Characteristics and treatment outcomes of adolescents and young adults living with HIV with drug-resistant tuberculosis co-infection in Uganda: a retrospective cohort study

Ivaan Pitua (iD), Marvin Kirya, Denis Kiberu, Shivan Nabaasa, Amelia Margaret Namiiro, Michael Collins Segawa, Patrick Semakula, Sarah Maria Najjuka, Joseph Baruch Baluku (iD) and Ronald Olum (iD)

Abstract

Background: Tuberculosis (TB) remains a significant global health challenge, especially among people living with HIV. Drug-resistant TB (DR-TB) complicates treatment outcomes in high-burden countries like Uganda, particularly for adolescents and young adults living with HIV (AYALH).

Objectives: We described the characteristics, treatment outcomes, and factors associated with treatment success among AYALH and DR-TB at a TB treatment unit in Mulago National Referral Hospital, Kampala, Uganda.

Design: A retrospective cohort study was conducted.

Methods: Medical records of AYALH treated for DR-TB between January 2013 and December 2021 were reviewed. Descriptive statistics and multivariable logistic regression were used to analyze treatment outcomes and associated factors.

Results: Among 327 participants (mean age: 28.2 years, SD: 4.75; 52.6% male), the treatment success rate was 65.7%. A body mass index (BMI) $\geqslant 18.5 \, kg/m^2$ (adjusted odds ratio [aOR]: 0.53, 95% CI: 0.33–0.83, $p = 0.005$), Efavirenz-based antiretroviral therapy (ART) regimens (aOR: 0.56, 95% CI: 0.35–0.89, $p = 0.014$), and primary DR-TB (aOR: 0.42, 95% CI: 0.28–0.64, $p < 0.001$) were significantly associated with treatment success.

Conclusion: The study revealed a treatment success in only two-thirds of participants emphasizing persistent challenge of achieving optimal treatment outcomes for AYALH. The findings highlight that a higher BMI and Efavirenz-based ART regimens are significantly associated with improved treatment success pointing to the necessity for addressing nutritional needs and optimizing ART regimens to improve the management of DR-TB among AYALH.

Correspondence to:
Ronald Olum
Makerere University
School of Public Health,
Kampala, Uganda
**olum.ronald@gmail.com;
ronald.olum@mak.ac.ug**

**Ivaan Pitua
Marvin Kirya
Denis Kiberu
Shivan Nabaasa
Amelia Margaret Namiiro
Michael Collins Segawa
Patrick Semakula**
College of Health
Sciences, Makerere
University, Kampala,
Uganda

Sarah Maria Najjuka
Infectious Diseases
Institute, Kampala,
Uganda

Joseph Baruch Baluku
Division of Pulmonology,
Kiruddu National Referral
Hospital, Kampala, Uganda

Plain language summary

Treatment outcomes of young Ugandans with HIV and drug-resistant tuberculosis

This study examined adolescents and young adults living with HIV in Uganda who had drug-resistant tuberculosis. Among 327 participants treated at Mulago National Referral Hospital from 2013 to 2022, about two-thirds had treatment success. The study found that having a healthier weight and being on an HIV regimen that included Efavirenz were associated with better treatment outcomes. Additionally, those with primary DR-TB had

better outcomes than those who aquired drug resistance during treatment. The findings highlight the need to address nutritional needs and optimize HIV treatments to improve outcomes in this group.

Introduction

Drug-resistant tuberculosis (DR-TB) remains a significant challenge, particularly among people living with HIV (PLWH). Tuberculosis (TB) has regained its position as the leading cause of death globally from a single infectious agent, overtaking COVID-19 after a 3-year span. TB currently accounts for nearly twice as many fatalities as HIV/AIDS. Annually, more than 10 million individuals are diagnosed with TB, with incidence rates showing an upward trend since 2021.[1] The burden of TB is disproportionately distributed, with over 95% of cases and deaths occurring in low- and middle-income countries, predominantly in Africa and Asia.[2,3] Moreover, the emergence of DR-TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), has further complicated TB management and control efforts, posing a significant threat to global health.[4]

