death, default and failure were considered as unfavourable outcome.[10]

Statistical methods

Data analysis used SPSS® v.12.0.1 for Windows® (SPSS Inc., Chicago, USA) and SAS/STAT® v 9.1 for windows (SAS Institute Inc., Cary, NC, USA). Results are presented as count (proportions) and median (interquartile range, IQR). Group comparisons used chi square test and equivalents for qualitative variables, and analysis of the variance (ANOVA) and equivalents for quantitative variables. Cox proportional hazard regression models were used to relate baseline characteristics with treatment discontinuation during follow-up. Exploratory analyses were adjusted for age and sex; then all significant predictors identified ($p < 0.05$) were entered into the same multivariable model adjusted for sex and age. All Cox models were stratified by type of patients (i.e. new patient, retreatment) to account for differences in the duration of treatment. Kaplan-Meier estimator was also used to depict the

probability of treatment discontinuation across strata of significant predictors and group comparisons made with the use of the log-rank test. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

Study population and antituberculosis treatment discontinuation rate

Between January and December 2009, 1688 patients with tuberculosis were registered at the Centre for Diagnosis and Treatment of tuberculosis. Their demographic, clinical profile and outcomes are summarised in Table 1. They were aged 32 years (interquartile range: 25-42 years) and 954 (56.5%) were men. Clinical forms of tuberculosis were: 1231 (73%) for PTB+, 168 (10%) for PTB- and 289 (17%) for EPTB. The cumulative incidence rate of antituberculosis treatment discontinuation was 20% and the treatment success rate was 68.4%.

Table 1: Characteristics of patients with tuberculosis according to the treatment outcome at the Yaounde Jamot Hospital in 2009

Characteristics	Categories	Total	Outcomes of tuberculosis treatment					
			Treatment success*	Failure	Deaths	Defaulted	Transferred	P-value
N(%)		1688	1155 (68.4)	6 (0.4)	86 (5.1)	337 (20.0)	104 (6.2)	
Age, years	≤15	39 (2.3)	33 (84.6)	0 (0)	0 (0)	5 (12.8)	1 (2.6)	<0.031
	>15-59	1554 (92.1)	1067 (68.7)	5 (0.3)	75 (4.8)	310 (19.9)	97 (6.2)	
	≥ 60	95 (5.6)	55 (57.9)	1 (1.1)	11(11.6)	22 (23.2)	6 (6.3)	
	Median (IQR)	32 (25-42)	32 (24-42)	35 (26-48)	45 (32-54)	32 (25-42)	35.5 (24-42)	<0.001
Men		954 (56.5)	650 (68.1)	4 (0.4)	50 (5.2)	195 (20.4)	55 (5.8)	0.882
Residence	Urban	1423/1662 (85.6)	995 (69.9)	5 (0.4)	72 (5.1)	283 (19.9)	68 (4.8)	<0.001
	Rural	239/1662 (14.4)	144 (60.3)	1 (0.4)	13 (5.4)	47 (19.7)	34 (14.2)	
Place of screening	This centre	1625 (96.3)	1115 (68.6)	6 (0.4)	84 (5.2)	319 (19.6)	101 (6.2)	0.269
	Elsewhere	63 (3.7)	40 (63.5)	0 (0)	2 (3.2)	18 (28.6)	3 (4.8)	
Setting of intensive	Hospitalisation	1098 (65.0)	772 (70.3)	3 (0.3)	69 (6.3)	179 (16.3)	75 (6.8)	<0.001
phase of treatment	Outpatient	590 (35.0)	383 (64.9)	3 (0.5)	17 (2.9)	158 (26.8)	29 (4.9)	
Clinical forms	PTB+	1231 (72.9)	860 (69.9)	6 (0.5)	16 (4.5)	239 (19.4)	70 (5.7)	0.012
	PTB-	168 (10.0)	95 (56.5)	0 (0)	16 (9.5)	45 (26.8)	12 (7.1)	
	ETB	289 (17.1)	200 (69.2)	0 (0)	14 (4.8)	53 (18.3)	22 (7.6)	
Type of patient	New cases	1543 (91.4)	1059 (68.6)	5 (0.3)	81 (5.2)	299 (19.4)	99 (6.4)	0.20
	Retreatment cases	145 (8.6)	96 (66.2)	1 (0.7)	5 (3.4)	38 (26.2)	5 (3.4)	
HIV serology	Not done	241 (14.3)	122 (50.6)	2 (0.8)	20 (8.3)	72 (29.9)	25 (10.4)	<0.001
	Negative	942 (55.8)	703 (74.6)	4 (0.4)	17 (1.8)	166 (18)	50 (5.4)	
	Positive	497/1419 (35)	330 (65.3)	0 (0)	49 (9.7)	97 (19.2)	29 (5.7)	
Sputum smear conversion £	Yes	1378/1471 (93.7)	1072 (77.8)	0 (0)	13 (0.9)	229 (16.6)	64 (4.6)	<0.001
	No	93/1471 (6.3)	82.8)	4 (4.3)	0 (0)	10 (10.8)	2 (2.2)	

