Timing of default from tuberculosis treatment: a systematic review

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Summary

OBJECTIVES To provide a systematic assessment of the timing of default from tuberculosis (TB) treatment which could help to quantify the potential contribution of new shorter duration TB drugs to global TB control.

METHODS We performed a systematic review following QUOROM guidelines. MEDLINE was searched from 1998 to the present using the terms *TB* and *default* or *drop-out* or *compliance* or *adherence* and *therapy*. A total of 840 articles were returned. A further detailed manual review selected 15 randomized trials and observational studies that reported timing of drop-out and focused on developing countries.

RESULTS The selected studies comprised randomized controlled trials, retrospective record reviews, and qualitative assessments and spanned 10 countries. Both directly observed treatment (DOT) and non-DOT programs were represented. Thus results were highly heterogeneous and not statistically aggregated. Data suggest, but do not conclude, that the majority of defaulters across the studies completed the 2-month intensive phase of treatment.

CONCLUSIONS There is insufficient high-quality comparable information on the timing of default from TB treatment to permit any firm conclusions on trends in default. However, a substantial proportion of defaulters appear to leave treatment in the later stages of the current 6-month regimen, suggesting that new TB chemotherapeutic agents which can reduce the length of treatment have the potential to improve global TB treatment success rates.

keywords tuberculosis therapy, directly observed treatment, default, time of default, temporal trends

Introduction

Tuberculosis (TB) is a global health emergency, killing nearly 1.6 million people each year, mostly in low- and middle-income countries (Stop-TB Partnership 2006). TB cases in Africa have more than quadrupled since 1990, as a result of co-infection with HIV (WHO 2005). The World Health Organization (WHO) – recommended treatment strategy, directly observed treatment or direct observation (DOT), which forms the basis of the Stop TB Strategy, is a 6- to 8-month regimen with a combination of anti-TB agents (Lienhardt & Ogden 2004). This regimen is also known as short-course chemotherapy (SCC). The first 2 months of SCC, known as the intensive phase, generally involve a combination of four drugs and the 4- to 6-month follow-up period, known as the continuation phase, involves two drugs. Both the drugs used in treatment and the duration of the intensive phase may vary within SCC programs.

While cure rates with this combination under optimal conditions approach 95%, actual global treatment success in 2005 was 84% (Borgdorff *et al.* 2002; WHO 2007). This figure is much lower in some regions: In Africa, the overall cure rate for smear-positive TB was 74% and as low as 54% in some areas (WHO 2007.) Further, *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, or multi-drug resistant TB, is now diagnosed in an estimated 4.3% of all new and previously treated TB patients (Zignol *et al.* 2006).

A major contributor to both treatment failure and the rise of multidrug-resistant TB is inadequate and incomplete treatment (Borgdorff *et al.* 2002; Sharma & Mohan 2006). While structural factors such as interruptions in drug supply play a role, patient default or drop-out from TB treatment is one of the most important reasons for not completing treatment (Borgdorff *et al.* 2002). Default is defined by the WHO as a treatment interruption of two consecutive months or more and is often used

synonymously with drop-out from treatment before completion (WHO 2003). One of the first reviews of adherence to TB therapy published in 1989 found non-adherence rates of 20–50% (Cuneo & Snider 1989). More recent estimates of default rates in DOT programs range from 6% to 30% (Jaiswal *et al.* 2003; Balasubramanian *et al.* 2004; Kaona *et al.* 2004).