About one in four TB-related deaths occur in the African region, and more than 60% of 15 million cases of HIV/TB co-infection have been reported in the region.[5,6] Studies have demonstrated an increased risk of DR-TB among PLWH, likely due to factors such as inadequate TB treatment, poor adherence to anti-TB medications, poor adherence to antiretroviral therapy (ART), and the high prevalence of HIV-associated immunosuppression.[7] Uganda is a high-burden TB/HIV country, with an estimated annual TB incidence of 253 cases per 100,000 population and an HIV prevalence of 6.2% with up to 45% among all reported TB cases.[8] Furthermore, PLWH have a 20-fold higher risk of developing TB compared to their peers without HIV.[9] The emergence of DR-TB in Uganda is a growing concern, with an estimated 1.4% of new TB cases and 12.1% of previously treated cases being classified as MDR-TB or rifampicin-resistant TB (RR-TB) in 2020.[10] The prevalence of rifampicin resistance was significantly higher in PLWH with TB (32%) than in HIV-negative individuals with TB (12%) at the National Referral Hospital, suggesting an increased risk of DR-TB among PLWH.[11] Over the study period, significant advances were made in DR-TB management, including the adoption of shorter, more effective treatment regimens in 2017, such as the Bedaquiline-based 9-month regimen.[12] Similarly, ART transitioned to Dolutegravir (DTG)-based regimens starting in 2018, replacing older Efavirenz (EFV)-based regimens.[13] These changes reflect ongoing efforts to optimize treatment outcomes for PLWH co-infected with DR-TB.

Previous studies among patients with DR-TB/HIV examined gender differences, noting higher mortality rates among men,[14] while also highlighting high treatment success among pregnant women with DR-TB despite a high prevalence of HIV co-infection.[15] Similarly, a study by Bayowa et al.[16] focused solely on mortality as an outcome, reporting a mortality rate of 33%, but included a broad age range of 1–80 years with a mean age of 35. However, these studies did not specifically address the unique age group of adolescents and young adults living with HIV (AYALH) who face distinct biological, psychological, and social challenges that differ significantly from those of younger children or older adults living with HIV. These gaps in existing literature indicate that characteristics and treatment outcomes of adolescents and young adults living with DR-TB/HIV are not well documented, stressing the need for a study in this specific population as this group represents a vulnerable population with unique challenges. The purpose of this study was to describe the characteristics, treatment outcomes, and factors associated with treatment success among AYALH and DR-TB at a TB treatment unit in Mulago National Referral Hospital, Kampala, Uganda.

Methods

Study design

We conducted a retrospective cohort study reviewing medical records of patients who initiated DR-TB treatment or received care at Mulago National Referral Hospital (MNRH) during their treatment course between January 2013 and December 2021 with a minimum follow up period of 12 months, ensuring comprehensive capture of treatment outcomes. The reporting of this study was in accordance with the STROBE guidelines.[17]

Study area

The study was conducted at the TB unit of MNRH, Uganda. MNRH is a tertiary care referral center providing comprehensive healthcare services, including specialized care for TB and PLWH. It is also Uganda's largest TB Treatment Center, managing an estimated 200 patients per quarter and offering care to referrals (about 40%) and non-referral cases. MNRH primarily manages DR-TB cases referred from across Uganda. These referrals often include patients with severe disease, failed previous DR-TB regimens, or those requiring specialized care unavailable at lower-level facilities.

Study population

Our target population was AYALH aged 10–35 years with a diagnosis of DR-TB, focusing on those who attended the TB unit of MNRH between January 2013 and December 2021.

Selection criteria

We included AYALH who had a confirmed diagnosis of DR-TB and excluded those with missing data on age and sex.

Study variables

Dependent variables. According to the standard definitions of the WHO Definitions and reporting framework for tuberculosis 2013 revision,[18] the following treatment outcome definitions were used:

- Cured: Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
- Treatment completed: Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
- Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions.
- Died: A patient who dies for any reason during the course of treatment.
- Lost to follow-up: A patient whose treatment was interrupted for two consecutive months or more.
- Treatment success: The sum of cured and treatment completed
- Unsuccessful treatment: The sum of loss to follow-up, death and treatment failure.

Independent variables. These included demographic characteristics such as age, sex, marital status, and employment status, as well as clinical characteristics like body mass index (BMI), TB regimen (Table 1), smoking, alcohol use, ART regimen, and TB treatment adherence. The adherence was based on reports from clinic-based directly observed therapy (DOT), home-based DOT, and patient self-reports and was categorized as "good" or "poor" based on clinic- and home-based DOT reports combined with patient self-reports throughout the treatment period as noted in the patients' records. Good adherence was defined as ≥90% of prescribed doses taken, while poor adherence was <90%. Reports from clinic- and home-based DOT were treated as verified doses, while patient self-reports were included only when cross-validated using methods like pill counts, diaries, or follow-up interviews. All sources were integrated into a composite adherence percentage, prioritizing directly observed doses. This 90% threshold aligns with adherence standards in clinical research and therapeutic guidelines. Other factors considered were comorbid conditions such as diabetes mellitus and cancer, site of DR-TB (pulmonary tuberculosis or extra-pulmonary tuberculosis), and mode of HIV acquisition (vertical or horizontal transmission) based on past

Table 1. The TB treatment regimens.

