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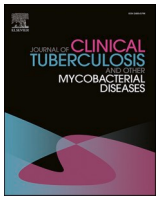

Low treatment success rate among previously treated persons with drug-susceptible pulmonary tuberculosis in Kampala, Uganda

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ABSTRACT

Rationale: In 2017, the treatment regimen for previously treated persons with tuberculosis (TB) changed to a shorter regimen that lasts six months and consists of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. Few studies have examined treatment success rate (TSR) among previously treated persons with TB including the associated factors.

Objective: To determine TSR and the associated factors among previously treated persons with bacteriologically confirmed pulmonary TB on a six-month treatment regimen in Kampala, Uganda.

Methods: We retrieved data (January 2012 and December 2021) across six TB clinics in the Kampala Metropolitan area for all previously treated persons with bacteriologically confirmed pulmonary TB. TSR was defined as cure or treatment completion. Frequencies and percentages for categorical data, and the mean and standard deviation for numerical data were computed. Multivariable modified Poisson regression analysis was performed to identify factors associated with TSR, reported as adjusted risk ratio (aRR) with a 95% confidence interval (CI).

Measurements and main results: We enrolled 230 participants with a mean age of 34.8±10.6 years. TSR was 52.2% and was associated with *Mycobacterium tuberculosis* (MTB) sputum smear load of ≥2+ (1–10 or >10 Acid Fast Bacilli (AFB)/Field) (aRR = 0.51; 95% CI, 0.38–0.68), TB/human immunodeficiency virus (HIV) (aRR = 0.67; 95% CI, 0.51–0.88) or unknown HIV serostatus (aRR = 0.42; 95% CI, 0.26–0.68), and digital community-based directly observed therapy short-course (DOTS) (aRR = 0.42; 95% CI, 0.20–0.88).

Conclusions: The TSR among previously treated persons with bacteriologically confirmed pulmonary TB on a six-month treatment regimen is suboptimal. TSR is less likely for people with TB/HIV co-infection or unknown HIV serostatus, high MTB sputum smear load, and on digital community-based DOTs. We recommend strengthening of TB/HIV collaborative activities and people with TB with high MTB sputum smear load should receive targeted treatment support, and the contextual barriers to digital community DOTS should be addressed.

1. Introduction

Successful treatment of tuberculosis (TB) is an important indicator for measuring the optimal performance of TB control programs, and the World Health Organization has set the target to at least 90%[1]. Achieving the target of ≥90 treatment success rate reduces the transmission of TB at both household and community levels and prevents mortality and complication at the personal level. In Uganda, people with drug-susceptible TB (excluding people with TB meningitis and osteoarticular TB), both new and previously treated persons, are currently treated with a six-month regimen consisting of two months of Isoniazid, rifampicin, Pyrazinamide, and ethambutol (HRZE) and four months of HR, which is shortened as 2HRZE/4RH. The 2022 World Health Organization (WHO) guideline recommends using a four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin, with the standard six-month regimen as the alternative option when treating persons with drug-susceptible pulmonary TB[2]. However, the guideline has not been fully operationalized in Uganda and across several TB Control Programs. The six-month regimen, which has similar performance in terms of efficacy and safety to the four-month regimen [3], is presently used to treat persons with drug-susceptible pulmonary TB.

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Most studies on treatment success rates have measured this outcome among newly diagnosed patients with TB [4–8]. The studies have shown variable treatment success rates, with the lowest at 61.3%[4] and the highest at 90.6%[5], while others have reported treatment success rates in the range of 80–85%[6–8]. While the performance of the six-month treatment regimen among persons with a new diagnosis of TB is known, little is known about previously treated persons with TB across TB control programs in developing countries. Moreover, previous studies have reported that previously treated persons with TB are less likely to achieve treatment success[9,10].

To the best of our knowledge, no study has examined the treatment success rate among previously treated persons with TB managed with the six-month regimen (2RHZE/4RH) in Uganda. Understanding the magnitude of treatment success is important because unsuccessful treatment of TB leads to the emergence of drug resistance and transmission of TB at the household and community levels, including death and complications at a personal level. We, therefore, investigated the magnitude of treatment success and the associated factors among previously treated persons with bacteriologically confirmed pulmonary TB who received the six-month regimen (2RHZE/4RH) in Kampala, Uganda.

