

# A review of compliance to anti tuberculosis treatment and risk factors for defaulting treatment in Sub Saharan Africa

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## Abstract

**Background:** The aim of this study is to assess anti TB treatment compliance and the factors predictive for poor adherence in Sub-Saharan Africa in the last 10 years.

**Methods:** We searched Medline for articles written in English using the terms: “Patient Compliance”[Mesh] OR “Medication Adherence”[Mesh]) AND “Tuberculosis”[Mesh] AND “Africa South of the Sahara”[Mesh].

**Results:** We identified 4 published manuscript and we included 1 study from the Infectious Diseases Institute. The proportion of patients defaulting varied from 11.3% (8) to 29.6%. Risk factors for defaulting treatment were: distance from the hospital, not being on the first course of TB medications, lack of repeated smears, unit transfer after the intensive phase, experiencing side effects, having no family support, poor knowledge about TB treatment, being more than 25 years old, and use of public transport.

**Conclusions:** This review reveals high rate of losses to follow up in Sub-Saharan Africa; the information currently available is however too heterogeneous to draw conclusions on the reasons for this high rate of defaulters. It is imperative to understand predictive factors for treatment default so that programs can implement specific measure to target the population at risk

## Key words:

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## Introduction

In 2007, nine million new cases of tuberculosis (TB) were diagnosed worldwide, and in the same year TB has killed 1.8 million people<sup>1</sup>.

In Sub Saharan Africa TB cases have markedly increased as a consequence of the HIV epidemic<sup>2,3</sup>. TB treatment usually consists of 2 phases: an intensive phase with a combination of four drugs for 2 months and a continuation phase with 2 drugs for 4 to 6 months. Drugs used for treatment and the duration of the intensive and continuation phases may vary within TB programs. In Africa the cure rate is lower than the global cure rate (54%-74% in Africa for smear positive pulmonary TB as compared to 84% world wide) due to adherence issues and the emerging of multi-drug resistant strains of *Mycobacterium tuberculosis*<sup>3</sup>.

Poor compliance and patients defaulting anti TB treatment contribute to the increase of multi-drug-resistant mycobacteria in the continent<sup>4</sup>.

Default is defined by the WHO as a treatment interruption of two consecutive months or more

after at least one month on treatment<sup>5</sup> but the definition of defaulters can vary within national programs.

The aim of this study was to assess anti TB treatment compliance and the factors predictive for poor adherence in Sub-Saharan Africa in the last 10 years.

## Methods

### Data sources

We searched Medline (<http://www.ncbi.nlm.nih.gov/mesh?itool=sidebar>) for articles using the terms: “Patient Compliance”[Mesh] OR “Medication Adherence”[Mesh]) AND “Tuberculosis”[Mesh] AND “Africa South of the Sahara”[Mesh]. We searched for articles written in English and we restricted the search to articles from the last 10 years (1999 – May 2009).

Conference abstracts were not searched.

### Selection criteria

Studies were excluded if the population was pediatric, if adherence described in the study regarded tuberculosis prophylaxis, if the adherence evaluated was to drugs other than tuberculosis drugs, if patients were lost to follow up between diagnosis and treatment start, if the research was conducted in

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geographical areas other than Sub Saharan Africa, if the primary endpoint was not treatment default, if studies were qualitative, and if articles were not found in HINARI.

One study from the Infectious Diseases Institute (IDI), Kampala, Uganda, was included; the data was presented at the Implementers Meeting 2009, Windhoek, Namibia, and although the publication did not fulfill the inclusion criteria described above, the author felt this data was valuable, as it was the only study on TB-HIV co-infected patients.

### Outcome measure

We assessed adherence to TB treatment as the proportion of patients defaulting anti TB drugs; we also looked at the factors predictive for non compliance to anti TB drugs.

### Data abstraction

Data abstraction was done by the author.