Regimen	Composition
Individualized (IND)	Administered over 18 months, with a 6-month intensive phase of Bedaquiline, Levofloxacin, Cycloserine, Clofazimine, and Linezolid, followed by a 12-month continuation phase using Levofloxacin, Cycloserine, Clofazimine, and Linezolid
Modified Shorter Treatment Regimen (mSTR)	9-month daily administration of Bedaquiline, Linezolid, Levofloxacin, Clofazimine, and Cycloserine
Long Term Standardized Treatment Regimen (LTR/STD)	Administered over 20 months, starting with a 6-month intensive phase of Kanamycin, Levofloxacin, Cycloserine, Ethionamide, and Pyrazinamide, followed by a 14-month continuation phase with Levofloxacin, Cycloserine, Ethionamide, and Pyrazinamide
Standardized Short Treatment Regimen (STR/STD)	Administered over 4–6 month intensive phase with Kanamycin, Moxifloxacin, Prothionamide, Clofazimine, Pyrazinamide, Ethambutol, and high-dose Isoniazid, followed by a 5-month continuation phase with Moxifloxacin, Clofazimine, Pyrazinamide, and Ethambutol
Short Treatment Regimen (STR)	Administered over 4-month intensive phase with Kanamycin, Isoniazid, Clofazimine, Ethambutol, Prothionamide, Pyrazinamide, and Gatifloxacin, followed by an 8-month continuation phase with Clofazimine, Ethambutol, Pyrazinamide, Gatifloxacin, and Prothionamide

medical records, facility records, and self-reporting. Additionally, documentation of AIDS-defining illness was sought for (any of *Pneumocystis jirovecii* pneumonia, esophageal or tracheal candidiasis, toxoplasmosis, cryptococcosis, Kaposi's sarcoma, non-Hodgkin lymphoma, invasive cervical cancer, and molluscum contagiosum), and the diagnostic category (primary or acquired DR-TB) was included. Also, ART regimen was noted based on whether it was DTG-based regimen (Tenofovir Disoproxil Fumarate + Lamivudine + DTG), EFV-based regimen (Cobicistat + EFV, Tenofovir Disoproxil Fumarate + Lamivudine + EFV), or other regimens such as Abacavir + Lamivudine + Lopinavir/ritonavir, Zidovudine + Lamivudine + Nevirapine, and Tenofovir Disoproxil Fumarate + Lamivudine + Nevirapine. The type of DR-TB was classified as RR-TB (resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs), MDR-TB (resistance to at least both Rifampicin and Isoniazid), or XDR-TB (TB caused by *Mycobacterium tuberculosis* strains that fulfill the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug, that is levofloxacin, moxifloxacin, bedaquiline, and linezolid). Uganda adopted WHO-recommended shorter treatment regimens for DR-TB in 2017, which include a 9-month treatment course involving Bedaquiline, Linezolid, Levofloxacin, Clofazimine, and Cycloserine. Prior to 2017, treatment regimens were individualized and often included injectable agents like kanamycin. Regimens were assigned based on the national guidelines active during each calendar year. Patients were started on a regimen following the national policy recommendations for their specific clinical presentation, drug susceptibility test results, and prior treatment history. The decision to initiate a particular regimen was determined by considering the availability of drugs, patient tolerability, and coexisting medical conditions, including HIV. The regimen described in the study was the starting regimen that patients were initiated on at the beginning of their DR-TB treatment. Changes to the initial regimen during follow-up, if any, were made in response to adverse drug reactions, lack of clinical improvement, or detection of additional drug resistance. While such changes were documented in individual patient records, our analysis focused on the initial regimens. The regimens obtained from the patient records are summarized in Table 1.

Sample size. We reviewed all available medical records for AYALH with DR-TB co-infection who attended the TB unit of MNRH between January 2013 and December 2021.

Study procedures. Data were collected from routinely existing health facility records into structured forms by a team of trained research assistants. Sources of data included TB physical registers and patient files, in cases of missing data, the online register was accessed. Reported DR-TB cases in this population were diagnosed using GeneXpert MTB/RIF assay and confirmed through sputum culture where required. The data collected from these registers included information on patient demographics, clinical characteristics, and their treatment outcomes.