In 2006, the Stop TB Partnership launched the Global Plan to Stop TB 2006–2015 at the World Economic Forum in Davos. This plan calls for a series of measures to help eliminate TB as a public health threat, including new drugs that will shorten the treatment course. After decades of little innovation in TB drug development, today there are more than 40 compounds in the TB drug pipeline at various stages of development (Stop-TB Working Group on New Drugs 2006). The first new TB drug in 40 years is expected to be introduced by 2010 and a 1- to 2-month treatment regimen may become available in the by 2015 (Stop-TB Partnership 2006). If a shorter regimen can substantially decrease default and improve treatment success, it could make an important contribution to reducing the global health burden of TB. Understanding the timing of default in current TB treatment can help quantify the size of this contribution. While much has been written on the determinants of default, there has been no systematic review of timing of default from TB treatment programs. Much of the TB program literature notes that patients may be inclined to leave TB treatment when they begin to feel markedly better, which implies a steep drop-off after 2 months or the intensive phase of therapy (Healthlink Worldwide 1999; Tissera 2003; International Union Against Tuberculosis and Lung Disease 2007).

The aim of this paper is to examine evidence from published literature on the timing of default from TB therapy in developing (low- and middle-income) countries and, where possible, to assess the determinants of default at different points over the treatment course.

Methods

This was a systematic review following QUOROM guidelines to the extent possible given the dearth of data on this topic (Moher *et al.* 1999). Medline was searched for peer-reviewed articles published since 1998 using combinations of the terms *TB* and *default* or *drop-out* or *compliance* or *adherence* and *therapy*. A total of 840 articles were returned from this search strategy and the abstracts were reviewed by two of the authors. Papers written in languages other than English, those from high-income countries and those in which default was not the primary study endpoint were excluded. The remaining 111 articles were manually reviewed by two of the authors and

papers that presented any temporal data on TB treatment default, such as mean time to default and default by day, week, or month of treatment were selected. A variety of criteria for defining TB default were accepted (e.g. non-completion of treatment, an interruption of 2 or more months). The types of papers excluded from the analysis were analyses of TB treatment options, TB treatment guidelines, articles that focused on outcomes other than adherence, reports from national TB programs, articles focusing on default rates or determinants of default without mention of timing of default, and articles focusing on antiretroviral rather than TB treatment adherence. Further, articles that compared default from different length regimens were excluded when they did not present timing of default.

Given the limited number of studies reporting temporal data on default, all study types identified in the final stage of selection (from randomized controlled trials to retrospective chart reviews) were included in the analysis. While we explicitly comment on study quality and generalizability below, quality was not explicitly used as a criterion to deselect studies. Given that in most of the studies selected for final review timing of default was not the primary outcome of interest, we did not explicitly explore the possibility of publication bias. While it is possible that studies with extremely high default rates or those not finding a difference between default-averting interventions might be less likely to be published, there is no *a priori* reason to believe that the timing of default in those programs would be systematically different from published studies. Two major types of publications were identified: studies reporting temporal trends in default and those reporting the mean timing of default from therapy. Aggregate estimates of the time of default or mean default rates by week/month of therapy were not calculated given the large heterogeneity of study populations, therapeutic approaches and study designs. Instead the study results were summarized in a table and a figure showing individual study estimates.