### Study characteristics

In this review we describe the following characteristics: reference, country and location (urban/rural), type of health facility, sample size, demographics of study patients (age, gender), study design and methods, definition of the primary

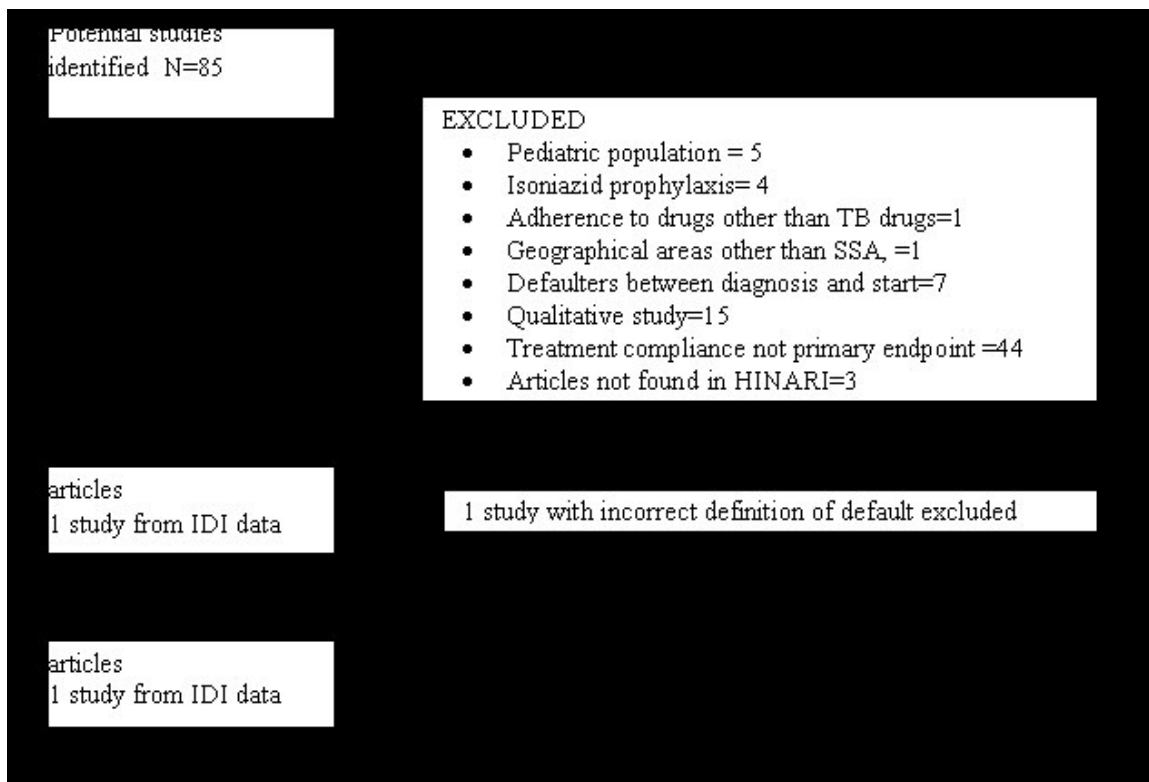
outcome (treatment defaulter), drugs used, use of direct observed therapy (DOT), proportion of patients completing anti TB treatment, timing of default, risk factors for defaulting treatment.

A meta-analysis was not performed because the studies were too heterogeneous and used different definitions of TB treatment defaulter.

### Results

We found a total of 85 published articles. After reviewing the abstracts, 80 papers were excluded: 5 assessed pediatric population, 4 regarded compliance to isoniazid and 1 to drugs other than anti TB drugs, 1 study was conducted in Israel, 15 described patients defaulting between diagnosis and treatment start, 15 were qualitative studies, in 44 treatment compliance was not primary endpoint, and 3 articles were not found in HINARI. We remained with 5 papers and data from the IDI study for a total of 6 studies (Figure 1). One of the papers was excluded after reading it because it had an incorrect definition of defaulters.

