Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study

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Summary

Background Long-term treatment-related outcomes in patients with extensively drug-resistant (XDR) tuberculosis are unknown. We followed up a cohort of patients to address knowledge gaps.

Methods Between March, 2008, and August, 2012, we prospectively followed up a cohort of 107 patients from three provinces in South Africa, who had been diagnosed with XDR tuberculosis between August 2002, and February, 2008. Available isolates from 56 patients were genotyped to establish strain type and used for extended susceptibility testing.

Findings All patients were treated empirically as inpatients with a median of eight drugs (IQR six to ten). 44 patients (41%) had HIV. 36 (64%) of 56 isolates were resistant to at least eight drugs, and resistance to an increasing number of drugs was associated with the Beijing genotype (p=0·01). After 24 months of follow-up, 17 patients (16%) had a favourable outcome (ie, treatment cure or completion), 49 (46%) had died, seven (7%) had defaulted (interruption of treatment for at least 2 consecutive months), and 25 (23%) had failed treatment. At 60 months, 12 patients (11%) had a favourable outcome, 78 (73%) had died, four (4%) had defaulted, and 11 (10%) had failed treatment. 45 patients were discharged from hospital, of whom 26 (58%) had achieved sputum culture conversion and 19 (42%) had failed treatment. Median survival of patients who had failed treatment from time of discharge was 19·84 months (IQR 4·16–26·04). Clustering of cases and transmission within families containing a patient who had failed treatment and been discharged were shown with genotypic methods. Net sputum culture conversion occurred in 22 patients (21%) and median time to net culture conversion was 8·7 months (IQR 5·6–26·4). Independent predictors of probability of net culture conversion were no history of multidrug-resistant tuberculosis (p=0·0007) and use of clofazamine (p=0·0069). Independent overall predictors of survival were net culture conversion (p<0·0001) and treatment with clofazamine (p=0·021). Antiretroviral therapy was also a predictor of survival in patients with HIV (p=0·003).

Interpretation In South Africa, long-term outcomes in patients with XDR tuberculosis are poor, irrespective of HIV status. Because appropriate long-stay or palliative care facilities are scarce, substantial numbers of patients with XDR tuberculosis who have failed treatment and have positive sputum cultures are being discharged from hospital and are likely to transmit disease into the wider community. Testing of new combined regimens is needed urgently and policy makers should implement interventions to minimise disease spread by patients who fail treatment.

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Introduction

Tuberculosis remains a major global problem: the estimated number of new cases in 2011 was almost 9 million.[1] Sustained control is undermined by the growing threat of drug-resistant tuberculosis. Of 12 million cases of tuberculosis worldwide in 2010, 650 000 (5·4%) were estimated to be of multidrug-resistant disease.[2] 5–10% of the cases of multidrug-resistant tuberculosis are thought to be extensively drug-resistant (XDR) disease—defined as multidrug-resistant disease with resistance to a fluoroquinolone and either capreomycin, amikacin, or kanamycin.[3]

In South Africa—where the incidence of tuberculosis is 948 per 100 000 individuals per year[1]—surveys indicated that the percentage of tuberculosis cases that were multidrug-resistant disease increased in the country from 3·1% in 2002, to 9·6% in 2008.[4–6] In 2011, more than 8000 culture-confirmed cases of multidrug-resistant tuberculosis were identified, of which about 500 were culture-confirmed XDR disease.[1,7] According to South African guidelines,[8] patients with XDR tuberculosis should be admitted to designated treatment facilities and empirically treated with a para-aminosalicylic acid and capreomycin-based regimen (until 2010, capreomycin resistance profiling was not available in the public sector).

The issue of drug-resistant tuberculosis is important because it predominantly affects economically productive young adults and is associated with a high mortality.[9] Additionally, the high treatment-related costs are unsustainable in the low-income and middle-income countries where it is most prevalent. For example, in 2010, despite drug-resistant tuberculosis being officially responsible for less than 3% of the total case load in South Africa, it consumed almost 45% of the national tuberculosis budget of about US$280 million.[10] Such disproportionate

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and prohibitive costs threaten to destabilise tuberculosis control programmes in South Africa and other countries with similar resource constraints. Cogent intervention strategies and public policies are needed to control XDR tuberculosis, but rational planning of interventions and allocation of public health resources are hampered by the scarcity of long-term outcome data relating to mortality, cure, and treatment failure.

In view of the long treatment duration and scarcity of outcome data, how treatment failure should be defined is also unknown. The present practice, by which patients who do not achieve culture conversion after 12 months are deemed to have failed treatment, is not well supported by robust evidence. Few data are available for the proportion of patients with XDR tuberculosis who fail treatment, their outcomes after treatment failure, and their long-term potential for disease transmission. Therefore, long-term outcomes of XDR tuberculosis and the fate of patients with treatment failure, and how these outcomes differ by HIV status, remain unknown. To address these knowledge gaps, and particularly those from a high burden African setting, we prospectively followed up a cohort of patients, and now report the long-term treatment outcomes.

