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Tb Knowledge And Outcomes In A Routine Care Setting In Kampala, Uganda

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Sincerely,

Tyler Johnson

Abstract

TB education and counseling (TEC) is universally recommended for individuals initiating treatment for active TB in Uganda. The effectiveness of routine TEC in Kampala and the association between specific knowledge domains and treatment outcomes is unknown. We sought to (1) to evaluate the effectiveness of routine TEC in helping individuals to increase and retain TB-specific knowledge and (2) to examine the association between TB knowledge and treatment outcomes among individuals diagnosed with TB. We enrolled adults (age ≥18) initiating treatment for active TB at Kisenyi Health Centre in Kampala, Uganda into a prospective, observational cohort study. We administered a verbal survey before and after TEC and at three refill appointments. We analyzed change in knowledge at three hierarchically-organized levels. We used Poisson and logistic regression models to describe associations with nonadherence and final treatment outcome, respectively. Eighty patients were enrolled. After TEC, TB disease-specific and treatment-specific knowledge increased significantly overall and across each of the eight sub-domains. Nine of 17 disease-specific questions and 11 of 13 treatment-specific questions changed significantly after TEC. For disease-specific knowledge, scores did not change significantly at two of three follow-up interviews; for treatment-specific knowledge, scores did not change significantly at any of the follow-up interviews. Disease- and treatment-specific scores were significantly associated with nonadherence at two weeks and two months. At least two of the eight sub-domains were significantly associated with nonadherence at each time point. Routine TEC was effective at increasing knowledge, and this knowledge was generally retained. Individual question scores were heterogeneous and show where TEC can be improved. Further, domains associated with nonadherence provide insight into areas where TB knowledge may be most important and where TEC should be targeted in future interventions.

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Table 1. Study participant characteristics

Characteristic	Frequency (n=80)	Percent
Sex		
Male	58	73%
Female	22	28%
Age		
<29	38	48%
30-39	23	29%
40-49	16	20%
>50	3	4%
Occupation		
Self-employed	36	45%
Formally employed	27	34%
Not employed	15	19%
Student	2	3%
Education		
No schooling at all	5	6%
Literacy classes only	2	3%
Some primary school	23	29%
Completed primary school	19	24%
Some secondary school	20	25%
Completed secondary school	5	6%
Higher education	6	8%
HIV Status		
Positive	29	36%
Negative	51	64%
Previous TB Status		
Yes	24	30%
No	56	70%
TEC Type		
Group	43	54%
Individual	37	46%
Received TEC with Visual Aid		
Yes	45	56%
No	35	44%
TB Diagnosis		
GeneXpert	56	70%
Sputum smear microscopy	2	3%
Clinical diagnosis	17	21%
Extrapulmonary	4	5%
Data missing	1	1%

Table 2. Knowledge content domains: within-patient difference of means

Content Domain[1]	Pre-Test Mean (95% CI) (%)	Post-Test Mean (95% CI) (%)	Difference (95% CI) (%)	p-value[2]
Disease-Specific Knowledge				
Prevention	47 (36-59)	83 (74-91)	35 (22-48)	<0.0001
Microbiology	49 (44-54)	65 (60-70)	16 (8-23)	0.0001
Transmission	54 (48-61)	69 (63-74)	14 (8-21)	<0.0001
Warning signs	71 (66-76)	80 (76-84)	9 (3-14)	0.002
TB vs HIV	77 (72-83)	85 (81-89)	7 (2-13)	0.0087
Treatment-Specific Knowledge				
Treatment monitoring	20 (14-27)	75 (69-81)	54 (47-62)	<0.0001
How to take medications	32 (27-37)	74 (69-79)	42 (37-47)	<0.0001
How treatment works	72 (67-76)	96 (94-98)	24 (20-29)	<0.0001

[1]Content domains are listed in descending order of magnitude of difference within each construct
[2]p-value for dependent t-test of difference in means

Table 3. TB disease-specific knowledge individual question scores

Content Domain	Question	Pre	Post	p-value[1]
Microbiology	TB attacks the lungs*	87%	96%	0.01
	*TB can attack other parts of the body outside of the lungs**	*34%*	*68%*	*<0.0001*
	*Everyone who is exposed to TB germs does not become ill**	*30%*	*31%*	*0.85*
Warning signs	A cough that does not go away for two weeks is a warning sign of TB*	88%	96%	0.03
	A cough that goes away after a few days not is a warning sign of TB*	82%	93%	0.04
	Loss of weight is a warning sign of TB*	91%	90%	1.00
	*General weakness is a warning sign of TB**	*57%*	*64%*	*0.10*
	*Vomiting is not a warning sign of TB**	*46%*	*56%*	*0.05*
Transmission	TB can be spread through the air*	99%	98%	1.0
	How are TB germs released?	*60%*	*86%*	*<0.0001*
	If you breathe in TB germs, where do they settle and grow?	*47%*	*71%*	*0.0002*
	*TB cannot be spread through food**	*39%*	*46%*	*0.32*
	*TB cannot be spread through drinking water**	*32%*	*41%*	*0.10*
TB vs HIV	Can you have HIV only (without TB)?	92%	99%	0.06
	Can you have TB only (without HIV)?	90%	99%	0.02
	*Unprotected sex cannot spread TB**	*50%*	*58%*	*0.30*
Prevention	How can you stop the spread of TB?	49%	83%	<0.0001

*Question was answered in a "Yes/No" format
[1]p-value for McNemar's test
(Italicized questions have sub-optimal post-test scores)

Table 4. TB Treatment-specific knowledge individual question scores

Content Domain	Question	Pre	Post	p-value[1]
How treatment works	How often can TB be cured if treatment is started in time?	91%	100%	0.008
	When do you take your TB medications?	27%	99%	<0.0001
	If you stop treatment before the full course of therapy, your TB becomes harder to cure*	96%	96%	1.0
	If you stop taking the TB medication before the treatment period is finished, what might happen?	93%	96%	0.48
	When can you stop taking the TB medication?	*51%*	*89%*	*<0.0001*
How to take medications	What do your TB medications look like?	26%	96%	<0.0001
	If you have TB, how long do you take the medication?	53%	91%	<0.0001
	What should you do if your TB medication gives you yellow or red eyes, too much vomiting, intense body rash, or issues with sight?	*55%*	*89%*	*<0.0001*
	What should you do if your TB medication gives you joint pain?	*31%*	*56%*	*<0.0001*
	Name two potential side effects of TB treatment	*5%*	*65%*	*<0.0001*
	What should you do if your TB medication gives you nausea?	*26%*	*44%*	*0.001*
Treatment monitoring	When should you come to the clinic for your next appointment?	11%	95%	<0.0001
	After starting the medication, how long does it usually take to start feeling better?	*31%*	*54%*	*0.0001*

*Question was answered in a "Yes/No" format
[1]p-value for McNemar's test
(Italicized questions have sub-optimal post-test scores)

Table 5. TB knowledge retention in relation to post-test at diagnosis

Construct	Time Point	Mean Change	95% CI	p-value[1]
Disease-Specific	Two weeks	-1.2%	-5.1% to +2.7%	0.54
	Two months	-10%	-15% to -5.7%	<0.0001
	Five months	-2.9%	-7.1% to +1.3%	0.17
Treatment-Specific	Two weeks	+2.6%	-2.5% to +7.7%	0.31
	Two months	-3.0%	-7.6% to +1.5%	0.19
	Five months	-3.6%	-8.7% +1.4%	0.15

[1]p-value for dependent t-test of difference in means

Table 6. Self-reported nonadherence over the last week

Appointment	Number of patients reporting (n)	Mean number of days	Standard deviation	*Percent missing x number of doses in last week (%)*							
				0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Two weeks	73	2.1	1.9	22	22	21	15	8	5	3	4
Two months	67	1.2	1.6	51	16	9	16	4	1	0	1
Five months	54	0.78	1.5	69	11	9	2	7	0	0	2

Table 7. Self-reported difficulties with treatment

Experience	Two weeks, n=73 Mean (%)	Standard Error (%)	Two months, n=67 Mean (%)	Standard Error (%)	Five months, n=54 Mean (%)	Standard Error (%)
Felt worse after taking pills	43	6.0	24	5.3	11	4.2
Forgot to take pills	4.3	2.4	1.5	1.5	5.5	3.1
Ran out of pills	7.1	3.1	9.1	3.6	11	4.2
Was away from home	10	3.6	4.5	2.6	0	0
Too busy	2.9	2.0	0	0	0	0
Had trouble taking pills at specified times	59	5.9	26	5.4	15	4.8
Was confused about how to take pills	7.1	3.1	1.5	1.5	0	0

Table 8. Bivariate associations between knowledge measures (scaled 0-10) and self-reported non-adherent days in the last week

Variable	Two weeks, n=73 IRR (95% CI)	p-value[1]	Two months, n=67 IRR (95% CI)	p-value[1]	Five months, n=54 IRR (95% CI)	p-value[1]
Disease-specific	**0.86 (0.76-0.98)**	**0.02**	**0.82 (0.67-0.97)**	**0.02**	0.93 (0.73-1.20)	0.58
Microbiology	0.95 (0.89-1.02)	0.16	0.98 (0.90-1.08)	0.73	**0.87 (0.76-0.99)**	**0.04**
Warning signs	0.96 (0.89-1.05)	0.36	0.94 (0.83-1.05)	0.26	1.19 (0.99-1.43)	0.07
Transmission	**0.92 (0.85-0.98)**	**0.01**	**0.87 (0.79-0.97)**	**0.01**	0.90 (0.78-1.03)	0.14
TB vs HIV	0.94 (0.86-1.03)	0.12	0.98 (0.86-1.11)	0.74	0.87 (0.74-1.03)	0.10
Prevention	1.00 (0.96-1.04)	0.83	0.97 (0.92-1.02)	0.25	1.07 (0.96-1.18)	0.22
Treatment-specific	**0.88 (0.80-0.97)**	**0.01**	**0.80 (0.70-0.90)**	**<0.0001**	0.99 (0.83-1.19)	0.95
How treatment works	0.87 (0.73-1.04)	0.13	0.85 (0.66-1.09)	0.21	**1.82 (1.01-3.28)**	**0.05**
How to take meds	**0.90 (0.84-0.96)**	**0.001**	**0.89 (0.81-0.97)**	**0.01**	0.97 (0.85-1.11)	0.66
Treatment monitoring	0.96 (0.91-1.02)	0.20	**0.88 (0.81-0.94)**	**0.001**	0.98 (0.88-1.09)	0.72