A summary of the studies including location, study design, sample size and authors' findings are presented in Table 1



**Table 1: A summary of the studies including location, study design, sample size and authors' findings**

Reference	Country Year Location Hospital	Sample size	Age Gender	Study design and methods	Definition of defaulters	TB regimen DOT
Nuwaha 1999	Uganda 1995 Rural District H and local HFs	1,783	Na Na	Retrospective cohort Data extracted from TB registers of 2 districts(M and R)	At least 4 w interruption	2 months S+E+R+H +P or S+H+T6 months T+H DOT in the first 2 months M: admitted for 2 m in the district hospital, then transferred out R: referred to the nearest clinic for both phases
Tekle B2002	Ethiopia 1997-99 Rural Local HF	1,367	48% between 15-29 years Males: 55%	Matched case control Cases=defaulters Controls= cured or treatment completed Hospital records and interviews	At least 4 w on treatment and >8 w interruption or cumulative period > 12w	2 months S/E +R+H+P 6 months T+E DOT
Kaona 2004	Zambia  Urban District H	382	-	Cross sectional study	Anybody that had stopped TB drugs	Not available DOT
Shargie EB 2007	Ethiopia 2002-04 Rural Local HF	404	Age: majority (27%) 25-34 Males: 56.9 %	Prospective cohort of smear positive TB patients	At least 4 w on treatment and > 8 w interruption	2 months S/E+ R+H+P 6 months H + E DOT
Katabira 2009	Uganda 2007 Urban Referral H	348	Median, IQR 36 (19-16) Males 52%	Retrospective cohort of HIV-TB co infected patients Data extraction from hospital records	Discontinuation of medication > 2 consecutive w within the first 6 months.	2 months E+R +H+P 6 months H+ENo DOT

DOT: directly observed therapy; HF: health facility; TB: tuberculosis; w: week; S: streptomycin; E: ethambutol; R: rifampicin, H: isoniazid; P: pyrazinamide; T: Thiocetazone

### Study characteristics

Two studies were from Uganda<sup>6,7</sup>, two from Ethiopia<sup>8,9</sup> and 1 from Zambia<sup>10</sup>. Three studies were conducted in rural areas<sup>6,8,9</sup> and two in an urban setting<sup>7,10</sup>; three studies were conducted in local health facilities<sup>6,8,9</sup>, one in a district hospital<sup>10</sup> and one in the referral national hospital<sup>7</sup>. Regarding the study design, two studies were retrospective cohorts<sup>6,7</sup>, one a prospective cohort<sup>9</sup>, one a cross-sectional study<sup>10</sup> and one a case control study<sup>8</sup>. The definitions of defaulters were different across the studies, with two

studies using the WHO definition<sup>8,9</sup> and three studies defining treatment defaulters with more stringent criteria<sup>6,7,10</sup>. In only one study DOT was not used as the strategy to deliver TB treatment and a treatment supporter was instead used to enforce adherence<sup>7</sup>.

### Proportion and timing of defaulting

The proportion of patients defaulting varied from 11.3% (8) to 29.6% (6). In four studies the majority of the patients defaulted treatment during the

continuation phase<sup>6,8-10</sup>, while in one study 59% of the patients were lost to treatment during the first 2 months intensive phase<sup>7</sup>. One study assessed seasonality of defaulting and found an association with the rainy season<sup>7</sup>.

### **Determinants of default**

Risk factors for defaulting treatment were: distance from the hospital<sup>7,9</sup>, not being on the first course of TB medications<sup>6</sup>, lack of repeated smears (6), unit transfer after the intensive phase<sup>6</sup>, experiencing side effects<sup>8</sup>, having no family support<sup>8</sup>, poor knowledge about TB treatment<sup>8</sup>, being more than 25 years old<sup>9</sup>, and use of public transport<sup>9</sup>.

### **Discussion**

This review shows overall a high proportion of patients defaulting TB treatment in Sub-Saharan Africa. Four out of the five studies report proportion of default above 20%<sup>6,7,9,10</sup> with 3 studies close to 30%<sup>6,7,10</sup>. The use of DOT<sup>6,8,9,10</sup> or the introduction of newer, better tolerated regimens in the last years<sup>7,9,10</sup> don't seem to improve this alarming rate of patients defaulting TB treatment.

The studies used different definition of defaulters. Of note, the studies that used the WHO definition of TB treatment defaulter, registered a lower rate of defaulting<sup>8,9</sup>.

The WHO definition, (being off drugs for more than 8 weeks after completing at least one month of treatment), is an operational definition to guide health workers in the decision of using a re-treatment/second line regimen if the patient comes back to the health facility after defaulting; three studies found this definition not enough stringent and formulated their own definition of treatment default, resulting in higher proportion of patients defaulting<sup>6,7,10</sup>.