Data analysis. The demographic data were summarized using descriptive statistics, including frequencies, percentages, and means. The aim of the analysis was to identify independent predictors of treatment outcomes (treatment success vs unsuccessful treatment). Multivariable logistic regression was used to identify these predictors, incorporating those with p-values <0.20 in bivariate analysis. We considered clinically relevant interactions a priori, particularly the site of DR-TB and ART regimen, based on prior studies and expert opinion. Other interactions were assessed post-hoc. However, none of these interaction terms significantly improved model fit, suggesting that no key interactions were present. Adjusted odds ratios (aORs) were calculated to quantify the strength of these associations, allowing for a robust evaluation of the factors influencing the outcome. All statistical analyses were conducted using IBM SPSS Statistics v27 software.[19]

Results

Characteristics of AYALH with DR-TB

Of the 340 participant data retrieved, 13 were excluded due to missing data on age (4) and sex (9). Of the 327 participants were included, a majority were male ($n = 172$) with over half of participants married ($n = 180$). The mean age was 28.2 years (range 10–35) with 150 (45.9%) having a BMI under 18.5kg/m^2 and majority having RR-TB (92.7%). 200 (61.2%) were on EFV-based ART regimens and 179 (54.7%) had primary DR-TB (Table 2).

Treatment outcomes of AYALH with DR-TB

Treatment completion was documented in 118 (36.1%), 56(17.1%) patients died and 46 (14.1%) were lost to follow-up. A total of 97 (29.7%)

patients were cured, and only 10 (3.1%) were treatment failure. This translated to 215 (65.7%) patients with treatment success and 112 (34.3%) with unsuccessful treatment outcomes.

Factors associated with DR-TB treatment success in AYALH

Participants with a BMI $\geq 18.5 \text{ kg/m}^2$ (54.1%) had higher odds of treatment success compared to those with a BMI below 18.5kg/m^2 (aOR: 0.53, 95% CI: 0.33–0.83, $p = 0.005$). Similarly, individuals on EFV-based ART regimens (61.2%) demonstrated the greatest likelihood of successful outcomes, with lower odds observed for those on DTG-based (aOR: 0.56, 95% CI: 0.35–0.89, $p = 0.014$) or other regimens (aOR: 0.25, 95% CI: 0.11–0.55, $p = 0.001$). Participants with primary DR-TB (54.7%) had significantly higher odds of achieving treatment success compared to those with secondary DR-TB (aOR: 0.42, 95% CI: 0.28–0.64, $p < 0.001$; Table 3).

Discussion

In this study, we aimed at describing characteristics and treatment outcomes of AYALH with DR-TB. We found that 65.7% of patients achieved treatment success, while 34.3% had unsuccessful treatment outcomes. Our finding is almost identical to the nationwide data of treatment success in HIV/DR-TB reported at 66%[14] and also similar to those reported in other studies conducted in resource-constrained settings in sub-Saharan Africa, where treatment success rates often fall short of the WHO target of 90%.[20,21]

Our results indicated that a BMI $\geq 18.5 \text{kg/m}^2$ was significantly associated with higher odds of treatment success compared to a BMI $< 18.5 \text{kg/m}^2$. This finding conforms to existing knowledge that nutritional status plays a crucial role in TB treatment outcomes. Underweight patients are often at higher risk of adverse outcomes due to their compromised immune systems, which makes them less able to fight off infections effectively.[22] A low BMI at the start of treatment for RR-TB or MDR-TB is associated with poor treatment outcomes.[23] Looking at Bayowa et al. study, having a BMI $< 18.5 \text{kg/m}^2$ was a risk factor to mortality. There was a 9% reduced likelihood in mortality among persons on treatment who had a BMI $\geq 18.5 \text{kg/m}^2$ than those who had a BMI $< 18.5 \text{kg/m}^2$.[16] Hanrahan et al. concluded that

Table 2. Characteristics of participants.

Variable	Categories	2013–2015	2016–2018	2019–2021	Mean/N (%)
		N = 108	N = 98	N = 121	N = 327
Age	Mean (SD)				28.20 (4.75)
	<20	5	8	4	17 (5.2)
	≥20	103	90	117	310 (94.8)
Gender	Male	45	65	62	172 (52.6)
	Female	63	33	59	155 (47.4)
Marital status	Single	25	46	30	101 (30.9)
	Married	70	38	72	180 (55.0)
	Separated	9	8	12	29 (8.9)
	Widowed	4	6	7	17 (5.2)
Employment status	Employed	61	48	58	167 (51.1)
	Unemployed	47	50	63	160 (48.9)
BMI	Mean (SD)				19.01 (3.35)
	<18.5 kg/m^2	42	30	78	150 (45.9)
	≥18.5 kg/m^2	66	68	43	177 (54.1)
TB regimen	IND	56	50	50	156 (47.7)
	STR	8	7	8	23 (7.0)
	mSTR	12	13	15	40 (12.2)
	LTR/STD	26	20	40	86 (26.3)
	STR/STD	6	8	8	22 (6.7)
Type of DR-TB	RR	100	88	115	303 (92.7)
	MDR-TB	6	8	6	20 (6.1)
	XDR-TB	2	2	0	4 (1.2)
Smoking	Yes	15	9	27	51 (15.6)
	No	93	89	94	276 (84.4)
Alcohol	Yes	22	18	25	65 (19.9)
	No	86	80	96	262 (80.1)
TB Treatment adherence	Good	95	89	99	283 (86.5)
	Poor	13	9	22	44 (13.5)
Comorbid condition	Cancer	2	1	1	4 (1.2)