Methods

Participants

We previously reported the retrospective analysis of short-term outcomes of 114 adults (aged >16 years) with culture-proven XDR tuberculosis diagnosed between August, 2002, and February, 2008,[9] and who were initiated on XDR tuberculosis treatment with an empirical capreomycin and para-aminosalicylic acid-based regimen (other drugs used were at the discretion of the attending physician, outlined in table 1, and guided by susceptibility data where relevant). From the censor date of the previous study (February, 2008),[9] we prospectively followed up 107 of these patients from three provinces in South Africa (three were lost to follow-up and four transferred out [ie,

	Whole cohort (n=107)	Patients with HIV (n=44)	Patients without HIV (n=63)	p value*
Age at diagnosis (years)	33 (27–43)	33 (28–40)	32 (25–46)	0·66
Male sex	58 (54%)	19 (43%)	39 (62%)	0·08
Mixed ancestry	54 (50%)	9 (20%)	45 (71%)	<0·0001
Ever smoker†	48 (53%)	14 (36%)	34 (65%)	0·01
CD4 count (cells per mL)‡	..	365 (157–414)	..	..
Previous diagnosis of culture-confirmed multidrug-resistant tuberculosis	95 (89%)	35 (80%)	60 (95%)	0·03
Number of drugs used	8 (6–10)	8 (7–9)	9 (6–10)	0·51
Weight (kg)§	49 (40–58)	50 (42–60)	48 (40–52)	0·46
Drugs used				
High-dose isoniazid (10 mg/kg)	30 (28%)	16 (36%)	14 (22%)	0·17
Isoniazid	39 (36%)	17 (39%)	22 (35%)	0·85
Pyrazinamide	83 (78%)	33 (75%)	50 (79%)	0·77
Ethambutol	48 (45%)	18 (41%)	30 (48%)	0·62
Ethionamide	68 (64%)	26 (59%)	42 (67%)	0·55
Ofloxacin	39 (36%)	16 (36%)	23 (37%)	1
Ofloxacin and moxifloxacin	8 (7%)	5 (11%)	3 (5%)	0·37
Streptomycin	1 (1%)	0	1 (2%)	..
Amikacin	4 (4%)	2 (5%)	2 (3%)	1
Capreomycin	98 (92%)	40 (91%)	58 (92%)	1
Dapsone	43 (40%)	12 (27%)	31 (49%)	0·04
Amoxicillin plus clavulanic acid	65 (61%)	22 (50%)	43 (68%)	0·09
Para-aminosalicylic acid	96 (90%)	41 (93%)	55 (87%)	0·51
Clofazamine	22 (21%)	14 (32%)	8 (13%)	0·03
Azithromycin	9 (8%)	8 (18%)	1 (2%)	0·01
Rifabutin	1 (1%)	0	1 (2%)	..
Amoxicillin	38 (36%)	10 (23%)	28 (44%)	0·04
Moxifloxacin	16 (15%)	12 (27%)	4 (6%)	0·01
Clarithromycin	80 (75%)	29 (66%)	51 (81%)	0·12
Terizidone (cycloserine derivative)	100 (93%)	43 (98%)	57 (90%)	0·27

Data are median (IQR) or n (%), unless otherwise stated. *Comparison between patients with and without HIV, calculated with Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. †Data available for 91 patients in whole cohort, 39 patients with HIV, and 52 patients without HIV. ‡CD4 counts available at diagnosis for only 21 patients with HIV. §Weight at diagnosis available for only 68 patients in whole cohort, 29 patients with HIV, and 39 without HIV.

Table 1: **Characteristics of the cohort**

left the region and treatment outcome unknown]) from March, 2008, to August, 2012, from three designated XDR tuberculosis facilities in South Africa (Brooklyn Chest Hospital, Cape Town, Western Cape; Gordonia Hospital, Upington, Northern Cape; and Sizwe Tropical Diseases Hospital, Johannesburg, Gauteng province). All patients were admitted to one of the facilities until culture conversion, death, or discharge because of treatment failure. At discharge, treatment in the continuation phase was directly observed. Data were captured on a quarterly basis by a trained researcher using a standardised case record form. CD4 counts in patients infected with HIV were recorded at the time of initial diagnosis for the purposes of outcome analysis. All patients had smear microscopy and culture at monthly intervals. Ethics approval was obtained from the human research ethics committees at the University of Cape Town and the University of Witwatersrand.

Procedures

Information about regimens, start and stop dates of treatment, adverse events, and treatment outcomes were recorded. Isolates were obtained every month to establish smear and culture status. Phenotypic routine testing for susceptibility to rifampicin, isoniazid, ofloxacin, amikacin, and ethionamide was done at the discretion of each patient's doctor in the centralised National Tuberculosis Programme reference laboratory (National Health Laboratory Service) as previously described.[11] WHO does not recommend susceptibility testing for para-aminosalicylic acid in routine diagnostic laboratories because this method has not been standardised.[12] To establish the profile and extent of drug resistance, available isolates from a subset of patients biobanked at diagnosis (n=56; from the Western Cape) were also genotyped to establish strain type by spoligotyping[13] and IS*6110* DNA fingerprinting,[14] and targeted DNA sequencing of the *inhA* promoter and the *katG*, *rpoB*, *embB*, *pncA*, *gyrA*, and *rrs* genes was used to identify mutations conferring resistance.[15] Resistance to para-aminosalicylic acid was determined with a culture-based method[16] (see appendix for detailed methods).