[1]p-value for bivariate Poisson regression test

Table 9. Bivariate associations between demographic measures, clinical measures, and intermediate treatment variables and self-reported non-adherent days in the last week

Variable	Two weeks, n=73 IRR (95% CI)	p-value[1]	Two months, n=67 IRR (95% CI)	p-value[1]	Five months, n=54 IRR (95% CI)	p-value[1]
Demographic/Clinical Measures						
Female[2]	0.88 (0.62-1.26)	0.49	0.78 (0.47-1.3)	0.34	1.80 (0.98-3.30)	0.06
Age[3]	1.01 (1.00-1.03)	0.15	0.98 (0.96-1.01)	0.18	0.99 (0.95-1.02)	0.38
Person living with HIV[2]	1.30 (0.94-1.79)	0.11	1.15 (0.73-1.80)	0.55	0.94 (0.50-1.78)	0.86
Prior history of TB[2]	0.70 (0.48-1.01)	0.06	**0.43 (0.23-0.77)**	**0.005**	0.90 (0.47-1.72)	0.74
Individual counseling[2]	0.84 (0.61-1.15)	0.27	1.52 (0.97-2.40)	0.07	0.77 (0.42-1.41)	0.39
Completed primary school[2]	0.81 (0.59-1.11)	0.19	1.31 (0.82-2.10)	0.26	1.27 (0.67-2.42)	0.46
Intermediate treatment variables						
Number of late appointments[3]	1.09 (0.99-1.20)	0.10	1.00 (0.86-1.16)	0.99	**1.59 (1.28-1.96)**	**<0.0001**
Felt worse after taking the pills[2]	**2.01 (1.46-2.76)**	**<0.0001**	**1.62 (1.02-2.58)**	**0.04**	1.60 (0.71-3.60)	0.26
Forgot to take the pills[2]	0.76 (0.31-1.86)	0.55	1.69 (0.42-6.89)	0.46	**2.83 (1.19-6.72)**	**0.02**
Ran out of pills[2]	**2.10 (1.37-3.22)**	**0.001**	**3.25 (1.99-5.31)**	**<0.0001**	**4.92 (2.64-9.18)**	**<0.0001**
Was away from home[2]	**1.67 (1.11-2.54)**	**0.02**	1.42 (0.58-3.52)	0.45	--	--
Too busy[2]	**2.81 (1.70-4.65)**	**<0.0001**	**--**	--	--	--
Trouble taking pills at specified times[2]	**1.75 (1.25-2.47)**	**0.001**	**3.5 (2.25-5.44)**	**<0.0001**	**2.30 (1.18-4.49)**	**0.02**
Confused about how to take pills[2]	1.43 (0.84-2.43)	0.19	2.60 (0.81-8.15)	0.11	--	--

[1]p-value for bivariate Poisson regression test
[2]Binary variable
[3]Continuous variable
[4]Count variable (range: 0-6)

Table 10. Multivariate adjusted associations with self-reported nonadherence

Variable	Two weeks, n=73 Adjusted IRR (95% CI)	p-value[1]	Two months, n=67 Adjusted IRR (95% CI)	p-value[1]	Five months, n=54 Adjusted IRR (95% CI)	p-value[1]
Disease-specific						
Microbiology	--	--	--	--	**0.88** (0.77-1.0)	0.05
Warning signs	--	--	--	--	**1.2** (0.96-1.5)	0.11
Transmission	**0.93** (0.87-1.0)	0.04	**0.92** (0.83-1.0)	0.13	--	--
TB vs HIV	--	--	--	--	**0.82** (0.68-0.98)	0.03
Prevention	--	--	--	--	--	--
Treatment-specific						
How treatment works	--	--	--	--	**1.6** (0.85-2.9)	0.15
How to take meds	**0.91** (0.85-0.98)	0.008	--	--	--	--
Treatment monitoring	--	--	**0.90** (0.84-0.97)	0.008	--	--
Demographic/Clinical Measures						
Female	--	--	--	--	**2.0** (1.1-3.8)	0.03
Age	--	--	--	--	--	--
Person living with HIV	**1.3** (0.94-1.8)	0.12	--	--	--	--
Prior history of TB	--	--	**0.52** (0.28-0.96)	0.04	--	--
Individual counseling	--	--	**1.6** (1.0-2.5)	0.05	--	--
Completed primary school	--	--	--	--	--	--

[1]p-value for coefficient in multivariate Poisson regression test

Table 11. Frequency of patients classified under each final treatment outcome

Outcome	Frequency (n=80)	%	Coding for analysis
Treatment completed	49	68	Completed treatment
Died	2	2.8	Did not complete treatment
Lost to follow up	17	24	
Treatment failed	4	5.6	

Table 12. Bivariate associations with final treatment outcome

Variable	Mean (Did not complete treatment)	Mean (Completed treatment)	OR (95% CI)	p-value[1]
Disease-specific knowledge	75%	76%	1.11 (0.74-1.66)	0.61
Microbiology	65%	63%	0.96 (0.77-1.20)	0.73
Warning signs	80%	80%	0.99 (0.75-1.30)	0.93
Transmission	**63%**	**71%**	**1.17 (0.95-1.46)**	**0.14**
TB vs HIV	87%	85%	0.94 (0.70-1.25)	0.66
Prevention	78%	82%	1.02 (0.90-1.15)	0.74
Treatment-specific knowledge	81%	82%	1.04 (0.76-1.44)	0.79
How treatment works	97%	96%	0.85 (0.45-1.61)	0.62
How to take medications	73%	74%	1.01 (0.80-1.26)	0.96
Treatment monitoring	72%	76%	1.05 (0.88-1.26)	0.59
Demographic/Clinical Measures				
Female	**18%**	**33%**	**2.30 (0.67-7.90)**	**0.19**
Age (years)	31.0	31.5	1.01 (0.96-1.07)	0.70
Persons living with HIV	41%	31%	0.69 (0.24-1.93)	0.48
Prior history of TB	**18%**	**37%**	**2.76 (0.81-9.39)**	**0.10**
Individual counseling	**32%**	**55%**	**2.81 (0.98-8.03)**	**0.06**
Completed primary school	59%	61%	1.02 (0.37-2.80)	0.98
Number of appointments late	**2.45**	**1.53**	**0.69 (0.50-0.96)**	**0.03**
Self-reported nonadherence				
Two weeks (days over last week)	**2.6**	**1.8**	**0.78 (0.58-1.06)**	**0.11**
Two months (days over last week)	**1.9**	**1.0**	**0.72 (0.49-1.04)**	**0.08**

[1]p-value for bivariate logistic regression test

Table 13. Multivariate adjusted associations with final treatment outcome

Variable	Adjusted OR (95% CI)	p-value[1]
Disease-specific knowledge		
Microbiology	--	--
Warning signs	--	--
Transmission	**1.18** (0.94-1.49)	0.16
TB vs HIV	--	--
Prevention	--	--
Treatment-specific knowledge		
How treatment works	--	--
How to take medications	--	--
Treatment monitoring	--	--
Demographic/Clinical Measures		
Female	**2.40** (0.67-8.65)	0.18
Age (years)	--	--
Persons living with HIV	--	--
Prior history of TB	--	--
Individual counseling	**2.73** (0.93-8.02)	0.07
Completed primary school	--	--

[1]p-value for bivariate logistic regression test

Figures

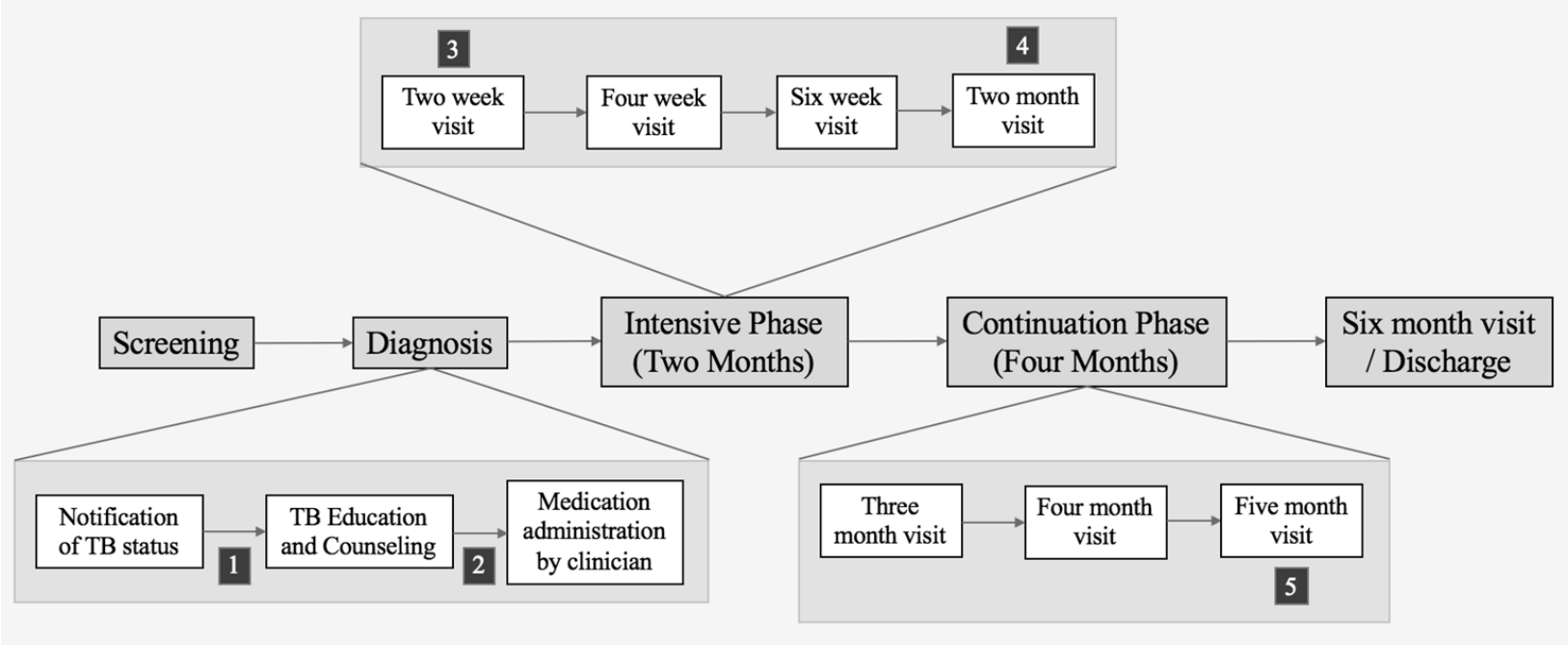

Figure 1. TB treatment timeline at Kisenyi Health Centre

(Study interview points indicated by numbered boxes)

