High rates of culture conversion and low loss to follow-up in MDR-TB patients managed at Regional Referral Hospitals in Uganda

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Research article

Keywords: Multi-drug resistant tuberculosis, regional referral hospitals, Uganda

Posted Date: April 22nd, 2019

DOI: <https://doi.org/10.21203/rs.2.9187/v1>

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Abstract

Background: Multi-drug resistant – tuberculosis (MDR-TB) is an emerging public health concern in Uganda, with only just over 200 new cases notified by 2014. Prior to 2013, MDR-TB treatment in Uganda was only being provided at the national referral hospital and two private-not-for profit clinics. From 2013, MDR-TB treatment was scaled up to seven regional referral hospitals (RRH). We analyzed data on the first cohort of patients started on MDR-TB treatment at the seven RRH. **Methods:** This study was a retrospective descriptive analysis of data collected on a cohort of 69 patients started on MDR-TB treatment at 7 RRHs between 1st April 2013 and 30th June 2014. **Results:** Of the 69 patients, 21 (30.4%) were female and 39 (56.5%) were HIV-negative. Thirty (43.5%) were resistant to both isoniazid and rifampicin and 57 (82.6%) were category 1 or 2 failures. Median age at the start of MDR-TB treatment was 35 years (SD 13.5), mean time-to-treatment initiation was 96.1 days and out of the 30 HIV-positive patients, 27 (90.0%) were on anti-retroviral treatment with a mean CD4 count of 258. Within six months of treatment, 59 (86.0%) patients' culture converted, of which 45 (65.2%) converted by the second month and 14 (20.3%) by the sixth month, one (1.5%) did not culture convert, three (4.4%) died and six (8.8%) were lost-to-follow up. Thirty-two (46.4%) patients experienced at least one severe drug adverse event, while 40 (67.8%) gained weight (mean 4.7 kilograms). **Conclusions:** Despite MDR-TB treatment initiation delays, most patients culture converted early, while few were lost to follow-up. These interim outcomes indicate a successful scale-up of MDR-TB treatment at RRH. Reasons for the high proportion of HIV-negative patients on MDR-TB treatment should be investigated.

Background

The diagnosis and treatment of Multidrug Resistant Tuberculosis (MDR-TB) remains a global challenge (1). MDR-TB is defined as *Mycobacterium Tuberculosis* that is resistant to two of the most efficacious first line anti-TB medicines (Isoniazid and Rifampicin) (2). According to the World Health Organization (WHO), MDR-TB remains a crisis. In 2014, it is estimated 480,000 new cases MDR-TB occurred and, of those, only 123,000 cases were diagnosed, while 190,000 died (3). Globally, the treatment outcomes of MDR-TB are less favorable, with only a 50% treatment success rate (3), partly due to the long duration of treatment, extending up to 24 months, treatment adherence difficulties and common adverse events (2,4). Until recently, the limited availability of second line drugs for the treatment of MDR-TB has been a major barrier to treatment access. According to WHO, there was an estimated 480,000 incidence cases of MDR-TB globally, of which only 123,000 (26%) were notified (3). The gap in MDR-TB treatment coverage globally has been attributed to inadequacies within the health system, including but not limited to lack of skilled human resources for health, lack of MDR-TB medicines and other logistics for MDR-TB patient management, inadequate infrastructure for in-patient care and suboptimal TB infection control practices, lack of funding for patient social support and limited access to laboratory and other monitoring tests (2). Currently, through support from the WHO, access to MDR-TB drugs in TB high burden countries has been on the increase, however implementing MDR-TB treatment programs is new in most high TB burden countries, with limited experience.

Uganda was one of the 22 high burden TB countries in the world with approximately 44,187 incident TB cases in 2014 (161/100,000). Additionally, 50 - 60% of TB patients are co-infected with HIV, and the country suffers a generalised HIV epidemic with a national prevalence of 7.3% (5). It is estimated that approximately 1.4% of new sputum positive cases and 12.1% of previously treated TB cases are MDR-TB, which translates to approximately 1,100 new MDR-TB cases in 2014 alone (3). However, the MDR-TB case notification rate was notably much higher than the MDR-TB treatment enrollment rate (6), indicating gaps in access to MDR-TB treatment. In order to improve access to MDR-TB treatment, it was necessary to further decentralise MDR-TB services. To that end, the National TB and Leprosy Programme (NTLP) mobilized partner support to decentralize treatment of drug resistant TB (DR-TB) from National Referral to the regional referral hospitals (RRH) to increase coverage and make treatment more accessible.