Results

The review identified 15 papers that reported the timing of default from TB treatment (Figure 1). The range of study designs represented is shown in Table 1. Table 2 summarizes the design, sample size and findings from the selected papers. It also notes whether or not the patients were enroled in programs that administer DOT. Reporting of timing of default varied substantially among the studies even within the two categories. Default rates were variously reported as either cumulative or incremental percentages of all patients or only of defaulters. These results
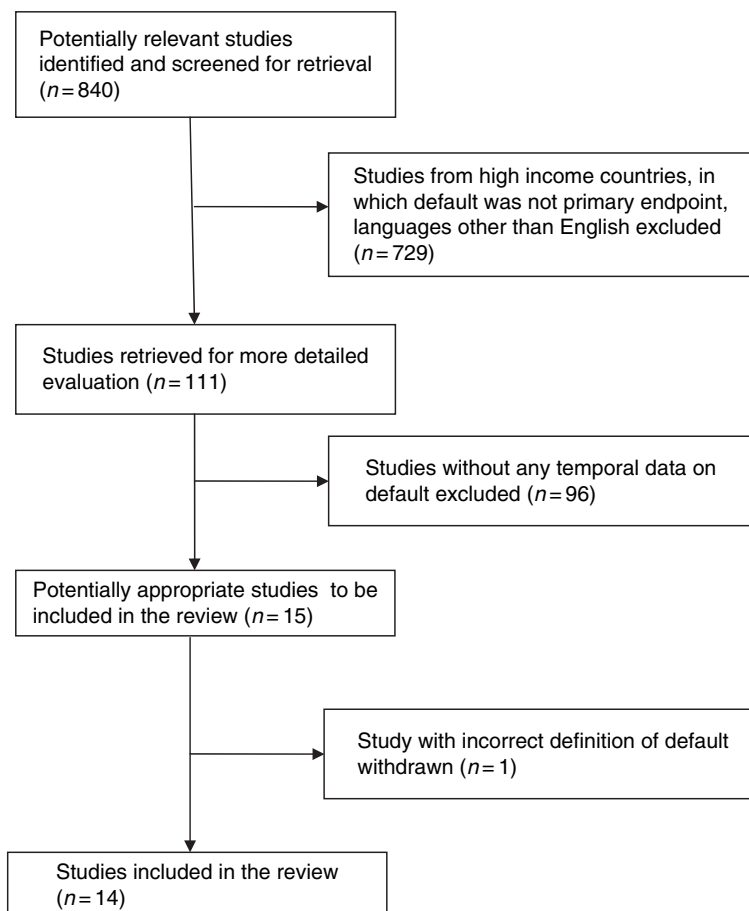
Figure 1 Trial flow.

are reported as stated in the study with an explanation of the method of reporting. None of the studies focused on determinants of default specifically at different durations of treatment in the treatment.

Eleven of the studies reported on DOT programs. These were generally situated within National TB Programs,

Table 1 Study types in final review

Study design (number of studies)

Prospective
  Observational studies without a randomly selected control
    group (2)
  Randomized controlled trials of strategies to improve adherence
    (1)
Retrospective
  TB program record reviews (one or more clinics) (6)
  Case–control studies comparing characteristics of defaulters and
    non-defaulters (3)
  Cross-sectional surveys of former TB patients (1)
  Qualitative semi-structured interviews with defaulters (1)

which are TB control programs run by national governments that generally follow standard international treatment protocols. The three non-DOT studies were from Singapore, India and Pakistan. One of these was conducted within a government treatment program (Chee *et al.* 2000). Uplekar *et al.* reviewed adherence among patients of private physicians in Maharashtra, India and Liefooghe *et al.* assessed the performance of the TB program in a mission hospital in Sialkot, Pakistan (Uplekar *et al.* 1998; Liefooghe *et al.* 1999).

All of the studies evaluated adult TB patients and most included a broad range of patients including treatment naïve, previously treated, smear positive, smear negative and extrapulmonary TB. Two studies (Santha *et al.* 2002; Holtz *et al.* 2006) involved MDR-TB patients and two studies included HIV+ patients (Lienhardt *et al.* 1998; Connolly *et al.* 1999).

The endpoints of interest in the majority of the reviewed publications were determinants or predictors of default, with temporal data on default reported as a secondary