Data are number (%) unless otherwise indicated; IQT, interquartile range; ETB, extra-pulmonary tuberculosis; PTB+, smear positive pulmonary tuberculosis; PTB-, smear negative pulmonary tuberculosis; *treatment success = cured+completed; £ at the end of intensive phase (applicable only to patients with smear positive tuberculosi

Time to tuberculosis treatment discontinuation

Antituberculosis treatment interruption in 210 patients (62.3%) occurred during continuation phase of treatment (Figure 1) and the median (IQR) duration to tuberculosis treatment discontinuation was 90 days (30-150). Tuberculosis treatment discontinuation was more likely to occur during continuation phase in those hospitalised during intensive phase than in those treated as outpatients [134 (74.9%) vs. 77 (48.7%), p<0.0001].

Determinants of treatment discontinuation

The probability of treatment discontinuation according to setting for intensive treatment and whether HIV test was done is depicted in Figure 2. At each time point during follow-up the probability of treatment discontinuation was always lower in patients hospitalized during intensive treatment phase than in those treated as outpatients during intensive phase. Similarly, discontinuation probability was always lower in patients with known status for HIV infection than in those with unknown status.

Cox regression models were used to examine predictors of treatment discontinuation using the observed follow-up duration for all participants in the overall cohort. In models adjusted for age and sex, hospitalisation during intensive phase reduced the risk of treatment discontinuation [hazard ratio (HR) 0.58, 95% confidence interval (95% CI): 0.46-0.72], while having PTB- [1.59 (1.15-2.21)] or unknown status for HIV infection [1.28 (1.17-1.41)] significantly increased the risk of treatment discontinuation. With further adjustment for those variables that were significant in basic models, ambulatory treatment during intensive phase and unknown status for HIV infection were the main determinants of antituberculosis treatment discontinuation (Table 2).

Table 2: Hazard ratio (HR) and 95% confidence interval (95% CI) for predictors of antituberculosis treatment discontinuation from Cox regression analysis

Characteristics	Basic models		Final models	
	HR (95% CI)	p	HR (95%CI)	p
Age (per year)	1.01 (1.00-1.01)	0.121	1.01 (1.00-1.01)	0.133
Sex (women vs. men)	0.96 (0.77-1.20)	0.723	0.99(0.79-1.23)	0.922
Hospitalised intensive phase	0.58 (0.46-0.72)	<0.0001	0.69 (0.54-0.89)	0.004
Residence (urban vs. rural)	0.92(0.67-1.26)	0.596	/	/
Clinical form of tuberculosis				
Positive smear (Reference)	1.00 (reference)		1.00 (reference)	
Negative smear	1.59(1.15-2.21)	0.005	1.25 (0.89-1.76)	0.192
Extra-pulmonary	0.99(0.73-1.34)	0.948	0.96(0.71-1.30)	0.780
Unknown status for HIV	1.28 (1.17-1.41)	<0.0001	1.65 (1.24-2.21)	0.0007

HIV, Human Immunodeficiency Virus; Basic models are adjusted for age and sex; and final models further adjust for all significant predictors in basic models. All Cox models are stratified by type of patients (i.e. new patient, retreatment) to account for difference in the duration of treatment.

DISCUSSION

In this study, we have assessed the incidence of antituberculosis treatment discontinuation and predictors of treatment discontinuation in a large cohort of patients treated for tuberculosis in a major referral centre in Cameroon. Treatment success rate was 68.4% and the cumulative incidence of treatment discontinuation was 20% overall and 19.4% among patients with smear-positive pulmonary tuberculosis. Discontinuation was most likely to occur during continuation phase of treatment and mostly among those treated as outpatients during intensive phase and patients with unknown status for HIV infection.

