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Association between patient and programmatic characteristics and smear conversion among pulmonary TB patients in South Africa

By

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Association between patient and programmatic characteristics and smear conversion among pulmonary TB patients in South Africa

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Abstract

Association between patient and programmatic characteristics and smear conversion among pulmonary TB patients in South Africa

By Emily Wong

BACKGROUND: South Africa has one of the worst tuberculosis epidemics in the world, with disease rates more than double those observed in other countries. Evaluation by sputum smear microscopy after the intensive phase of treatment is commonly used as a predictor for treatment outcome. However, little is known about patient and programmatic factors that may influence conversion after the intensive phase or at the end of treatment.

STUDY OBJECTIVES: To identify patient and programmatic factors that influence non-conversion after the intensive phase of treatment and the association between non-conversion and other factors and a poor final treatment outcome.

METHODS: In this retrospective cohort study sociodemographic, clinical, and TB program management information data previously collected as part of a national systematic evaluation aiming to evaluate the TB surveillance system and Electronic TB Register (ETR) system in South Africa was used to evaluate the risk of non-conversion after the intensive phase of treatment, and poor outcome at the end of treatment.

RESULTS: The only factor found to be associated with non-conversion after the intensive phase was treatment in a rural setting. Factors found to be associated with poor outcome were: male gender, treatment in a rural setting, and receiving directly observed therapy (DOT) during the intensive phase.

CONCLUSIONS:
These findings add to a growing body of literature that identifies simple predictive factors that could be used by TB control programs to identify patients who are less likely to convert after the intensive phase and have poor treatment outcomes. The results of this study indicate a need for greater monitoring of patients treated in rural settings during both the intensive phase and the continuation phase of treatment. Additionally, males may need to be monitored more closely during the continuation phase of treatment. Further, more emphasis should be placed on better adherence and management of DOT. Future studies should emphasize the need for complete follow-up results at the end of the intensive phase.

Association between patient and programmatic characteristics and smear conversion among pulmonary TB patients in South Africa

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INTRODUCTION

The global burden of death and disease cause by tuberculosis (TB) is immense and concentrated in low income countries. In 2010, an estimated 8.8 million new cases occurred with 1.1 million deaths worldwide with an additional 0.35 million deaths from Human immunodeficiency virus (HIV) associated TB (1). About 95% of cases and 98% of deaths occur in developing countries. Africa accounts for 24% of the world's case notifications. South Africa has one of the worst tuberculosis epidemics in the world, with disease rates more than double those observed in other countries (2). In 2010 South Africa reported an incidence of 490,000 cases, reflecting a rate of 981 cases per 100,000 and a prevalence of 400,000 cases reflecting a rate of 795 cases per 100,000 (1). The situation is further complicated by high incidence of HIV. In 2010, 54% of tuberculosis cases in South Africa were co-infected with HIV.

Sputum smear microscopy for acid-fast bacilli (AFB) is currently the most important and widely available technique for the diagnosis of pulmonary TB in low and middle income countries (3). AFB utilizes stained smears of sputum specimens from symptomatic patients to examine the presence of *Mycobacterium tuberculosis* microscopically. AFB detects those cases that are epidemiologically most important, i.e., those that are most likely to transmit infection to their close contacts. It is also relatively inexpensive, can be accomplished under field conditions, can be done quickly, and is highly specific (4). The specificity of AFB in the diagnosis of pulmonary TB is over 98% thus, more aggressive diagnostic tests are not normally necessary (5).

A six month long "short-course" chemotherapy is currently the most effective treatment for most patients with tuberculosis, and direct observational therapy, short-course (DOTS) helps many patients to complete the 6 month or more treatment regimen (6). A new case refers to a patient who has never had treatment for tuberculosis or who has taken antituberculosis drugs for less than one month. A retreatment case is one that was previously treated for tuberculosis, undergoing treatment for a new episode, usually of bacteriologically-positive tuberculosis. The standard short course treatment for a new TB patient begins with the intensive phase where isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) are taken daily for two months (7). TB treatment is monitored by periodic sputum examinations after treatment initiation (4). Both the International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organization (WHO), TB treatment guidelines recommend that control programs evaluate sputum smears after this initiation phase (two months for a new patient and three months for retreatment case) for conversion to a negative AFB sputum smear (8, 9). Conversion to a negative AFB sputum smear allows for assessment of the effectiveness of treatment and determines whether or not the treatment regimen can be switched to the continuation phase. If conversion is not achieved the patient is given an additional month of intensive phase treatment (10). At the continuation phase the prescription changes to isoniazid and rifampicin alone for another four months (for new cases) or 6 months (for retreatment cases).

Smear examination is performed again at the last month of the prescribed treatment course (at month 5 for new patients and month 7 for retreatment patients) to determine final treatment outcomes. The WHO has set international standard definitions

for determining treatment outcomes based on smear microscopy (1). South Africa has also adopted these definitions in identifying outcomes for patients (11). The six outcome definitions of interest are: cured, completed, died, failed, defaulted, and transferred. Cured is a patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion. Completed treatment is a patient who completed treatment but did not meet the criteria for cure or failure. This definition applies to pulmonary smear-positive and smear-negative patients and to patients with extrapulmonary disease. Died is a patient who died from any cause during treatment. Failed is a patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment. Defaulted is a patient whose treatment was interrupted for 2 consecutive months or more. Transferred out refers to a patient who transferred to another reporting unit and for whom the treatment outcome is not known.

Risk factors for failure to convert to negative AFB at 2 or 3 months (end of intensive phase)

Several patient factors have been associated with non-conversion (13-23). Many studies agree that age over 42.8 (13), increasing age (14), age over 45 (15), age over 41(16), or age over 35 (17) are less likely to convert. Most studies agree that females are more likely to convert than males (15, 18, 19). Sociodemographic characteristics such as illiteracy (20) or lack of formal education (21) are significantly associated with non-conversion. Behavioral characteristics such as smoking (13, 15, 19, 22), recent weight loss (17, 21), alcoholism (15, 21, 22), non-injectable drug use (23) are all significantly associated with non-conversion. Some authors report co-infection with HIV as a significant predictor for sputum non-conversion at two or three months (17, 18, 21, 23).

However, other studies have shown that HIV patients do not have this association (24-27). In a study of time to conversion, it was found that HIV infection is not associated with increased an increase in time required to convert (25). Similarly, a study in Spain that found HIV co-infection was associated with a shorter time to sputum conversation (27). The authors of this study hypothesize that the presence of cavitation may supersede presence of HIV. Low platelet level was also associated with non-conversion (13). Several studies have shown that previous TB treatment has been shown to be significantly associated with non-conversion (15, 18, 19, 21, 28). However, others have not identified any association (25, 29). Many authors have suggested that the key factor in conversion is the presence of absence of cavitation (13, 25, 27). In one study, patients with cavitary disease and extensive radiological disease were likely to have longer conversion times than those without these factors (13). This study is unique in that all patients were HIV negative, allowing the opportunity to evaluate these other clinical risk factors that may prolong infection. Initial AFB grading is also commonly seen to be significantly associated with conversion. Patients with weakly positive smears have been demonstrated to be more likely to convert than patients with strongly and moderately positive smears (29, 30). Similarly, Rieder described conversion of 90.9%, 77.9%, and 61.7% among patients with initial weak, moderate, and strong positivity respectively (10). In Gambia, it was observed that conversion at 2 or 3 months increased with decreasing smear grading at diagnosis (12). In Tanzania, an initial AFB grading of 3+ was associated with not converting (31) Drug resistant TB is associated with conversion in some studies (16, 29), but not in others (13).

Program factors have also been found to affect conversion (14, 23, 32). Patients were more likely to convert if treatment was provided by TB control staff in main health centers rather than my nurses or village health workers at peripheral level (14). In North Carolina, use of DOT and a four drug therapy regimen were significant predictors of conversion (23). Additionally, past studies have identified that the inability to complete or correctly adhere to the lengthy DOTS treatment is one of the major reasons for non-conversion (32).

The understanding of these patient characteristics is salient in the effort to ensure positive treatment outcomes (4). Current research lacks simple predictive factors affecting sputum conversion that could be used by treatment programs in resource limited countries to identify patients who are likely to not convert (29).

Relationship between conversion and final treatment outcome

Sputum examination after the intensive phase of treatment for sputum positive pulmonary TB is essential for assessing the quality of patients' treatment and management (13). Smear positive cases are, by definition, able to infect other. Most studies have determined that sputum positivity at the end of the 2 or 3 month intensive phase of treatment is a strong predictor for treatment failure (13, 14, 27, 30, 33, 34, 35, 37). In a study from the Gambia, it was found that after controlling for gender, failure to convert at two months was associated with treatment default (14). However, in this study non-conversion was not associated with other poor treatment outcomes like death and treatment failure. In India, it was found that the risk of adverse outcomes (failed, died, relapse or default) was significantly higher in those who were smear positive at 2 month

evaluation (34). Similarly, in Burkina Faso, cure rates were higher among those who converted at the end of two months when compared to those who did not convert, however, HIV status and other clinical factors were not considered (35). In Madagascar, the majority of treatment failures were observed in patients who were smear positive at two months (27). In contrast to the majority of literature, one study in South Africa concluded that the 2 or 3 month smear could be safely omitted. The authors of this study found that most patients who relapsed had been smear negative at 2 or 3 months (38). In addition, they observed a low positive predictive value of 2 or 3 month conversion for treatment failure. The increased risk of defaulting among non-converters at two months is of serious concern as these patients are able to spread drug-resistant organisms (39). This underlines the fundamental importance of the intensive phase of therapy where most of the bacilli population is killed. However, many of these studies state that smear non-conversion at the end of the intensive phase is not by itself sufficiently specific for predicting treatment failure (27, 34, 37).