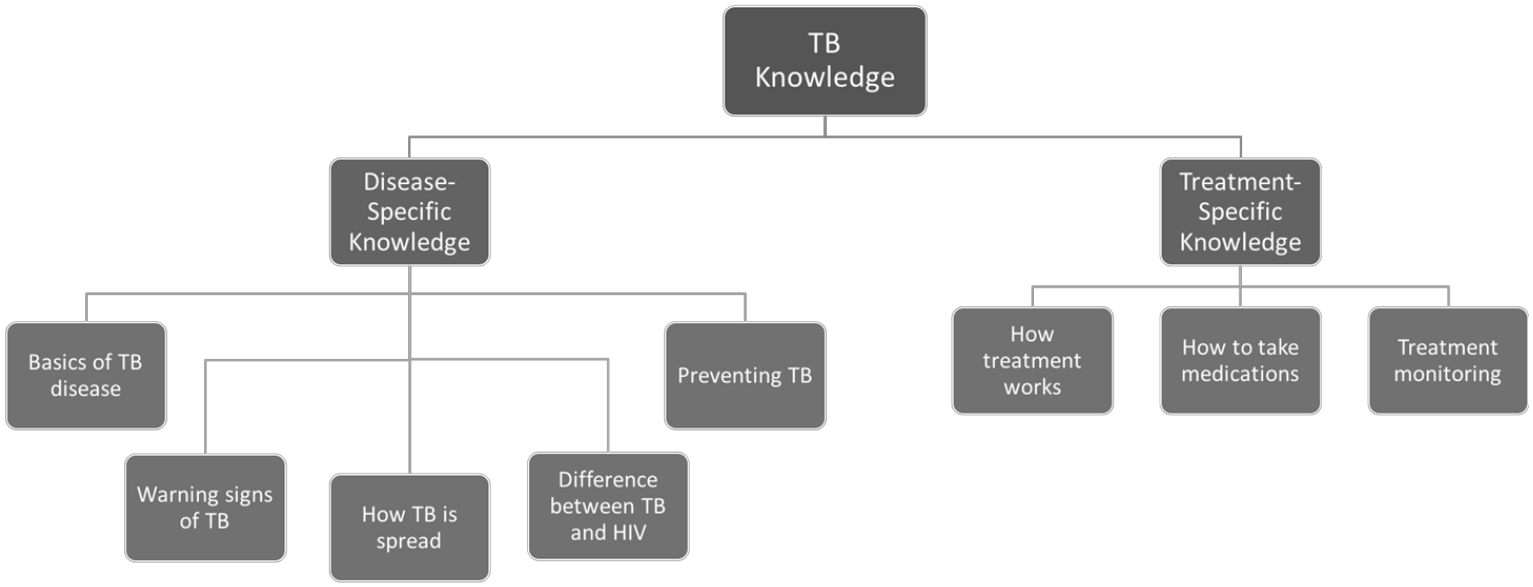

Figure 2. Schematic delineating the two constructs and eight content domains of TB knowledge