Outcomes

Early treatment outcomes (ie, within 12 months of treatment initiation) were sputum culture conversion and reversion. Late treatment outcomes (ie, after 24 months) were treatment completion, treatment cure, all-cause mortality (not necessarily secondary to progression of tuberculosis), default (interruption in treatment for at least 2 consecutive months for any reason), treatment failure, and transfer out (appendix).[17] Culture conversion was defined as two consecutive negative sputum cultures at least 30 days apart. Culture reversion was defined as two consecutive positive sputum cultures at least 30 days apart after initial sputum culture conversion. Patients were deemed to have achieved net conversion if their last sputum culture event (conversion or reversion) during follow-up was conversion, even if they had had one (or occasionally more than one) previous episode of reversion. Patients were deemed to be net reverters if their last sputum culture event was reversion. Patients were deemed to have failed treatment if at least two of five sputum cultures were positive in the previous 12 months, if any of the final three sputum cultures in the previous 12 months were positive, or if their treatment was stopped earlier than suggested by national programmatic guidelines because of inadequate response or adverse events.

See Online for appendix

	Genotypic resistance	Phenotypic resistance
Rifampicin (*rpoB*)	55/56 (98%)	56/56 (100%)
Isoniazid (*katG*)	38/56 (68%)	56/56 (100%)
Isoniazid (*katG* plus *inhA* promoter)	56/56 (100%)	..
Aminoglycosides, kanamycin, and capreomycin (*rrs*)	46/56 (82%)	56/56 (100%)
Ofloxacin (*gyrA*)	50/56 (89%)	56/56 (100%)
Pyrazinamide (*pncA*)	47/56 (84%)	..
Ethambutol (*embB*)	49/56 (88%)	..
Ethionamide (*inhA* promoter)	39/56 (70%)	..
Para-aminosalicylic acid	..	3/48 (6%)

Data are number resistant/isolates tested (%). Genes and promoters sequenced given alongside drugs.

Table 2: **Number of biobanked isolates with drug-specific genotypic and phenotypic resistance**

	24 months	36 months	48 months	60 months
Died	49 (46%)	61 (57%)	74 (69%)	78 (73%)
Treatment default*	7 (7%)	6 (6%)	5 (5%)	4 (4%)
Treatment cure	7 (7%)	6 (6%)	5 (5%)	5 (5%)
Treatment failure	25 (23%)	19 (18%)	14 (13%)	11 (10%)
Treatment completion	10 (9%)	10 (9%)	6 (6%)	7 (7%)
Insufficient information	9 (8%)	5 (5%)	3 (3%)	2 (2%)

Data are n (%). *Interruption of treatment for at least 2 consecutive months for any reason; once patient classified as a default, the classification remained unless individual died; all other categories (except died) needed a minimum of 24 months' treatment.

Table 3: **Outcomes of 107 patients with extensively drug-resistant tuberculosis after treatment, by duration of follow-up**

	Treatment failure (n=19)	Achieved culture conversion (n=26)
Smear microscopy positive	6 (35%)*	1 (5%)†
Unfavourable outcome	17 (89%)	13 (50%)
Died	14 (74%)	6 (23%)
Treatment failure	3 (16%)	2 (8%)
Defaulted	0	4 (15%)
Readmitted to hospital	0	1 (4%)
Favourable outcome	2 (11%)	13 (50%)
Cured	2 (11%)	13 (50%)

Data are n (%). *Smear microscopy requested for 17 patients. †Smear microscopy requested for 19 patients.

Table 4: **Outcomes of the 45 patients who were discharged into the community**

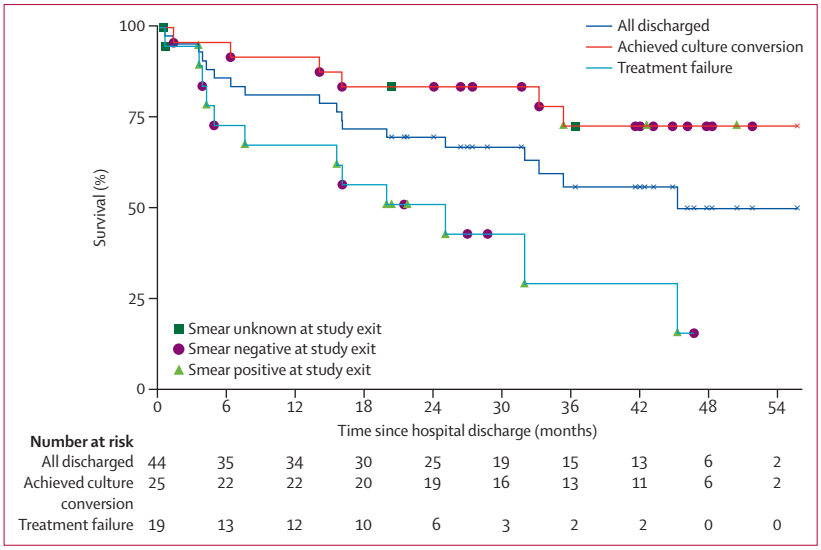

Figure 1: **Kaplan-Meier for probability of survival since discharge from hospital**
Crosses indicate censoring.