Patient factors have also been linked to adverse final treatment outcomes. Lower cure rate is significantly associated with increasing age (14). Some studies specify patients over 45 are more likely to experience failure (15, 30). Being male is often found to be associated with poor treatment outcomes (14, 15, 18, 30). Sociodemographic factors associated with treatment failure include illiteracy (15, 20, 30) and poor patient knowledge of TB (30). Behavioral factors like alcoholism (14, 15, 20, 22, 30) and smoking (15, 22, 30) have also been independently determined to be associated with final TB treatment failure.

One study found that a baseline weight of less than 35 kilograms is associated with death (15). Patients with a history of previous TB treatment are less likely to achieve cure (15, 20) and are associated with relapse (28) and death (18). Additionally, patients with multidrug- resistant TB (MDR TB) are more likely to fail treatment (15) and have recurrence of disease (21, 22, 28). Some studies have found that patients with pulmonary TB (15) or mixed clinical form (18) are at significantly higher risk of adverse treatment outcomes and death. Increasing initial smear grading is often significantly associated with decreasing cure rate (14, 20). TB patients with diabetes also have greater risk for treatment failure and death (13, 38).

The literature is divided concerning the association between HIV infection and adverse TB treatment outcomes (14, 15, 18, 26, 37, 40, 41,42). In India the risk of death weas more common among older patients and patients that were positive for HIV (14, 15, 32). Similarly in The Gambia, after adjusting for age and gender, the risk of death for HIV positive individuals was higher than in HIV negative patients (14). However the authors note that HIV infection status records were often incomplete. Similarly, a study in San Francisco found that HIV infected subjects had significantly higher rates of relapse (40). In contrast, a study of gold miners in South Africa reported similar likelihood of cure among HIV positive and HIV negative individuals (41). These authors attributed these findings to a focused and resourced TB program, and concluded that acceptable cure rates can be achieved even in a population with a very high incidence of TB and HIV infection. In Brazil, researchers observed that the recovery rate for pulmonary TB patients with HIV were similar to expected rates for patients without HIV

(42). However, the authors noted that worse outcomes were more often seen in extrapulmonary TB patients infected with HIV.

Program factors are also likely to contribute to treatment failure (14,15). In Gambia, cure was more likely when treatment was provided by TB control staff in main health centers rather than by nurses or village health workers at peripheral level (14).

Adherence to TB treatment has been shown to predict final outcome (15, 18, 30). Non completion of TB treatment leads to the persistence of TB and facilitates drug resistance and micro-epidemics. It has been estimated that treatment non completion is required to fall below 10% in order to achieve treatment success of 85% one of the health related indicators of the Millennium Development goals (2). In New York, non-adherence to TB treatment is most important predictor of treatment failure (30). In India irregularity of treatment during the intensive phase (versus regular treatment) was associated with higher default rates (15). It has been suggested that treatment default or dropout is a marker for other confounding variables like worse health status, adverse drug effects, or difficult access to health (18).

Identification of factors related to persistent sputum positivity at the end of the intensive treatment phase may inform programs of patient groups that require more vigilant attention to ensure treatment adherence during the intensive phase. Further, understanding the relationship between the interim outcome of failure to convert to a negative AFB sputum smear and final treatment outcomes may provide an indicator of patients more likely to have poor outcomes. Establishing other patient and programmatic

factors associated with treatment default, failure and death will help guide and target program interventions aiming to improve treatment adherence and treatment outcomes.

STUDY OBJECTIVES

The objectives of the current analysis are:

1. To describe completeness of availability of sputum smear results for evaluating smear conversion after the intensive phase of TB treatment (2 months for new TB patients, 3 months for retreatment patients);

2. Among patients who had a sputum smear result determining sputum conversion status, to determine patient and program factors associated with sputum conversion;

3. Among patients who had a sputum smear collected and result determining sputum conversion status, to evaluate the association between sputum conversion status after the intensive phase and final treatment outcomes.

METHODS

Study Population

The current study utilized sociodemographic, clinical, and TB program management information data previously collected as part of a national systematic evaluation aiming to evaluate the TB surveillance system and Electronic TB Register (ETR) system in South Africa (43). The current analysis aimed to explore patient and programmatic factors associated with sputum collection to monitor TB treatment progress after the intensive phase of treatment, conversion to a negative AFB sputum smear after the intensive phase of treatment, and final treatment outcomes.

Parent Study

A retrospective cohort analysis was conducted to determine the completeness, reliability, and utility of data collected for TB surveillance in South Africa. In brief, 3 of 9 provinces in South Africa were selected based on tertile of cure rates as reported in the ETR. Gauteng, Mpumulanga, and KwaZulu-Natal provinces were included in the evaluation. Within each province, three subdistricts or local government units were randomly selected. Geographic characteristics (urban, rural) and type of health facility (hospital, community health center, health clinic) were used to categorize facilities within each subdistrict, and one facility type from each urban and rural area within the subdistrict was randomly selected for inclusion, for a total of 54 facilities. In each facility, TB records of up to 30 patients (all patients if <30; random selection of 30 patients if >30) who were diagnosed with TB in the first quarter (Q1) of 2009 were reviewed.

Current Study

The current analysis included all patients in the parent study with information available on collection of sputum for determination of smear conversion after the intensive phase of treatment. The analysis evaluating factors associated with failure to convert to a negative AFB sputum smear after the intensive phase of treatment (non-conversion) was restricted to patients that had a sputum specimen collected at that time and that had sputum smear results recorded. The evaluation of the association between sputum non-conversion and final TB treatment outcomes included patients with both sputum conversion status after the intensive phase and a final treatment outcome recorded.

Data Collection

Patient record reviews included the primary TB treatment card (blue card), the paper TB register, and the ETR at the subdistrict, district, province, and national level. Data was abstracted from each source on sociodemographic and key TB clinical and management variables. Information related to the TB facility and program was also collected based on questionnaires administered to TB staff.

Variables for Data Analysis

Outcomes

Sputum collection, results, and conversion after the intensive phase of treatment

Information is recorded in the TB surveillance system and ETR reflecting whether or not a sputum specimen was collected at the end of the intensive phase for each patient.

Based on NTP guidelines, at least 2 sputum specimens are to be collected at the end of two months of treatment for newly registered patients (no previous TB treatment) and at the end of three months of treatment for retreatment patients (11). There is a field in the paper surveillance sources and in the ETR to also record the laboratory testing result as positive or negative for AFB.

Patients whose sputum specimen laboratory results after the intensive phase of treatment are absent of AFB (negative) are considered to have converted to a negative AFB, and their treatment regimen is changed to the continuation phase. Patients that have one or more specimens positive for AFB are considered to have failed to convert (non-conversion) and often their current treatment regimen is extended until further assessment.

Final Treatment Outcomes

Data on final treatment outcomes is recorded in the various data sources based on international and national definitions (11, 44). At the end of the prescribed treatment course (at month 5 for new patients and month 7 for retreatment patients), at least 2 sputum specimens are collected for laboratory testing for the presence of AFB. Patients whose final smears are all negative that had a negative smear on at least one previous occasion are classified as cured; patients with a persistent positive AFB smear in the last month of treatment are considered treatment failures. If a patient has completed treatment but does not provide a sputum specimen are considered as treatment completed. Patients are also assigned a final treatment outcome as defaulted if they have missed 2 or more months of consecutive treatment, and patients who die during the treatment course

are recorded as died. Patients who transfer or move are often missing a final treatment outcome.

The current analysis only included patients with a final treatment outcome recorded, including: cured, completed treatment, failed treatment, defaulted, and died. Patients with outcomes indicating transferred or moved, or who were missing an outcome were excluded. Patients who were cured or completed treatment were considered to have successful outcomes; patients who failed treatment, defaulted, or died were categorized as having poor outcomes.

Patient and Programmatic Variables

Patient Factors

Several patient factors were considered in the current analysis to evaluate the association with interim and final TB treatment outcomes. Information on sociodemographic, clinical, treatment management and TB indicator variables was abstracted from each data source (Appendix A). Sociodemographic variables included age, date of birth, and gender. Variables related to TB diagnosis and management included information on patient category (new, retreatment), classification of the site of TB (pulmonary or extrapulmonary based on international classification of disease (ICD) codes), pre-treatment sputum results for the presence of AFB, treatment regimen, and directly observed therapy (DOT). Each data source also had fields to record the patient's HIV status.

Program Factors

Each health facility was categorized by type, as hospital, community health center, or clinic. Health facilities were also characterized according to geographic setting as urban or rural.

Data Coding/Recoding for Analysis

Decision Rules for Recoding/Deriving Values for Each Variable

As described, the parent study collected information on key TB indicators across multiple data sources. For the current analysis, only information from the first three primary sources, the TB blue card, the TB paper register, and the initial ETR were utilized, as these sources are used for patient management and therefore the most complete and reflective of patient information. Further, information on key indicators was often missing in the district, provincial, and national ETR databases.

For sociodemographic, clinical, and treatment management variables, the TB register was used as the primary source document, with the TB blue card and the initial ETR (e.g., subdistrict) as secondary sources. This determination was based on results from the parent study reflecting the TB register as the most complete data source. When comparing data sources, the following decision rules were applied to derive a single value for each variable: 1) if all 3 data sources were available, the value reflected in 2 of 3 sources was selected; 2) if 3 or 2 data sources were available with differing results, the value from the TB register was selected; 3) if only 1 source was available, the value was selected that source.

Data Recoding

Outcomes

Information on sputum results after the intensive phase was categorized as patients who converted to a negative AFB smear (converted) or who failed to convert to a negative AFB smear (non-conversion). Final treatment outcomes were collapsed into a binary outcome, as a successful outcome (cured, completed treatment) or poor outcome (failed treatment, defaulted, died).