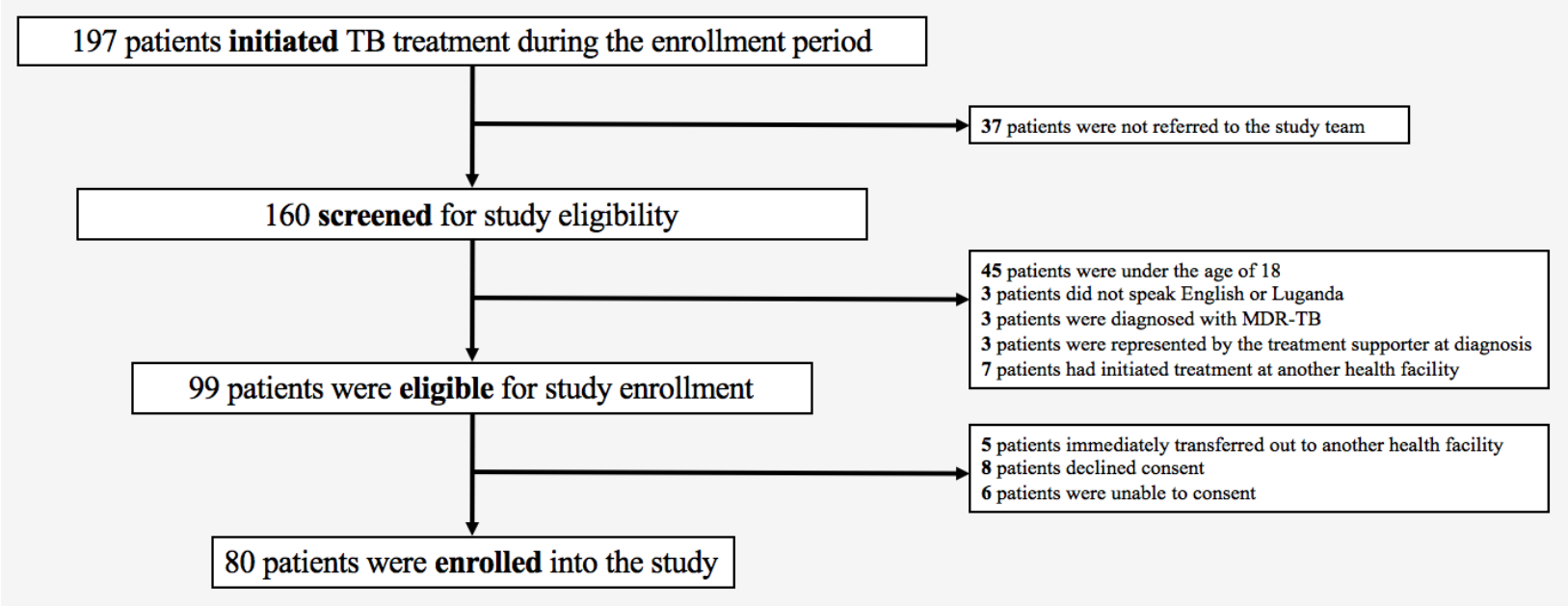

Figure 3. Results of screening and enrollment process

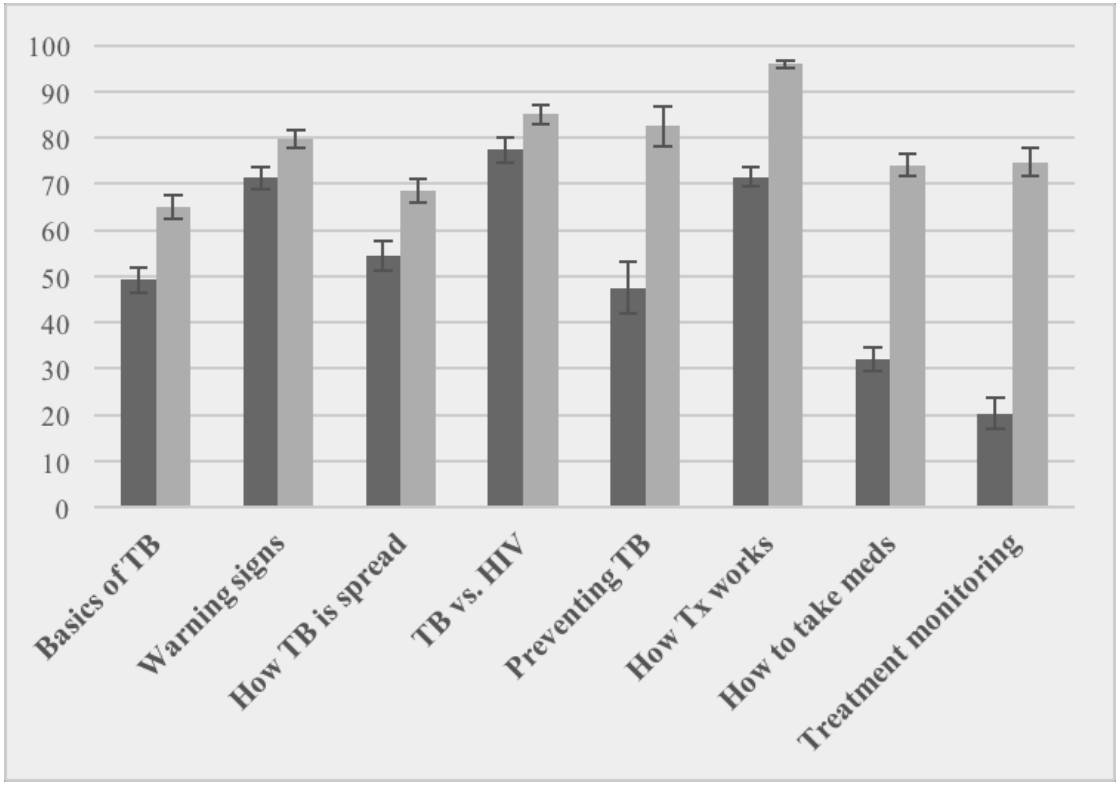

Figure 4. Mean TB knowledge content domain scores before and after TEC

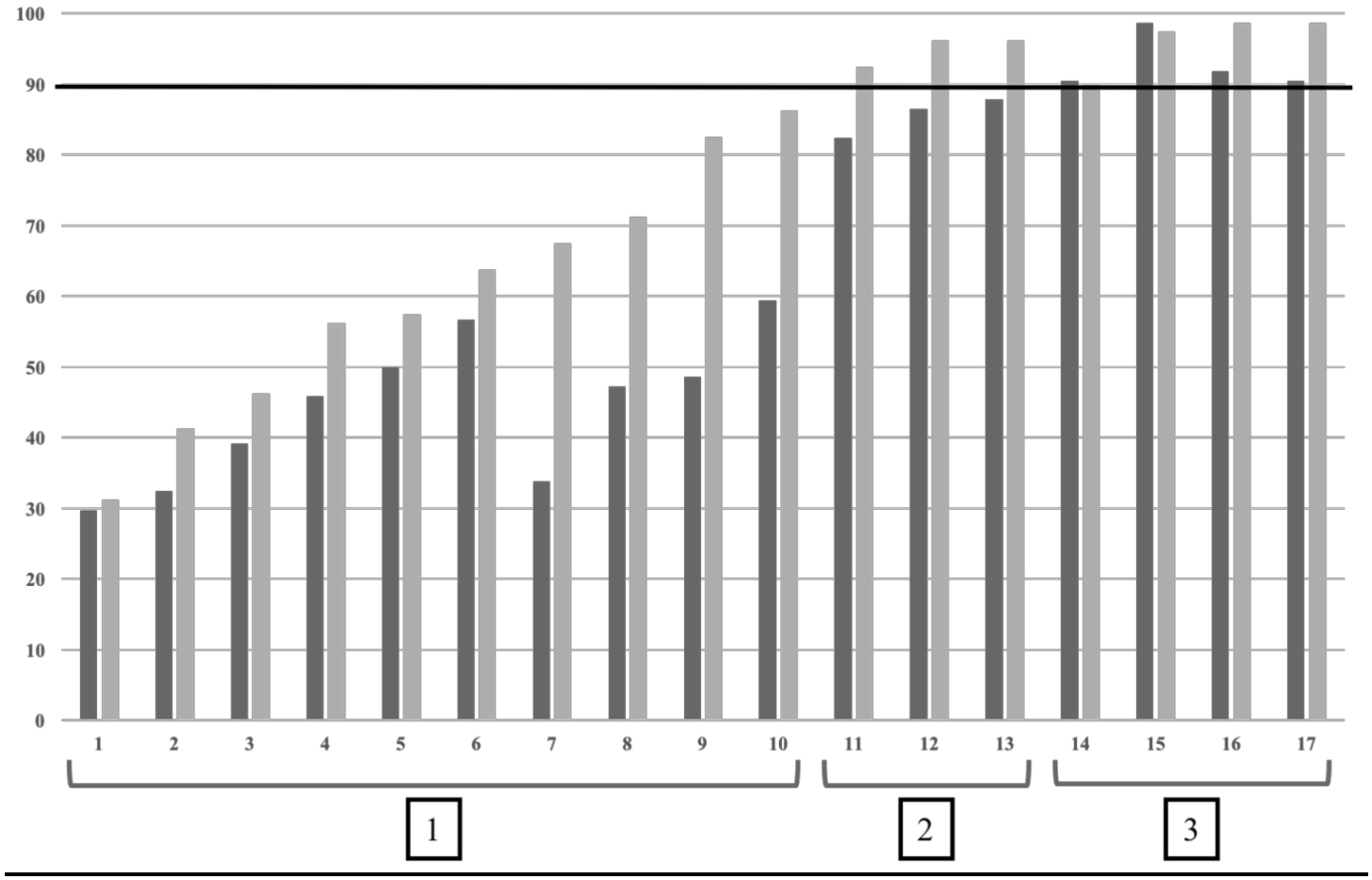

Figure 5. Mean TB disease-specific individual question scores before and after TEC *(Question legend on next page)*

Block 1: Pre-test and post-test score are below 90%

Block 2: Pre-test score is below 90%/post-test score is above 90%

Block 3: Pre-test and post-test score are above 90%

Figure 5 Question Legend

Block	Question Number	Question
1	1	Everyone who is exposed to TB germs does not become ill
	2	TB cannot be spread through drinking water
	3	TB cannot be spread through food
	4	Vomiting is not a warning sign of TB
	5	Unprotected sex cannot spread TB
	6	General weakness is a warning sign of TB
	7	TB can attack other parts of the body outside of the lungs
	8	If you breathe in TB germs, where do they settle and grow?
	9	How can you stop the spread of TB?
	10	How are TB germs released?
2	11	A cough that goes away after a few days is not a warning sign of TB
	12	TB attacks the lungs
	13	A cough that does not go away for two weeks is a warning sign of TB
3	14	Loss of weight is a warning sign of TB
	15	TB can be spread through the air
	16	Can you have HIV only (without TB)?
	17	Can you have TB only (without HIV)?

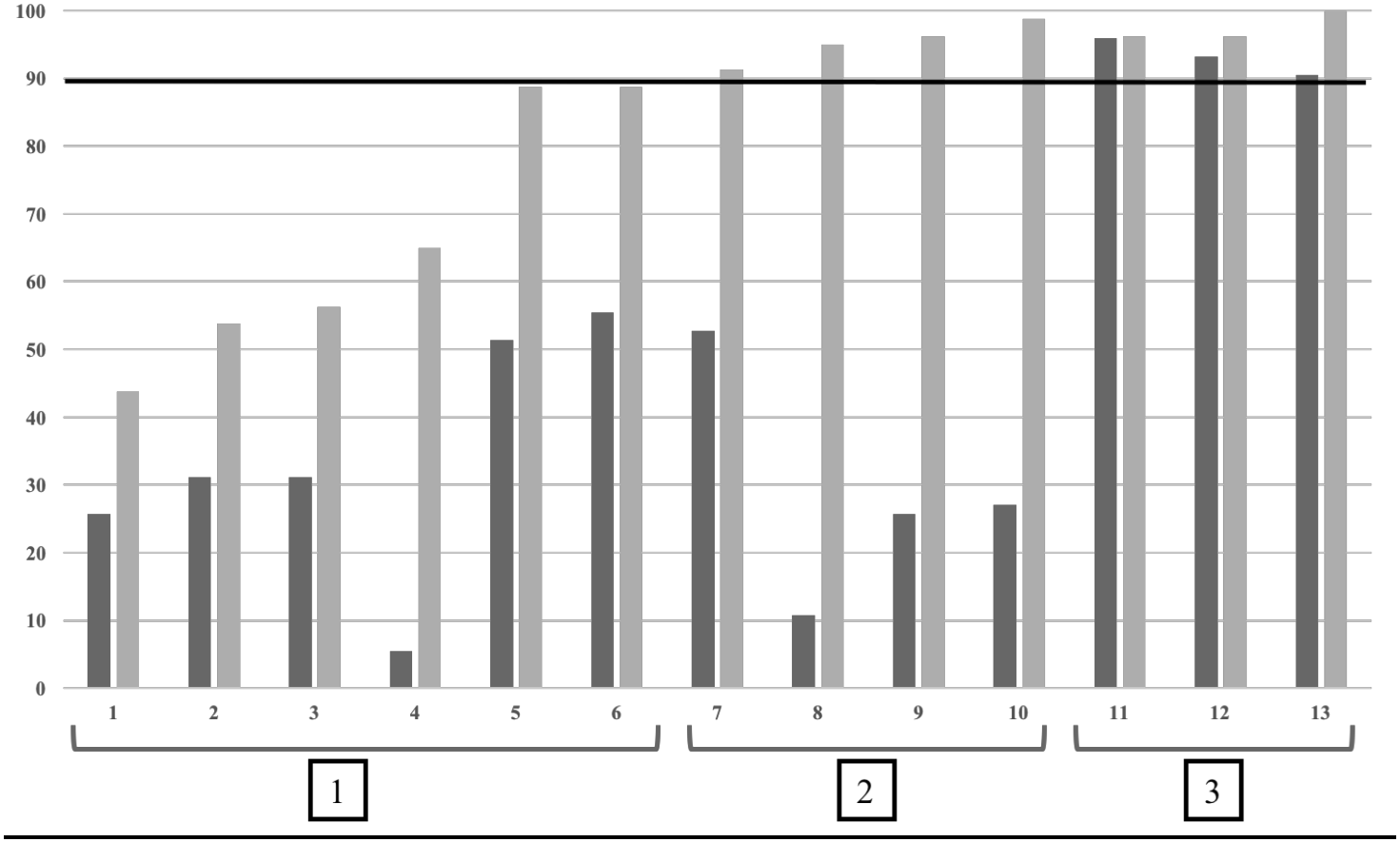

Figure 6. Mean TB treatment-specific individual question scores before and after TEC *(Question legend on next page)*
Block 1: Pre-test and post-test score are below 90%
Block 2: Pre-test score is below 90%/post-test score is above 90%
Block 3: Pre-test and post-test score are above 90%

Figure 6 Question Legend

Block	Question Number	Question
1	1	What should you do if your TB medication gives you nausea?
	2	After starting the medication, how long does it usually take to start feeling better?
	3	What should you do if your TB medication gives you joint pain?
	4	Name two potential side effects of TB treatment
	5	When can you stop taking the TB medication?
	6	What should you do if your TB medication gives you yellow or red eyes, too much vomiting, intense body rash, or issues with sight?
2	7	If you have TB, how long do you take the medication?
	8	When should you come to the clinic for your next appointment?
	9	What do your TB medications look like?
	10	When do you take your TB medications?
3	11	If you stop treatment before the full course of therapy, your TB becomes harder to cure
	12	If you stop taking the TB medication before the treatment period is finished, what might happen?
	13	How often can TB be cured if treatment is started in time?

Introduction

Tuberculosis (TB) is one of the largest contributors to global mortality and recently surpassed HIV as the leading cause of death from a single pathogen [1]. In 2014, the member states of the World Health Organization (WHO) and the United Nations (UN) signed on to the WHO's END TB Strategy, which calls for large reductions in global TB mortality and incidence by 2030 [1]. In 2017, it was estimated that 10 million incident active TB cases occurred globally, with 25% of these occurring in the WHO African Region [1]. While the global TB disease incidence rate is steadily falling at around 2% per year, the rate of decline is not sufficient to meet the END TB Strategy goal of 4-5% per year by 2020 [1, 2]. Additionally, the END TB Strategy calls for a reduction of the global TB case fatality ratio to 10% by 2020; in 2017, this number was still at 16% [1, 2]. What must be done, then, to achieve the END TB Goals? In addition to structural changes at the policy and health system level and research into new treatments and prevention strategies, the END TB Strategy states that existing interventions must be expanded and streamlined to focus on high-impact and patient-centered approaches [2].