Table 2 Summary of studies reporting temporal data on default from TB treatment

References	Country	Study population	DOT	Sample size	Methods	Overall default rate	Timing of default
Chee *et al.* (2000)	Singapore	New and previously treated smear-positive, smear-negative, and EPTB patients	No	44	Case–control study with review of records of patients attending a TB control unit over 1 year, with follow-up of 1 year; default defined as failure to attend treatment appointments	N/A – all defaulters	Incremental rates of default (as % of all defaulters): 30.2% of defaulters defaulted within 2 months, 27.9% between 2 and 4 months of treatment, and 41.9% after 4 months
Connolly *et al.* (1999)	South Africa	New and previously treated smear-positive, smear-negative, EPTB and HIV patients	Yes	3610	Extraction of data from the TB control program database over a 5-year period; default reported as failure to complete treatment within 7 months of starting	17.0%	Incremental rates of default (as 5 of all patients): Approximately 1% rate of treatment interruption for each 2-week period after the initial 2–3 weeks of hospitalization
Dodor (2004)	Ghana	New and previously treated smear-positive, smear-negative, and EPTB patients	Yes	1061	Retrospective review of TB clinic records over 2 years for defaulters and non-defaulters and their characteristics; default defined as drop-out from treatment	13.9%	Cumulative rates of default (as % of defaulters): 42.9% defaulted by 2 months and 96.4% de faulted by 5 months. (Rates at other time points estimated from graph) Mean time of default was 3.4 months.
Holtz *et al.* (2006)	South Africa	MDR-TB defaulters and non-defaulters	Yes	370	Case–control study over a 2-year period with data collection from TB registers for treatment outcome and administration of a patient questionnaire; default defined as 2 or more consecutive months of treatment interruption	N/A – all defaulters	Default rates (as % of all defaulters): 30% of defaulters defaulted in the first 6 months of treatment, 31% defaulted between 6 and 12 months, and 39% defaulted after 12 months
Kaona *et al.* (2004)	Zambia	New and previously treated TB patients	Yes	382	Cross sectional study with a household survey of former TB patients; patients identified over a 6-month period; default defined as dropping out before completing 8 months of treatment	29.8%	Estimated incremental rates of default (as % of all defaulters): 7.5% in the first month, 27% in the second month, 22% in the third month, 16% in the fourth month, 15% in the fifth month, and 8% in the sixth month.
Liefooghe *et al.* (1999)	Pakistan	New and previously treated smear-positive, smear-negative, and EPTB patients (non-DOT)	No	1019	Randomized controlled prospective trial of counselling to improve adherence; default defined as not collecting drugs for 2 months or more over 1 year of treatment	46.6% treatment group; 53.6% control group	Cumulative default rates (as % of all patients): Estimated 22% default by 2 months, thereafter linear defaulting to 1 year (control group)

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Table 2 (*Continued*)

References	Country	Study population	DOT	Sample size	Methods	Overall default rate	Timing of default
Nyirenda *et al.* (2003)	Malawi	New and previously treated smear-positive, smear-negative, and EPTB patients	Yes	3761	Prospective comparative operational study; default defined as dropping out before completing 8 months of treatment	7.6–19.4%	Cumulative rates of default (as % of all patients):2.4% by 2 months and 7.6% by 8 months; another 8.1% and 11.9% had unknown outcomes at 2 and 8 months, respectively
Salaniponi *et al.* (2003)	Malawi	New and previously treated smear-positive, smear-negative, and EPTB patients	Yes	6634	Review of TB register; default defined as dropping out before completing 8 months of treatment	7–14%	Cumulative rates of default (as % of all patients): 2% by 2 months and 7% by 8 months, another 5% and 7% had unknown outcomes (cards lost) at 2 and 8 months, respectively
Tekle *et al.* (2002)	Ethiopia	New smear-positive, smear-negative, and EPTB patients	Yes	1367	Case–control study with review of patient records over a 30-month timeframe; Default defined as more than 8 consecutive weeks or 12 total weeks of treatment interruption for patients after at least 4 weeks of treatment	11.3%	Incremental rates of default (as % of all defaulters): 18.7% of defaulters defaulted between weeks 4–8; 31% between weeks 9–12; 15.5% between weeks 13–16; 18.7% between weeks 17–20; 9% between weeks 21–24; and 7.1% between weeks 25–28
Uplekar *et al.* (1998)	India	New pulmonary TB patients (non-DOT)	No	173	Prospective study of patients seeking care from private providers; treatment completion defined as completing 80% of 6-month short course therapy	41%	Estimated cumulative default rates (as % of all patients): 12% of patients defaulted by 2 months, 19% by 3 months, 22% by 4 months, 35% by 5 months and 41% by 6 months
Mean default rate studies							
Jaiswal *et al.* (2003)	India	New and previously treated smear-positive, smear-negative, and EPTB patients	Yes	40	Retrospective chart review, interviews, focus groups; timing of default data collected from 40 defaulting patients via interviews	N/A – all defaulters	Mean time to default: 6 ± 3 weeks after beginning chemotherapy
Lienhardt *et al.* (1998)	The Gambia	New and previously treated smear-positive, smear-negative, EPTB and HIV patients	Yes	1588	Retrospective review of records from the national TB Control Program for treatment outcome over 2 years; default defined not completing treatment	13.3%	Mean time to default among smear-positive patients: 85.4 days