Risk Factors

Information on HIV status was recorded as HIV positive, HIV negative, or unknown. HIV was recoded into a dichotomous variable as either HIV known positive or other, which included all other patients. Directly observed treatment (DOT) was recorded in data sources as whether or not the patient was on DOT during the intensive phase and whether or not the patient was on DOT during the continuation phase. For evaluation of factors for sputum conversion, DOT was dichotomized into DOT during the intensive phase or no DOT during the intensive phase. For assessment of factors associated with final treatment outcomes, DOT was categorized into four categories: intensive DOT only, continuation DOT only, full DOT (intensive and continuation), or no DOT.

Statistical Analysis

Descriptive statistics were used to describe the completeness of sputum collection after the intensive phase of treatment, availability of smear results (among those with sputum collected), smear conversion (among those with sputum collected and a result available), and final treatment outcomes. Chi square statistics were calculated to evaluate

difference between patients who had a sputum collected and those that did not, as well as differences between patients with a smear result available and those that did not have a smear result recorded. All patient information and programmatic factors were considered as potential risk factors for each of the interim outcomes. Logistic regression adjusting for factors found to be confounders was carried out to evaluate risk factors associated with sputum conversion and final outcome. An *a priori* analysis was conducted to evaluate the association between non-conversion and final treatment outcome. For the purpose of logistic regression dummy variables were used for independent variables with more than two categories. For all analyses, stratified models were examined to evaluate potential effect modification. Finally, the association between factors and each outcome was analyzed by multivariate logistic regression with factors found to be significant at a p-value <0.20 in univariate analysis. All multivariate models were initially adjusted by age as a dichotomous variable (<35 or ≥35 years of age). In the final models, a p-value of 0.05 was used as the cut-off indicating statistical significance. All analyses were conducted using SAS version 9.2.

ETHICAL CONSIDERATIONS

The present analysis utilized data previously collected as part of a parent study evaluating the TB surveillance and ETR in South Africa. The database does not contain any patient identifying information and there was no additional data collected as part of this evaluation. The information collected in the parent study was collected as part of the routine TB diagnosis and management of TB patients and monitoring and evaluation of

the National TB Program in South Africa. The project was reviewed and approved by the ethical review boards of the Centers for Disease Control and Prevention, the South African Medical Research Council, and Emory University Rollins School of Public Health.

RESULTS

Study population

A total of 1339 smear positive TB patients were included as part of the parent study cohort. Seven hundred eighty nine patients (58.9%) did not have a sputum result available for evaluation of conversion to a negative AFB smear at the end of the intensive phase of treatment (after 2 months for new patients and 3 months for retreatment patients) (Figure 1). The majority of patients with a conversion result (n=550) recorded had a final treatment outcome recorded (n=502; 91.8%). Of the 48 patients with a conversion result but no final outcome result, 24 had moved, 18 transferred out, and 6 did not have a final treatment outcome recorded.

Availability of sputum results at the end of the intensive phase of treatment

When comparing the patients with a smear status result after the intensive phase to patients without a conversion result, there were no significant differences noted by gender or patient type (Table 1). There were significant differences in availability of smear result in patients according to age, site of disease, HIV status, treatment regimen, DOT, geographic setting and facility type. The majority (90.6%) of young patients aged 0-14 did not have a smear result recorded, which was significantly greater than the proportion missing a result in other age groups (range 50.0-58.6%). The proportion of extrapulmonary TB patients missing a smear result was significantly greater than the proportion among pulmonary patients (73.8 vs. 54.1%, $p<0.0001$). Patients known to have HIV infection had a greater proportion of results available than patients who were HIV negative or whose HIV status was unknown (45.0 vs. 36.3%). Patients seen in

urban settings were more likely to have missing sputum results than patients treated in rural facilities (61.3 vs. 51.5%, p<0.0001). Patients treated at community health centers had a higher proportion of sputum results recorded (58.4%) compared with patients treated at hospitals (49.9%) or clinics (20.3%).

The analytic study population therefore included the 550 patients who had sputum smear results available at the end of the intensive treatment phase. The majority of these patients were aged 25-34 (35.1%) or 35-44 (26.4%) (Table 2). There were 286 (52%) males and 264 (48%) females. Most were pulmonary TB patients (88.4%), new cases (84.4%), co-infected with HIV (60.2%), prescribed category I treatment regimen (80.7%), and on DOT during both the intensive and continuation phase (63.2%). Most patients were treated in a rural setting (57.6%) and in a clinic (69.5%).

Smear conversion

Of the 550 patients analyzed based on sputum smear availability, sputum smear conversion to negative AFB was observed in 482 (87.4 %) patients. Sixty-nine (12.5 %) patients did not convert.

When examining factors associated with non-conversation at the end of the intensive phase, patients aged 15-24, 35-44, and greater than 55 years were at an increased risk for non-conversion when compared to the 45-54 year old age group (Table 3). Patients treated in a rural setting had a higher risk for non-conversion compared to patients treated in urban facilities (OR 1.9, 95% CI 1.1-3.1; p=0.02). There were no significant differences observed according to gender, patient type, HIV status, treatment regimen, or facility type. All extrapulmonary patients converted to a negative AFB smear after the

intensive phase (vs. 85.9% among pulmonary TB patients). All patients that did not receive DOT during the intensive phase also converted (compared to 92.2% of patients who did receive DOT during the intensive phase). An odds ratio estimating the magnitude of association between these variables (site of disease and DOT) and sputum conversion could not be calculated due to zero cells.

To assess effect modification, patients were stratified by patient type (new versus retreatment). The risk of non-conversion was not significantly different in the two groups.

In the multivariate regression model the only factor that remained significantly associated with sputum non-conversion at the end of the intensive phase while adjusting for age was being treated in a rural setting (OR_{adj} = 2.0, 95% CI 1.2- 3.4, p= 0.01) (Table 4).

Association between non-conversion to negative AFB smear and final treatment outcomes

Among patients with a conversion smear result available at the end of the intensive phase (n=550), 48 (8.7%) did not have a final outcome available. Of the patients missing a final outcome, 24 (50%) were recorded as moved, 18 (37.5%) transferred out, and 6 (12.5%) did not have an outcome recorded. Of the 502 patients with both smear conversion results and a final outcome recorded, over half (305/502; 60.8%) were cured, 136 (27.1%) completed treatment, 35 (6.8%) defaulted, 22 (4.4%) died, and 4 (0.8%) failed treatment. In total 441 (87.9%) had a successful outcome while 61 (12.2%) patients had a poor final outcome.

In univariate analysis, failure to convert to a negative AFB sputum smear after the intensive phase of treatment was significantly associated with having a poor final outcome (OR 1.8, 95% CI 0.9-3.7; p=0.11) (Table 4). Additionally, patients who were male (OR 1.8, 95% CI 1.1-3.2; p=0.03), had been previously treated for TB (retreatment; OR 1.6, 95% CI 0.8-3.2; p=0.19), were treated in a rural setting (OR1.8, 95% CI 1.0-3.0; p=0.04), or who received DOT during the intensive phase only (when compared to patients receiving DOT during both intensive and continuation phase; OR 2.7, 95% CI 1.4-5.2; p=0.004) were at a significantly higher risk for a poor treatment outcome. Patients treated at a community health center were significantly more likely to have a poor outcome (OR 2.1, 95% CI 0.8-5.5; p= 0.15) when compared to being treated in a hospital, however, there was no increased risk associated with receiving treatment in a clinic (OR 1.0, 95% CI 0.4- 2.5; p=0.99). No significant associations were identified between patient age, site of disease, HIV status, or treatment regimen and poor treatment outcomes.

To assess effect modification, patients were stratified by patient type (new versus retreatment). The risk of poor outcome was not significantly different in the two groups.

In the final multivariate regression model, sputum conversion was not significantly associated with poor treatment outcome. After adjusting for age, factors that remained significantly associated with a poor final treatment outcome were male gender (OR_{adj} 1.9, 95% CI 1.1-1.4; p=0.02), patients treated in a rural setting (OR_{adj} 1.8, 95% CI 1.0-3.1; p=0.04), and patients treated with DOT only during the intensive phase were more likely to have poor outcomes (OR_{adj} 2.8, 95% CI 1.5-5.2; p=0.002).

DISCUSSION

In this study of 1339 patients across three provinces of South Africa, less than half (41%) had a sputum smear result recorded for evaluation for conversion to a negative AFB smear after the intensive phase of treatment. Patients without sputum results in the TB surveillance records tended to be between 0-14 years old and male. The majority of the patients without a sputum result had extrapulmonary TB, as well as an unknown or negative reported HIV status. A greater proportion of patients without a sputum smear result were treated in urban settings or hospitals. There were also a greater proportion of patients who were not on DOT in those who did not have a sputum smear results.

Among this select cohort, 12.4% failed to convert to a negative AFB smear after the intensive phase of treatment. In our study, all extrapulmonary TB patients that had sputum collected converted. Since only 26.3% of extrapulmonary patients had a specimen result available, the observed smear conversion of extrapulmonary patients may only reflect those that had the capacity to produce a sputum specimen and not generalizable to all extrapulmonary patients. The large percentage of extrapulmonary patients that did not have a sputum smear result available may indicate that measures other than sputum smear positivity and negativity should be used in these patients to evaluate the effect of treatment during the intensive phase. Previous studies have also shown that extrapulmonary TB patients are more likely to have unknown 2 month outcomes compared to smear positive pulmonary TB patients (56). It has been suggested that the diagnosis and monitoring of extrapulmonary TB is difficult because of a shortage of trained health personnel, poor diagnostic facilities, and lack of appropriate and specific diagnostic guidelines (46). These factors may contribute to the difficulties in following

and evaluating treatment of extrapulmonary TB patients, and so it may be that extrapulmonary TB patients would be less likely to demonstrate conversion using the AFB method, regardless of actual treatment effect.