The United States Agency for International Development (USAID) funded Strengthening Uganda's System for Treating AIDS Nationally (SUSTAIN) project supported selected RRH and General Hospitals to provide comprehensive quality HIV and TB prevention, care and treatment services, initiated activities, including building capacity of seven of the RRH to manage drug resistant TB. In 2013, in collaboration with NTLP, SUSTAIN embarked on a phased approach to scale up ambulatory MDR-TB care to the seven SUSTAIN-supported RRHs with the highest incidences of MDR-TB. Scale-up included training of multi-disciplinary teams at each RRH to initiate and manage MDR-TB treatment, dissemination of guidelines for management of MDR-TB, and facilitation of follow-up of patients and their household contacts.

WHO recommends MDR-TB models that are ambulatory, in which patients receive medicines from a local health facility close to their homes, or have the medicines delivered daily by a health worker to the patient's home, as compared to hospital-based models of care in which patients are admitted into a centralized setting for an intensive phase of treatment or more, lasting a minimum of six months (2,7). In Uganda, the NTLP recommends a mixed model of care that combines both ambulatory and hospitalisation approaches.

To understand if scale up of MDR-TB treatment to RRH was successful in ensuring favorable interim (sputum conversion at six months) treatment outcomes, we conducted a retrospective analysis for the early treatment outcomes for the first cohort of MDR-TB patients started on MDR-TB treatment at seven RRH. To our knowledge, this is the first analysis of this kind in the country.

Methods

We retrospectively examined clinical records from a case series of 69 DR-TB patients started on treatment at six RRHs between 1st April 2013 and 30th June 2014. This included all patients diagnosed with MDR-TB using culture based drug susceptibility testing (DST) or rifampicin resistance (RR) through rapid test Xpert® MTB/RIF.

Mycobacteria Culture and Drug Susceptibility Testing

Prior to the study period, participating laboratories collected sputum samples and delivered them to the National TB Reference Laboratory (NTRL) through an existing laboratory network for culture and sensitivity. Samples were from presumptive MDR-TB cases, defined as patients who:

1. Have failed on WHO category 1 or 2 (pulmonary bacteriologically confirmed at 5 months of) TB treatment;
2. Have relapsed (previously treated and cured of TB and returned with a pulmonary bacteriologically confirmed TB);
3. Have returned after loss to follow-up (returning to TB care after taking TB treatment for 1 month and interrupting treatment for 2 months) or;
4. Are household contacts of confirmed MDR-TB cases (8)

Results were returned to the requesting health facilities through the same network for patient care and support. The NTRL conducted cultures on BACTEC MGIT 960 or Lowenstein-Jensen solid medium, while conventional DST or line probe assays (LPA), a rapid molecular method for detecting first and second line drug resistance were used.

The MOH/NLTP adopted Xpert MTB/RIF in 2011 and installed at RRHs as the rapid DST for screening for Rifampicin Resistance (RR) as a proxy to MDR-TB. All cases of RR had sputum samples referred to the NTRL for baseline culture prior to treatment initiation (9,10).

MDR-TB Regimen and Treatment Follow-up

Health facilities linked or referred newly diagnosed MDR-TB patients to one of the seven RRH MDR-TB treatment initiation sites where baseline history, physical exam, chest radiography, haematological and chemistry tests were conducted. Multidisciplinary panels conducted pre-treatment preparation and counselling, after which a standardised MDR-TB regimen was initiated in accordance with Uganda National MDR-TB guidelines (9). The standardised regimen consisted of five drugs; one injectable agent – Kanamycin or Capreomycin or Amikacin substituted depending on need, a fluoroquinolone (levofloxacin), Pyrazinamide, Ethionamide and Cycloserin. Para-amino salicylic acid (PAS) was available for substitution when Cycloserin was not tolerated. An empiric regimen is recommended for patients previously exposed to second-line TB medicines, until a full DST profile was available to guide regimen modification. Daily directly observed therapy (DOT) was administered, except the injectable that was given for only six days in a week (9).