	No conversion (n=68)	Net conversion (n=22)	Net reversion (n=17)
Time from treatment start date to outcome or last sputum culture event (months)	16·8 (4·5–32·5)	8·7 (5·6–26·4)	23·5 (15·2–27·6)
With HIV	30 (44%)	10 (45%)	4 (24%)
Favourable outcome	1 (1%)	15 (68%)	1 (6%)
Completed treatment	1 (1%)	7 (32%)	1 (6%)
Cure	0	8 (36%)	0
Unfavourable outcome	67 (99%)	7 (32%)	16 (94%)
On treatment	1 (1%)	1 (5%)	1 (6%)
Defaulted	2 (3%)	2 (9%)	0
Treatment failure	3 (4%)	0	5 (29%)
Died	61 (90%)	4 (18%)	10 (59%)

Data are median (IQR) or n (%).

Table 5: **Treatment-related outcomes by conversion status**

Statistical analysis

Continuous variables were summarised by median and IQR, using Wilcoxon rank sum for p values, categorical variables by counts and percentages using Fisher's exact test for p values. Variables with a large percentage of missing data are noted. Durations were calculated in days and converted to number of months by days/30·4 (as the number in days of an average month) for simplicity. Univariate Cox proportional hazards models were used to assess the relation between explanatory variables and time-to-event outcomes (including time to death, time to net sputum culture conversion, and time to net sputum culture reversion). Variables considered included HIV status (positive or negative), combined HIV and antiretroviral therapy status (HIV negative, HIV positive on antiretroviral therapy, or HIV positive not on antiretroviral therapy), sex, ethnic origin (mixed ancestry or black), treatment outcome (positive or negative), adverse drug reactions, cavitation (yes or no), bilateral disease (yes or no), strain family (Beijing or other), smoking (yes or no), cohort (Western Cape, Northern Cape, or Siswe), weight less than 50 kg at diagnosis, weight (kg) at diagnosis, age at diagnosis, number of drugs prescribed, history of tuberculosis (none, confirmed, or unknown), history of multidrug-resistant tuberculosis (yes or no), and a binary variable for each of the drugs prescribed. Unless otherwise noted, the time to event was taken as days from treatment start date. Kaplan-Meier curves were estimated for probability of survival by various strata. Tests between strata were done by the log-rank test. Cumulative incidence curves under competing risks assumptions were estimated for cumulative probability of net conversion and net reversion. Cause-specific Cox proportional hazard regression models in competing risk were fitted to risk of net conversion and reversion with death as a competing risk. Multivariate Cox proportional hazards models for mortality included variables that were significantly associated with outcome ($p<0·05$) and additional prespecified variables (eg, sex). In some cases, important variables (eg, weight) were omitted from multivariate models because of the high percentage of missing data; these cases were noted. All statistical analysis was done in R (version 3.0) and graphics generated with the package ggplot2. A simple cost analysis was done to determine the cost relative to net gain in culture conversion rate when longer treatment duration was used as a cutpoint to define treatment failure (see appendix for methods, assumptions, and detailed results).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

By August, 2012, 79 patients (74%) had died, of whom 32 (41%) had HIV infection. 17 patients (16%) were still alive, of whom seven (41%) had HIV infection. The other 11 patients (10%) were lost to follow-up, of whom five (45%) had HIV infection. 63 patients (59%) were not infected with HIV. 35 (80%) of 44 patients with HIV infection were on ART (a combination of lamivudine, stavudine, efavirenz, nevirapine, zidovudine, and lopinovir–ritonavir; frequency and dosing of ART is outlined in detail by Shean and colleagues[18]). The median follow-up from diagnosis to mortality or censor date was 28·5 months (IQR 13·8–49·3) and the median duration of in-patient stay was 13·29 months (8·27–23·89).

All participants were treated as inpatients with directly observed therapy. Median treatment duration was 22·1 months (8·8–34·3). Because linezolid was unavailable, access to capreomycin susceptibility testing

was poor, and second-line phenotypic susceptibility testing was unreliable, patients were treated empirically with a combination of drugs (table 1). The three most frequently prescribed drugs were capreomycin, para-aminosalicylic acid, and terizidone (a cycloserine derivative; table 1).

Isolates from all 107 patients were phenotypically resistant to rifampicin, isoniazid, amikacin, and ofloxacin. According to national policy, isolates resistant to isoniazid and rifampicin are sent for some second-line testing (resistance to ethionamide, ofloxacin, amikacin, and occasionally streptomycin). We did extended molecular and phenotypic susceptibility testing for the 56 biobanked isolates. 20 isolates (36%) had genotypic resistance (phenotypic resistance to para-aminosalicylic acid) to up to seven drugs, 18 (32%) had resistance to eight drugs, 17 (30%) to nine drugs, and one (2%) to all ten drugs tested (resistance beyond XDR tuberculosis or so-called totally drug-resistant tuberculosis).[15,19–21] We recorded some discordance between genotypic and phenotypic resistance patterns (table 2). In a multivariable model, resistance to an increasing number of drugs was associated with the Beijing genotype (odds ratio 2·66, 95% CI 1·18–17·35; p=0·01), but not with mortality or non-conversion status (appendix).

