

Outcomes in Adolescents Undergoing Treatment for Drug-Resistant Tuberculosis in Cape Town, South Africa, 2008-2013

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Received: January 30, 2014; Revised: March 1, 2014; Accepted: March 15, 2014

Background: There is limited data on outcomes of adolescents with drug-resistant tuberculosis (DR-TB).

Objectives: To describe patient outcomes and factors associated with outcomes of adolescents diagnosed with DR-TB in Khayelitsha, South Africa.

Patients and Methods: A retrospective analysis of data for adolescents aged 10-19 years who were diagnosed with DR-TB between January 2008 and August 2013 was conducted. The proportions of adolescents with treatment success (cure and treatment completion), failure of treatment, those lost from treatment, and those who died were calculated and compared by HIV status. Proportions and odd ratios are presented.

Results: Seventy-one adolescents were diagnosed with DR-TB. Six (8%) were lost to care before treatment could be initiated. The median age of those started on treatment was 18 years (IQR 15.8-18.9). Eighteen (27.7%) were HIV infected. Of the 44 adolescents with final treatment outcomes, 36.4% (n=16) were successfully treated, 9.1% (n=4) died, 11.4% (n=9) failed treatment and 43.2% (n=19) were lost from treatment (treatment interrupted for ≥ 2 consecutive months). Three of the four patients who died, died within two months of starting therapy. Loss from treatment, and treatment success (cure or treatment completion) did not differ between HIV infected and un-infected adolescents, OR: 2.0, (95% CI 0.56-7.50), P=0.27; and OR: 1.2 (95% CI 0.37-4.43), P=0.71, respectively. All five patients who failed treatment and one of those lost from treatment subsequently died. Overall mortality was 12.1/100 person years.

Conclusions: HIV infected and uninfected adolescents with DR-TB experienced poor outcomes with high proportions of mortality, treatment failure and loss from treatment. Mortality occurred early in the treatment period suggesting delayed presentation and/or diagnosis. Innovative and targeted strategies are needed to encourage early presentation and improve adherence to treatment among adolescents.

Keywords: Extensively Drug-Resistant Tuberculosis; Adolescent; Patient Outcome Assessment

1. Background

Drug-resistant tuberculosis (DR-TB) defined as strains of tuberculosis with any resistance to rifampicin, is a growing public health concern, across the world (1, 2). According to World Health Organization (WHO) estimates, there are more than 650,000 prevalent cases of DR-TB in the world (3). It is estimated that at least 10% of these occur among children (4), and although excellent treatment outcomes have been reported in pediatric populations (5), thousands of children die from this disease each year, largely due to lack of access to diagnosis and treatment (6, 7).

There has been a recent increased interest in pediatric DR-TB, with efforts being made to increase access to time-

ly diagnosis and prompt initiation of care (8-10). While the pediatric population is often written about as a homogenous group, children along the age spectrum have different needs in terms of diagnosis and treatment that merit special attention (11). The period of adolescence defined by the WHO as between the ages of 10-19 years (12) may pose significant challenges to the management of DR-TB (13, 14). One of the only studies of DR-TB in adolescents was of HIV co-infected adolescents in Mumbai which found that poor treatment outcomes were common, with 64% experiencing death, treatment failure, or default (15).

There may be several factors related to the poor treat-

Implication for health policy/practice/research/medical education:

There is limited data on outcomes of adolescents with drug-resistant tuberculosis (DR-TB). This study shows poor outcomes in HIV infected and un-infected adolescents with DR-TB and highlights the need for adolescent specific interventions and support to encourage early presentation and retention on treatment.

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ment outcomes seen in adolescents with DR-TB. Studies of other diseases in this population have shown that adolescents face specific developmental challenges that may make adherence to complicated medical regimens difficult (16, 17). Second, adolescents may be experiencing rapid periods of growth that render dosing inadequate (18). Third, adolescents may not always engage well with standard services, which are usually adult orientated, and finally, adolescence is a time of major life changes such as geographic dislocation, finding work, developing significant relationships (e.g. long term commitments), that may also make treatment of chronic diseases more complicated (19-21).