Patients were initiated on an ambulatory or hospitalisation model depending on severity of the illness. The very sick patients were initiated on a hospitalization model and when they stabilised on treatment, they chose a health facility nearest to his/her place of abode, which was visited by a team of health workers from the RRH, assessed and staff trained in MDR-TB management. The patient was then transferred to the peripheral health facility to continue receiving ambulatory DOT, adherence monitoring and psychosocial support. The initiating RRH conducted monthly visits to the peripheral sites, provided supervision and mentorship. A monthly supply of MDR-TB and ancillary medicines and personal protective equipment for TB infection control were delivered to the DOT follow-up health facility.

The initial phase was administered for a minimum of four months following culture conversion, defined as two consecutive negative cultures one month apart, after which up to 18 months' continuation phase ensues upon discontinuation of the injectable agent (9). During the intensive phase, all MDR-TB patients were counselled and tested for HIV. MDR-TB/HIV co-infected patients, if not already on treatment, were linked to integrated TB/HIV services and initiated on an ART regimen containing a backbone of either Zidovudine/Lamivudine or Tenofovir/Emtricitabine and a tail of Efavirenz or Nevirapine within 2 months of MDR-TB treatment initiation, regardless of CD4+ count (11). Also, during this phase, health workers conducted home visits to provide patient and family education, assess for adherence to infection control practices, screen household contacts for TB symptoms and collect sputum samples for Xpert® MTB/RIF test.

At the RRH initiating treatment, the patients received a comprehensive monthly review in which sputum samples were collected for monthly follow-up cultures, kidney and liver functions were analysed, blood samples were collected and delivered to a private laboratory for thyroid function tests and patients were assessed for hearing impairment. During the treatment, the patients were monitored for adverse events and managed through with dose adjustments, substitution of the offending drug, treatment withdrawal and/or by reassurance. For co-infected MDR-TB/HIV patients, all services integrated MDR-TB and HIV care, such as screening and management of opportunistic infections, response to ART, Immune Reconstitution Syndrome, repeat CD4+ and Viral load testing after 6 months) according to WHO HIV treatment guidelines (11). Also, during the monthly review, the patients received nutritional assessment, counselling and support.

All confirmed MDR-TB patients provided sputum samples for smears and baseline DST before treatment initiation. Subsequently, sputum was collected and tested every month during the six months of treatment. All patients were provided with a month's stipend to cater for treatment related travel costs, while the peripheral DOT health workers were provided with a transport re-imbursement and mobile phone credit to facilitate provision of weekend DOT and to conduct phone patient follow-ups, respectively.

Data collection and analysis

Demographic data, previous TB treatment history, HIV status and previous exposure to ART, CD4+ count, drug resistance patterns, MDR-TB treatment regimen, time to treatment initiation, monthly weights, occurrence of adverse events, monthly smear and culture monitoring were collected.

Patient follow-up ended when an outcome was recorded or on 30th June 2014 for all patients still on treatment. The primary treatment outcome was the proportion of patients that culture converted at 6 months of treatment. Culture conversion is considered a useful indicator of MDR-TB programme

effectiveness as treatment outcomes are available after 18-24 months (2,12). Culture conversion is defined as two consecutive negative cultures taken one month apart (12). Secondary outcomes included time to culture conversion - time from treatment initiation to the date of the first of two consecutive negative cultures (13). Univariate analysis (χ^2 test) were performed to determine the associations between type of patient and treatment outcome. STATA/SE software version 14.0 was used for all the analysis.

Results

A total of 73 patients were started on MDR-TB treatment from 1st April 2013 through 30th June 2014 (Figure 1). Four patients started on an empiric MDR-TB treatment regimen were excluded from the analysis because two of the patients were found without MDR-TB following a culture and Drug Susceptibility Testing (DST), while the other two were culture negative. The tests were carried out at the National TB Reference Laboratory.