At 60 months, few patients had a favourable outcome, many had died, and a tenth had failed treatment (table 3). The persistently high frequency of treatment failure represents patients who exhausted treatment options and were discharged from inpatient care to reside in the community. 56 patients died before discharge from hospital and six transferred out of the region. The remaining 45 patients were discharged into the community, of whom 26 (58%) had achieved sputum culture conversion. Notably, more than a third of patients deemed to have failed treatment were smear microscopy positive at discharge and almost 90% had an unfavourable outcome (>80% died; table 4). Median survival of patients who had failed treatment from time of discharge was 19·84 months (IQR 4·16–26·04). Patients discharged after culture conversion had significantly longer survival (36·1 months, IQR 21·23–46·25; p=0·0015; figure 1). Notably, two female patients who had failed treatment at discharge had a favourable outcome despite withdrawal of therapy: both are alive, well, and fulfilling duties in the community.

Net sputum culture conversion occurred in 22 patients (21%; table 5). More than half of these patients achieved net sputum culture conversion by 9–12 months (table 6), although the overall mortality of this group—six of whom had HIV infection—was 27% (appendix). Favourable outcomes were more common in patients who achieved net culture conversion than in those with net culture reversion or who did not achieve culture conversion (table 5). Time to culture conversion was not associated with improved outcome (appendix). Independent predictors of probability of net culture conversion were no history of multidrug-resistant tuberculosis and use of clofazamine (table 7). Culture reversion occurred in 17 (44%) of 39 initial converters (appendix) and 94% of net reverters had an unfavourable outcome (table 5).

A separate analysis of treatment costing showed that substantial cost would be expended for little gain in

	First conversion (n=39)		Net conversion (n=22)		Net reversion (n=17)	
	During timeframe	Cumulative	During timeframe	Cumulative	During timeframe	Cumulative
<2 months	1 (3%)	1 (3%)	1 (5%)	1 (5%)	0	0
2–4 months	3 (8%)	4 (10%)	1 (5%)	2 (9%)	0	0
4–6 months	6 (15%)	10 (26%)	4 (18%)	6 (27%)	1 (6%)	1 (6%)
6–9 months	9 (23%)	19 (49%)	5 (23%)	11 (50%)	1 (6%)	2 (12%)
9–12 months	4 (10%)	23 (59%)	1 (5%)	12 (55%)	1 (6%)	3 (18%)
12–18 months	7 (18%)	30 (77%)	2 (9%)	14 (64%)	3 (18%)	6 (35%)
18–24 months	3 (8%)	33 (85%)	2 (9%)	16 (73%)	3 (18%)	9 (53%)
≥24 months	6 (15%)	39 (100%)	6 (27%)	22 (100%)	8 (47%)	17 (100%)

Follow-up time is calculated from treatment start date and all periods are up to and including the upper limit.

Table 6: **Number of patients achieving first culture conversion, net conversion, or net reversion, by follow-up time**

	Full cohort (n=107)		Patients with HIV (n=44)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Net conversion				
Age at diagnosis	0·99 (0·95–1·04)	0·87	0·95 (0·88–1·04)	0·26
Male sex	1·48 (0·58–3·78)	0·39	0·76 (0·21–2·82)	0·69
Mixed ancestry	0·59 (0·14–2·58)	0·5	1·59 (0·27–9·24)	0·61
HIV infection	1·48 (0·50–4·39)	0·46	..	..
Antiretroviral therapy	..	..	0·93 (0·10–8·82)	0·95
No history of multidrug-resistant tuberculosis	10·21 (2·64–39·38)	0·0007	1·61 (0·37–6·96)	0·53
Clofazamine	0·14 (0·034–0·59)	0·0069	..	..
Mortality				
HIV infection	1·51 (0·87–2·63)	0·147	..	..
Antiretroviral therapy	..	..	0·13 (0·03–0·50)	0·003
Male sex	0·86 (0·54–1·37)	0·526	0·42 (0·15–1·17)	0·096
Mixed ancestry	0·66 (0·37–1·18)	0·159	0·46 (0·16–1·29)	0·138
Net conversion	0·14 (0·06–0·34)	<0·0001	0·12 (0·03–0·53)	0·005
Net reversion	0·24 (0·12–0·48)	<0·0001	0·36 (0·07–1·99)	0·242
Age at diagnosis	0·98 (0·95–1·00)	0·052	0·95 (0·89–1·01)	0·113
Clofazamine	0·38 (0·16–0·87)	0·021	2·26 (0·57–8·99)	0·247
Azithromycin	..	..	0·53 (0·11–2·62)	0·434
Para-aminosalicylic acid	..	..	0·68 (0·14–3·36)	0·638
Ethambutol	..	..	3·12 (1·01–9·67)	0·048
Ofloxacin plus moxifloxacin	..	..	2·70 (0·78–9·32)	0·115

Many values for weight at diagnosis were missing in the full cohort (36%) and in patients with HIV (34%), so this variable was omitted from the final multivariate models. CD4 cell count at diagnosis was not included in multivariate models for patients with HIV because many values (52%) were missing. A complete case model was run including CD4 cell count (n=21; omitting azithromycin and clofazamine because used in few patients), ethnic origin, antiretroviral therapy, net conversion, and ethambutol, and remained significant at p<0·05. CD4 cell count had a hazard ratio of 0·99 (95 %CI 0·99–1·00), p=0·045.