Treatment discontinuation in our study was based on the World Health Organisation's definition, which refers to a defaulter as a patient who's treatment has been discontinued for at least two consecutive months.[2] Compared with other few studies from Africa that have used similar definition, discontinuation rate in our cohort was similar to that reported by Shargie and co-workers in South Ethiopia, [11] lower that the rate found by Kaona and his colleagues in Zambia,[12] and higher than the rate by Tekle et al in Arsi in Ethiopia.[13] The above studies however differs from our study in a number of respects. The largest of those studies had 20% fewer patients than our cohort,[13] while the two others had less than ¼ the number of participants in our sample. [11, 12]. Furthermore, the two studies in Ethiopia involved only rural participants, with one based only on patients with smear-positive tuberculosis,[13], while the study in Zambia was based on a cross-sectional sample of urban dwellers.[12] In general, it has been recognised that using a stricter definition for treatment discontinuation results in much higher rates than when using the World Health Organisation's definition.[7]

Before the reorganisation of the fight against tuberculosis in Cameroon and roll out of the DOT strategy, antituberculosis treatment discontinuation rate was 31.7% among adults with PTB+ in the Yaounde Jamot Hospital.[14] Our study would tend to suggest that implementation of the DOT strategy has positively impacted on antituberculosis treatment discontinuation, with a 12% drop, although much efforts are still needed to bring the rate below 10%. The currently observed discontinuation rates are twice higher than the expected <10%, a requirement if the 85% antituberculosis treatment success rates prescribed in the millennium development goals are to be achieved.[15] Treatment discontinuation is a major challenge to programmes against tuberculosis, in the sense that non-adherence to antituberculosis treatment is associated with reoccurrence of the disease, preservation of reservoirs for micro-organism dissemination, emergence of drug resistant species of mycobacterium and increased tuberculosis related deaths.[16]

Two out of three patients who defaulted to treatment in our study did so during the continuation phase of tuberculosis treatment. Predominantly late antituberculosis treatment discontinuation (i.e. after the intensive phase) has also been confirmed in a systematic review.[17] This late discontinuation could partly be explained by the improved condition of the patient following the intensive phase of antituberculosis treatment. It is possible that patients who feel clinically better following this phase are less motivated to continue the treatment as they don't feel the need to do so.[16]

Tuberculosis treatment on the outpatient basis during the intensive phase and unknown status for HIV were the main determinants of treatment discontinuation found in our study. This would tend to suggest that direct daily supervision reduces the risk of drop out. This could be explained at least in part by the fact that those who receive antituberculosis treatment as in-patient during intensive phase also receive more education on the disease, the duration and outcome of care and are therefore more motivated to observe the treatment for the required duration. Two studies from Zambia and Ethiopia have reported that poor knowledge of antituberculosis treatment duration among patients was associated with high risk of treatment discontinuation.[12,13] Unlike our results however, another study in Spain found no protective effect of DOT on antituberculosis treatment discontinuation.[18] Patients with unknown status for HIV in our study are more likely to be those who did not consent for the test, since cost is not a constraint for HIV screening in our setting. It is possible that faced with the persisting invitation from healthcare personnel to accept HIV screening, some of the non-consenting patient would prefer to stop the antituberculosis treatment and walk away from the programme. The stigmatisation of people living with HIV is a reason for not-consenting for screening.[19,20] We can also speculate that antituberculosis treatment discontinuation is not the direct consequence of not-consenting for HIV screening, but the latter is just an indicator of the profile of those patients who will adhere less to any medical prescription. The effects of non-consenting for HIV screening on antituberculosis treatment discontinuation have not been investigated by other studies.[7] In agreement with a previous study in Cameroon,[14] and unlike findings from elsewhere,[11] age, gender and living and rural area were not associated with antituberculosis treatment discontinuation in our study.