(Continued)

Table 2. (Continued)

Variable	Categories	2013–2015	2016–2018	2019–2021	Mean/*N* (%)
	DM	2	3	2	7 (2.1)
	None	104	94	118	316 (96.6)
ART regimen	DTG based	33	30	40	103 (31.5)
	EFV based	66	61	79	200 (61.2)
	Others	9	7	8	24 (7.3)
Site of DR-TB	PTB	104	95	119	318 (97.2)
	EPTB	4	3	2	9 (2.8)
Mode of HIV acquisition	Horizontal	97	85	102	284 (86.9)
	Vertical	11	13	19	43 (13.1)
Documentation of AIDS defining illness	Yes	4	4	6	14 (4.3)
	No	104	94	115	313 (95.7)
Diagnostic category	Primary DR-TB	61	53	65	179 (54.7)
	Acquired DR-TB	47	45	56	148 (43.3)

ART, antiretroviral therapy; BMI, body mass index; DM, diabetes mellitus.; DR-TB, drug-resistant tuberculosis; DTG, dolutegravir; EFV, efavirenz; EPTB, extra-pulmonary tuberculosis; IND, individualized; LTFU, loss to follow-up; LTR/STD, long-term regimen/standardized; MDR-TB, multidrug-resistant tuberculosis; mSTR, modified short-term regimen; PTB, pulmonary tuberculosis; RR, rifampicin-resistant; STR, short-term regimen; STR/STD, short-term regimen/standardized; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

Table 3. Factors associated with treatment success.

Variable	Categories	*N* (%)	Successful outcome (*N*)	Bivariate cOR (95% CI)	*p*-Value (bivariate)	Multivariable aOR (95% CI)	*p*-Value
Age	≥20	310 (94.8)	207	1.00			
	<20	17 (5.2)	8	0.44 (0.14–1.34)	0.095		
BMI	≥18.5 kg/m^2	177 (54.1)	133	1.00		1.00	
	<18.5 kg/m^2	150 (45.9)	82	0.47 (0.28–0.77)	0.002	0.53 (0.33–0.83)	0.005
Gender	Male	172 (52.6)	111	1.00			
	Female	155 (47.4)	104	1.12 (0.69–1.8)	0.626		
Marital status	Married	180 (55.0)	117	1.00			
	Single	101 (30.9)	69	1.16 (0.67–2.03)	0.573		
	Separated	29 (8.9)	16	0.66 (0.28–1.60)	0.307		
	Widowed	17 (5.2)	13	1.75 (0.511–7.66)	0.340		

(Continued)

Table 3. (Continued)