Table 7: **Cox cause-specific hazards model of time from treatment start to net conversion (under competing risk of death) and multivariate Cox proportional hazards model for risk of death from treatment start**

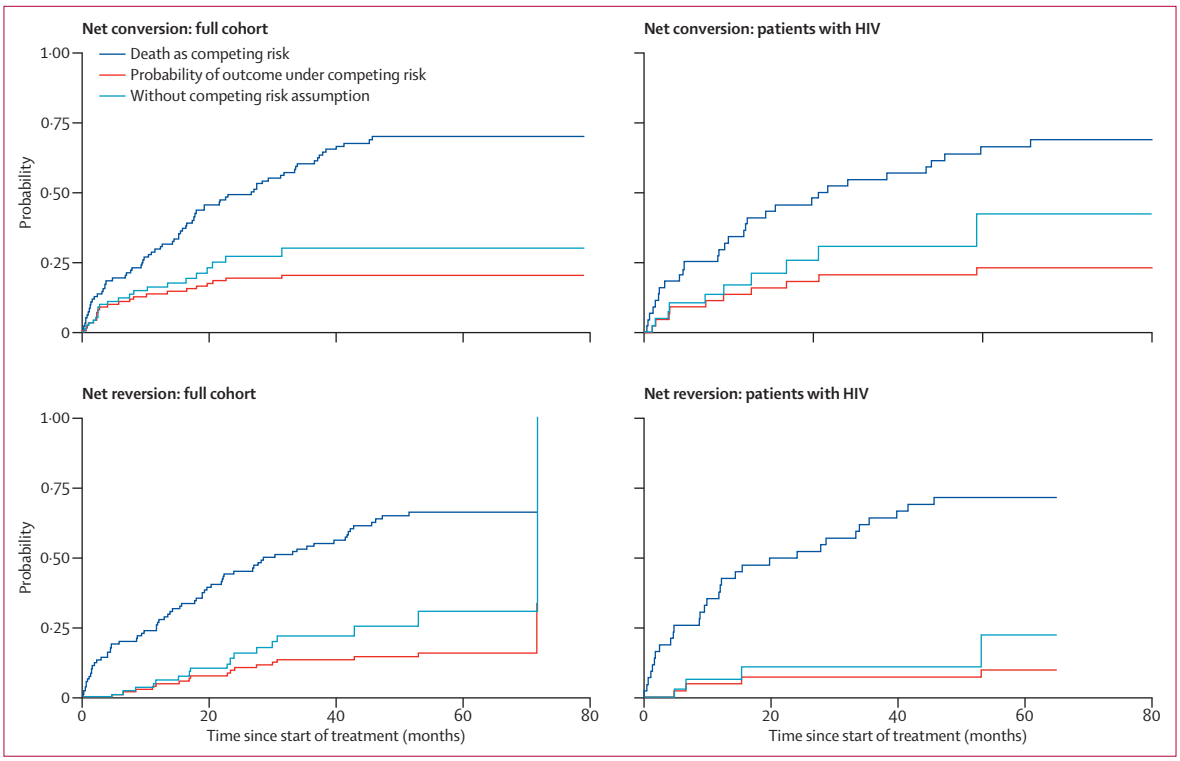

Figure 2: **Cumulative incidence estimates under competing risks assumptions of culture conversion and culture reversion, and cumulative incidence estimates without assumption of competing risks**

sputum culture conversion rates: in a hypothetical cohort of 100 patients with XDR tuberculosis, the cost of treatment would be US$363 886 if it were extended to 18 months (rather than 12 months) and an additional 2·2 patients would achieve sputum culture conversion by 18 months. Cost would increase to $726 760 if treatment were extended to 24 months, and an additional 4·4 patients would achieve sputum culture conversion (appendix).[10]

When plotting cumulative incidence estimates under competing risks, the probability of net culture conversion rises to about 20% in the first 24 months and stabilises (figure 2). Probability of net culture reversion increases more slowly, needing about 40 months to stabilise (figure 2). Without the competing risk assumption, the probability of net culture conversion would be significantly overestimated (see appendix for univariate analysis).

Almost half the patients in the cohort died within 24 months of treatment (figure 3A, table 3). 24 (69%) of 35 patients living with HIV and receiving antiretroviral therapy had died by the end of follow-up, compared with 46 (73%) of 63 patients not infected with HIV (p=0·77) and all nine patients with HIV not taking antiretroviral therapy (p=0·0069; figure 3B). CD4 count of <200 cells per mL was also associated with increased mortality (p=0·069; figure 3C).

In a multivariate Cox proportional hazards model, net culture conversion status and treatment with clofazamine were associated with decreased risk of death in the overall cohort (table 7; see appendix for univariate analysis). In patients with HIV, net culture conversion and use of antiretroviral therapy were associated with improved survival (table 7). Net culture reversion was a predictor of survival in the full cohort despite the high frequency of unfavourable outcomes in patients with net culture reversion, because unfavourable outcomes were even more common in patients who did not achieve conversion (table 5; appendix).

We identified three families in which at least three members had been diagnosed with any type of drug-resistant tuberculosis in the previous 10 years (appendix). Strain typing and parallel mutational analysis of available isolates in one family showed evidence of transmission from one individual—B28, a treatment failure residing in the community—to his brother who also eventually died in the community as a treatment failure.