This information will support TB control programs to understand the performance of the six-month treatment regimen in a real-world setting and design context-relevant measures to address suboptimal treatment success rates.

2. Methods and materials

2.1. Data source

Data for the present study are from a parent study[11], the anti-TB regimen (ATTIRE) study, designed to evaluate the effectiveness of the six-month treatment regimen (2RHZE/4RH) on treatment success. The dataset is published in the parent study[11]. The parent study was approved by Clarke International University Research Ethics Committee (CIU-REC) in Kampala, Uganda (CLARKE-2021–101) and received administrative clearance from the Kampala Capital City Authority (KCCA) Directorate of Public Health and Environment (DPHE/KCCA/1301). A need for informed consent was waived by the ethics committee since it was logistical impractical to reach the participants. Findings are reported following the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[12,13].

The parent study used a standardized data abstraction tool to retrieve data from TB unit registers at all six large TB clinics in the Kampala metropolitan area, Uganda. The data were on all previously treated persons with bacteriologically confirmed pulmonary TB aged ≥15 years who had received and completed treatment between January 2012 and December 2021. A person with a bacteriologically confirmed pulmonary TB is one from whom a biological specimen is positive by smear microscopy, culture or a WHO-recommended rapid diagnostic like Xpert MTB/RIF. In the parent study, people with confirmed or intermediate rifampicin resistance based on GeneXpert test results were excluded as they have drug-resistant TB and had received a second-line TB treatment regimen. Also, people with unknown rifampicin resistance status were excluded since their drug-resistant TB status was not known. Overall, the study focused on previously treated persons with bacteriologically confirmed pulmonary TB who are drug-susceptible.

The data were retrieved between January and February 2022 on the following: 1) the patient's sociodemographic characteristics such as age, sex, treatment supporter availability, baseline weight in kilograms, and baseline nutritional status measured using the mid-upper arm circumference (MUAC) as green, yellow, and red to signify no, moderate, and severe malnutrition, respectively; 2) the health facility characteristic included the level of care thus level III versus level IV; 3) the clinical factors included the TB treatment regimen, baseline *Mycobacterium bacilli* (MTB) sputum smear load, sputum smear conversions at 2, 5 and 6 months, mode of TB treatment, and human immunodeficiency virus (HIV) serostatus amongst others; 4) the treatment outcomes included cure, treatment completed, treatment failed, dead, lost-to-follow-up, and transfer out. MTB sputum smear load was graded as follows: 1 + if 10–99 Acid Fast Bacilli per 100 Field), 2+ if 1–10 AFB/Field, and 3+ if >10 AFB/Field. All persons with TB/HIV were on anti-retroviral therapy (ART) and cotrimoxazole prophylaxis (CPT). We adopted the WHO standard definition for treatment outcomes (S1 Table 1).

2.2. Measurements

This study utilized the following covariates from the parent study: the level of health facility (Health Center III versus Health Center IV), age in years, sex (male or female), type of previously treated person with bacteriologically confirmed pulmonary TB (relapse or treatment after failure), HIV serostatus (positive, negative, and unknown), baseline MUAC, and baseline weight in kilograms, type of directly observed therapy short-course (DOTS) namely digital community, health facility, and non-digital community, treatment supporter availability (yes versus no), and treatment outcome data. Treatment success was defined on a dichotomous scale of yes or no, computed as cure or treatment completed. Conversely, people with the treatment outcomes of death, treatment failure, and lost-to-follow-up were considered unsuccessfully treated.

2.3. Statistical analysis

We summarized the data descriptively using means and standard deviations for numerical data, and for categorical data, we used frequencies and percentages. We used the Chi-square test to assess differences in treatment success when the cell counts were large (≥5), otherwise, Fisher's exact test was used. We assessed mean differences in treatment success for numerical data such as age using the Student's *t*-test when the data had normal distribution, otherwise, for skewed data, we used the Wilcoxon-rank sum test.