In addition, all patients in our study not receiving any DOT during the intensive phase converted to a negative sputum smear at the 2 or 3 month follow-up. However, most literature indicates that not having DOT is a strong indicator of non-conversion (32). It is possible that the results from this study reflect good adherence to treatment during this time, even among patients not receiving DOT. This may be because clinical symptoms are often present in the initial months of treatment, and so the patient is motivated to adhere to the treatment regimen without the close supervision provided by DOT. Previous studies have cited that an improvement in patient symptoms is a main contributor to non-adherence and non-completion of treatment (32, 53).

In addition, patients who were treated in a rural setting had almost 2-fold the risk for non-conversion (OR_{adj} 1.9, 95% CI 1.2-3.2, p=0.01) compared to patients treated in urban settings. Studies have shown that patients living in urban areas have better access to care and rural patients often face challenges with financial and transportation constraints (51, 52). These barriers may contribute to lower rates of treatment adherence as well as less likelihood of sputum conversion.

Retreatment patients, despite having a different therapy regimen did not have a significantly different risk of non-conversion when compared to new TB patients. This is similar to a study done in Saudi Arabia where it was found that prior history of TB treatment was not a significant predictor for sputum smear positivity at the end of 2

months of treatment (16). These findings, as well as the findings of our study, contrast a previous study that reported new patients had delayed times to conversion compared to patients that had been previously treated (49). Authors suggest that this association may be explained in part by retreatment patients having a greater number of immunologically specific T cells. The T-cells produce lymphokines that can accelerate macrophage accumulation and activation which, in turn, more rapidly destroy the bacilli. However, most studies have demonstrated that previous TB treatment is a significant risk factor for non-conversion (15, 18-20, 28). It is thought that retreatment patients are more likely to have drug resistance making conversion more difficult (18). In our analysis patients treated with Category II regimen were not associated with non-conversion. This is consistent with our previous findings that retreatment patients were no more likely to non-convert than new patients.

No association was identified between HIV status and non-conversion in the present analysis, similar to several previous reports (24, 36, 45). Though lower rates of conversion among HIV positive patients may be expected, it has been suggested that similar conversion rates among HIV positive and HIV negative patients may be attributed to enhanced supervision received by HIV positive patients for treating both diseases (36). Yet other studies that have identified differences have had varied results, with some citing lower rates of conversion among TB patients co-infected with HIV (23), and others reporting accelerated times to conversion among HIV positive patients (25). A study done in North Carolina reported a 46% lower rate of conversion among HIV positive patients compared to non-HIV infected patients (23). In a contrasting study reporting HIV positive patients converting more rapidly than HIV negative patients, authors

postulated that since HIV positive patients are less likely to have cavitary disease and tend to have lower AFB grading, they lack risk factors that have been found to be highly associated with non-conversion or delayed conversion (25).

There was no significant association identified between failure to convert to a negative AFB after the intensive phase of treatment and final treatment outcomes in the present study. This is in contrast to many studies that have found non-conversion to be a significant predictor of outcome. In Gambia, smear positivity at two months was an indicator of treatment default (14). Smear positivity remained significant after controlling for gender. However, non-conversion in Gambia was not associated with other poor treatment outcomes included in our analysis such as death and treatment failure. In India, it was found that the rate of adverse outcomes (failed, died, relapse or default) was significantly higher in those who were smear positive at 2 month evaluation (34). Similarly, in Burkina Faso, cure rates were higher among those who converted at the end of two months when compared to those who did not convert, however, HIV status and other clinical factors were not considered (35). A study in Madagascar observed that the rate of treatment failure significantly increased in patients failing to convert (27). However, the authors note that the failure rate they observed was relatively high and that the high failure rate could be due to application of the treatment regimen or quality of the sputum smear. A study in South Africa found that patients who did not convert were more than four times more likely to experience treatment failure (38). However, in an extensive follow up it was observed that most patients who relapsed had been smear negative at 2 or 3 months. Further, a low positive predictive value for smear positivity was found for adverse outcomes including death, failure, default and relapse.

However, within the population of patients that were monitored after the intensive phase and had a final treatment outcome recorded, males (versus females; OR_{adj} 1.9, 95% CI 1.1-3.4, p=0.02) and patients treated in a rural setting (versus urban; OR_{adj} 1.8, 95% CI 1.0-3.1, p=0.04) were significantly more likely to have a poor outcome. These findings are consistent with several previous studies reporting an association between poor outcome and male gender (14, 15, 18, 30, 47). In Gambia, it was found that males were less likely to achieve cure than females (14). A study in Brazil found that males were more likely to die (18). In India, being male was associated with default (15, 30). In South Africa, males were more likely to fail treatment than females, possibly due to work responsibilities that increased the likelihood of treatment interruptions, making successful outcome less likely (47). Patients in rural settings were significantly more likely to have poor outcomes than those in urban settings. In a study of urban-rural disparities in England, univariate analysis showed a significantly higher level of treatment non-completion in rural areas (50). However, these results became non-significant after adjusting for the confounding effects of ethnic group and age. The authors of this study suggest that this indicates equal access to care between urban and rural areas, and that socioeconomic status is a greater driver of non-completion. However, this may not be generalizable to the situation in South Africa. The current finding of patients in rural settings being significantly more likely to have poor outcomes than those in urban settings is similar to several previous studies (22, 32, 51), and challenges with access to care may underlie the observed association. A study in Ethiopia found a significant association between living in rural residence and treatment non-completion (22). In a study of anthropological factors relating to effective TB control, authors identified living

in a rural area as having an impact on patients' access to care, as there are often difficulties in reaching the health center because of long distances and poor transportation infrastructure (51). This is consistent with the study in Ethiopia, where significant factors for defaulting from treatment were distance from home to treatment center and necessity to use public transport to get to a treatment center (32). Additionally in Jordan it was found that rural TB patients were less likely to seek care, and patients commonly cited economic constraints as reasons for delayed care seeking behavior (52).

While the current study did not identify any differences in poor treatment outcome risk between new and retreatment patients, most literature has demonstrated retreatment patients as significantly more likely to have poor outcomes (55-57). A study in India found that retreatment patients were more likely to experience default and failure and have lower cure rates (55). This is consistent a study in Uganda where it was found that a high proportion of retreatment patients (20%) had unsuccessful outcomes (56). In Hong Kong, retreatment patients were less likely to complete treatment when compared to new patients (57). It has been suggested that patients who require retreatment may have issues with drug susceptibility (55). Thus, retreatment patients pose a difficult challenge to TB control.

Our study showed no difference in outcomes between HIV positive and negative patients. This result has been seen in several other studies (14, 18, 21, 47, 48), yet contrasts most findings that have reported higher rates of treatment failure and mortality among HIV infected patients (14, 18, 31, 36, 47, 48).

The current study allowed for careful examination of the association between patient and program factors and failure to convert to a negative AFB sputum after the intensive phase of treatment and with final treatment outcomes. Information was collected on a large cohort of smear positive TB patients across multiple health facilities in three provinces of South Africa. Patient-level data were collected across multiple sources utilized in the programmatic management of TB patients; multiple sources allowed for the establishment of values for key TB indicators that may have otherwise been missing had the study included only a single data source.

However, the current study is not without limitations. This study was a retrospective cohort design, thus investigators were not able to verify or complete missing information. However, multiple data sources helped to maximize completeness, and data decision rules aimed to identify the most reliable, and ideally valid, value for each variable. This study was also hindered by issues of the large proportion of patients missing a sputum result after the intensive phase or missing a final treatment outcome. It is possible that if all missing data were complete the identification of risk factors would be significantly different than what was observed in the present analysis**.** Additionally, small cell sizes prevented consideration of some variables in multivariate analysis. Age and gender were adjusted for in each analysis; however, other confounders that were not measured in the present analysis may still exist. Factors relating to socioeconomic status are often observed to influence treatment outcomes. However, this information is unavailable in the present analysis. Our study contained a portion of individuals whose HIV status was unknown. Our findings would likely be affected if outcomes in those individuals were significantly different than the observed outcomes of known HIV

positive and negative patients. Additionally small sample sizes in some age categories may have contributed to bias. The current analysis was based on a sample of patients in South Africa, but may not be generalizable beyond the current sample. In addition, the diversity of people, overall socioeconomic status, and prevalence of HIV may or may not differ significantly from other studies conducted elsewhere.

CONCLUSIONS

The current evaluation found that a large proportion of TB smear positive patients are not being adequately monitored over the course of treatment. It is critical for programs to emphasize the need for assessing treatment efficacy through sputum collection, particularly after the intensive phase of treatment. This enables programs to appropriately manage patients and identify patients that may be at risk for treatment interruptions or default or that may have drug-resistant strains of TB. This study helped identify patient and programmatic factors that may influence sputum conversion and final outcome. Specifically, patients who are treated in rural settings have an increased risk for non-conversion and poor treatment outcomes compared to patients treated in urban settings. TB programs, particularly in rural settings, need to evaluate key barriers to treatment adherence and consider interventions that may optimize treatment compliance and successful outcomes. Future studies should more carefully examine factors that influence sputum collection after the intensive phase of treatment as well as factors that may impact treatment adherence and outcomes among patients in rural settings.

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Figure 1. Flow chart of patients from three provinces in South Africa in 2009 included in analysis of factors related to sputum non-conversion and final treatment outcome.