Discussion

We have shown that long-term outcomes in patients with XDR tuberculosis are poor, irrespective of HIV status (panel), although antiretroviral therapy has improved survival in patients with HIV. Many patients in our cohort who were discharged from hospital had positive sputum cultures, had failed treatment, and had no further therapeutic options. These patients survive for long periods living in the community and are likely to

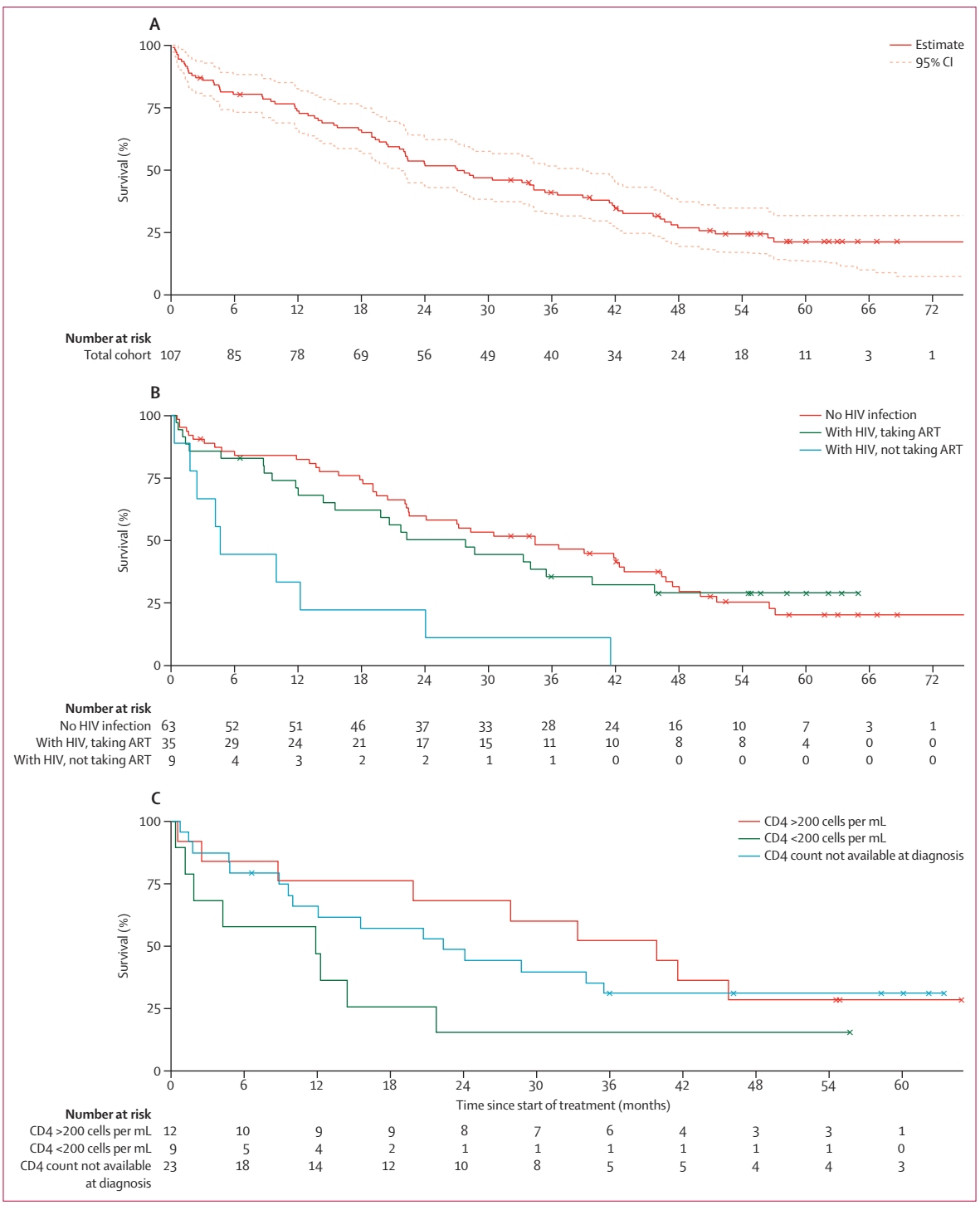

***Figure 3*: Kaplan-Meier survival estimates**
(A) Probabilities of survival in all patients. (B) Probabilities of survival stratified by HIV infection and ART. (C) Probabilities of survival in patients with HIV stratified by CD4 cell count. Crosses indicate censoring. ART=antiretroviral therapy.

contribute to community-based spread of XDR tuberculosis. Overall net culture conversion was fairly infrequent and only two-thirds of patients who achieved net conversion had a favourable outcome. Therefore, some initial responders subsequently relapse. Additionally, only slightly more than half of patients who achieved sputum culture conversion did so by 12 months. The proportion increased slightly to 24 months, but a cost analysis indicated that additional gains that would result from an extension would be small and costly.