2. Objectives

This paper reports on the treatment outcomes for a group of adolescents undergoing treatment for DR-TB in Khayelitsha, Cape Town, South Africa between 2008 and 2013. The outcomes for the entire cohort have been reported elsewhere in the literature (22). The adolescent outcomes are presented separately here given the poor treatment outcomes seen in the Mumbai cohort (15) and since this is to our knowledge one of the largest cohorts of adolescent patients reported in the literature.

3. Patients and Methods

Khayelitsha township is situated about 30 km outside Cape Town and has an estimated population of approximately 400000 (23) people. It has a high burden of HIV and TB with a 69 % HIV/DR-TB confection rate in 2011 (22). Antenatal HIV prevalence was 33% in 2010 (24). The TB case notification rate was 1500/100000 in 2008 (25). A survey conducted in the same year found DR TB in 3.3% and 7.7% of new and previously treated TB cases respectively, and estimated DR-TB notification rate at 51/100,000/year (25, 26).

This study is a retrospective review of a cohort of adolescents who were diagnosed with DR-TB in Khayelitsha, South Africa between January 2008 and August 2013. The details of the entire DR-TB cohort in Khayelitsha and a description of the methodology have been described in detail elsewhere (22, 27). In summary, the following elements were added to the existing TB programme at primary care level: - DR-TB specific staff training and clinical support, DR-TB counseling, social assistance, programme supervision and evaluation, TB infection control support and advice, a local sub-acute short stay facility and specialist outreach services for pediatrics and audiometry screening (22). In addition to primary care services that include HIV testing and counselling, DR-TB services provided at the primary care clinics include nurse and medical officer consultation, sputum collection for diagnosis and treatment monitoring, DR-TB specific counselling, directly observed therapy (DOT) and administration of injectable drugs where they have been prescribed. The sub-acute facility is available for patients who do not need hospital care but require support to take their med-

ication, deal with side effects, or overcome other difficulties to receiving treatment at home.

Drug susceptibility testing (DST) was initially only available for TB cases considered at high DR-TB risk, who were defined as patients who had been previously treated for TB, those not responding to first-line TB treatment, close contacts of patients diagnosed with DR-TB, health care workers and those with a history of being in prison. From late 2011, all individuals with suspected TB underwent testing with the Xpert MTB/Rif assay (28, 29), a molecular based test for rapid and simultaneous detection of tuberculosis and rifampicin resistance endorsed by the WHO, and is being rolled out in South Africa (28, 29). A standard treatment regimen in line with the South African National Department of Health recommendations aligned to WHO recommendations was used (29, 30). This was adapted based on second line DST results or when treatment was failing. Available drugs included second line injectable agents (kanamycin, capreomycin), ethambutol, ethionamide and pyrazinamide, terizidone, fluoroquinolones (ofloxacin, moxifloxacin) and P-aminosalicylic acid (PAS), clofazimine, and high dose isoniazid. Treatment duration was for at least 18 months (29, 30). Treatment outcome definitions follow WHO recommendations, as follows (29, 31):

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 success: The sum of cured and treatment completed.

Treatment failed: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of culture conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).

Died: A patient who dies for any reason during the course of treatment.

Lost to follow up: A patient whose treatment was interrupted for 2 consecutive months or more (previously defined as default (30)).

3.1. Data Collection and Analysis

Routine DR-TB programme data was initially collected from paper registers at primary care clinics and entered into a MS Access database. From February 2013, data was directly imported from an electronic database of all DR-TB patients (EDR. Web), in the Khayelitsha district.

Analyses were conducted using STATA v. 12.0 (Stata Corp, College Station, TX, USA). Continuous variables were compared using the Mann-Whitney test. Proportions were compared using with the Chi2 test. 95% CI and p values are presented. Evaluation of the Khayelitsha DR-TB program was approved by the University of Cape Town, Faculty of Health Sciences Human Ethics review committee (ref 540/2010).