Table 2 (*Continued*)

References	Country	Study population	DOT	Sample size	Methods	Overall default rate	Timing of default
Santha *et al.* (2002)	India	New and previously treated smear-positive, smear-negative, MDR-TB and EPTB patients	Yes	676	Retrospective review of treatment cards along with patient interviews over a 12-month study period; default not defined	19.0%	Median time to default was 66 days; 76% of defaulters defaulted at the end of the intensive phase of treatment
Wares *et al.* (2003)	Nepal	TB defaulters from sample of new smear-positive or smear-negative patients	Yes	30	Semi-structured interviews with non-adherent patients in short-course and long-course regimens over 3 months; non-adherence defined as over 60 days late in collecting medication	N/A – all defaulters	Mean time to default: 80 days (no significant difference between short-course and long-course)

outcome. Ten of the papers reported temporal trends in default (category 1). Four reported mean time of default as their primary outcome (category 2). One additional paper, which defined default as after diagnosis but before treatment, was excluded from analysis (Buu *et al.* 2003). The findings on timing of default from the 14 studies selected are presented in Table 2 below.

Temporal trend studies

Studies that presented temporal trends in default encompassed a wide variety of methods. Three were retrospective data reviews in which TB registers were analysed for rates and timing of default (Connolly *et al.* 1999; Salaniponi *et al.* 2003; Dodor 2004). Three were case–control studies that compared defaulters and non-defaulters using data from TB registers or interviews (Chee *et al.* 2000; Tekle *et al.* 2002; Holtz *et al.* 2006). Three studies used a prospective design: Nyirenda *et al.* (2003) and Uplekar *et al.* (1998) followed patients beginning TB therapy and Liefooghe *et al.* (1999) performed a randomized-controlled trial of a counselling intervention to improve adherence. The remaining study in this category was a household survey of former TB patients and included both defaulters and non-defaulters (Kaona *et al.* 2004).

The range of findings from the temporal trend papers is shown in Figure 2. This figure includes studies that presented at least one default data point within the first 6 months of treatment – the typical length of standard short-course therapy. The rates in Figure 2 represent cumulative default over 6 months in the defaulter population. Study results were converted to cumulative default rates where necessary to permit comparison. Between 18.7% and 49.3% of defaulters left treatment before the end of 8 weeks (nine studies). By the end of 12 weeks the cumulative default rate in the five studies that reported 12-week results ranged between 46.3% and 61.0%, indicating that a substantial proportion of patients drop out in the later stages of treatment. One of the temporal trend studies, Holtz *et al.* (2006), which focused on MDR-TB patients and thereby longer treatment regimens, reported default rates only for six, 12 and >12 months and so is not included in this figure.