Figure 1: Flow chart for patients initiated on MDR-TB treatment from April 2013 to June 2014

Baseline characteristics of the remaining 69 patients are shown in Table 1. Twenty-one (30.4%) patients were female, with a median age of 36.8 (Standard Deviation (SD) ± 13.1). Median time to MDR-TB treatment initiation was 96.1 days (Inter Quartile range (IQR) 1 - 930). The drug susceptibility patterns were as follows; 30 (43.5%) patients were resistant to both isoniazid and rifampicin on culture based DST and 39 (56.5%) were MTB/RIF based on Xpert®. A total of 66 (95.6%) patients were on a standardised treatment regimen. Thirty (43.5%) patients were HIV-positive, of which which 27 (90.0%) were already receiving anti retroviral treatment (ART) at baseline, with median CD4 count of 238 cells/ul (IQR214 to 307) at baseline. Only five (7.3%) patients did not have a history of previous TB treatment while 64 (92.7%) patients had been previously treated as failures, with twenty (29.0%) Category 1 failures, 37 (53.6%) Category 2 failures, one (1.5%) relapse and six (8.7%) returns after lost to follow-up. A total of 59 patients had a record of weight at baseline and after six months of treatment, 40 (67.8%) patients experienced weight gain (mean: 4.7 kilograms; SD: ± 3.2), one maintained the same weight while the other eighteen (30.5%) lost weight (mean: 2.8 kilograms and SD ± 2.3).

Table 1: Baseline characteristics of the MDR-TB patients

Variable	All patients (n=69) N (%)	Male (n=48) N (%)	Female (n=21) N (%)
Age			
Median (SD)	36.8 (13.1)	37.4 (13.1)	35.2 (13.4)
Time to treatment initiation (in days)			
Median (IQR)	27.5 (1 - 930)	26 (1 - 930)	43 (1 - 415)
Sex			
Female	21 (30.4%)	NA	NA
Male	48 (69.6%)	NA	NA
Drug susceptibility resistance profile			
Isoniazid and Rifampicin	10 (14.5%)	6 (12.5%)	4 (19.0%)
Isoniazid, Rifampicin & other 1st line	20 (29.0%)	14 (29.2%)	6 (28.6%)
MTB/Rif based on Gene expert result	39 (56.5%)	28 (58.3%)	11 (52.4%)
Treatment regime			
Individualized	3 (4.4%)	1 (2.1%)	2 (9.5%)
Standardized	66 (95.6%)	47 (97.9%)	19 (90.5%)
HIV status			
Negative	39 (56.5%)	29 (60.4%)	10 (47.6%)
Positive**	30 (44.5%)	19 (39.6%)	11 (52.4%)
CD4 Cell count/mm3			
CD4 cell count is known	28 (93.3%)	19 (100%)	9 (81.8%)
CD4 cell count is not known	2 (6.7%)	0 (0%)	2 (18.2%)
Median CDC cell count (IQR)	206	268 (49-809)	130 (10-307)
TB treatment history/patient type			
Category 1 failure	20 (29.0%)	16 (33.3%)	4 (19.1%)
Category 2 failure	37 (53.6%)	24 (50.0%)	13 (61.9%)
New	5 (7.3%)	1 (2.1%)	4 (19.1%)
Relapse	1 (1.5%)	1 (2.1%)	0 (0.0%)
Treatment after loss-to-follow up/defaulters	6 (8.7%)	6 (12.5%)	0 (0.0%)
Current treatment hospital			
Treatment Initiating hospital (RRH)	21 (30.4%)	35 (72.9%)	13 (61.9%)
Follow up health facility	48 (69.6%)	13 (27.1%)	8 (38.1%)
Weight measurement			
Weight gain: Number (Mean, SD)	40 (4.7, ± 3.2)	26 (4.9, ± 3.3)	14 (4.1, ± 3.1)
Weight loss: Number (Mean, SD)	18 (2.8, ± 2.3)	13 (2.5, ± 2.6)	5 (3.5, ± 0.9)
No change in weight: Number (Mean, SD)	1 (0, NA)	1 (0, NA)	0 (NA, NA)

** - All HIV positive patients received ART and Cotrimoxazole prophylaxis

Adverse Events and Interim Treatment Outcomes

Just over 75% of the cohort experienced some type of adverse event associated with MDR-TB medicines as presented in Table 2. The most prevalent adverse event was hearing impairment (30.4%).