Outcomes up to August 2013 were analysed. The proportion of adolescents with treatment success (cure and treatment completion), failure of treatment, those lost from treatment, and those who died were calculated and compared by HIV status. For this analysis, patients who interrupted treatment for ≥ 2 consecutive months were defined as lost from treatment. Patients who did not return to care or were never traced after diagnosis were regarded as lost to follow up. Information on deaths was obtained from regular cross linkage of available civil identifiers with the national death registry, and from DR-TB counsellors who are active in the area and become aware of deaths among DR-TB patients.

Extensive drug-resistance (XDR) was defined as resistance to any fluoroquinolone and one of two second-line injectable drugs (capreomycin and kanamycin), in addition to multidrug resistance (31). Pre-extensive drug-resistance (pre-XDR TB) was defined as tuberculosis resistance to either any fluoroquinolone or one of two second-line injectable drugs (capreomycin and kanamycin), in addition to multidrug resistance (32).

4. Results

Seventy-one (71) adolescents, aged 10-19 years, median age 18 years (IQR 15.7-18.9), were diagnosed with DR-TB between January 2008 and August 2013 in Khayelitsha. Six of these (8%) did not start treatment: two could not be traced after diagnosis, one out-migrated, two refused treatment, one is known to have died before treatment was started. There was no significant difference in age between the adolescents who started treatment and those who did not, $P = 0.8$. The demographic features of the 65 adolescents who started treatment are shown in Table 1. Treatment was started at a primary care clinic in 67.7% of these adolescents.

HIV co-infection was 27.7%. There was no significant difference in HIV infection between adolescent males and

females, OR: 0.4 (95% CI 0.12-1.28), $P = 0.13$. Seventeen of the 18 (94%) HIV infected adolescents were on antiretroviral therapy (ART) at the time of DR-TB diagnosis. Median CD4 count at diagnosis was 168 cells/mm³ (IQR 97-457). Of the 12 adolescents with known resistance to second line drugs, 8 (66.7%), had resistance to both an injectable agent (kanamycin) and a fluoroquinolone (ofloxacin). Table 2 shows details of the six patients who did not start treatment. In all six patients this was their first episode of DR-TB, and none had resistance to second line agents. The patient known to have died before commencing treatment was HIV infected and died within a month of DR-TB diagnosis.

Table 1. Demographic Features of Adolescents Diagnosed and Started on DR-TB Treatment for 2008-2013 (n = 65)^{a, b}

Variable	Value
Age, y, IQR	18 (15.8-18.9)
Gender	
Male	29 (45)
Female	36
HIV status	
+ve	18 (27.7)
-ve	45 (69.2)
unknown	2 (3.1)
Site of treatment initiation	
Primary Care Clinic	44 (67.7)
Subacute facility	7 (10.8)
Hospital ^c	14 (21.5)
Drug Susceptibility Testing pattern	
Presumed MDR-TB	1 (1.5)
Rifampicin mono resistance	20 (30.8)
MDR & no 2nd line resistance ^d	30 (46.2)
MDR & 2nd line resistance ^d	12 (18.5)
MDR 2nd line resistance unknown ^d	2 (3.1)

^a Abbreviations: IQR, Interquartile range; MDR-TB, multidrug resistant tuberculosis.

^b Data are presented as No. (%).

^c District and specialist TB hospitals with specialist care services.

^d MDR-TB -multidrug resistant tuberculosis (resistant to rifampicin and isoniazid).