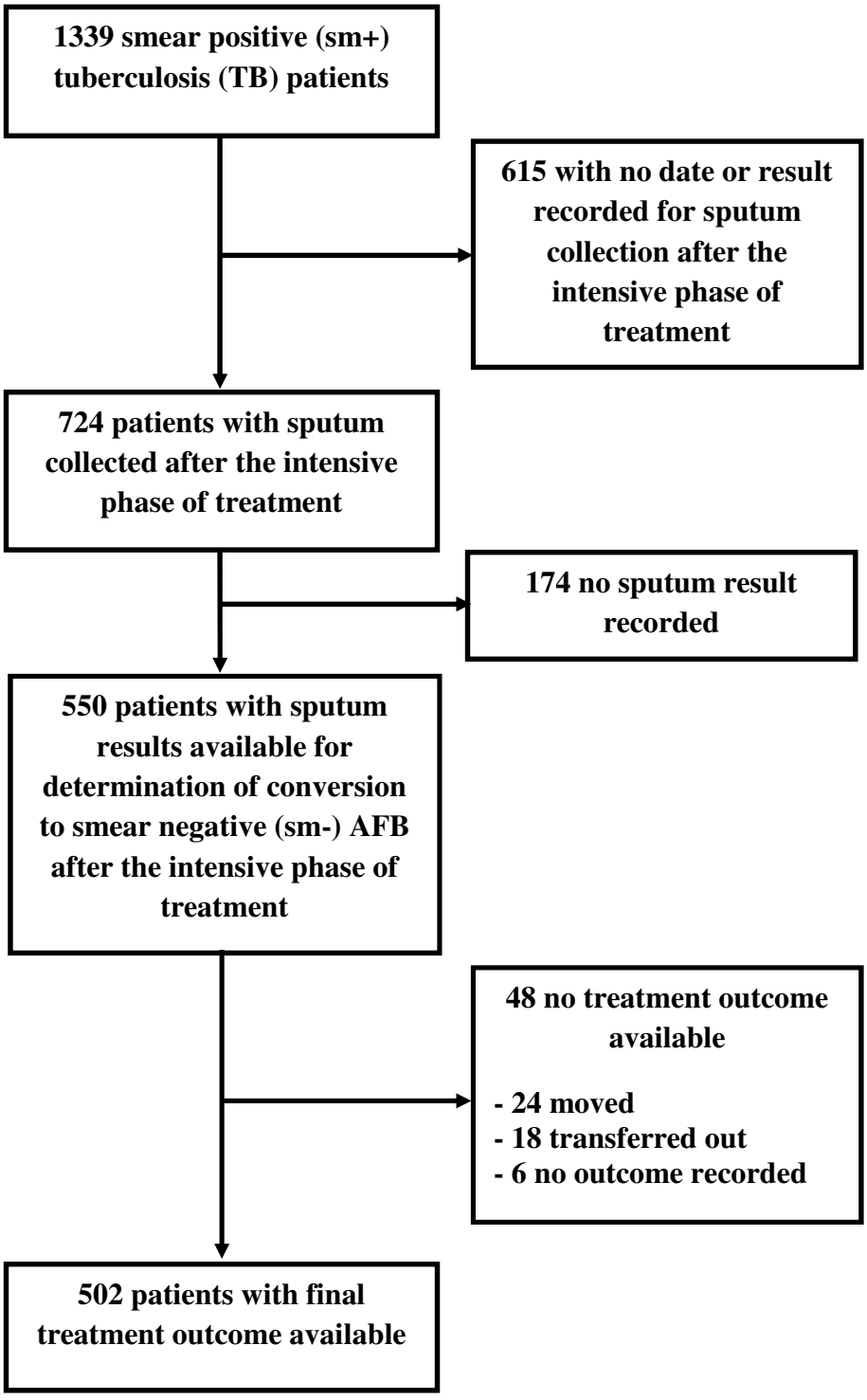

Table 1. Comparison of sociodemographic, clinical, and program characteristics of TB patients who had a sputum smear collection and result after the intensive phase (N=1339).

Variable	Total N=1339	Result n=550 (41.1%)	No Result n=789 (58.9%)	p-value
Age Category, years				<0.0001
0-14	149	14 (9.4)	135 (90.6)	
15-24	145	60 (41.4)	85 (58.6)	
25-34	419	193 (46.1)	226 (53.9)	
35-44	340	145 (42.7)	195 (57.4)	
45-54	176	83 (47.2)	93 (52.8)	
≥55	110	55 (50.0)	55 (50.0)	
Gender				0.27
Male	719	286 (39.8)	433 (60.2)	
Female	617	264 (60.2)	353 (57.2)	
Site of disease				<0.0001
Pulmonary	1048	481(45.9)	567 (54.1)	
Extrapulmonary	240	63 (26.3)	177(73.8)	
Patient type				0.31
New	1071	448 (41.8)	623 (58.2)	
Retreatment	178	83 (45.9)	95 (54.14)	
HIV status				0.001
Known positive	735	331 (45.0)	404 (55.0)	
Other	604	219 (36.3)	385(63.7)	
Treatment regimen				<0.0001
Cat I 2RHEZ 4RH	1006	444 (44.1)	562 (55.9)	
Cat II 2RHZES 1RHEZ 5RHE	195	95 (48.7)	100 (51.3)	
Cat III RHZ 4RH	125	9 (7.2)	116 (92.8)	
Other	2	0 (0)	2(100)	
DOT				<0.0001
None	26	6 (24.0)	19 (76.0)	
Intensive phase only	864	141 (37.7)	723 (61.3)	
Continuation phase only	60	10 (50.0)	50 (50.0)	
Both intensive and continuation phase	465	278 (59.5)	187 (40.2)	
Geographic setting				<0.0001
Urban	859	317 (36.9)	542 (61.3)	
Rural	507	233 (48.5)	274 (51.5)	
Facility type				<0.0001
Hospital	457	93(20.3)	364(79.7)	
Community health center	185	108(58.4)	77(41.6)	
Clinic	694	346(49.9)	348(50.1)	

Due to missing values totals may not equal 1339

Table 2. Patient and programmatic characteristics for the analytic population of patients who had a sputum smear collected and a result available for determination of conversion status at the end of the intensive phase of treatment (n=550). Percentages reflect proportion of analytic sample population.

Variable	n (%)
Age Category, years	
0-14	14 (2.6)
15-24	60 (10.9)
25-34	193 (35.1)
35-44	145 (26.4)
45-54	83 (15.1)
≥55	55 (10.0)
Gender	
Male	286 (52.0)
Female	264 (48.0)
Site of disease	
Pulmonary	481(88.4)
Extrapulmonary	63 (11.6)
Patient type	
New	448 (84.4)
Retreatment	83 (15.6)
HIV status	
Known positive	331 (60.2)
Other	219 (39.8)
Treatment regimen	
Cat I 2RHEZ 4RH	444 (81.0)
Cat II 2RHZES 1RHEZ 5RHE	95 (17.3)
Cat III RHZ 4RH	9 (1.6)
Other	0 (0)
DOT	
None	6 (1.4)
Intensive phase only	141 (32.4)
Continuation phase only	10 (2.3)
Both intensive and continuation phase	278 (63.9)
Geographic setting	
Urban	195 (42.4)
Rural	233 (30.1)
Facility type	
Hospital	93 (16.9)
Community health center	108 (19.6)
Clinic	346 (63.5)

Due to missing values totals may not equal 502

Table 3. Univariate association between patient and program characteristics and sputum conversion after the intensive phase of TB treatment, among patients with a sputum smear result (n=550).

Variable	Converted to AFB- n=482 87.4 (%)	Did not convert n=69 12.5 (%)	OR (95% CI)	p-value
Age, years				
0-14	14 (100.0)	0 (0.0)	--	
15-24	49 (81.7)	11 (18.3)	6.0 (1.6, 19.0)	0.008
25-34	175 (90.7)	18 (9.3)	2.7 (0.8, 9.6)	0.11
35-44	120 (82.8)	25 (17.2)	5.6 (1.6, 19.0)	0.006
45-54	80 (96.9)	3 (3.6)	1.0	
≥55	44 (80.0)	11 (20.0)	6.7 (1.8, 25.2)	0.005
Gender				
Female	244 (85.3)	42 (14.7)	1.0	
Male	238 (90.2)	26 (9.8)	1.6 (0.9, 2.7)	0.09
Site of disease				
Pulmonary	413 (85.9)	68 (14.1)	--	
Extrapulmonary	63 (100.0)	0 (0.0)	--	
Patient type				
New	391 (89.3)	57 (12.7)	1.0	
Retreatment	74 (89.2)	9 (10.8)	1.2 (0.6, 2.5)	0.63
HIV status				
Other	187 (85.4)	32 (14.6)	1.0	
Known positive	295 (89.1)	36 (10.9)	1.4 (0.8, 2.3)	0.19
Treatment regimen				
Cat I 2RHEZ 4RH	385 (86.7)	59 (13.3)	1.0	
Cat II 2RHZES 1RHEZ 5RHE	86 (90.5)	9 (9.5)	1.5 (0.7, 3.5)	0.40
Cat III RHZ 4RH	9 (100.0)	0 (0.0)	--	
DOT				
Intensive phase	130 (92.2)	11 (7.8)	--	
None	6 (100.0)	0 (0.0)	--	
Geographic setting				
Urban	195 (83.7)	38 (16.3)	1.0	
Rural	287 (90.5)	30 (9.5)	1.9 (1.1, 3.1)	0.02
Facility type				
Hospital	79 (85.0)	14 (15.1)	1.0	
Community health center	100 (92.6)	8 (7.4)	2.2 (0.9, 5.5)	0.09
Clinic	303 (86.8)	46 (13.2)	1.0 (0.9, 1.1)	0.64

OR=Odds Ratio; CI=confidence interval; Due to missing values, columns may not equal 550

Table 4. Factors significantly associated with non-conversion to a negative AFB sputum smear after the intensive phase of treatment in the final multivariate model (n=502).