Table 2: Frequency of drug reactions and how they were managed

Adverse event	Reaction	Male	Female	Reaction	Management of adverse events		
	N (%)	N (%)	N (%)	N (%)	Clinically	Regimen changed	Others
Nausea/Vomiting	14 (20.3%)	9 (64.3%)	5 (35.7%)	14 (20.3%)	14 (100%)		
Headache	15 (21.7%)	11 (73.3%)	4 (26.7%)	15 (21.7%)	15 (100%)		
Diarrhea	2 (2.9%)	0 (0.0%)	2 (100.0%)	2 (2.9%)	2 (100%)		
Burning pains in the lower limbs	20 (29.0%)	15 (75.0%)	5 (25.0%)	20 (29.0%)	18 (90%)	1 (5%)	1 (5%)
Arthralgia	12 (17.4%)	9 (75.0%)	3 (25.0%)	12 (17.4%)	12 (100%)		
Seizures	1 (1.4%)	1 (100.0%)	0 (0.0%)	1 (1.4%)	1 (100%)		
Rash	1 (1.4%)	3 (50.0%)	3 (50.0%)	1 (1.4%)	1 (100%)		
Psychiatric manifestations	9 (13.0%)	6 (66.7%)	3 (33.3%)	9 (13.0%)	9 (100%)		
Hypothyroidism	2 (2.9%)	2 (100.0%)	0 (0.0%)	2 (2.9%)	2 (100%)		
Visual disturbances	10 (14.5%)	7 (70.0%)	3 (30.0%)	10 (14.5%)	10 (100%)		
Hearing disturbance	21 (30.4%)	16 (76.2%)	5 (23.8%)	21 (30.4%)	21 (100%)		
Dizziness	13 (18.8%)	7 (53.9%)	6 (46.2%)	13 (18.8%)	13 (100%)		

With exception of burning pains in the lower limbs, the adverse events were managed symptomatically without need for treatment discontinuation. Figure 2 shows the time at which each of the 59 patients with favourable treatment outcomes culture converted. Majority (27: 46%) of the 59 patients culture converted within 2 months of treatment initiation. 57 (97%) of the 59 patients that eventually culture converted achieved culture conversion within 3 months of treatment initiation. The mean time to culture conversion was 1.98 months (SD 0.86).

Figure 2: Time to sputum culture conversion among 59 patients with favorable interim treatment outcomes

Six months after starting treatment ten patients had not achieved favourable treatment outcomes. Of these, three (4.4%) patients had died, three (4.4%) patients were lost to follow up, three patients (4.4%) did not have their culture results known, and one did not culture convert (Table 3).

Table 3: Six-months interim treatment outcomes, culture conversion time and adverse events profiles

Variable	All patients (n=69) N (%)	Male (n=48) N (%)	Female (n=21) N (%)
Six months interim treatment outcomes			
Favourable outcome	59 (87.0%)	41 (85.3%)	18 (85.7%)
Culture converted	1 (1.5%)	0 (0.0%)	1 (4.8%)
Unfavourable outcome	3 (4.4%)	3 (6.3%)	0 (0.0%)
Remained culture positive	3 (4.4%)	1 (2.1%)	2 (9.5%)
Culture unknown	3 (4.4%)	3 (6.3%)	0 (0.0%)
Died			
Lost-to-follow up			
Culture conversion time (by the sixth month of treatment)			
By two months	45 (76.3%)	10 (24.4%)	4 (22.2%)
After two months	14 (23.7%)	31 (75.6%)	14 (77.8%)
Adverse events			
Yes	53 (76.8%)	36 (75.0%)	17 (80.9%)
No	16 (23.2%)	12 (25.0%)	4 (19.1%)
Median (IQR)	1.0 (1 - 3)	1.0 (0.5-3.0)	2.0 (1.0-2.0)
Mean (SD)	1.8 (1.69)	1.77 (1.79)	1.90 (1.48)
Range	(0.0 – 7.0)	(0.0 – 7.0)	(0.0 – 5.0)

Relationship between patient category and treatment outcome

Table 4 shows that 86.4% of the MDR-TB patients with favourable outcomes (had sputum culture conversion) had been treatment failures on 1st line (susceptible TB) treatment, compared to 60% of MDR-TB patients with unfavorable outcomes (did not culture convert, were lost to follow-up). Overall, there was a statistically significant association between patient type and treatment outcomes (Chi-square = 8.5, and p-value = 0.037). Table 4 shows associations between patient type and six-month treatment outcomes. It was observed that patients who were failures on 1st line treatment were less likely to experience unfavorable treatment outcomes by six months of MDR-TB treatment compared to defaulters, new and relapse patients (p = 0.04).