Mean time of default studies

Four studies presented the average time of default from TB treatment as their primary or only temporal finding (Lienhardt *et al.* 1998; Santha *et al.* 2002; Jaiswal *et al.* 2003; Wares *et al.* 2003). One additional study that focused on temporal trends and was discussed above, Dodor (2004), also included data on mean time of default. Three of the five studies reporting mean timing of default involved reviews of
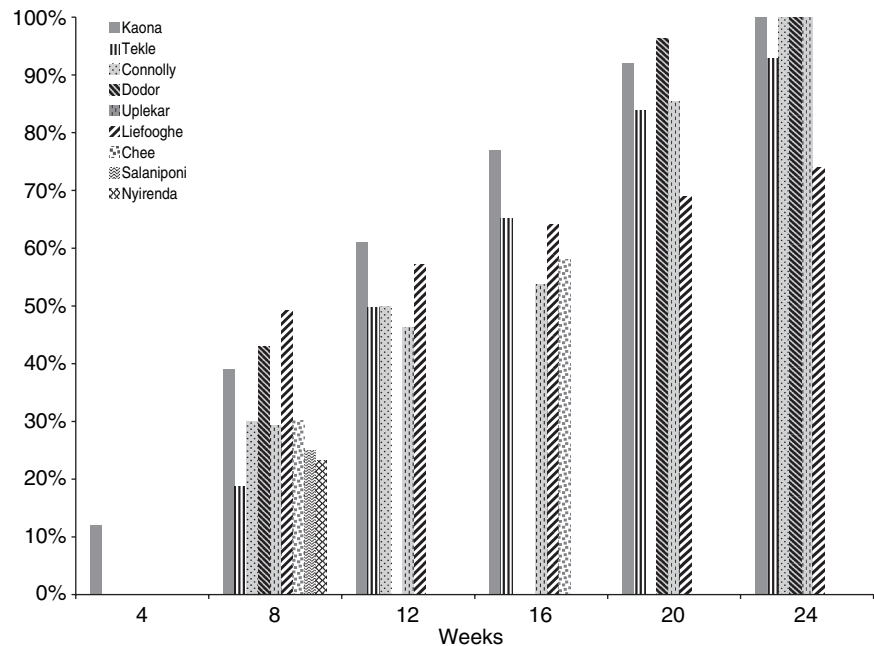
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Figure 2 Temporal trends in cumulative rates of default in published studies.

TB registers and treatment records and were complemented by interviews to identify the timing and reasons of default from treatment (Santha *et al.* 2002; Jaiswal *et al.* 2003; Wares *et al.* 2003). The remaining two were based on record review alone (Lienhardt *et al.* 1998; Dodor 2004). The timing of default across the four studies ranged from 6.0 weeks (Jaiswal *et al.* 2003) to 13.6 weeks (Dodor 2004).

Determinants of default

The studies did not in general discuss determinants of default at different points of the treatment regimen; rather factors predisposing to default were reported as a separate endpoint and applied to all defaulters regardless of time of default. Thus it was not possible to assess determinants of default at different stages in treatment.

Discussion

Default has been linked to the length and complexity of treatment as well as to the fact that most patients feel markedly better after the first or second month of treatment (Demissie & Kebede 1994; Jaiswal *et al.* 2003; Bam *et al.* 2006; Shargie & Lindtjorn 2007). There is thus a perception that a substantial proportion of patients leave treatment in the early phase. Because of the relatively few studies reporting timing of default and the wide heterogeneity in study design among those that do, we were unable to compute an aggregate estimate of temporal trends in

default. However, visual inspection of the available data from the studies reviewed here, which included randomized-controlled trials, retrospective record reviews and qualitative interviews with defaulters, suggests that the majority of default occurred after the 2-month intensive phase.

In the four studies the reported mean time of default, the number of weeks that patients stayed in treatment before defaulting ranged from 6.0 to 13.6. Two of these studies, Jaiswal *et al.* (2003) and Wares *et al.* (2003), were relatively small (*n* = 40 and *n* = 30 respectively) and had wide confidence intervals. The remaining two studies (Lienhardt *et al.* 1998 and Santha *et al.* 2002) reported results of retrospective record reviews and were relatively comparable (large, DOT programs, similar patient profiles). Their reported default times were 85.4 days (SD 7.1 days) (Lienhardt) and 66 days (no SD reported) (Santha). Santha and colleagues' figure is the median time whereas the Lienhardt figure is the mean time; the latter is therefore more sensitive to outliers. These two studies appear to support the notion that defaulters tend to leave treatment after the first 2 months.