Variable	Categories	N (%)	Successful outcome (N)	Bivariate cOR (95% CI)	p-Value (bivariate)	Multivariable aOR (95% CI)	p-Value
Employment status	Employed	167 (51.1)	121	1.00		1.00	
	Unemployed	160 (48.9)	94	0.54 (0.33–0.88)	0.009	0.45 (0.22–0.93)	0.053
TB regimen	IND	156 (47.7)	104	1.00			
	STR	23 (7.0)	11	0.46 (0.17–1.23)	0.078		
	mSTR	40 (12.2)	22	0.61 (0.29–1.33)	0.170		
	LTR/STD	86 (26.3)	47	0.60 (0.34–1.07)	0.065		
	STR/STD	22 (6.7)	31	10.5 (1.59–442.35)	0.006		
Smoking	No	276 (84.4)	182	1.00			
	Yes	51 (15.6)	33	0.95 (0.49–1.89)	0.864		
Alcohol	No	262 (80.1)	177	1.00		1.00	
	Yes	65 (19.9)	38	0.68 (0.37–1.23)	0.167	0.75 (0.40–1.39)	0.360
TB Treatment adherence	Good	283 (86.5)	184	1.00			
	Poor	44 (13.5)	31	1.28 (0.62–2.80)	0.480		
Comorbid condition	No	316 (96.6)	207	1.00			
	Yes	11 (3.4)	8	1.40 (0.33–8.37)	0.620		
Site of DR-TB	PTB	318 (97.2)	209	1.00			
	EPTB	9 (2.8)	6	1.04 (0.22–6.57)	0.953		
Mode of HIV acquisition	Horizontal	284 (86.9)	195	1.00		1.00	
	Vertical	43 (13.1)	20	0.40 (0.20–0.80)	0.004	0.75 (0.39–1.43)	0.390
Type of DR-TB	RR	303 (92.7)	201	1.00			
	MDR/XDR-TB	24 (7.3)	14	0.71 (0.28–1.86)	0.426		
ART regimen	EFV based	200 (61.2)	134	1.00		1.00	
	DTG based	103 (31.5)	70	1.04 (0.61–1.80)	0.870	0.56 (0.35–0.89)	0.014
	Others	24 (7.3)	11	0.42 (0.16–1.07)	0.040	0.25 (0.11–0.55)	0.001
AIDS defining illness	No	313 (95.7)	207	1.00		1.00	
	Yes	14 (4.3)	8	0.68 (0.20–2.46)	0.490	2.30 (0.85–6.23)	0.110
Diagnostic category	Primary DR-TB	179 (54.7)	142	1.00		1.00	
	Secondary DR-TB	148 (45.3)	73	0.25 (0.15–0.42)	<0.001	0.42 (0.28–0.64)	<0.001

ART, antiretroviral therapy; BMI, body mass index; DR-TB, drug-resistant tuberculosis; DTG, dolutegravir; EFV, efavirenz; EPTB, extra-pulmonary tuberculosis; IND, individualized; LTFU, loss to follow-up; LTR/STD, long-term regimen/standardized; MDR-TB, multidrug-resistant tuberculosis; mSTR, modified short-term regimen; PTB, pulmonary tuberculosis; RR, rifampicin-resistant; STR, short-term regimen; STR/STD, short-term regimen/standardized; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

individuals living with HIV who are obese and overweight BMI have a significantly reduced risk of both mortality and TB, after adjusting for highly active antiretroviral therapy use and CD4 cell count whereas those with underweight BMI had an increased risk of mortality.[24] Shuter et al. identified an inverse link between BMI and mortality, regardless of baseline CD4 cell count, in a group of PLWH and using intravenous drug in Miami.[25] Shuter et al.[25] observed that overweight individuals experienced slower disease progression and lower viral loads among AIDS-free PLWH in New York City, after accounting for baseline CD4 cell count and the time to start antiretroviral therapy in a multisite US study of women living with HIV. The importance of addressing malnutrition in TB patients is emphasized by global health guidelines, which recommend nutritional support as part of comprehensive TB care.[26] There are still gaps in our knowledge of what specific supplementation macro and micronutrients would improve TB outcomes.

Patients with primary DR-TB were more likely to achieve treatment success compared to those with acquired DR-TB. Primary resistance develops when patients are exposed to and infected with an already drug-resistant strain. Secondary resistance or acquired resistance develops due to poor adherence to medication, drug malabsorption, and inadequate regimen among patients taking TB medication.[27] Secondary DR-TB often involves patients with a history of TB treatment, potentially leading to more extensive drug resistance and compromised immune responses, especially in the context of HIV.[28] This could explain the poorer outcomes observed in secondary DR-TB cases. Early and accurate detection of drug resistance and personalized treatment regimens, particularly for those with a history of TB can improve treatment outcomes in this high-risk group.

EFV-based regimens were associated with higher odds of treatment success. Up to June 2018, the preferred first-line therapy for HIV-1 infection was an EFV-based regimen (with a 400 mg dose of EFV),[29] meaning that this regimen was most widely adopted in the first half of our study period. The superior outcomes observed with EFV-based regimens may be attributed to its minimal interaction with rifampin, a key anti-TB drug. Unlike DTG, which has been reported to reduce rifampin absorption, EFV maintains stable plasma levels, ensuring sustained therapeutic efficacy. These

pharmacological differences likely explain the observed treatment success, highlighting the need for careful regimen selection in managing HIV/DR-TB co-infections. The observed advantage of EFV-based regimens in achieving higher treatment success conforms with other studies that showed its effectiveness in HIV/DR-TB management as EFV's potent antiviral properties and favorable pharmacokinetics likely contribute to improved outcomes.[30,31] Our findings, however, support the continued use of EFV-based regimens in case DTG-based regimens are unavailable as the NAMSAL study showed people with HIV on DTG- and EFV-based regimens showed long-term efficacy and safety of both ARTs.[32] Moving forward, focus should be on addressing barriers to adherence among AYALH with DR-TB to further enhance treatment success. Given the poorer outcomes associated with secondary resistance, we recommend implementation of robust adherence counseling strategies tailored to adolescents and young adults. This includes addressing stigma, enhancing social support, and utilizing digital tools to ensure consistent medication use.