Table 4. Relationship between interim 6-months treatment outcome and type of patient

Type of patient	Unfavourable outcome (N=10)		Favourable outcome (N=59)		Chi-square		p-Value
	N	%	N	%			
Treatment failure	6	60.0%	51	86.4%	4.2		0.04*
Defaulter	2	20.0%	4	6.8%	1.9		0.17
New	1	10.0%	4	6.8%	0.13		0.72
Relapse	1	10.0%	0	0%	6.0		0.01*

Discussion

This manuscript describes the first cohort of patients treated for MDR-TB at the RRHs following scale up to 7 RRH in Uganda. Only one patient died and was not able to complete the intensive phase of MDR-TB treatment.

There is a paucity of literature on MDR-TB treatment outcomes among cohorts on treatment on the African continent (14,15). Some cohorts have been described in South Africa, Lesotho, Nigeria and Tanzania (16–20). Our findings showed an exceptionally high sputum culture conversion rate (87%) compared to other studies done elsewhere (70%) in the following 5 countries: Estonia, Latvia, Peru, the Philippines, and the Russian Federation (21).

Despite scaling up MDR-TB treatment services to RRH in order to bring services closer to the population, the majority of the population affected by MDR-TB are too poor to afford the reduced transport costs. SUSTAIN provided transport to the patients to enable them visit the MDR-TB drug collection centers. The 4.4% loss to follow up rate in this intervention is low compared to previous community based cohorts (22,23). We postulate that the transport stipend provided to patients to offset travel related expenses re-enforced adherence and retention in care, while the decentralisation of MDR-TB management from NRH to RRH, coupled with utilisation of perihelal health facilities nearest to patient homes for daily directly observed therapy (DOT) broadened MDR-TB treatment coverage and access.

Most (76.8%) experienced some sort of drug adverse events, although only one patient required a regimen change. Adverse events like hearing impairment were mostly due to the MDR-TB medicines in the treatment regimen, like Kanamycin. Routine audiometry and Kanamycin substitution may therefore benefit the patient. Other adverse events like peripheral neuropathy are known ethionamide and cycloserine associated events, potentiated by HIV related peripheral neuropathies. We postulate that the increased frequency of adverse events observed were associated with poor clinical condition of the patients and existing TB/HIV coinfection. Further research is need to elucidate adverse events predictors among MDR-TB patients on treatment.

Generally, mortality was low (4.4%) occurring in only three patients - all HIV co-infected. This trend in mortality among HIV co-infected patients compares with observations in previous studies (18). In our study, mortality occurred early-within 4 weeks of MDR-TB treatment initiation, underscoring the need for expedited treatment initiation among MDR-TB patients. A meta-analysis by Wells et al. reported death among MDR-TB patients on treatment occurring within 4-8 weeks of MDR-TB diagnosis and also demonstrated higher mortality rates among HIV co-infected patients, even among those on ART (24). Interestingly, the majority of our patients were HIV-negative, while those that were HIV-positive were on ART. Further studies need to be conducted to identify factors contributing to a higher MDR-TB prevalence among HIV seronegative patients. We noticed most of the patients upon diagnosis had remained on long pre-treatment lists, up to 31 months, prior to the decentralisation of treatment from NRH to RRH's. We therefore postulate that high prevalence of HIV seronegative patients were as a result of MDR-TB/HIV co-infected patients dying during the long time-to-treatment initiation periods.

In Uganda, MDR-TB treatment was, until recently (2012), only provided at the National Referral Hospital (NRH), Arua RRH and Kitgum government general hospital, the latter two being Médecins Sans Frontières (MSF) run MDR-TB clinics (25). At that time, the Regional Referral Hospitals (RRH) only had capacity to do surveillance and referral to the three sites for treatment. Patients diagnosed at RRH had challenges accessing treatment, due to long distances to the centers, lack of social/family support and lack of food packages during the mandatory hospitalization phase of treatment. The SUSTAIN project supported 7 RRH's MDR-TB treatment sites have been trying to address the access and coverage challenges since 2013. The early treatment outcomes from our study indicate a successful scale up of MDR-TB treatment from NRH to RRH for both HIV-positive and HIV-negative patients.