Variable	OR	95% CI	P value
Rural setting	2.0	1.2 - 3.4	0.01

OR, Odds Ratio. CI, confidence interval.

Model also adjusted for patient age.

Table 5. Univariate associations between smear conversion status and patient and program factors and final treatment outcome, among TB patients with smear conversion results and final treatment outcome recorded (n=502).

	Final Treatment Outcome			
Variable	**Success n=441 87.8 (%)**	**Poor n=61 12.2 (%)**	**OR (95% CI)**	**p-value**
Smear conversion status				
Converted	393 (88.7)	50 (11.3)	1.0	
Did not convert	48 (81.4)	11 (16.6)	1.8 (0.9, 3.7)	0.11
Age, years				
0-14	13 (92.9)	1 (7.1)	1.0	
15-24	51 (92.7)	4 (7.3)	1.0 (0.1, 9.9)	0.99
25-34	150 (84.8)	27 (15.3)	2.3 (0.3, 18.6)	0.42
35-44	116 (85.9)	19 (14.1)	2.1 (0.3, 17.2)	0.48
45-54	67 (91.8)	6 (8.2)	1.2 (0.1, 10.5)	0.89
≥55	44 (91.7)	4 (8.3)	1.2 (0.1, 11.5)	0.89
Gender				
Female	217 (84.8)	39 (15.2)	1.0	
Male	244 (91.1)	22 (8.9)	1.8 (1.1, 3.2)	0.03
Site of disease				
Pulmonary	390 (88.2)	52 (11.8)	1.0	
Extrapulmonary	48 (84.2)	9 (15.8)	1.4 (0.7, 3.0)	0.38
Patient type				
New	369 (88.5)	48 (11.5)	1.0	
Retreatment	58 (82.9)	12 (17.1)	1.6 (0.8, 3.2)	0.19
HIV status				
Other	268 (87.0)	40 (13.0)	1.0	
Known positive	173 (89.2)	12 (10.8)	1.2 (0.7, 2.2)	0.47
Treatment regimen				
Category I	367 (88.9)	46 (11.1)	1.0	
Category II	64 (82.1)	14 (18.0)	1.8 (0.91, 3.4)	0.96
Category III	8 (88.9)	1 (1.1)	1.0 (0.1, 8.2)	0.96
DOT				
Both intensive and continuation phases	246 (92.0)	22 (8.2)	1.0	
Intensive phase only	101 (80.8)	24 (19.2)	2.7 (1.4, 5.2)	0.004
Continuation phase only	9 (90.0)	1 (10.0)	1.2 (0.1, 10.3)	0.96
None	5 (100.0)	0 (0.0)	--	1.0
Geographic setting				
Urban	257 (90.5)	27 (9.5)	1.0	
Rural	184 (84.4)	34 (15.6)	1.8 (1.0, 3.0)	0.04
Facility type				
Hospital	52 (89.7)	6 (10.3)	1.0	
Community health center	84 (80.8)	20 (19.2)	2.1 (0.8, 5.5)	0.15
Clinic	305 (89.7)	35 (10.3)	1.0 (0.4, 2.5)	0.99

OR=Odds Ratio; CI=confidence interval

Successful outcomes included cured and completed. Poor outcomes included failure, default, and death. Patients whose outcome could not be determined were excluded.

Due to missing values totals may not equal 502

Table 6. Factors significantly associated with a poor final treatment outcome in the final multivariate model (n=502).

Variable	OR	95% CI	p-value
Male gender	1.8	1.0 - 1.3	0.04
Rural setting	1.7	1.0 - 2.9	0.05
DOT during intensive phase	2.8	1.5 - 5.2	0.002

OR, Odds Ratio. CI, confidence interval.

Model also adjusted for patient age.

APPENDIX A: SOUTH AFRICA SURVEY EVALUATION FORM

Form 4: Paper Audit Validation (Health Facility and Sub-District Level)

Complete as much information as available

Patient Study ID	
TB Register No.	
Patient Name	
ID Number	
Date of Birth (DD/MM/YYYY)	
Age (years)	
Patient Address	

PATIENT IDENTIFIERS FOR DATA COLLECTION PURPOSES ONLY

DETACH AND DESTROY TOP PAGE AFTER VALIDATION IS COMPLETE

Form 4: Paper Audit Validation _

Facility Name District	Subdistrict		
Date of Audit			
	Patient File/TB Blue Card	**TB Register**	**ETR**
Available for review		☐Y ☐N (not in register)	☐Y ☐N (not in ETR)
TB Register No.	☐☐☐☐☐☐	☐☐☐☐☐☐	☐☐☐☐☐☐
Date of birth	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded
Age	☐☐ ☐NR Not recorded	☐☐ ☐NR Not recorded	☐☐ ☐NR Not recorded
Gender	☐M ☐F ☐NR	☐M ☐F ☐NR	☐M ☐F ☐NR
Patient Category	☐ **N** New (<4 wks prev tx) ☐ **RC** Relapse ☐ **RF** Retreat after failure ☐ **RD** Retreat after	☐ **N** New (<4 wks prev tx) ☐ **RC** Relapse ☐ **RF** Retreat after failure ☐ **RD** Retreat after	☐ **N** New (<4 wks prev tx) ☐ **RC** Relapse ☐ **RF** Retreat after failure ☐ **RD** Retreat after

	default ☐ **OR** Other prev tx ☐ **NR** Not recorded	default ☐ **OR** Other prev tx ☐ **NR** Not recorded	default ☐ **OR** Other prev tx ☐ **NR** Not recorded
	Patient File/TB Blue Card	**TB Register**	**ETR**
Classification of Disease	☐☐☐☐☐ ICD code ☐ **NR** Not recorded	☐☐☐☐☐ ICD code ☐ **NR** Not recorded	☐☐☐☐☐ ICD code ☐ **NR** Not recorded
Treatment start date	☐☐-☐☐-☐☐ D D – M M – Y Y	☐☐-☐☐-☐☐ D D – M M – Y Y	☐☐-☐☐-☐☐ D D – M M – Y Y
Treatment regimen (initial)	☐ 1 2RHEZ 4RH ☐ 2 2RHZES 1RHEZ 5RHE ☐ 3 RHZ 4RH ☐ Other Treatment: _____ ☐ H INH Chemoprophylaxis ☐ O Other Chemoprophylaxis ☐NR not recorded ☐NA not applicable (not started on tx)	☐ 1 2RHEZ 4RH ☐ 2 2RHEZS 1RHEZ 5RHE ☐ 3 RHZ 4RH ☐ Other Treatment: _____ ☐ H INH Chemoprophylaxis ☐ O Other Chemoprophylaxis ☐NR not recorded ☐NA not applicable (not started on tx)	☐ 1 2RHEZ 4RH ☐ 2 2RHEZS 1RHEZ 5RHE ☐ 3 3 RHZ 4RH ☐ Other Treatment: _____ ☐ H INH Chemoprophylaxis ☐ O Other Chemoprophylaxis ☐NR not recorded ☐NA not applicable (not started on tx)

	TB Blue Card	**TB Register**	**ETR**
Pretreatment smear date	☐☐-☐☐- ☐☐ D D – M M – Y Y ☐NR Not recorded ☐NA not applicable	☐☐-☐☐- ☐☐ D D – M M – Y Y ☐NR Not recorded ☐NA not applicable	☐☐-☐☐- ☐☐ D D – M M – Y Y ☐NR Not recorded ☐NA not applicable
Pretreatment smear result	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable

End 2mth smear date	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded
End 2mth smear result (new cases only)	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable
End 3mth smear date	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded
	TB Blue Card	**TB Register**	**ETR**
End 3mth smear result	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable
End of treatment smear date	☐☐-☐☐-☐☐	☐☐-☐☐-☐☐	☐☐-☐☐-☐☐

	D D – M M – Y Y	D D – M M – Y Y	D D – M M – Y Y
End of treatment smear result	☐pos ☐neg ☐contam ☐NR not recorded	☐pos ☐neg ☐contam ☐NR not recorded	☐pos ☐neg ☐contam ☐NR not recorded
Other diagnosis (check only if indicated used in diagnosis)	☐ **Aspiration** ☐ **CSF** ☐ **Skin Test** ☐ **X-rays** ☐ Other ☐ Not done	☐ **Aspiration** ☐ **CSF** ☐ **Skin Test** ☐ **X-rays** ☐ Other ☐ Not done	☐ **Aspiration** ☐ **CSF** ☐ **Skin Test** ☐ **X-rays** ☐ Other ☐ Not done
	TB Blue Card	**TB Register**	**ETR**
Culture date	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐NR Not recorded
Culture result	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable	☐pos ☐neg ☐contam ☐NR not recorded ☐NA not applicable

DST done	☐Y ☐N ☐NR	☐Y ☐N ☐NR	☐Y ☐N ☐NR
DST result	**R** ☐Suscept ☐Res ☐NR **H** ☐Suscept ☐Res ☐NR **E** ☐Suscept ☐Res ☐NR **Z** ☐Suscept ☐Res ☐NR **S** ☐Suscept ☐Res ☐NR	**R** ☐Suscept ☐Res ☐NR **H** ☐Suscept ☐Res ☐NR **E** ☐Suscept ☐Res ☐NR **Z** ☐Suscept ☐Res ☐NR **S** ☐Suscept ☐Res ☐NR	**R** ☐Suscept ☐Res ☐NR **H** ☐Suscept ☐Res ☐NR **E** ☐Suscept ☐Res ☐NR **Z** ☐Suscept ☐Res ☐NR **S** ☐Suscept ☐Res ☐NR
On DOT - Intensive phase	☐Y ☐N ☐NR	☐Y ☐N ☐NR	☐Y ☐N ☐NR
	TB Blue Card	**TB Register**	**ETR**
- DOT Type	☐ **1** Facility ☐ **2** Community	☐ **1** Facility ☐ **2** Community	☐ **1** Facility ☐ **2** Community