Table 2. Patients Who Did Not Commence Treatment (n = 6)^a

Age, y	Gender	HIV Status	Resistance Profile	Previous TB History	Outcome
13.8	female	positive	MDR TB- no second line resistance	none	LTFU (did not return to care and never found)
15.3	male	unknown	Rifampicin mono resistance	none	Out-migrated
16.4	female	negative	Rifampicin mono resistance	none	Refused treatment and LTFU
18.1	female	positive	MDR-TB- no second line resistance	none	LTFU (did not return to care and never found)
18.5	female	Positive	MDR-TB- no second line resistance	none	Died before start of treatment
19.9	male	unknown	MDR-TB- no second line resistance	none	Refused treatment and LTFU

^a Abbreviations: LTFU, lost to follow up.

4.1. Treatment Outcomes

Final treatment outcomes were available for 44 adolescents. (Three patients were transferred out of the area during treatment and 18 are still on treatment), Table 3. Treatment success was achieved in 36.4%, 43% were lost from treatment, 9% died while on treatment and treatment failed in 11.4% (Table 3).

Among those who died, three died within two months of starting treatment, and one within four months. All four patients had resistance to second line drugs (three had XDR TB 31 and one had pre-XDR TB 32), and were HIV negative. All the five patients in whom treatment failed are known to have subsequently died. All five were female, (age range 16-19 years), and all except one were HIV negative. Nineteen patients were lost from treatment, and among these one restarted treatment again, and one is known to have subsequently died. The median duration of treatment of those who were lost from treatment was 8.9 months (IQR 4.8-13.3).

Overall mortality ($n = 10$) among those who started treatment was 12.1/100 person years, over the period of observation. Loss from treatment and treatment success (cure or treatment completion) was not significantly different between HIV infected and un-infected adolescents, OR: 2.0, (95% CI 0.56-7.50), $P = 0.27$, and OR: 1.2 (95% CI 0.37-4.43), $P = 0.71$ respectively. Only one of the 12 patients with known resistance to second line drugs was successfully treated.

5. Discussion

We observed poor treatment outcomes in the majority of adolescents undergoing treatment for DR-TB treatment in Cape Town with a treatment success rate of only 36%. Nine percent of adolescents died while on treatment, while 11% experienced treatment failure, and 43% were lost from treatment. Treatment was not initiated in 8% of those diagnosed.

Our treatment success rate is comparable to that reported among HIV positive adolescents in India (36% had favourable outcomes) (15). However we observed much lower mortality in a larger cohort of patients with final treatment outcomes 15. Our loss from treatment proportion of 43% was 1.6 times that seen in the Mumbai cohort (15). It is possible that the high proportion of those

lost from treatment masked some deaths in our cohort (only one of these is known to have died); therefore overall mortality is likely to be higher than presented here. Nonetheless, overall mortality over the period of observation was high, with 15.4% of all patients who started treatment and had treatment outcomes known to have died during the period of observation.

Six patients were lost to care before therapy could be initiated: - one died, while two refused treatment and one out-migrated from the area, and three were lost to follow-up. Analysis of the outcomes of the entire Khayelitsha DR-TB cohort found that the majority of patients who did not initiate treatment died prior to receipt of their diagnosis and thus initiation of treatment (22). In the present analysis only one adolescent is known to have died before treatment could be initiated. At inception of the decentralized Khayelitsha DR-TB programme in 2007, the median time from diagnosis to initiation of treatment was 54 days, time during which patients could experience further deterioration and/or death. In 2011 this delay had been reduced by 50% (27 days) and is expected to have been further reduced since the introduction of Xpert MTB/Rif testing for MDR-TB diagnosis in the district (22, 28). In Gauteng, South Africa, Xpert testing at point-of-care resulted in same day treatment initiation in all those with a positive result (33).

Two adolescents refused treatment, an observation previously reported in TB patients (15, 34). In this population this can be attributed to a myriad of reasons including the physical and emotional changes, and the pressures associated with life during this period. Adolescents have to contend with peer pressure, competing demands for time (school attendance, work and social activities), have to navigate relationships with parents, peers and partners, may have genuine difficulties in understanding complex treatment, or may believe that they do not need treatment, among many other reasons that have been cited as barriers to adherence to treatment for chronic diseases in this population (13, 21, 35). These factors potentially contributed to the exceptionally high loss from treatment that we observed. Further research should therefore investigate strategies targeted at adolescent specific needs and challenges within DR-TB programs. A potential useful intervention to encourage acceptance of and adherence to treatment could be modeled along the "Youth group patient support" model aimed at decreasing loss from HIV and ART care among the youth that has been piloted in Khayelitsha, South Africa (36). In the pilot only 4% of patients had been lost to care over a period of 8 months (36).