Variables with a probability value (p-value) of < 0.1 at the bivariate analysis level and those deemed clinically relevant for treatment success were considered for the multivariable analysis. Here, we fitted a modified Poisson regression with robust standard errors since the outcome was large, with the reference category as the most frequent variable level. We excluded variables that did not improve the model fit as measured by the log-likelihood and retained those with $p < 0.05$. We assessed model fit using the Akaike Information Criteria (AIC) and selected a model with the lowest value, and a statistically nonsignificant Hosmer-Lemeshow goodness-of-fit Chi-square test. We reported both unadjusted and adjusted risk ratios (RR) with the corresponding 95% confidence interval (CI).

3. Results

3.1. Characteristics of the participants

We analyzed data from 230 participants with an overall mean age of 34.8±10.6 years (Table 1). The majority of the participants were males (68.7%), aged 25–34 years (33.5%), 59.6% had ≥2+ MTB sputum smear load (1–10 or >10 AFB/Field), and 82.6% had received treatment through a health facility-based DOTS and had a treatment supporter (82.6%). Treatment outcomes were distributed as follows: 117 (50.9) cure, 3 (1.3) treatment completed, 82 (35.7) treatment failed, 8 (3.5) dead, 7(3.0) lost to follow-up, and 13 (5.7) transfer-out. Therefore, of the 230 participants, 120 (52.2%) achieved treatment success. The highest proportion of treatment success was among participants who had received treatment at a Health Centre III level (67.5%), males (76.7%), 25–34 years (35.8%), 1+ MTB sputum smear load (10–99 AFB/100 Field) (84.9%), without HIV (60.8%), those treated under health facility-based DOTS (92.5%), and those with a treatment supporter

Table 1
General characteristics of the participants.

Variable	Level	Overall (n = 230)	Treatment success rate		P-value
			No (n = 110)	Yes (n = 120)	
		No. (%)	No. (%)	No. (%)	
Level of health facility	Health Centre III	117 (50.9)	36 (32.7)	81 (67.5)	<0.001
	Health Centre IV	113 (49.1)	74 (67.3)	39 (32.5)	
Sex	Female	72 (31.3)	44 (40.0)	28 (23.3)	0.01
	Male	158 (68.7)	66 (60.0)	92 (76.7)	
Age groups (years)	15–24	37 (16.1)	16 (14.5)	21 (17.5)	0.735
	25–34	77 (33.5)	34 (30.9)	43 (35.8)	
	35–44	73 (31.7)	39 (35.5)	34 (28.3)	
	45–54	31 (13.5)	16 (14.5)	15 (12.5)	
	≥55	12 (5.2)	5 (4.5)	7 (5.8)	
	mean (SD)	34.8 (10.6)	35.1 (10.8)	34.5 (10.4)	0.662
MTB sputum smear load	1+ (10–99 AFB/100 Field)	93 (40.4)	14 (15.1)	79 (84.9)	<0.001
	≥2+ (1–10 or > 10 AFB/ Field)	137 (59.6)	96 (70.1)	41 (29.9)	
Baseline weight	mean (SD)	51 (16.4)	52.9 (13.7)	49.3 (18.5)	0.104
HIV serostatus	Negative	92 (40.0)	19 (17.3)	73 (60.8)	<0.001
	Positive	87 (37.8)	52 (47.3)	35 (29.2)	
	Unknown	51 (22.2)	39 (35.5)	12 (10.0)	
Type of DOTS	Digital community	29 (12.6)	24 (21.8)	5 (4.2)	<0.001
	Health facility	191 (83.0)	80 (72.7)	111 (92.5)	
	Non-digital community	10 (4.3)	6 (5.5)	4 (3.3)	
Treatment supporter availability	No	40 (17.4)	10 (9.1)	30 (25.0)	0.003
	Yes	190 (82.6)	100 (90.9)	90 (75.0)	
MUAC	Green		372 (80.9)	17 (89.5)	0.583
	Yellow		27 (5.9)	1 (5.3)	
	Red		61 (13.3)	1 (5.3)	

(75.0%).