	☐ NR Not recorded	☐ NR Not recorded	☐ NR Not recorded
On DOT - End of Treatment	☐Y ☐N ☐NR	☐Y ☐N ☐NR	☐Y ☐N ☐NR
- DOT type	☐ **1** Facility ☐ **2** Community ☐ NR Not recorded	☐ **1** Facility ☐ **2** Community ☐ NR Not recorded	☐ **1** Facility ☐ **2** Community ☐ NR Not recorded
HIV status *(If HIV NEG or UNK, skip to bottom page 10)*	☐POS ☐NEG ☐UNK ☐ NR Not recorded	☐POS ☐NEG ☐UNK ☐ NR Not recorded	☐POS ☐NEG ☐UNK ☐ NR Not recorded
On ARV at TB treatment initiation	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded
	TB Blue Card	**TB Register**	**ETR**
CD4 result (last CD4 if on	☐☐☐☐☐ cells/uL	☐☐☐☐☐ cells/uL	☐☐☐☐☐ cells/uL

ART/current CD4 if not on ART)	☐NA not applic (not HIV+) ☐ND not done ☐ NR Not recorded	☐NA not applic (not HIV+) ☐ND not done ☐ NR Not recorded	☐NA not applic (not HIV+) ☐ND not done ☐ NR Not recorded
On CPT	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (specific children) ☐ NR Not recorded
On ARV	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded	☐Y ☐N ☐NA not applic (not HIV+) ☐NE not eligible (CD4 >200, specific children) ☐ NR Not recorded
	TB Blue Card	**TB Register**	**ETR**

Treatment outcome date	☐☐-☐☐-☐☐ D D – M M – Y Y ☐ NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐ NR Not recorded	☐☐-☐☐-☐☐ D D – M M – Y Y ☐ NR Not recorded
Treatment outcome	☐ **C** Cured ☐ **TC** Treatment Completed ☐ **DF** Treatment Defaulted ☐ **F** Treatment Failure ☐ **D** Died ☐ **TF** Transferred Out ☐ **MO** Moved Out ☐ **NR** Not recorded	☐ **C** Cured ☐ **TC** Treatment Completed ☐ **DF** Treatment Defaulted ☐ **F** Treatment Failure ☐ **D** Died ☐ **TF** Transferred Out ☐ **MO** Moved Out ☐ **NR** Not recorded	☐ **C** Cured ☐ **TC** Treatment Completed ☐ **DF** Treatment Defaulted ☐ **F** Treatment Failure ☐ **D** Died ☐ **TF** Transferred Out ☐ **MO** Moved Out ☐ **NR** Not recorded

Remarks

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APPENDIX B: SAS OUTPUT FOR MODELING NON-CONVERSION AND POOR OUTCOME

Multivariate modeling for non-conversion

In determining factors associated with non-conversion after the intensive phase, all two way interactions were evaluated. However, site of disease, and type of DOT was excluded from consideration in the model because of small cell sizes. Important two way interactions were gender and geographic setting (poptype).

The results of gender in a two way analysis while adjusting for age, show that the interaction term age*gender is significant and should be included in the final model.

The LOGISTIC Procedure

Model Information

Data Set	WORK.CONVERT
Response Variable	converted
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	550
Number of Observations Used	550

Response Profile

Ordered Value	converted	Total Frequency
1	1	68
2	0	482

Probability modeled is converted=1.

Class Level Information

Class	Value	Design Variables
age3	1	0

		2	1
gender		1	1
		2	0

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	413.519	404.941
SC	417.829	422.181
-2 Log L	411.519	396.941

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	14.5779	3	0.0022
Score	14.3767	3	0.0024
Wald	13.3918	3	0.0039

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
age3	1	3.6520	0.0560
gender	1	1.6204	0.2030
age3*gender	1	9.8096	0.0017

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-1.8918	0.2461	59.0917	<.0001
age3	2	1	-0.8806	0.4608	3.6520	0.0560
gender	1	1	-0.5241	0.4117	1.6204	0.2030
age3*gender	2 1	1	1.8794	0.6001	9.8096	0.0017

Association of Predicted Probabilities and Observed Responses

Percent Concordant	50.6	Somers' D	0.271
Percent Discordant	23.4	Gamma	0.367
Percent Tied	26.0	Tau-a	0.059
Pairs	32776	c	0.636

The results of a two way analysis of age and geographic setting (poptype) show that geographic setting is significant and should be included in the final model

The LOGISTIC Procedure

Model Information

Data Set	WORK.CONVERT
Response Variable	converted
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	550
Number of Observations Used	550

Response Profile

Ordered Value	converted	Total Frequency
1	1	68
2	0	482

Probability modeled is converted=1.

Class Level Information

Class	Value	Design Variables
age3	1	0
	2	1
poptype	Rural	1
	Urban	0

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

	Intercept	Intercept and

Criterion	Only	Covariates
AIC	413.519	410.140
SC	417.829	423.070
-2 Log L	411.519	404.140

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	7.3788	2	0.0250
Score	7.4308	2	0.0243
Wald	7.2665	2	0.0264

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
age3	1	1.6293	0.2018
poptype	1	6.2334	0.0125

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.4571	0.2529	94.3836	<.0001
age3	2	1	0.3377	0.2646	1.6293	0.2018
poptype	Rural	1	0.6570	0.2632	6.2334	0.0125

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
age3	2 vs 1	1.402	0.835	2.354
poptype	Rural vs Urban	1.929	1.152	3.231

Association of Predicted Probabilities and Observed Responses

Percent Concordant	47.8	Somers' D	0.205
Percent Discordant	27.2	Gamma	0.274
Percent Tied	25.0	Tau-a	0.045
Pairs	32776	c	0.603

The intermediate model showed that the interaction term age*gender is not significant and was dropped from the model.

The LOGISTIC Procedure

Model Information

Data Set	WORK.CONVERT
Response Variable	converted
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	550
Number of Observations Used	550

Response Profile

Ordered Value	converted	Total Frequency
1	1	68
2	0	482

Probability modeled is converted=1.

Class Level Information

Class	Value	Design Variables
age3	1	-1
	2	1
poptype	Rural	1
	Urban	-1
gender	1	1
	2	-1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	413.519	400.193
SC	417.829	421.742
-2 Log L	411.519	390.193

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	21.3261	4	0.0003
Score	20.9949	4	0.0003
Wald	19.5277	4	0.0006

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
poptype	1	6.6679	0.0098
age3	1	0.1726	0.6778
gender	1	2.1243	0.1450
age3*gender	1	9.9847	0.1016

Analysis of Maximum Likelihood Estimates

Parameter			DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept			1	-2.1176	0.1515	195.4654	<.0001
poptype	Rural		1	0.3454	0.1338	6.6679	0.0098
age3	2		1	0.0629	0.1514	0.1726	0.6778
gender	1		1	0.2199	0.1509	2.1243	0.1450
age3*gender	2	1	1	0.4766	0.1508	9.9847	0.0570

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
poptype Rural vs Urban	1.995	1.181	3.371

Association of Predicted Probabilities and Observed Responses

Percent Concordant	61.1	Somers' D	0.351
Percent Discordant	26.0	Gamma	0.403
Percent Tied	13.0	Tau-a	0.076
Pairs	32776	c	0.676

The intermediate model showed gender was not significant and was dropped from the model.

The LOGISTIC Procedure

Model Information

Data Set	WORK.CONVERT

Response Variable	converted
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	550
Number of Observations Used	550

Response Profile

Ordered Value	converted	Total Frequency
1	1	68
2	0	482

Probability modeled is converted=1.

Class Level Information

Class	Value	Design Variables
poptype	Rural	1
	Urban	0
gender	1	1
	2	0
age3	1	0
	2	1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	413.519	409.266
SC	417.829	426.506
-2 Log L	411.519	401.266

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	10.2531	3	0.0165

Score	10.2337	3	0.0167
Wald	9.9612	3	0.0189

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
gender	1	2.8146	0.0934
poptype	1	6.4881	0.0109
age3	1	1.1506	0.2834

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.6911	0.2957	82.8128	<.0001
gender	1	1	0.4519	0.2694	2.8146	0.0934
poptype	Rural	1	0.6728	0.2641	6.4881	0.0109
age3	2	1	0.2863	0.2669	1.1506	0.2834

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
gender	1 vs 2	1.571	0.927	2.664
poptype	Rural vs Urban	1.960	1.168	3.289
age3	2 vs 1	1.332	0.789	2.247

Association of Predicted Probabilities and Observed Responses

Percent Concordant	54.6	Somers' D	0.222
Percent Discordant	32.4	Gamma	0.255
Percent Tied	13.0	Tau-a	0.048
Pairs	32776	c	0.611

The final model included geographic setting and was adjusted for age.

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The LOGISTIC Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	7.3788	2	0.0250
Score	7.4308	2	0.0243

Wald	7.2665	2	0.0264

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
age3	1	1.6293	0.2018
poptype	1	6.2334	0.0125

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.4571	0.2529	94.3836	<.0001
age3	2	1	0.3377	0.2646	1.6293	0.2018
poptype	Rural	1	0.6570	0.2632	6.2334	0.0125

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
age3	2 vs 1	1.402	0.835	2.354
poptype	Rural vs Urban	1.929	1.152	3.231

Association of Predicted Probabilities and Observed Responses

Percent Concordant	47.8	Somers' D	0.205
Percent Discordant	27.2	Gamma	0.274
Percent Tied	25.0	Tau-a	0.045
Pairs	32776	c	0.603

Confounding was assessed by dropping age and comparing odds ratios. The odds ratio was not significantly different. Therefor there was no confounding.