Three of the four patients who died while on treatment died within two months of initiating treatment. These patients who had resistance to second line drugs and were HIV negative demonstrate very poor outcomes and early mortality in extensive resistance. They could however also be disease that presented and was diagnosed and

Table 3. Final Treatment Outcomes for Adolescents ($n = 44$)^a

Final Outcomes	No. (%)
Cured	11 (25)
Completed treatment	5 (11.4)
Treatment success	16 (36.4)
Failed treatment	5 (11.4)
Lost from treatment	19 (43.2)
Died	4 (9.1)

^a Data are presented as No. (%).

treated late in its course as has been described in other settings (15, 37). In the Indian adolescent cohort, three of the four reported deaths occurred prior to treatment initiation and one within three weeks of initiation, and were ascribed to delayed diagnosis and treatment rather than treatment failure (15). The three adolescents who died while on treatment in study were diagnosed with DR-TB before the roll out of Xpert MTB/Rif testing, strongly supporting this hypothesis of delayed diagnosis rather than treatment failure.

The TB/HIV co-infection rate of 27.7% while lower than the 69% that has reported for the entire DR-TB cohort in Khayelitsha (22) shows a high HIV burden in this age group in our setting. This could have implications for treatment adherence since it has been shown a high pill burden and adverse drug effects are associated with loss from DR-TB treatment (38): treatment for both conditions entails a large number of tablets which have significant adverse drug events which may overlap resulting in additive drug toxicities (39). However we found no difference in loss from treatment rates between HIV infected and un-infected adolescents in this analysis.

Our study had several limitations. First, it is based on routine DR-TB program data and is subject to limitations associated with such data, mainly that we may have missed some cases. However, these would be very few given the extensive monitoring and evaluation system and clinical support implemented as part of the decentralized program. Second, the cohort described is from a township in Cape Town and may not be generalizable to other populations. Lastly, were not able to analyse data on viral load in HIV infected patients. In spite of these limitations, the analysis has several important findings. It shows very poor outcomes among HIV un-infected and infected adolescents, with very high proportions of loss from treatment, treatment failure and mortality. It highlights the need for targeted interventions to support treatment adherence among adolescents a high risk group facing different challenges to those faced by adults and young children. Lastly it underscores the need for integration of HIV and DR-TB care among adolescents since a significant proportion of adolescents with DR-TB will be HIV infected in high HIV burden settings.

Acknowledgements

We are grateful to the healthcare staff in Khayelitsha, the City of Cape Town and Province of the Western Cape health departments for the tireless efforts in this program, and we acknowledge the adolescents affected by DR-TB in Khayelitsha.

Authors' Contributions

Study concept and design: Sizulu Moyo, Jennifer J Furin, JH; Acquisition of data: Jennifer Hughes, Odella Muller; Statistical analysis and interpretation of data: Sizulu Moyo; drafting of manuscript- Sizulu Moyo, Jennifer J

Furin, HC, Vivian Cox, Leigh Snyman, Helen Cox, Amir Shroufi; critical revision of manuscript: Sizulu Moyo, Helen Cox, Vivian Cox, AM; study supervision: Helen Cox, Vivian Cox, Leigh Snyman, Sizulu Moyo.

Financial Disclosure

The study was part of Medecins Sans Frontieres decentralised DR-TB programme in Khayelitsha, South Africa. No other funding was obtained.

Funding/Support

Implementation of the Khayelitsha DR-TB programme was funded by Medecins Sans Frontieres (MSF Belgium).

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