Statistically significant differences in treatment success rate were observed concerning the level of health facility, sex, MTB sputum smear load, HIV serostatus, mode of treatment, and treatment supporter presence, all had $p < 0.05$.

3.2. Factors associated with treatment success rate at univariable and multivariable analysis

Table 2 presents the univariable and multivariable analysis results. In the univariable analysis, treatment success rate was significantly less likely among females compared to males (RR = 0.67; 95% CI, 0.49–0.92), less likely among people with MTB sputum smear load of ≥2+ (1–10 or >10 AFB/Field) compared to people with MTB sputum smear load of 1+ (10–99 AFB/100 Field) (RR, 0.35; 95% CI, 0.27–0.46), and less likely among people with TB/HIV (RR = 0.51; 95% CI, 0.38–0.67) or unknown HIV serostatus (RR = 0.30; 95% CI, 0.18–0.49) compared to those without HIV. Treatment success rate was more likely among people with TB who had received treatment at the Health Center III level compared to the Health Center IV level (RR = 2.01; 95% CI, 1.51–2.66). Compared to health facility-based DOTS, digital community

Table 2
Factors associated with treatment success rate among previously treated persons with bacteriologically confirmed pulmonary TB on a six-month regimen.

Variable	Level	Modified Poisson regression analysis	
		Univariable	Multivariable
		RR (95% CI)	aRR (95% CI)
Level of health facility	Health Centre IV	1	
	Health Center III	2.01*** (1.51–2.66)	
Sex	Male	1	1
	Female	0.67* (0.49,0.92)	0.82 (0.64–1.07)
Age groups (years)	15–24	1	
	25–34	0.98 (0.70–1.39)	
	35–44	0.82 (0.56–1.19)	
	45–54	0.85 (0.54–1.35)	
	≥55	1.03 (0.59–1.79)	
MTB sputum smear load	1+ (10–99 AFB/100 Fields)	1	1
	≥2+ (1–10 or > 10 AFB/Field)	0.35*** (0.27–0.46)	0.51*** (0.38–0.68)
Baseline weight	1-kg increase	0.99 (0.99–1.00)	
HIV serostatus	Negative	1	1
	Positive	0.51*** (0.38–0.67)	0.67** (0.51–0.88)
	Unknown	0.30*** (0.18–0.49)	0.42*** (0.26–0.68)
Type of DOTS	Health facility	1	1
	Digital community	0.30** (0.13–0.67)	0.42* (0.20–0.88)
	Non-digital community	0.69 (0.32–1.49)	0.71 ([0.45–1.12)
Treatment supporter availability	No	1	
	Yes	0.63*** (0.50–0.80)	

Note: 1) Risk ratios are exponentiated coefficients at a 5% significant level; 2) 95% confidence intervals in brackets; 3) *$p < 0.05$, ***$p < 0.01$, ***$p < 0.001$; 4) RR: Risk ratio; 5) aRR: Adjusted risk ratio.

DOTS (RR = 0.30; 95% CI, 0.13–0.67) and non-digital community-based DOTS (RR = 0.69; 95% CI, 0.32–1.49) were associated with a lower likelihood of treatment success rate.

In the multivariable analysis, people with MTB sputum smear load of ≥2+ (1–10 or >10 AFB/Field) compared to 1+ (10–99 AFB/100 Field) (Adjusted risk ratio (aRR) = 0.51; 95% CI, 0.38–0.68), people with TB/HIV (aRR = 0.67; 95% CI, 0.51–0.88) or unknown HIV serostatus (aRR = 0.42; 95% CI, 0.26–0.68) compared to those without HIV, and people treated under the digital community DOTS compared to health facility DOTS (aRR = 0.42; 95% CI, 0.20–0.88) had a lower likelihood of treatment success rate.