This study used administrative data routinely collected for the monitoring of the national programme against tuberculosis. Because such data collection is not comprehensive, we were unable to investigate the effects of some potential determinants of antituberculosis treatment discontinuation such as patient's knowledge about tuberculosis, distance from Centre for Diagnosis and Treatment of tuberculosis to patient's residence, side effects of antituberculosis treatment and chronic alcohol abuse.[8, 9, 21-23] That no systematic effort was in place to trace patients who interrupted their treatment during the year of the study has probably introduced some biases in our ranking of patients according to the outcome of care. For instance, some patients who died in-between drugs collection visit would have been inappropriately classified as defaulters, particularly among HIV infected patients [24-26]. Our

study also has major strengths including the large population and inclusion of common forms of tuberculosis in this setting. Unlike recent studies on this topic in Africa, assessment of predictors of treatment discontinuation used robust methods to account both for the observed time to treatment discontinuation as well as differences in the duration of treatment for various forms of tuberculosis.[7] Those studies have either been based in patients with HIV and tuberculosis, or lacked information on status for HIV. Accordingly, none has investigated the effects of HIV testing on the outcome of care for tuberculosis; what our study has successfully done.

In conclusion, antituberculosis treatment discontinuation in this setting is relatively high, and tends to occur more during the continuation phase of the treatment. Patients who receive treatment on the outpatient basis during the intensive phase and those who do not consent for HIV screening are more likely to be those who will interrupt their antituberculosis treatment. Specific actions targeting these subgroups would likely improve the outcomes of care for tuberculosis in this centre. That patients treated entirely on ambulatory basis were less like to achieve good outcomes of care as compared to those hospitalised during intensive treatment phase, together with much higher discontinuation rates in the same setting in the pre-DOT era, all suggest that DOT strategy is associated with improved outcomes of care for tuberculosis in this setting. Prospective studies are needed to investigate other determinants of antituberculosis treatment discontinuation and refine the incidence data based on a more objective ascertainment of the outcomes of care.

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Authors' contribution – EWPY conceived the study, supervised data collection, co-analysed the data and drafted of the manuscript; APK contributed to study designed, data analysis, drafting and critical revision of the manuscript; CK supervised the data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	5,7
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	7,8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	/

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10,11
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

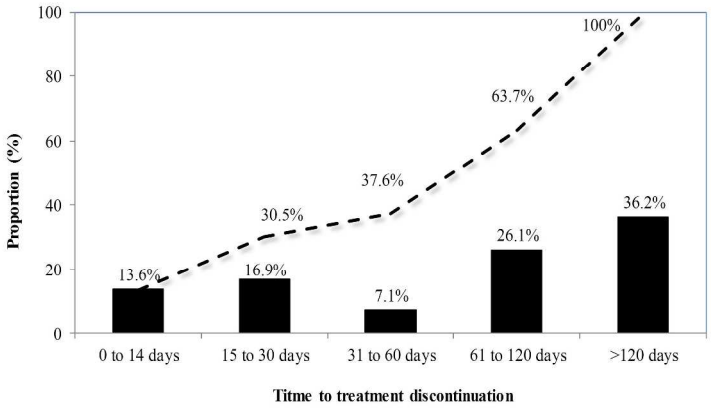

Figure 1 - Time to antituberculosis treatment discontinuation in 337 defaulters at the Yaounde Jamot Hospital in 2009

The vertical bars are proportional to the number of participants who stopped their treatment within the indicated time frame. The doted superimposed curve is for the cumulative number of defaulter across time. Within each time frame, the frame specific proportion of defaulters is shown, together with the cumulative proportion of defaulters up to that time limit.

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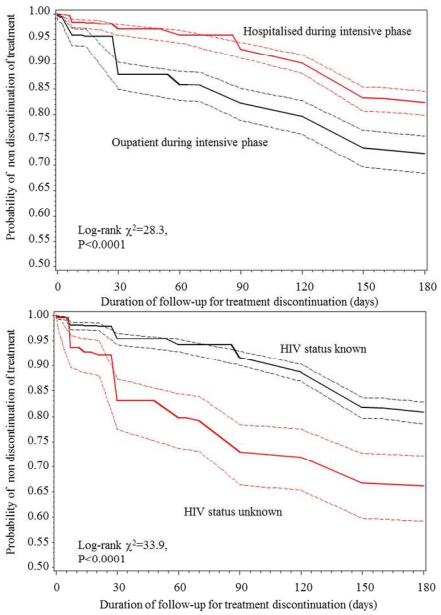

Figure 2 – Kaplan-Meier curves showing the probability of dropping out in subgroups defined by the setting of intensive treatment (upper panel) and knowledge of the status for HIV (lower panel)
For each figure panel, the log-rank test results comparing the probability between subgroups are also shown.

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