With timely diagnosis and treatment, active drug-susceptible TB disease can be easily cured [1]. Despite this, in low- and middle-income countries with a high burden of TB disease and death, poor adherence to TB treatment persists. Poor adherence has been shown to result in both a decline in treatment effectiveness and the development of antimicrobial resistance [3, 4]. In Uganda, 25,000 people died from TB in 2017, and the most recent data show that 1.6% of new TB cases in the country are resistant to at least rifampin, the most effective first-line drug for TB [1]. The specific impact of partial nonadherence was demonstrated in a recent pooled analysis of three clinical trials of novel 4-month treatment regimens [5]. Compared to those who did not miss a single dose, participants who missed approximately one dose per week had 2.4-fold

increased risk of unfavorable outcomes, and those that missed two doses per week had 29 times the risk of unfavorable outcomes compared to those who did not miss any doses [5].

A systematic review of qualitative studies uncovered a number of broad themes that may influence adherence [3]. While some factors such as poverty and gender discrimination can reduce treatment adherence even in patients willing to adhere, the review discerned a number of factors that could be directly attributed to individual patient factors, including knowledge and beliefs about TB and its treatment [3]. Patient knowledge can interact with structural and health care service factors (e.g. drug stock-outs, long wait times and transport difficulties) as well as social factors (e.g. stigma and motivation to complete treatment) to either encourage or dissuade adherence [3]. Uganda is one of 20 countries that account for 83% of global incident TB disease cases among people living with HIV (PLHIV), and HIV status has also been documented as a potential risk factor for nonadherence [1, 3]. The complex nature of these determinants suggests a need for more patient-centered approaches to promote positive treatment outcomes [3]. To this end, Pillar One of the END TB strategy calls for a focus on integrated, patient-centered care and prevention, and specifically states that "patient-centered care and support, sensitive and responsive to patients' educational, emotional and material needs, is fundamental to the new draft global tuberculosis strategy" [2]. We hypothesize that a combination of patient-centered interventions will be necessary to address different barriers to adherence, including TB knowledge and beliefs, TB-related stigma, and TB treatment intentions. One intervention that has been utilized in this effort is patient TB education and counseling (TEC) delivered by health workers. TEC aims to increase patient knowledge around TB disease and treatment, ensure that the patient understands the outcomes associated with adherence behavior, and provide the patient with a sense of self-efficacy to adhere to medication and complete treatment [6].

It is universally advised that TEC be administered to individuals initiating treatment for active TB. The WHO guidelines for treatment of drug-susceptible TB strongly recommend health education for all patients initiating treatment, with this intervention specifically defined as a method of encouraging treatment adherence [7]. There is evidence that TEC may be important in influencing positive treatment outcomes when combined with a larger set of patient-centered adherence interventions, including reminders, incentives, and digital technologies such as SMS messages and video-observed therapy (VOT) [6]. A systematic review and meta-analysis of studies examining the impact of these adherence interventions found three randomized controlled trials and one cohort study that demonstrated an association between TEC and increased rates of treatment adherence, completion, and cure [6, 8-11]. However, the nature of the interventions in these studies focused either exclusively on psychotherapy or on education related to treatment processes [8-11]. Additional studies on the independent effect of patient education and counseling on medication adherence have been sparse in number and have generally focused on treatment for latent TB [12]. There is a gap in the literature examining the independent impact of TEC interventions that focus on adherence counseling. Furthermore, there is a lack of studies evaluating the effectiveness of TEC in delivering education around both TB disease and treatment.

Previous studies have examined the association between TB knowledge and a variety of outcomes. Two cross-sectional studies in Ethiopia found associations between TB knowledge and health-seeking behavior [13, 14]. Additionally, a cross-sectional study in Nigeria found that unsatisfactory knowledge was associated with patient delay in treatment initiation, and a case-control study in Morocco found that poor knowledge resulted in an increased risk of defaulting from treatment [15]. There is reason to believe that TB knowledge influences a number of

treatment outcomes, but the specific domains of knowledge that drive this association are unknown.

We found only one study that conducted an evaluation of routine TEC prescribed by the country's National TB Program, which took place in Vietnam [16]. While TEC is universally recommended, the effectiveness of its implementation in practice has not been systematically evaluated. Previous qualitative studies conducted in Kampala with patients and health workers highlighted that there was a perceived importance placed on TEC in encouraging patient adherence, but there was a need for improvements in routine TEC administered to patients [17, 18]. This project seeks to determine if routine practice is effective in increasing TB disease and treatment knowledge, and, if so, which aspects are associated with favorable TB treatment outcomes. We conducted this study as part of a larger assessment of individual-level barriers to treatment adherence. The results of the project will inform the development of a tailored adherence intervention to be piloted in Kampala.

Methods

Study Design and Setting

We performed a prospective cohort study to describe the antecedents of TB treatment behaviors and their associations with outcomes among adult patients receiving treatment for active TB in Kampala, Uganda. The study was conducted at Kisenyi Health Centre, an urban, public, primary health clinic operated by the Kampala Capital City Authority (KCCA) on behalf of the Ugandan Ministry of Health (MoH). At Kisenyi Health Centre and other similar clinics nationwide, the Uganda National TB and Leprosy Programme (NTLP) offers free TB diagnosis and treatment services in dedicated TB Units with WHO-approved, short-course treatment regimens through community-based directly observed therapy [7]. Laboratory technicians employed by KCCA perform on-site diagnostic testing using GeneXpert molecular testing and sputum smear microscopy. Full-time KCCA nurses dispense medications. Generally, TEC is administered by part-time community health workers (CHWs) rather than by clinicians. This task-shifting adaptation was introduced by external implementing partners who provide technical assistance with USAID funding. Through this mechanism, CHWs are employed to conduct contact investigation and other TB programmatic activities.

The Uganda NTLP recommends TB health education for all individuals diagnosed with active TB [19]. Specifically, the Ugandan MoH Guidelines for Tuberculosis Infection Control state that "it is necessary to promptly initiate adequate TB treatment and support adherence education to ensure completion of treatment for persons diagnosed with TB disease" [20]. No specific guidance on the format of counseling (e.g. group vs. individual) is provided. The NTLP has made education and counseling materials available through a partnership with USAID [21]. After diagnosis, patients return to the clinic for medication refills every two weeks for the first

two months of treatment (the intensive phase) and every month for months three to six of treatment (the continuation phase). The timeline of treatment from diagnosis to discharge is outlined in Figure 1.

Participants

We considered consecutive adults (age ≥18) newly diagnosed with active TB for inclusion into the study if they spoke English or Luganda and were diagnosed with drug-susceptible TB. A protocol for enrollment was established under the supervision of the KCCA TB Unit Nurse In-Charge at Kisenyi Health Centre. Patients were referred to the study team by any staff member in the TB unit once they were determined to be initiating TB treatment, either as a result of positive GeneXpert testing, positive smear microscopy testing, or a clinical diagnosis made by a trained clinician. All patients who were registered in the Uganda NTLP Register as incident TB disease cases during the study period were considered eligible for inclusion. We enrolled patients consecutively, with up to 5 new patients enrolled daily; the research team decided *a priori* that it would not be feasible to conduct more interviews than this in one day. We automatically excluded patients if they initiated treatment when the study team was not present (outside of the hours of 9 a.m. to 4 p.m., Monday-Thursday), or if the TB unit staff did not refer the patient to the study team before they received TEC. We also excluded individuals if they transferred in from another health center, declined consent, were unable to consent, or had immediate plans to transfer out to receive treatment at a different health center.

Measurements

We collected data through audits of the treatment register and a survey that was verbally administered by a Ugandan community health worker. Survey data were recorded into a Qualtrics survey that was loaded onto an electronic tablet. The survey instrument is included in Appendix A. Throughout the study period, we collected appointment attendance data and final treatment outcomes from routine clinic registers.

We interviewed patients before they received routine TEC, collecting demographic and clinical information as well as a baseline knowledge assessment. After the initial interview, the patient received TEC, was given his or her first dose of medication, and was entered into the NTLP Treatment Register. Before the patient left the clinic, we conducted a follow-up knowledge assessment. Upon enrollment into the study, patients agreed to participate in 45-minute follow-up interviews at three of their eight follow-up appointments (specifically, at two weeks, two months, and five months). These interviews consisted of the knowledge assessment and an adherence self-assessment. If a study participant missed an appointment, a member of the study team called the patient to determine the reason they had not come to the clinic and, if applicable, reminded them that the study interview would be completed at the next follow-up visit. A schematic showing the timing of interviews is provided in Figure 1.

Survey Design

TB Literacy

We formulated the TB knowledge assessment to measure two major constructs: TB disease-specific knowledge and TB treatment-specific knowledge. We used two sources to formulate content domains for the assessment questions, with each source representing one of the

major constructs. We adapted five disease-specific content domains utilizing TB counseling guidelines published by Médecins Sans Frontières and learning objectives from the TB and HIV Health Education Flipchart developed by USAID and the Ugandan MoH [21, 22]. These five domains included (with shorthand in parentheses): Basics of TB (Microbiology), Warning signs of TB (Warning signs), How TB is Spread (Transmission), Differentiation between TB and HIV (TB vs HIV), and Preventing TB (Prevention) [21]. We adapted the treatment-specific content domains from a rapid review of TB treatment literacy materials. [23]. In the review, the content domains were developed utilizing concepts that had previously been identified as key enablers of HIV treatment adherence. The three content domains under treatment-specific knowledge include: How Treatment Works (e.g. patients understand that TB is curable and why adherence is important), How to Take Medications (e.g. patients can describe the appearance of TB drugs, length of treatment regimen, and side effect management), and Treatment Monitoring (e.g. patients understand what interactions with the health system they should expect and how they will know that treatment is working) [23]. We formulated individual questions in the assessment to reflect the content elements listed in the rapid review. We excluded the following content elements from the study's assessment questions: "Explains why TB regimen includes multiple drugs," "States which TB drugs are in the patient's regimen," and "Lists the names of individual TB drugs" [23]. TB drugs were administered in single tablets as a fixed-dose combination, so these content elements would have been irrelevant to the assessment. A schematic of the TB constructs and corresponding content domains used in the knowledge survey is provided in Figure 2.

We designed the following scoring algorithm to aid in analyzing TB knowledge at three hierarchical levels: construct, content domain, and individual component (question). We

assigned each individual knowledge question to one of the eight content domains. There was an uneven distribution of questions across the content domains. To give each content domain an equal weight, we calculated the mean score for the questions answered correctly within each content domain. We standardized the total score for the content domains within each construct to a ten-point scale.