4. Discussion

Our study shows that slightly more than half of the participants achieved treatment success rate. The likelihood of treatment success rate is lower among people with a high baseline MTB sputum smear load, people with TB/HIV or unknown HIV serostatus, and if the treatment is under digital community DOTS compared to facility-based DOTS. Compared to the WHO desired target of at least a 90% treatment success rate[14], our study shows a suboptimal treatment success rate among previously treated persons with bacteriologically confirmed pulmonary TB treated with the six-month regimen. The treatment success rate is not far distant from 68.1% observed among previously treated persons with bacteriologically confirmed pulmonary TB in rural eastern Uganda[15]. Recent WHO data (2021/2022) show an 80% TSR among previously treated persons with TB compared to the 52.2% TSR we report in this study, which is an improvement although the TSR is arguably a snapshot and the data spanned relatively short period (1-year) to provide a strong conclusion. Overall, the suboptimal TSR should be a concern for TB control programs as it potentially leads to drug-resistant TB and unfavourable treatment outcomes and increased risk of complications at the individual level. However, implementation sciences research is needed to identify the contextual barriers to optimal treatment success rate among previously treated persons with bacteriologically confirmed pulmonary TB on a six-month regimen.

Our finding that a high MTB sputum smear load is associated with a lower likelihood of treatment success rate is not unique. Biologically, people with high MTB sputum smear load have a slow sputum smear conversion rate[16] leading to unsuccessful treatment outcomes. The finding underscores the importance of closely supporting treatment adherence to prevent treatment failure and achieve treatment success rate among previously treated persons with bacteriologically confirmed pulmonary TB.

Our finding of a lower likelihood of treatment success rate for people with TB/HIV and unknown HIV serostatus can be explained by several factors. HIV and TB interact in various ways. Untreated HIV weakens the immune system and increases vulnerability to opportunistic infections such as TB, accelerates the progression from latent TB infection to TB disease, increase the risk of TB relapse, slows the response to TB treatment, and hinders sputum smear conversion leading to unfavourable treatment outcomes, namely death and treatment failure[10]. People with TB/HIV are more likely to die compared to those without HIV[17] and are more likely to develop disseminated TB and to respond poorly to treatment. All these effects combined translate to unfavourable treatment outcomes hence lower treatment success rate. Besides the high mortality rates, people with TB/HIV have high rates of adverse drug reactions leading to increased loss-to-follow-up. Resultantly, many countries and TB control programs with high HIV prevalence do not achieve the global treatment success rate target of at least 90%[18].

The lower likelihood of treatment success rate and unknown HIV serostatus is reported in a few studies. One study showed that people with TB and unknown HIV serostatus are more likely to be lost to follow-up and to fail treatment[17] leading to a reduced treatment success rate. A study in Benin reported that people with TB and unknown HIV serostatus are less likely to achieve treatment success rate compared to those without HIV[19]. A systematic review and *meta*-analysis conducted in Ethiopia showed that 27% of people with TB have unknown HIV serostatus suggesting the problem is prevalent [20]. Unknown HIV serostatus could have arisen from several factors such as not recording one's HIV serostatus, not testing people with TB for HIV, or refusing to undertake an HIV test by people with TB, which we do not have the data for to verify. Regardless of the reasons, unknown HIV serostatus impact negatively people with TB and TB control programs.

For example, unknown HIV serostatus potentially leads to delayed initiation of HIV treatment, which might increase the risk of mortality and reduce the chance of treatment success rate among those with TB/HIV. Other negative consequences include a high risk of treatment failure and severe immunosuppression, with the latter leading to multiple opportunistic infections. Also, there is a possibility that people with unknown HIV serostatus might be having HIV and if this is the case, the high risk for treatment failure may be explained by the serostatus. However, it remains unclear whether people with unknown HIV serostatus had HIV or not so future studies should explore this relationship. Overall, since HIV fuels the TB epidemic, TB/HIV collaborative programs should be strengthened to ensure universal access to HIV testing and ART initiation while TB care and prevention should be a priority for HIV control programs.