In most of the studies the majority of the losses to follow up occurred during the continuation phase<sup>6,8-10</sup>; only the study by Katabira et al<sup>7</sup> shows that most of the patients default during the intensive phase. This could be explained by the fact that this study was conducted in a clinic in the national referral hospital; many patients discharged from the wards, if HIV positive, are referred to the clinic for treatment. It is likely that the patients that come from other areas, after starting the treatment and getting healthier, move back to their original location without informing the clinicians and getting referral forms.

Four studies looked also at risk factors for treatment default<sup>7,7,9</sup>; each study included different characteristics, therefore the factors identified are heterogeneous. A big role in this rate of patients lost to follow up is distance, money for transport or logistic in referring and transferring patients<sup>6,7,9</sup>; other challenges in adhering to treatment are side effects, poor knowledge of the disease and insufficient family support<sup>9</sup>.

This study has several limitations. The search was restricted to English written papers and abstracts of conferences were not searched. After searching, studies that were not available through HINARI were also excluded; we attempted to obtain the manuscripts from the John Hopkins University Library with no success.

Also, due to the heterogeneity of the TB programs, the study designs, and findings on risk factors these results cannot be generalized. There is need for new research studies with the main aim of identifying risk factor for defaulting TB treatment.

### **Conclusion**

This review of studies on patients' adherence to TB treatment reveals high rate of losses to follow up in Sub-Saharan Africa; the information currently available is too heterogeneous to draw conclusions on the reasons for this high rate of defaulters. It is imperative to understand predictive factors for treatment default so that programs can implement specific measure to target the population at risk, since other strategies such simpler treatment regimens and DOT have not given enough satisfactory results. Since distance from the clinics plays a big role in influencing adherence to TB treatment, national programs should consider making drugs more widely available, by either providing the TB treatment to smaller health centers, or organizing mobile TB clinics, especially in rural areas.

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### **References**

1. GlobalHealthFact.org. Available at:<http://www.globalhealthfacts.org/topic>. [Accessed 1<sup>st</sup> of July 2009].
2. WHO (2005) WHO declares TB an emergency in Africa. Press release. Available at: <http://>

- [www.who.int/mediacentre/news/releases/2005/africa\\_emergency/en/index.html](http://www.who.int/mediacentre/news/releases/2005/africa_emergency/en/index.html) (accessed 1 June 2009).
3. WHO (2007). Global tuberculosis control-surveillance, planning, financing. Available at: [http://www.who.int/tb/publications/global\\_report/2009/en/index.html](http://www.who.int/tb/publications/global_report/2009/en/index.html). Accessed July 15 2009
  4. Borgdorff, Floyd K and Broekmans JF. Intervention to reduce tuberculosis mortality and transmission in low- and middle-income countries. *Bulletin on the World Health Organization* 80, 217-227.
  5. WHO 2003. Treatment of tuberculosis. Guidelines for national programs. Available at: [http://www.who.int/tb/publications/cds\\_tb\\_2003\\_313/en/index.html](http://www.who.int/tb/publications/cds_tb_2003_313/en/index.html). Accessed July 15 2009.
  6. Nuwaha, F. Control of tuberculosis in Uganda: a tale of two districts. *Internal Journal of Tuberculosis and Lung Diseases* 1999; 224-230.
  7. Katabira C, Castelnuovo B, Bhushan A, Le E, Kambugu A, and Manabe Y. Examining Drug Default for Treatment of Tuberculosis in an Urban HIV Clinic in Uganda. Implementers meeting 2009. Windhoek, Namibia.[117]
  8. Tekle B, Mariam DH, and Ali A. Defaulting from DOTS and its determinants in three districts of Arsi Zone in Ethiopia. *Internal Journal of Tuberculosis and Lung Diseases* 2002; 573-579.
  9. Shargie EB, and Lindtjorn, B. Determinants of treatment adherence among smear-positive tuberculosis patients in Southern Ethiopia. *PLOS medicine* 2007; 4: 280-287 [PubMed](#) .
  10. Kaona ADF, Tuba M, Siziya S, and Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. *BMC Public Health* 2004; 4: 68.