Our study, however, had some limitations. The study is reliant on secondary data, which are limited by the availability and completeness of medical records. The varied durations of DR-TB regimens pose potential biases, as patients on longer regimens have greater risk exposure for death or loss to follow-up. Also, patients starting treatment in 2017 or later were more likely to receive shorter, Bedaquiline-based regimens, while earlier cases predominantly received individualized or standardized longer regimens hence interpretation of results should be done with caution. Grouping death and loss to follow-up as unsuccessful treatment may mask distinct risk factor patterns. Another limitation is in the analysis as there is variation in treatment durations across different ART regimens. The unequal follow-up times across participants could introduce bias, as individuals on longer regimens have more opportunities to experience the outcome (e.g., treatment failure, death, or lost to follow-up).

Conclusion

The study revealed a treatment success in only two-thirds of participants emphasizing persistent challenge of achieving optimal treatment outcomes for AYALH. The findings highlight that a higher BMI and EFV-based ART regimens are

significantly associated with improved treatment success pointing to the necessity for addressing nutritional needs and optimizing ART regimens to improve the management of DR-TB among AYALH. Optimizing adherence through structured counseling programs is crucial for improving outcomes, particularly among patients with secondary DR-TB. Future studies should consider time-dependent variables or survival analysis techniques to better account for variation in treatment duration.

Declarations

Ethics approval and consent to participate
Mulago Hospital Research Ethics Committee (MHREC) approved the study protocol and a waiver of informed consent. Approval number MHREC 2582. MNRH and National Tuberculosis and Leprosy Program granted permission to the study team to access the patient records. We maintained the confidentiality of the patients' data by using anonymized extracted data for further analysis.

Consent for publication
Not applicable.

Author contributions
Ivaan Pitua: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Marvin Kirya: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

Denis Kiberu: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Shivan Nabaasa: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Amelia Margaret Namiiro: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Michael Collins Segawa: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Patrick Semakula: Data curation; Investigation; Validation; Writing – original draft; Writing – review & editing.

Sarah Maria Najjuka: Conceptualization; Data curation; Formal analysis; Supervision; Validation; Writing – original draft; Writing – review & editing.

Joseph Baruch Baluku: Data curation; Formal analysis; Validation; Writing – original draft; Writing – review & editing.

Ronald Olum: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All data and materials related to the study are available upon reasonable request from the first author.

ORCID iDs
Ivaan Pitua https://orcid.org/0000-0003-0768-1315

Joseph Baruch Baluku https://orcid.org/0000-0002-5852-9674

Ronald Olum https://orcid.org/0000-0003-1289-0111

References

1. WHO. *Global Tuberculosis Report*. Geneva: WHO, 2024.

2. Bhutta ZA, Sommerfeld J, Lassi ZS, et al. Global burden, distribution, and interventions for infectious diseases of poverty. *Infect Dis Poverty* 2014; 3: 21.

3. Prem K, Pheng SH, Teo AKJ, et al. Spatial and temporal projections of the prevalence of active tuberculosis in Cambodia. *BMJ Glob Health* 2019; 4(1): e001083.

4. Chowdhury K, Ahmad R, Sinha S, et al. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) among children: where we stand now. *Cureus* 2023; 15(2): e35154.

5. Tesfaye B, Alebel A, Gebrie A, et al. The twin epidemics: Prevalence of TB/HIV co-infection and its associated factors in Ethiopia; A systematic review and meta-analysis. *PLoS One* 2018; 13(10): e0203986.

6. WHO. Tuberculosis (TB), https://www.afro.who.int/health-topics/tuberculosis-tb (2018, accessed 17 July 2024).

7. Nicholson TJ, Hoddinott G, Seddon JA, et al. A systematic review of risk factors for mortality among tuberculosis patients in South Africa. *Syst Rev* 2023; 12(1): 23.

8. Semitala FC, Chaisson LH, Dowdy DW, et al. Tuberculosis screening improves preventive therapy uptake (TB SCRIPT) trial among people living with HIV in Uganda: a study protocol of an individual randomized controlled trial. *Trials* 2022; 23(1): 399.

9. Aturinde A, Farnaghi M, Pilesjö P, et al. Spatial analysis of HIV-TB co-clustering in Uganda. *BMC Infect Dis* 2019; 19(1): 612.