The first TB knowledge block consisted of closed-ended questions to which the only possible answers were "yes" or "no." The second block consisted of open-ended questions. For these questions, we embedded decision rules into the survey questions to guide the interviewer in choosing "correct" or "incorrect" based on the response given. Decision rule criteria were initially composed of responses that members of the study team anticipated based on prior experience or that respondents gave during pilot testing of the TB knowledge assessment. If subjects gave new answers after initiation of the study, the study team agreed by consensus whether to include that answer in the 'correct' or 'incorrect' criteria for that question. We made this decision based on whether the response satisfactorily answered the question according to its reason for inclusion in the assessment (referencing the objectives and domains stated above). The study team then updated the response to include the new answer choice.

We specified scores greater than 90% as indicative of an adequate level of knowledge, whether at the construct, content domain, or individual component level. We set this operational definition of "adequate knowledge" to ensure that quality education had been administered. We selected a relatively high cutoff because each of these areas has been defined to be important in influencing TB treatment adherence and treatment completion. Our ultimate goal is the design of an intervention that delivers patient-centered care in which a patient understands the causes

and treatments for his or her illness. Ideally, patients would understand each of these knowledge components after receiving TEC.

TB Medication Adherence

We measured medication adherence in the survey through a self-assessment of nonadherence over the past 7 days. Previous evaluations of self-report methods have shown that this measure is a valid proxy for other adherence measures and can significantly predict clinical outcomes [24]. The self-assessment measures were taken at each of the three follow-up interviews, so analyses of association with nonadherence were conducted relative to each of the three measures. In addition, multiple possible explanations for nonadherence were surveyed (heretofore described as "difficulties with treatment"). We adapted the self-assessment questions from a tool used in an isoniazid preventive therapy (IPT) implementation study in South Africa [25].

Final Treatment Outcome

We defined final treatment outcome as a binary variable and coded WHO outcomes associated with treatment success (cured, treatment completed) as treatment completed and other WHO outcomes (died, treatment failed, and lost-to-follow-up) as treatment not completed [26].

Pilot Testing

Prior to initiation of study enrollment, we pilot tested each block of the assessment tool with patients already receiving treatment at Kisenyi Health Centre. Pilot testing was carried out by a Ugandan community health worker and included 12 patients. We revised questions if they

were determined to be difficult for patients to understand or vulnerable to misinterpretation. We tested different question types for each block to determine which method provided the most variance in patient responses. We timed each block and designed the final assessment tool used for the study to take no more than 45 minutes.

For the adherence self-assessment, we tested a Likert scale through which patients were asked to rate their adherence to medications since their last appointment. There was little variance in the answers given, with almost every respondent rating their adherence as "very good" or "excellent." In an effort to increase variance, we adapted the self-assessment to ask patients to estimate the number of days in the past week that doses were taken late or missed.

Analysis

We sought to answer four distinct questions in the analysis: (1) is routine TEC effective in increasing patients' TB-specific knowledge; (2) is knowledge gained from TEC retained throughout treatment; (3) is TB-specific knowledge associated with TB treatment nonadherence; and (4) is TB-specific knowledge associated with final treatment outcomes? We used STATA 14.1 (Stata Corporation, College Station, Texas) for all analyses. We conducted bivariate statistical tests at a significance level of $p<0.05$ and multivariate statistical tests at a significance level of $p<0.20$.

Effect of Routine TEC on TB Knowledge

We analyzed the difference in TB knowledge before and after each patient received TEC at three levels: construct, content domain, and knowledge component. For the constructs and content domains, we analyzed the differences in proportion of correct answers before and after

TEC using two-sided dependent t-tests. The null hypothesis was that there was no difference in the proportion of correct answers before and after TEC. For the individual questions, we compared the proportion of correct answers before and after TEC through McNemar's test. The null hypothesis was that the question was answered correctly at the same rate before and after TEC.

TB Knowledge Retention After Diagnosis

We analyzed retention of knowledge throughout each patient's treatment period stratified by construct (disease-specific and treatment-specific knowledge) and relative to the post-test at three time points after diagnosis: two weeks, two months, and five months. We analyzed the differences in proportion of correct answers using two-sided dependent t-tests. We compared the follow-up assessment results to the post-test to measure the extent to which within-patient knowledge was retained after receiving TEC.

Association Between TB Knowledge and Treatment Outcomes

We used Poisson regression models to describe the association between independent variables and TB treatment nonadherence. We conducted bivariate tests of association for the two knowledge constructs and each of the eight content domains using the post-test scores at diagnosis. We used the post-test scores because we found a general retention of knowledge from the post-test to each of the three follow-up time points. We also conducted bivariate tests of association for various demographic and clinical measures, including those that have been shown to be associated with adherence and TB outcomes. Factors previously shown to be associated with treatment outcomes include gender, age, HIV status and education level [3]. Additionally,

we examined bivariate associations with various intermediate treatment measures (e.g. number of late appointments and surveyed difficulties with treatment).

We used logistic regression models to describe the association between independent variables and final treatment outcome. We conducted bivariate tests of association between final treatment outcome and TB knowledge (at the level of constructs and content domains) and relevant demographic and clinical measures. We did not include patients who either transferred out of Kisenyi for treatment after enrolling into the study or had not yet completed treatment by March 1, 2019 in these analyses.

We used a multivariate Poisson regression model to estimate the adjusted relative risk of nonadherence and a multivariate logistic regression model to estimate the adjusted odds of treatment completion with increasing scores for individual knowledge content domains. We considered demographic and clinical variables for inclusion into the model if they have previously been shown to influence nonadherence or treatment completion or showed significant bivariate associations with the outcome. We did not consider variables for inclusion into the models if they could be considered intervening variables, as adjusting for these variables may have dominated the effect we intended to explore with the knowledge components. These variables included the various difficulties with treatment and the number of appointments attended late. After conducting bivariate tests of association, we included any variable into the model that showed an association at $p<0.20$. We used backward selection to remove nonsignificant variables.

Human Subjects

All patients provided written informed consent for participation. The study protocol was approved by the Makerere College of Health Sciences, the Uganda National Council for Science and Technology, and the Yale University Human Investigation Committee.

Results

Patients were recruited if they initiated treatment between June 5, 2018 and August 15, 2018. We enrolled a total of 80 patients during this period. The results of study enrollment are provided in Figure 3. The cohort was comprised of 28% female participants (n=22), 36% people living with HIV (n=29), and 30% who had experienced a prior TB disease episode (n=24). TEC was administered as part of a group for 54% of patients in the cohort. The USAID/MoH Educational Flipchart was used as a visual aid to supplement TEC for 56% of patients in the cohort. A summary of the study participants' characteristics is provided in Table 1.

Of the 80 subjects initially enrolled, two were lost to follow-up after the initial interviews at diagnosis because they elected to transfer out to receive treatment at another health center. They are included in analyses of within-patient change in knowledge before and after TEC but have been excluded from analyses involving nonadherence measurements and treatment outcomes.

Effect of Routine TEC on TB Knowledge

The mean TB disease-specific knowledge score at baseline was 61%, with baseline content domain scores ranging from 47% to 77%. Overall, there was a mean within-subject increase of 16% (95% CI: 12%-19%, $p<0.0001$) after TEC. There were modest but statistically significant within-subject increases across each of the five disease-specific content domains. In descending order of the magnitude of increases, knowledge related to 'Prevention' increased by 35% (95% CI: 22%-48%, $p<0.0001$); 'Microbiology' increased by 16% (95% CI: 8.2%-23%, $p=0.0001$); 'Transmission' increased by 14% (95% CI: 7.7%-21%, $p<0.0001$); 'Warning Signs' increased by 8.5% (95% CI: 3.2%-14%, $p=0.002$) and 'TB vs HIV' increased by 7.3% (95% CI:

1.9% to 13%, p=0.009). After TEC, the mean TB disease-specific knowledge score was 76%, with content domain scores ranging from 65% to 85%.

The mean TB treatment-specific knowledge score at baseline was 42%, with content domain scores ranging from 20% to 72%. Overall, there was a mean within-subject increase of 40% (95%CI: 36%-44%, p<0.0001) after TEC. There were statistically significant within-subject increases across each of the three treatment-specific content domains. In descending order of the magnitude of increases, 'Treatment Monitoring' increased by 54% (95% CI: 47%-62%, p<0.0001); 'How to Take Medications' increased by 42% (95% CI: 37%-47%, p<0.0001); and 'How Treatment Works' increased by 24% (95% CI: 20%-29%, p<0.0001). After TEC, the mean TB treatment-specific knowledge score was 82%, with content domain scores ranging from 74% to 96%. The mean pre-test and post-test scores, 95% confidence intervals and mean within-subject difference between pre- and post-test scores for each TB disease-specific and treatment-specific content domain are provided in Table 2. Figure 3 provides a bar graph depicting the pre- and post-test scores for each of the eight content domains.

Out of 17 disease-specific knowledge questions, the score on 9 questions changed significantly before and after TEC. Seven of the 17 questions were answered with a mean score greater than 90% on the post-test, representing an adequate level of knowledge. Of the 9 questions that showed a statistically significant improvement, 4 had mean post-test scores above 90%, and each of these questions had pre-test scores in the range of 80%-90%. There were 5 questions that showed no statistically significant improvement and had post-test means that were in the range of 41%-64%. These questions pertained to either TB transmission or warning signs. In Figure 5, the pre- and post-test score for each disease specific knowledge question are provided in a bar graph, in ascending order of the post-test score. Questions are grouped into

three blocks: (1) those with a pre- and post-test score below 90%, (2) those with a pre-test score below 90% but a post-test score above 90%, and (3) those with a pre- and post-test score above 90%.

Out of 13 treatment-specific knowledge questions, the score on 11 questions changed significantly before and after TEC. Seven of the 13 questions were answered with a mean score less than 90% on the post-test. Notably, out of three questions assessing patients' knowledge of potential treatment side effects and how to manage them, none reached a post-test score above 65%. Additionally, only 54% of patients knew how long it would take them to feel better after initiating treatment (compared to 31% at baseline). Figure 6 provides a bar graph of scores for each individual treatment-specific question, grouped in the same set of blocks as Figure 5. The mean scores on the pre- and post-test for each individual question, along with each question's p-value for the McNemar's test, are provided in Tables 3 (disease-specific knowledge questions) and 4 (treatment-specific knowledge questions).

Overall, 11% of patients had post-test scores above 90% for disease-specific knowledge, and 35% of patients had post-test scores above 90% for treatment-specific knowledge.