We attribute these outcomes; firstly, to utilization of an effective - standardized MDR-TB treatment regimen that made training, drug forecasting and management of drugs adverse events simpler; Secondly, to the existing DOT at peripheral health facilities supervised by the decentralized RRH MDR-TB sites enabled individual patients' access daily medication from facilities closest to their homes as compared to having the DOT site as the RRH and NRH as the treatment initiation site; Three, to the monthly satellite/review clinics run by the RRH multidisciplinary teams, that aided prompt identification and management of adverse events minimizing treatment interruptions and ultimately loss to follow-up; Four, to the monthly home visits and psychosocial support, adherence counselling and nutritional assessment counselling and support provide by the RRH multidisciplinary team; Five, the integrated MDR-TB/HIV services run by the MDR-TB clinics, which reduced patient waiting time and transport related expenses and also provided an opportunity to the multidisciplinary teams to screen for drug adverse events and interactions, and provide appropriate management. We further, think that the ambulatory care coupled with TB infection control measures and practices at the RRH during the early days of hospitalization may have contributed to prevention of reinfection with resistant strains.

The feasibility of MDR-TB models of care delivered through ambulatories is still debated (18,19,26). Equally, community based cohorts have demonstrated challenges with patient adherence, leading to high lost to follow-up rates (22,23). Our findings provide insights into the early outcomes of the mixed model of MDR-TB care in resource constrained settings. We adopt the best of both models of care, to identify risk patients to loss to follow-up.

This study was not designed to find if a mixed model of care is superior to other single dimensional model. However, the results point towards early success of the programme. We believe that delivering a decentralised MDR-TB care through RRH and peripheral DOT sites is feasible and could serve for resource limited settings. The final treatment outcomes needs to be evaluated as we push for the need for rapid scale up of coverage and access to MDR-TB care to lower level health facilities using this model. Further qualitative study is necessary to provide further insights into health workers' perspectives and patient's experiences regarding the mixed model of MDR-TB care in Uganda.

List Of Abbreviations

ART Anti-Retroviral Therapy

CHC Center for Health Services

DOT Directly Observed Treatment

DST Drug Susceptibility Test

HIV Human Immuno-Deficiency Virus

LPA Line Probe Assays

MDR Multi-Drug Resistance Tuberculosis

MSF Médecins Sans Frontières

NTLP National TB and Leprosy Program

NTRL National TB Reference Laboratory

PAS Para-Amino Salicylic Acid

REC Research and Ethics Committee

RR Rifampicin Resistance

RRH Regional Referral Hospital

SD Standard Deviation

SUSTAIN Strengthening Uganda Health Systems for Treating AIDS Nationally

TB Tuberculosis

URC Univesity Research Co., LLC

USAID United States Agency for International Development

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the University Research Co., LLC | Center for Human Services Research and Ethics Committee (URC-CHS REC), Mildmay Uganda Research and Ethics committee (MUREC) and the Uganda National Council of Science and Technology (UNCST). MUREC waived the need for informed patient consent as the study only involved routinely collected patient monitoring data.

Consent for publication

Not applicable

Availability of data and materials

The dataset used during this study is available and can be availed upon request from the corresponding author.

Competing Interests

All authors declare they have no competing interests.

Funding

The SUSTAIN project was funded by the United States Agency for International Development (USAID) under Cooperative Agreement number 617-A-10-00007-00.

Authors' contributions

MKM, OJP, AH, MKA, WC, GT and KSW conceived and designed the study. MKM and OJP wrote study protocol. OJP and WC collected the data. MKM, OJP and WC electronically captured the data and performed data cleaning. MKM analyzed the data; MKM and OJP interpreted the results and wrote the manuscript. MKM, OJP and SR reviewed the manuscript to ensure it meets the submission requirements: All authors reviewed the manuscript and approved it for final submission.

Acknowledgments

We are grateful to USAID for funding the SUSTAIN project. We are also grateful to the Ministry of Health and management of the Regional Referral Hospitals that participated in this study for supporting this study. We thank the healthcare providers who treat the MDR-TB patients at the study hospitals for supporting to the data collection process. We would also like to thank Beth Turesson and Chana Rabiner who reviewed an earlier version of this manuscript.

References

1. Gandhi NR, Nunn P, Dheda K, Schaaf HS, Zignol M, van Soolingen D, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet [Internet]*. 2010;375(9728):1830–43. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673610604102>
<http://www.ncbi.nlm.nih.gov/pubmed/20488523>
<http://linkinghub.elsevier.com/retrieve/S0140673610604102>
2. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 Update. *World Heal Organ*. 2011;WHO/HTM/TB/2008.402.
3. WHO. *Global TB Report 2015*. Geneva; 2015.
4. Shenoi S, Heysell S, Moll A, Friedland G. Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community. *Curr Opin Infect Dis*. 2009;22:11–7.
5. Uganda HM, ICF I. 2011 Uganda AIDS Indicator Survey Key Findings. Report. 2012;(Calverton, Maryland, USA):MOH and ICF International.