10. Kasozi S, Kirirabwa NS, Kimuli D, et al. Addressing the drug-resistant tuberculosis challenge through implementing a mixed model of care in Uganda. *PLoS One* 2020; 15(12): e0244451.

11. Baluku JB, Mugabe P, Mulwana R, et al. High prevalence of rifampicin resistance associated with rural residence and very low bacillary load among TB/HIV-coinfected patients at the national tuberculosis treatment center in Uganda. *Biomed Res Int* 2020; 2020: 2508283.

12. Dookie N, Ngema SL, Perumal R, et al. The changing paradigm of drug-resistant tuberculosis treatment: successes, pitfalls, and future perspectives. *Clin Microbiol Rev* 2022; 35(4): e0018019.

13. WHO. *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. World Health Organization, 2018.

14. Baluku JB, Mukasa D, Bongomin F, et al. Gender differences among patients with drug resistant tuberculosis and HIV co-infection in Uganda: a countrywide retrospective cohort study. *BMC Infect Dis* 2021; 21(1): 1093.

15. Baluku JB and Bongomin F. Treatment outcomes of pregnant women with drug-resistant tuberculosis in Uganda: a retrospective review of 18 cases. *Int J Infect Dis* 2021; 105: 230–233.

16. Bayowa JR, Kalyango JN, Baluku JB, et al. Mortality rate and associated factors among patients co-infected with drug resistant tuberculosis/HIV at Mulago National Referral Hospital, Uganda, a retrospective cohort study. *PLOS Global Public Health* 2023; 3(7): e0001020.

17. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147(8): 573–577.

18. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision: updated December 2014 and January 2020. Geneva: World Health Organization, 2013.

19. IBM CI. IBM SPSS Statistics for Windows Version 27.*0 IBM Corp*, 2020.

20. Izudi J, Tamwesigire IK and Bajunirwe F. Treatment success and mortality among adults with tuberculosis in rural eastern Uganda: a retrospective cohort study. *BMC Public Health* 2020; 20(1): 501.

21. Izudi J, Okello G and Bajunirwe F. Low treatment success rate among previously treated persons with drug-susceptible pulmonary tuberculosis in Kampala, Uganda. *J Clin Tuberc Other Mycobact Dis* 2023; 32: 100375.

22. Sahile Z, Tezera R, Haile Mariam D, et al. Nutritional status and TB treatment outcomes in Addis Ababa, Ethiopia: an ambi-directional cohort study. *PLoS One* 2021; 16(3): e0247945.

23. Oyewusi L, Zeng C, Seung KJ, et al. Low body mass index as a predictor of sputum culture conversion and treatment outcomes among patients receiving treatment for multidrug-resistant tuberculosis in Lesotho. *Global Health Action* 2024; 17(1): 2305930.

24. Hanrahan CF, Golub JE, Mohapi L, et al. Body mass index and risk of tuberculosis and death. *AIDS* 2010; 24(10): 1501–1508.

25. Shuter J, Chang CJ and Klein RS. Prevalence and predictive value of overweight in an urban HIV care clinic. *J Acquir Immune Defic Syndr* 2001; 26(3): 291–297.

26. WHO. *Guideline: nutritional care and support for patients with tuberculosis*. Geneva: World Health Organization, 2013.

27. Jang JG and Chung JH. Diagnosis and treatment of multidrug-resistant tuberculosis. *Yeungnam Univ J Med* 2020; 37(4): 277–285.

28. Otchere ID, Asante-Poku A, Akpadja KF, et al. Opinion review of drug resistant tuberculosis in West Africa: tackling the challenges for effective control. *Front Public Health* 2024; 12: 1374703.

29. Costa B and Vale N. Efavirenz: history, development and future. *Biomolecules* 2022; 13(1): 88.

30. Jacobs TG, Svensson EM, Musiime V, et al. Pharmacokinetics of antiretroviral and tuberculosis drugs in children with HIV/TB co-infection: a systematic review. *J Antimicrob Chemother* 2020; 75(12): 3433–3457.

31. Atwine D, Bonnet M and Taburet AM. Pharmacokinetics of efavirenz in patients on antituberculosis treatment in high human immunodeficiency virus and tuberculosis burden countries: a systematic review. *Br J Clin Pharmacol* 2018; 84(8): 1641–1658.

32. Mpoudi-Etame M, Tovar Sanchez T, Bousmah M-a-Q, et al. Durability of the efficacy and safety of Dolutegravir-based and low-dose Efavirenz–based regimens for the initial treatment of human immunodeficiency virus Type 1 infection in cameroon: week 192 data of the NAMSAL-ANRS-12313 Study. *Open Forum Infect Dis* 2023; 10(12): ofad582.