TB Knowledge Retention after Diagnosis

TB disease-specific knowledge did not significantly change relative to the post-test at two of the three follow-up interviews, and TB treatment-specific knowledge did not significantly change relative to the post-test at any of the follow-up interviews. For disease-specific knowledge, the change was -1.2% (95% CI: -5.1% to +2.7%, p=0.54) at two weeks; -10% (95% CI: -15% to -5.6%, p<0.0001) at two months; and -2.9% (95% CI: -7.1% to +1.3%, p=0.17) at five months. For treatment-specific knowledge, the change was +2.6% (95% CI: -2.5% to

+7.7%, p=0.31) at two weeks; -3.0% (95% CI: -7.6% to +1.5%, p=0.19) at two months; and -3.6% (95% CI: -8.7% to +1.4%, p=0.15) at five months. The results of the dependent t-tests for within-subject differences in means for the disease-specific and treatment-specific knowledge constructs are provided in Table 5.

Association Between TB Knowledge and Treatment Nonadherence

The mean number of pills late or missed in the last week was 2.1 at two weeks, 1.2 at two months, and 0.78 at five months. Table 6 displays the mean number of days of self-reported nonadherence over the last week and the proportion of patients who reported missing each possible value (range=0-7) at each time point. A summary of the mean percentage of "yes" answers for the questions assessing difficulties with treatment at each of the time points is provided in Table 7.

None of the previously-established risk factors for nonadherence showed bivariate associations with nonadherence in this cohort. However, at two months, patients who reported having TB before the current episode were 57% less likely to report nonadherence than patients experiencing their first TB episode (RR=0.43, 95% CI 0.23-0.77, p=0.05). The results of the bivariate Poisson regression analyses for demographic and various clinical variables are provided in Table 9.

The results for the bivariate tests of association with each knowledge element are provided in Table 8. Each of the knowledge constructs (disease-specific and treatment-specific knowledge) was significantly associated with nonadherence at two weeks and two months, but not at five months. For each 10% increase in disease-specific knowledge score, nonadherence decreased by 14% at two weeks (RR=0.86, 95% CI 0.76-0.98, p=0.021) and 18% at two months

(RR= 0.82, 95% CI 0.67-0.97, p=0.022). For each 10% increase in treatment-specific knowledge score, nonadherence decreased by 12% at two weeks (RR=0.88, 95% CI 0.80-0.97, p=0.010) and 20% at two months (RR=0.80, 95% CI 0.70-0.90, p<0.0001).

Among the eight content domains, at least two were significantly associated with self-reported nonadherence at each time point. Increasing score in "Transmission" knowledge was associated with decreasing rates of nonadherence at both two weeks (RR=0.92, 95% CI 0.85-0.98, p=0.011) and two months (RR=0.87, 95% CI 0.79-0.97, p=0.009). The same relationship was observed with knowledge related to "How to take medications" at two weeks (RR=0.90, 95% CI 0.84-0.96, p=0.001) and two months (RR=0.89, 95% CI 0.81-.97, p=0.010). At two months, increasing score in knowledge related to "Treatment monitoring" was significantly associated with decreasing rates of nonadherence (RR=0.88, 95% CI 0.81-0.94, p=0.001); this relationship was not observed at two weeks. Each of these content domains were no longer significantly associated with nonadherence at five months. At this point in treatment, for each 10% increase in score for the domain "Warning Signs," nonadherence decreased by 13% (RR=0.87, 95% CI 0.76-0.99, p=0.035), but for each 10% increase in score for the domain "How treatment works," nonadherence increased by 82% (RR=1.8, 95% CI 1.0-3.8, p=0.045).

Various intermediate treatment-related variables showed significant associations with nonadherence at each of the three time points. At five months, for each appointment that a patient had attended late (at least one day past their scheduled appointment date), he or she was 59% more likely to report nonadherence (RR=1.6, 95% CI 1.3-2.0, p<0.0001). In addition, multiple surveyed "difficulties with treatment" were significantly associated with nonadherence. For example, patients who had difficulty taking medication at specified times were more likely to report nonadherence at two weeks (RR 1.8, 95% CI 1.3-2.5, p=0.001), two months (RR 3.5,

95% CI 2.3-5.4, p<0.0001), and five months (RR 2.3, 95% CI 1.2-4.5, p=0.02). In addition, patients who reported feeling worse after taking their medication were more likely to report nonadherence at two weeks (RR 2.01, 95% CI 1.46-2.76, p<0.0001) and two months (RR 1.62, 95% CI 1.02-2.58, p=0.04), but this association was no longer observed at five months. The results of the bivariate Poisson regression analyses for intermediate treatment-related variables are provided in Table 9.

The adjusted relative risks for variables in the final multivariate Poisson regression models at each of the three time points are provided in Table 10. At two weeks, nonadherence decreased by 9% for each 10% increase in "How to take medications" score and 7% for each 10% increase in "Transmission" score, after adjusting for HIV status. At two months, nonadherence decreased by 10% for each 10% increase in "How treatment works" score and 8% for each 10% increase in "Transmission" score after adjusting for previous TB status and type of counseling received (group vs. individual). At five months, nonadherence decreased by 12% for each 10% increase in "Microbiology" score and 18% for each 10% increase in "TB vs HIV" score, but increased by 20% for each 10% increase in "Warning signs" score and 58% for each 10% increase in "How treatment works" score after adjusting for sex.

Association Between TB Knowledge and Final Treatment Outcome

We closed data collection on March 1, 2019. As of this date, 49 patients (68%) were classified as "Completed Treatment" and 23 patients (32%) were classified as "Did Not Complete Treatment." Notably, both patients who died were living with HIV when they initiated TB treatment. Detailed frequencies of patients in each classification are provided in Table 11.

We removed 8 patients from the analysis because they either transferred out after enrollment or did not have an outcome at the time that data collection closed.

None of the previously-established risk factors for nonadherence (sex, age, HIV status and education level) were significantly associated with final treatment outcome. Across all knowledge elements (both constructs and content domains), none showed significant bivariate associations with final treatment outcome. After adjusting for sex and type of counseling received (group vs. individual), patients had increased odds of completing treatment for each 10% increase in score on the "Transmission" content domain (OR=1.2, 95% CI: 0.94-1.5, p=0.16). Among the intermediate treatment measures, "number of late appointments" showed a statistically significant bivariate association with final treatment outcome (OR=0.69, 95% CI 0.50-0.96, p=0.03).

Discussion

TEC is a universally recommended adherence intervention for patients initiating treatment for active TB. Previous studies have demonstrated that education and counseling interventions play an important role in decreasing default rates and increasing adherence, treatment completion, and cure rates [8-10]. In this study, we sought to evaluate the effectiveness of routine TEC at a high-enrolling TB clinic and determine which specific TB knowledge domains are important in influencing medication adherence and treatment completion.

To our knowledge, a standardized, validated TB knowledge assessment for patients initiating TB treatment does not exist. We developed an instrument to measure domains of TB knowledge that have previously been indicated to be of importance in a TEC intervention [21-23]. We did not conduct a comprehensive instrument validation process, as this was outside the scope of the project. However, before implementing the knowledge questionnaire, we established face validity by having the questions reviewed by multiple parties; members of the Ugandan research team reviewed both English and Luganda versions of the instrument to assess question difficulty and consistency after translation, and a member of the U.S. research team with a background in survey validation reviewed individual questions to check for errors that could lead to bias. We also conducted a pilot test of the questionnaire with a group of participants totaling 15% of the intended sample size.

This study showed that routine TEC resulted in a statistically significant increase in knowledge across the eight surveyed content domains. However, none of the content domain means increased to a level reflective of high-quality education, revealing a need for improvement in the delivery of routine TEC. Both disease-specific and treatment-specific knowledge

increased after TEC and were generally retained at the two-week, two-month and five-month follow-up appointments. This retention was seen to a greater extent statistically for treatment-specific knowledge compared to disease-specific knowledge. This discrepancy might be explained by the statistical artifact of higher baseline scores for disease-specific knowledge, making the minimum detectable effect size smaller. Further, the magnitudes of the mean within-subject changes in score at each follow-up appointment are similar for both disease-specific and treatment-specific knowledge, suggesting that knowledge was retained to the same extent for both constructs (Table 5).

There were general patterns of heterogeneity at the individual question level. Scores varied based on baseline knowledge level; the extent to which scores increased after TEC; and whether the post-test score reflected an adequate level of knowledge (Figures 5 and 6). This suggests an importance for analyses related to TB knowledge to describe and account for this granular complexity.

Adherence is known to be an important predictor of TB treatment outcomes, but less is known about what factors predict adherence. This study showed that some content domains of TB knowledge may be more important than others in influencing medication adherence. This finding builds on previous facility-based studies that showed associations between unsatisfactory TB knowledge and both delay in initiating treatment and defaulting from treatment early [15, 27]. Our findings identify specific knowledge components that might help predict adherence. For example, higher scores on questions related to both "Transmission" and "How to take medications" were significantly associated with decreased nonadherence at both two weeks and two months. A recent study showed that missing even one pill per week resulted in double the

risk of unfavorable outcomes [5]. Improvements in TB knowledge could provide an effective avenue for improving adherence and, potentially, treatment outcomes.

Our finding that routine TEC was effective in increasing TB knowledge is in line with a cross-sectional study in Vietnam that sought to evaluate routine TEC delivered at TB clinics [16]. Our study was strengthened by the paired, pre/post design at diagnosis, as this allowed for analysis of within-patient increase in knowledge through dependent t-tests and increased our power. We also found that knowledge was retained throughout treatment. This differs from the results of a previous cross-sectional study in Ethiopia that compared knowledge scores among patients in different phases of treatment and found that patients in the intensive phase of treatment had a four-fold risk of poor knowledge compared to patients in continuation phase [14]. Measurement of each individual patient's TB knowledge at diagnosis and throughout treatment is a strength of our study design, as it provided more power and precision and allowed for a clear analysis of retention from diagnosis to multiple points in the treatment cascade.