Only two of the studies reviewed, Lienhardt *et al.* (1998) and Connolly *et al.* (1999) included patients co-infected with HIV and these did not report the impact of HIV on timing of default. Their findings on the impact of HIV on overall default from TB treatment are contradictory, with Lienhardt *et al.* reporting no impact of HIV on default and Connolly *et al.* reporting that HIV positive status was the

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only significant factor in predicting default. The studies had relatively comparable designs (retrospective TB register review) and were both large. Other work appears to support an association between HIV co-infection and default from TB treatment (Johnson *et al.* 2000; Rocha *et al.* 2003; Daniel *et al.* 2006).

Two of the studies included patients with MDR-TB of which one (Santha *et al.* 2002), did not examine temporal trends in withdrawal among the MDR group. The second study, by Holtz *et al.* (2006), was a case–control study of defaulters and non-defaulters and found that default was approximately evenly distributed between three time periods: 1–6 months, 6–12 months and after 12 months. Default rates before 6 months are not broken out, making comparison with non-MDR patient studies impossible. Three of the 14 studies were conducted in non-DOT programs (i.e. supervised and non-supervised administration of treatment) (Uplekar *et al.* 1998; Liefooghe *et al.* 1999; Chee *et al.* 2000). Overall default rates were 41% in Uplekar *et al.* (1998) and 53.6% in Liefooghe *et al.* (1999) The study by Chee *et al.* (2000) was a case–control study among defaulters. The timing of default in these three studies was similar to the timing of default in DOT programs.

Our findings have to be interpreted in light of several limitations. The first and most important issue is the limited generalizability of these findings due to limited and heterogeneous data. We found that there is little available research on temporal aspects of default from TB treatment. The majority of the trials reviewed here had other endpoints as their main focus and only reported temporal data as a secondary finding. The vast majority of studies returned by the search strategy focused on determinants of default and on different rates of default in different regimens with no mention of timing of default. Furthermore, the studies that did report on timing of default were highly heterogeneous. Six different study designs were used in the papers reviewed, ranging from semi-structured qualitative interviews with defaulters to randomized-controlled trials of adherence-promoting interventions. In addition, patient and program profiles differed across the studies. Hospital-based and outpatient, private and public sector and DOT and non-DOT programs, and programs with and without previously treated TB patients were represented. As a result, no statistical aggregation of study results was possible. New rigorous research focusing directly on temporal trends in default is essential to shed light on the question of timing of default. Secondly, some of the default time results were presented graphically and thus several of the values presented in Table 2 and in Figure 2 may not be precise as they are derived from graphs rather than tables in the original papers (indicated

in Table 2). Lastly, some of the research is now nearly 10 years old and treatment approaches, particularly as regards adherence promotion, have changed over the past decade. New, ideally prospective, studies across DOT programs with sufficient power to permit subgroup analysis (previously treated patients, HIV-positive patients, extra-pulmonary TB patients) are urgently needed to clarify the timing of default. Another important issue for future research is the degree to which timing of default varies with overall default rates.

Conclusions

This review of the literature suggests that there is a large gap in our understanding of the timing of default from TB treatment in the developing world. Current studies are too few and disparate to permit robust inference about temporal default trends. Knowledge of patterns of default could lead to better-focused adherence promotion strategies and better forecasts of the impacts of new, shorter therapies. For example, Salomon *et al.* (2006) calculated that assuming 6% default in the first 2 months of treatment, a 2-month regimen could reduce TB incidence 14% more than today's 6-month regimens. Evaluating the accuracy of this estimate requires more robust measures of the rate of default within the first 2 months. Using evidence-based adherence promotion measures to reduce default in the early months, together with accelerating development of new agents that can reduce treatment time are key components of the strategy to reduce treatment failure and the rising incidence of resistant TB – two key challenges to global TB control today.

Acknowledgements

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