We found a lower likelihood of treatment success rate among participants managed through the digital community DOTS compared to the health facility-based. Digital DOTS particularly video DOTS (VDOTS) is feasible and acceptable for monitoring and supporting TB treatment in Uganda and has shown high levels of treatment adherence [21]. However, several challenges such as phone malfunction, uncharged batteries, and app malfunctions have been reported as reasons for missed videos[21]. A study conducted in Vietnam among persons with bacteriologically confirmed pulmonary TB reported that the majority of the participants accepted VDOT but faced several challenges [22]. Findings from a qualitative study conducted in Cambodia showed that patients are willing to accept video DOT (in general, mobile technologies and apps) but prefer frequent in-person interactions with healthcare providers compared to VDOTS since the latter option does not offer interactions with healthcare providers[23]. The study reported that patients face technical challenges with VDOTS (or digital technologies) for treatment and adherence support including how to make the app suitable for those illiterate[23]. These challenges might have contributed to the present finding. With electronic DOT being non-inferior to in-person DOT despite providing evidence for inclusion in the standard of care[24], our findings suggest a need for additional evidence. Overall, there are barriers to implementing digital DOTS which should be addressed to optimize treatment success rate among people with TB.

4.1. *Implications of findings for practice, research, and policy*

To improve TSR among previously treated persons with TB, barriers to suboptimal TSR like inadequate food, stigma, lack of social protection, frequent drug stock-outs and transportation challenges among others[25] should be addressed. The notable strategies might include strengthening health education on the importance treatment adherence and treatment completion[26], and providing incentives like food support[27,28] and unconditional cash grants[29,30]. Strategies to assess treatment adherence like pill counts, three-day medication adherence recall, self-reported medication adherence, and pharmacy refills, which currently are not routinely used in TB care should be encouraged. In addition, treatment adherence support measures like adherence counseling, peer support systems, mobile phone calls and text messaging, reminder devices (calendars, pill boxes, cell phone alarms, and diaries), peer-led dialogues, and behavioral skills or medication adherence training might be useful in improving TSR. Future research should explore the effectiveness of the strategies to improve TSR and those for monitoring treatment adherence among previously treated persons with

bacteriologically confirmed pulmonary TB.

4.2. Study strengths and limitations

This is one of the few studies to examine treatment success rate among previously treated persons with bacteriologically confirmed pulmonary TB treated with the six-month regimen in Uganda. Based on the published studies [15,17,19] and given that these patients constitute a minority of the TB burden[11], our sample size of 230 participants is reasonably large. We abstracted data spanning nearly a decade (January 2012 to December 2021) which demonstrates a credible trend in treatment success rate. We computed treatment success rate based on standard WHO definitions to mitigate inaccuracies in the computation of cure and treatment failure as previously reported[31]. Our data show that the treatment success rate was 75.0% (30/40) among people without treatment support and 47.4% (90/190) among those with treatment support. We computed that the study has an 87.9% statistical power at a 5% significance level, which is acceptable. Limitations in the present study include the analysis of secondary data that is prone to transcription and transposition errors among others. Our analysis did not include several unmeasured confounders, namely travel distance, anthropometric measures such as body mass index, comorbidities other than HIV infection, diabetes mellitus, undernutrition and other immunosuppressive conditions that trigger TB relapse, and the level of treatment adherence amongst others.

We do not have data about the duration and outcomes of initial treatment, the status of sputum smear bacillary load, whether dead or alive, and time of previous TB episode. Besides, we do not have data on the pattern of resistance to first-line treatment among all the participants. However, previously treated persons with TB might benefit from testing for extremely resistant TB, both rifampicin and isoniazid resistance, with drug susceptibility testing if confirmed with isoniazid resistance in settings with a high prevalence of Isoniazid resistance. This is important since persons with isoniazid resistant TB are treated with REZ and levofloxacin for six months. The interpretation of the findings should consider these limitations.

5. Conclusion

We found a suboptimal treatment success rate among people with retreatment bacteriologically confirmed pulmonary TB treated with the six-month regimen. Treatment success rate is less among people with TB/HIV or unknown HIV serostatus, people with high baseline MTB sputum smear load, and people treated under digital community DOTS compared to health facility-based DOTS. We conclude that besides strengthening TB/HIV collaborative activities, people with TB who have a high MTB sputum smear load should receive targeted treatment support and the contextual barriers to digital community DOTS have to be addressed.

CRediT authorship contribution statement

Jonathan Izudi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Gerald Okello:** Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Francis Bajunirwe:** Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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