TB medication adherence is important in reducing treatment relapse, treatment failure, drug resistance and death. Individual-level predictors of adherence must be understood when designing behavior change interventions to improve adherence. Our findings suggest that specific content domains of TB knowledge may play an important role in encouraging adherence and, once identified, could be targeted through specific behavior change techniques as a part of routine TEC. The process followed in this study could be utilized at other health facilities as a potential quality improvement tool to identify areas in patient knowledge that need more focus. Once these areas have been identified, specific changes could be implemented to TEC at the facility that could significantly improve treatment outcomes. For example, we found that higher scores in "How to take medications" resulted in lower rates of nonadherence at multiple time

points in treatment, and that multiple questions assessing knowledge of side effects within this domain had low post-test scores. This suggests that there could be an opportunity to improve delivery of TEC in this setting as it relates to side effect management, and making this improvement could directly reduce nonadherence later in treatment.

While our study design had a number of strengths, there were some notable limitations. The pre/post nature of the knowledge assessment at diagnosis may have resulted in a greater increase in knowledge than would have occurred had there been no pre-test; if there were questions on the pre-test that patients did not know, they may have focused in on these areas during TEC, knowing that they would be asked the same questions on the post-test. We were unable to follow up with a number of patients who had been classified as "lost to follow up" to discern their actual outcomes. We classified these patients as "Did not complete treatment," per WHO guidelines. There is a chance that these patients transferred to another clinic and actually completed treatment, which would have resulted in non-differential misclassification of the outcome and a bias of the effect size toward the null. If this did occur, our results would be an underestimate of the true effect size.

The modest size of our study may have limited the ability to detect a statistically significant association between knowledge domains and treatment completion. Additionally, our nonadherence measure relied on self-report; this method could have been subject to social desirability bias, where patients who actually experienced a nonzero number of nonadherent days reported a lower number when asked this question. Finally, we designed our study to focus on individual-level predictors of nonadherence and treatment completion, but there are several potential structural barriers that also could have influenced these outcomes, including distance to

the clinic; absence of health workers to administer medication; and competing obligations with work or family.

There is a need for a standardized, validated TB knowledge survey that can be used to measure TB knowledge among patients initiating and receiving treatment for active TB. Other studies have found that TB knowledge in the community and among new TB patients varies based on a number of factors, including geographic region [14-16, 27]. Each of these studies measured knowledge with an original questionnaire and measured a range of domains through a variety of open and closed-ended questions [14-16, 27]. Because of this variation, it is difficult to compare results among these studies. A standardized assessment will be necessary to advance scientific understanding of TB knowledge among this population and design effective adherence interventions.

The source population from which the cohort was sampled has a higher HIV prevalence, a lower average socioeconomic status, and higher rates of adverse treatment outcomes relative to the rest of Kampala. Because of this, a multi-center study in a variety of settings is needed to determine which of our study's findings, if any, are generalizable to the general population. A larger sample size is necessary to increase power to detect an association between TB knowledge and final treatment outcome. Future studies should measure other individual-level predictors of adherence such as stigma and treatment intentions to better understand how these factors operate concurrently with knowledge in determining adherence and treatment outcomes.

This study was developed with the intention of informing the development of a tailored, patient-centered TEC intervention. Guidelines published by Médecins Sans Frontières will be used as a basis for intervention development [22]. The intervention will involve task shifting of TEC from nurses and CHWs to "expert clients," members of the community who have already

experienced TB treatment and are trained in delivering peer education and counseling. Through a "prompt card," expert clients will provide TEC with a standardized list of questions that should be addressed through counseling in order to influence key target behaviors, including daily adherence and completing treatment. The results from this study have informed this list, and specific behavior change techniques will be employed to address the areas we have identified to be important predictors of treatment adherence. For example, expert clients will educate patients about common side effects, and then counsel them on the salience of consequences if various side effects are not correctly handled. After receiving all of the necessary health education points, expert clients will work with patients to develop an individualized adherence plan. The results of our study suggested that there are common individual-level difficulties with treatment that need to be addressed through counseling, such as taking medication at specified times. Our hypothesis is that interventions tailored to meet individual patient needs as implemented through an individualized adherence plan are more likely to lead to successful treatment outcomes than simply providing knowledge alone.

Our study found that routine TB education and counseling was effective at increasing patient knowledge at a high-enrolling TB clinic in Kampala, and this knowledge was generally retained throughout multiple time points of treatment. In this cohort, specific content areas of TB knowledge were significantly associated with medication nonadherence later in treatment. Given these findings and the importance of adherence on TB treatment completion, as well as the likely modest cost of making targeted improvements to TEC, this is an area that warrants further study and investment.

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Appendices

Appendix A. Questionnaire

Respondent Information

1. Treatment initiation date
2. NTLP Register Number
3. Sex
4. Date of birth
5. What is the highest level of education you have completed?
6. What is your current occupation?
7. Referred to the TB unit from…
8. Did you receive TEC before coming to the TB unit for this TB episode?
9. What is your HIV status?
10. Have you ever had TB before?
11. Has someone in your household or anyone close to you had TB?
12. Have you ever received any information about TB?
    a. If yes, where have you received information about TB?
        i. Religious leaders (Yes/No)
        ii. Health workers (Yes/No)
        iii. Family and friends (Yes/No)
        iv. Teachers (Yes/No)
        v. Brochures, posters or other printed materials (Yes/No)
        vi. Media (Yes/No)

TB Knowledge: Closed-Ended Questions *(Content Domain in parentheses)*

1. TB attacks the lungs. *(Microbiology)*
2. TB can attack other parts of the body outside of the lungs. *(Microbiology)*
3. Everyone who is exposed to TB germs becomes ill. *(Microbiology)*
4. Answer "yes" if the condition is a warning sign of TB and answer "no" if it is not a warning sign of TB. *(Warning signs)*
    a. A cough that does not go away for two weeks
    b. Loss of weight
    c. A cough that goes away after a few days
    d. General weakness
    e. Vomiting
5. Answer "yes" if the statement is a way that TB can be spread and answer "no" if TB cannot be spread that way. *(Transmission)*
    a. Through drinking water
    b. Through the air
    c. Through food
6. Unprotected sex can spread TB. *(TB vs. HIV)*
7. If you stop treatment before the full course of therapy, your TB becomes harder to cure. *(How treatment works)*

TB Knowledge: Open-Ended Questions + Decision Logic (*Content Domain in parentheses)*

1. How often can TB be cured if treatment is started in time? *(How treatment works)*
    a. Correct (always, almost always, "I am pretty sure TB can be cured if you complete treatment")
    b. Incorrect (never, sometimes, doesn't know)
2. How are TB germs released? *(Transmission)*
    a. Correct (when a person with TB coughs, sneezes, spits)
    b. Incorrect (when a person with TB vomits, touches you; if you share a cup or food with someone who has TB; doesn't know)
3. If you breathe in TB germs, where do they settle and grow? *(Transmission)*
    a. Correct (lungs)
    b. Incorrect (anywhere else, doesn't know)
4. Can you have HIV only (without TB)? *(TB vs. HIV)*
    a. Correct (yes)
    b. Incorrect (no, doesn't know)
5. Can you have TB only (without HIV)? *(TB vs. HIV)*
    a. Correct (yes)
    b. Incorrect (no, doesn't know)
6. How can you stop the spread of TB? *(Prevention)*
    a. Correct (cover mouth with a handkerchief; cover mouth when coughing; avoid others for the first two weeks of treatment; don't go out in public for the first two weeks of treatment; don't spit on the ground in public)
    b. Incorrect (tell everyone that I have TB; interviewer uses judgement; doesn't know)
7. If you have TB, how long do you take the medication? *(How to take medications)*
    a. Correct (until you are discharged, 6-8 months; when they test me again and there is no more TB and the nurse tells me I can finish treatment)
    b. Incorrect (any other answer, doesn't know)
8. When can you stop taking the TB medication? *(How treatment works)*
    a. Correct (when you finish the full course of therapy, when you are discharged, after 6-8 months)
    b. Incorrect (when the cough stops, when you feel better, doesn't know
9. If you stop taking the TB medication before the treatment period is finished, what might happen? *(How treatment works)*
    a. Correct (the germs won't be fully killed and another TB episode can occur; the germs can develop resistance; you can die; you can end up taking the medication for a longer period of time)
    b. Incorrect (nothing, doesn't know)
10. Name two potential side effects of TB treatment. *(How to take medications)*
    a. Correct (skin rash, nausea, joint pain, color of urine changes, etc.—interviewer uses judgment)
    b. Incorrect (interviewer uses judgment; can only name one; doesn't know)
11. What should you do if your TB medication gives you nausea? *(How to take medications)*

    a. Correct (endure for a few weeks, try taking medication with food or other self-medication such as lemon)
    b. Incorrect (stop taking medication, come to the clinic, doesn't know)
12. What should you do if your TB medication gives you joint pain? *(How to take medications)*
    a. Correct (take pain killers, take pyridoxine, move around and do some light exercises, reduce on doing heavy work)
    b. Incorrect (stop taking medication, come to the clinic, doesn't know)
13. What should you do if your TB medication gives you yellow or red eyes, too much vomiting, intense body rash, or issues with sight? *(How to take medications)*
    a. Correct (talk to a health worker, come to the clinic)
    b. Incorrect (stop taking medication, sleep it off, nothing, doesn't know)
14. When should you come to the clinic for your next appointment? *(Treatment monitoring)*
    a. Correct (be able to say the date or the amount of time until the next appointment)
    b. Incorrect (when the health worker tells me to come back; can't tell the date or the amount of time until the next appointment; doesn't know)
15. What do your TB medications look like? *(How to take medications)*
    a. Correct (adequately explains what pills look like in color and shape)
    b. Incorrect (incorrectly explains what the pills look like; doesn't know)
16. When do you take your TB medications? *(How treatment works)*
    a. Correct (in the morning when you first wake up)
    b. Incorrect (any other time; multiple times throughout the day; doesn't know)
17. After taking the medication, how long does it usually take to start feeling better? *(Treatment monitoring)*
    a. Correct (any amount of time between 2 weeks and 1 month)
    b. Incorrect (any time outside of 2 weeks and 1 month; doesn't know)

Self-Reported Nonadherence

1. During the last week, how many days were you late or missed taking your TB medication?
2. Below are some reasons why people have difficulty taking their drugs. Answer "yes" or "no" to indicate whether or not each of the following reasons describes why you may have had difficulty taking your drugs in the last 7 days.
    a. I feel worse when I take the pills
    b. There are too many pills to take
    c. I forget to take the pills
    d. I ran out of pills
    e. I don't think I need the pills
    f. I was away from home
    g. I did not want others to notice
    h. I am too busy
    i. I had problems taking pills at specified times
    j. I was confused or uncertain about how to take the pills