The LOGISTIC Procedure

Model Information

Data Set	WORK.CONVERT
Response Variable	converted
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	550
Number of Observations Used	550

Response Profile

Ordered Value	converted	Total Frequency
1	1	68
2	0	482

Probability modeled is converted=1.

Class Level Information

Class	Value	Design Variables
poptype	Rural	1
	Urban	-1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	413.519	409.787
SC	417.829	418.406
-2 Log L	411.519	405.787

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	5.7323	1	0.0167
Score	5.8077	1	0.0160
Wald	5.6836	1	0.0171

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
poptype	1	5.6836	0.0171

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-1.9468	0.1306	222.0996	<.0001
poptype	Rural	1	0.3114	0.1306	5.6836	0.0171

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
poptype Rural vs Urban	1.864	1.117	3.111

Association of Predicted Probabilities and Observed Responses

Percent Concordant	33.3	Somers' D	0.154
Percent Discordant	17.8	Gamma	0.302
Percent Tied	48.9	Tau-a	0.033
Pairs	32776	c	0.577

Multivariate modeling for poor outcome

In determining factors associated with non-conversion after the intensive phase, all two way interactions were evaluated. Important two way interactions, adjusted for age were gender and geographic setting (poptype) and DOT.

The first important two way interaction analysis showed gender was a significant predictor of poor outcome while adjusting for age

The LOGISTIC Procedure

Model Information	
Data Set	WORK.OUTCOME
Response Variable	outcome
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	502

Number of Observations Used	502

Response Profile		
Ordered Value	**outcome**	**Total Frequency**
1	1	61
2	0	441

Probability modeled is outcome=1.

Class Level Information		
Class	**Value**	**Design Variables**
gender	**1**	1
	2	-1
age3	**1**	-1
	2	1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	373.410	373.816
SC	377.629	390.690
-2 Log L	371.410	365.816

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	5.5948	3	0.1331
Score	5.4019	3	0.1446
Wald	5.2274	3	0.1559

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
gender	1	4.9863	0.0255
age3	1	0.8441	0.3582
gender*age3	1	0.1547	0.6940

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.0314	0.1450	196.2328	<.0001
gender	**1**	1	0.3238	0.1450	4.9863	0.0255
age3	**2**	1	-0.1332	0.1450	0.8441	0.3582
gender*age3	**1 2**	1	0.0570	0.1450	0.1547	0.6940

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	46.1	**Somers' D**	0.176
Percent Discordant	28.6	**Gamma**	0.235
Percent Tied	25.3	**Tau-a**	0.038
Pairs	26901	**c**	0.588

The second important two way interaction showed type of DOT was a significant predictor of poor outcome while adjusting for age

The LOGISTIC Procedure

Model Information	
Data Set	WORK.OUTCOME
Response Variable	outcome
Number of Response Levels	2
Model	binary logit

Model Information	
Optimization Technique	Fisher's scoring

Number of Observations Read	502
Number of Observations Used	408

Response Profile

Ordered Value	outcome	Total Frequency
1	1	47
2	0	361

Probability modeled is outcome=1.

Note: 94 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information

Class	Value	Design Variables	
dot1	**1**	-1	-1
	2	1	0
	3	0	1
age3	**1**	-1	
	2	1	

Model Convergence Status
Quasi-complete separation of data points detected.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	293.510	291.817
SC	297.522	315.884
-2 Log L	291.510	279.817

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	11.6935	5	0.0392
Score	11.7313	5	0.0387
Wald	9.8992	5	0.0781

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
dot1	2	9.3758	0.0092
age3	1	0.0018	0.9663
dot1*age3	2	0.1765	0.9155

Analysis of Maximum Likelihood Estimates						
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept			1	-3.7889	44.0655	0.0074	0.9315
dot1	**2**		1	2.3496	44.0657	0.0028	0.9575
dot1	**3**		1	-3.7241	88.1308	0.0018	0.9663
age3	**2**		1	-1.8627	44.0655	0.0018	0.9663
dot1*age3	**2**	**2**	1	1.9958	44.0657	0.0021	0.9639
dot1*age3	**3**	**2**	1	-3.8585	88.1308	0.0019	0.9651

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	43.4	**Somers' D**	0.258

Association of Predicted Probabilities and Observed Responses			
Percent Discordant	17.6	**Gamma**	0.423
Percent Tied	39.0	**Tau-a**	0.053
Pairs	16967	**c**	0.629

The third important two way interaction analysis showed that geographic setting (poptype) was a significant predictor of poor outcome.

The LOGISTIC Procedure

Model Information	
Data Set	WORK.OUTCOME
Response Variable	outcome
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	502
Number of Observations Used	502

Response Profile		
Ordered Value	**outcome**	**Total Frequency**
1	1	61
2	0	441

Probability modeled is outcome=1.

Class Level Information		
Class	**Value**	**Design Variables**
age3	**1**	-1
	2	1
poptype	**Rural**	1

Class Level Information		
Class	**Value**	**Design Variables**
	Urban	-1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	373.410	373.985
SC	377.629	390.859
-2 Log L	371.410	365.985

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	5.4256	3	0.1432
Score	5.6326	3	0.1309
Wald	5.4797	3	0.1399

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
age3	1	0.0977	0.7546
poptype	1	3.8511	0.0497
age3*poptype	1	1.0156	0.3136

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-1.9911	0.1404	201.0905	<.0001
age3	**2**	1	-0.0439	0.1404	0.0977	0.7546

Analysis of Maximum Likelihood Estimates							
Parameter			**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
poptype	**Rural**		1	0.2755	0.1404	3.8511	0.0497
age3*poptype	**2**	**Rural**	1	-0.1415	0.1404	1.0156	0.3136

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	46.2	**Somers' D**	0.174
Percent Discordant	28.9	**Gamma**	0.231
Percent Tied	24.9	**Tau-a**	0.037
Pairs	26901	**c**	0.587

All important two way interactions were included in the first full model (gender, type of DOT, and geographic setting) while adjusting for age. All three remained significant and were included in the full final model.

The LOGISTIC Procedure

Model Information	
Data Set	WORK.OUTCOME
Response Variable	outcome
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	502
Number of Observations Used	408

Response Profile		
Ordered Value	**outcome**	**Total Frequency**
1	1	47
2	0	361

Probability modeled is outcome=1.

Note: 94 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information

Class	Value	Design Variables	
gender	**1**	1	
	2	-1	
age3	**1**	-1	
	2	1	
poptype	**Rural**	1	
	Urban	-1	
dot1	**1**	-1	-1
	2	1	0
	3	0	1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	293.510	288.397
SC	297.522	312.465
-2 Log L	291.510	276.397

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	15.1132	5	0.0099
Score	15.4884	5	0.0085
Wald	14.4899	5	0.0128

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
gender	1	3.9060	0.0481
age3	1	0.0063	0.9369
poptype	1	1.6272	0.2021
dot1	2	10.1411	0.0063

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.1780	0.3655	35.5069	<.0001
gender	**1**	1	0.3264	0.1651	3.9060	0.0441
age3	**2**	1	0.0127	0.1599	0.0063	0.9369
poptype	**Rural**	1	0.2037	0.1597	1.6272	0.0521
dot1	**2**	1	0.7150	0.3870	3.4139	0.0016
dot1	**3**	1	-0.4254	0.7032	0.3659	0.5452

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
gender 1 vs 2	1.821	1.005	1.269
age3 2 vs 1	1.026	0.548	1.920
poptype Rural vs Urban	1.503	1.004	2.860
dot1 2 vs 1	2.751	1.455	5.164
dot1 3 vs 1	0.873	0.108	7.060

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	63.8	**Somers' D**	0.334
Percent Discordant	30.4	**Gamma**	0.354
Percent Tied	5.8	**Tau-a**	0.068
Pairs	16967	**c**	0.667

Confounding was assessed by dropping and age comparing resulting odds ratios. The odds ratios were not significantly different. Therefore, there was no confounding.

The LOGISTIC Procedure

Model Information	
Data Set	WORK.OUTCOME
Response Variable	outcome
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	502
Number of Observations Used	408

Response Profile

Ordered Value	outcome	Total Frequency
1	1	47
2	0	361

Probability modeled is outcome=1.

Note: 94 observations were deleted due to missing values for the response or explanatory variables.

Class Level Information

Class	Value	Design Variables	
gender	**1**	1	
	2	-1	
poptype	**Rural**	1	
	Urban	-1	
dot1	**1**	-1	-1
	2	1	0

Class Level Information		
Class	**Value**	**Design Variables**
	3	0 1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	293.510	286.403
SC	297.522	306.460
-2 Log L	291.510	276.403

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	15.1070	4	0.0045
Score	15.4873	4	0.0038
Wald	14.4920	4	0.0059

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
gender	1	3.9935	0.0457
poptype	1	1.6210	0.0030
dot1	2	10.1358	0.0063

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.1774	0.3654	35.5118	<.0001
gender	**1**	1	0.3278	0.1641	3.9935	0.0457

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
poptype	**Rural**	1	0.2029	0.1593	1.6210	0.2030
dot1	**2**	1	0.7140	0.3867	3.4085	0.0649
dot1	**3**	1	-0.4240	0.7029	0.3638	0.5464

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
gender 1 vs 2	1.926	1.013	3.665
poptype Rural vs Urban	1.500	1.303	2.802
dot1 2 vs 1	2.729	1.455	5.120
dot1 3 vs 1	0.875	0.108	7.068

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	60.8	**Somers' D**	0.332
Percent Discordant	27.7	**Gamma**	0.375
Percent Tied	11.5	**Tau-a**	0.068
Pairs	16967	**c**	0.666