6. WHO. World Health Organization. Uganda country profile. Global Tuberculosis Control: WHO Report 2015. Geneva. 2015.
7. WHO. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response [Internet]. Geneva: World Health Organization. 2010. 57 p. Geneva;
8. Ugandan Ministry of Health. National Tuberculosis and Leprosy Programme Manual, 2nd edition. 2010.
9. Ugandan Ministry of Health. National Guidelines for the Programmatic Management of Drug Resistant-TB. 2nd edition 2015.
10. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: WHO/HTM/TB/2014.11; 2014.
11. World Health Organization. March 2014 Supplement. March 2014 Suppl to 2013 consolidated Guidel USe Antiretroviral Drugs Treat Prev HIV Infect [Internet]. 2014;(March). Available from: http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_march2014/en/
12. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: Treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2005;9(6):640–5.
13. The World Health Organization. Treatment of Tuberculosis: Guidelines. 4th edition. 2010. p. 2.3 Case definitions.
14. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9, 153 Patients. *PLOS Med* [Internet]. 2012;9(8):e1001300. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3429397&tool=pmcentrez&rendertype=abstract>
15. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: A systematic review and meta-analysis. *PLoS ONE*. 2009.
16. Laloo UG, Naidoo R, Ambaram A. Recent advances in the medical and surgical treatment of multi-drug resistant tuberculosis. *Curr Opin Pulm Med* [Internet]. 2006;12(3):179–85. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16582672>
17. Loveday M, Wallengren K, Voce a, Margot B, Reddy T. Comparing Early Treatment Outcomes of MDR-TB in a Decentralized Setting in KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis*. 2012;16(2):209–15.
18. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early Outcomes of MDR-TB Treatment in a High HIV-Prevalence Setting in Southern Africa. *PLoS One*. 2009;4(9):e7186.
19. Oladimeji O, Isaakidis P, Obasanya OJ, Eltayeb O, Khogali M, Van den Bergh R, et al. Intensive-phase treatment outcomes among hospitalized multidrug-resistant tuberculosis patients: results from a nationwide cohort in Nigeria. *PLoS One*. 2014;9(4):e94393.
20. Mpagama SG, Heysell SK, Ndusilo ND, Kumburu HH, Lekule IA, Kisonga RM, et al. Diagnosis and Interim Treatment Outcomes from the First Cohort of Multidrug-Resistant Tuberculosis Patients in Tanzania. *PLoS One*. 2013;8(5).
21. Nathanson E, Weezenbeek CL Van, Rich ML, Gupta R, Bayona J, Bl??ndal K, et al. Multidrug-resistant tuberculosis management in resource-limited settings. *Emerg Infect Dis*. 2006;12(9):1389–97.
22. Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcántara F, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med*. 2003;348:119–28.
23. Heller T, Lessells RJ, Wallrauch CG, Bärnighausen T, Cooke GS, Mhlongo L, et al. Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis*. 2010;14(4):420–6.
24. Wells C, Cegielski J, Nelson L, Laserson K, Holtz T, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis*. 2007;196 Suppl:S86–107.
25. Luyirika E, Nsobyia H, Batamwita R, Busingye P, Musoke W, Nabiddo L, et al. A home-based approach to managing multi-drug resistant tuberculosis in Uganda: A case report. *AIDS Res Ther* [Internet]. BioMed Central Ltd; 2012;9(1):12. Available from: <http://www.aidsrestherapy.com/content/9/1/12>
26. Isaakidis P, Cox HS, Varghese B, Montaldo C, Da Silva E, Mansoor H, et al. Ambulatory Multi-Drug Resistant Tuberculosis Treatment Outcomes in a Cohort of HIV-Infected Patients in a Slum Setting in Mumbai, India. *PLoS One*. 2011;6(12):e28066.

Figures

Figure 1: Flow chart for patients initiated on MDR-TB treatment from April 2013 to June 2014

Figure 1

Flow chart for patients initiated on MDR-TB treatment from April 2013 to June 2014

Figure 2

Flow chart for patients initiated on MDR-TB treatment from April 2013 to June 2014