***Panel:* Research in context:**

Systematic review

We searched PubMed for reports published in English before Sept 1, 2013, that presented results for treatment outcomes in patients with extensively drug-resistant (XDR), extremely drug-resistant, or totally drug-resistant tuberculosis. We combined search terms for drug-resistant tuberculosis ("MDR-TB", "XDR-TB", "XXDR-TB", and "TDR-TB") with those indicating outcome ("outcome", "mortality or death", "culture conversion"), molecular epidemiology ("strain type", "DNA fingerprinting", "spoligotyping", "IS*6110*", "mutational analysis", and "Beijing"), and drug susceptibility. Including systematic reviews, we identified 97 studies of treatment outcome, 51 related to molecular epidemiology, and 159 related to drug susceptibility. We identified no studies in which the frequency or long-term outcomes of patients with XDR tuberculosis who fail treatment was assessed.

Interpretation

To our knowledge, ours is the first prospective study in which 60-month treatment-related outcomes are recorded in patients with XDR tuberculosis, with further investigation of the frequency and outcomes of patients who failed treatment. We prospectively confirmed that in a setting where tuberculosis is endemic, long-term outcomes of patients with XDR tuberculosis are poor, irrespective of HIV status and despite an intensive injectable-based regimen. Alarmingly, we have shown for the first time that, by contrast with sporadic and isolated cases of treatment failure and near total or totally drug-resistant cases that have been reported in several countries, therapeutic failure is occurring systematically on a country-wide level. Patients who fail treatment, many of whom have high transmission potential, are being discharged back into the communities. Often survival is for months to years with substantial potential for disease transmission. Our data provide important information to policy makers to allow them to design appropriate interventional strategies. Although prevention of further cases is mandatory through improved regimens for multidrug-resistant tuberculosis and better functioning programmes, and fast-tracking of new drug regimens and improved diagnostics, the growing pool of treatment failures needs to be addressed with a coordinated strategy that involves supported home care interlinked with urgent building of long-term community stay and palliative care facilities.

Overall predictors of mortality included conversion status and treatment with clofazamine; in patients with HIV, an additional predictor was use of antiretroviral therapy. Survival of patients with HIV taking antiretroviral therapy was similar to that of patients without HIV infection, confirming previous findings[8] that antiretroviral therapy is mandatory in patients with HIV and XDR tuberculosis.

Isolates from patients in our cohort had a high level of resistance (almost two-thirds of the cohort had resistance to at least eight drugs) and we have confirmed the emergence of totally drug-resistant disease, as previously described.[15] Capreomycin resistance as defined by the *rrs* 1401 mutation[22] was common, but empirical treatment with capreomycin was given to most patients, despite its toxicity.[18] The Beijing strain type was associated with advanced resistance in our cohort.

Overall, despite apparently good adherence and intensive inpatient therapy with an empirical regimen of capreomycin and para-aminosalicylic acid, 5-year outcomes in our cohort were worse than previous estimates of short-term and 24-month outcomes in settings with intermediate-burden[23,24] and those with high burden, like South Africa.[9,25–27] These poor outcomes were probably due to high-grade resistance, meaning that no effective drugs were available to treat the disease.[18] One of the isolates showed resistance beyond XDR tuberculosis, a concerning clinical entity previously described in India, Iran, Italy, and more recently South Africa.[15,19–21] Only para-aminosalicylic acid and clofazamine were likely to be effective in these patients and active disease is unlikely to respond to only two active agents (both of which are fairly weak mycobacteriostatic drugs from the WHO class 4 category of drugs). New drugs such as linezolid, which could be effective against XDR tuberculosis,[28] are not yet available in the South African national tuberculosis programme. Other drugs approved by the US Food and Drug Administration (eg, bedaquiline[29,30]) have not yet been approved for use in South Africa. Therefore, linezolid should be introduced into the South African national tuberculosis programme. Studies assessing new multidrug regimens for XDR tuberculosis are urgently needed, although enthusiasm is tempered by concerns about reductions in their effective lifespan through use in regimens in which they are least protected (ie, drug resistance is most likely to develop). Other factors that could be driving poor outcomes include nutritional status, drug absorption, and host immunity, including HIV.

Consistent with other evidence,[31] the Beijing strain type was associated with increased resistance in our cohort. More detailed gene-based studies are now needed to identify the mechanisms by which this increased resistance might develop.

Many patients who fail treatment are being discharged back into the community because little bed space is available in designated tuberculosis hospitals, alternative long-term residential and palliative care facilities are scarce, and resources to support proper home-based care when appropriate are inadequate. A third of discharged patients were smear microscopy positive at discharge, suggesting high transmission potential. The identification of epidemiological clusters and primary spread by strain typing and mutational analysis in the initial cohort[9] and in our follow-up study suggest that community-based spread of drug-resistant tuberculosis is likely. There is an urgent need to connect home-based care with palliative care and long-term sheltered community stay facilities (modernised sanatoriums) where such patients can voluntarily reside, thus minimising continuing transmission.[32] Clearly, preventive strategies and testing of new drug regimens for XDR tuberculosis are also urgently needed. The findings we have outlined are likely to be relevant in several settings where XDR or totally drug-resistant tuberculosis has been described, such as Iran, India, Italy, Russia, and eastern Europe.[15,19–21] As described in prechemotherapeutic times, some patients who fail treatment were cured after discharge and withdrawal of therapy.

Our data challenge previous findings (in the context of short-term outcomes)[9] and the widespread national

policy of treatment withdrawal if patients do not achieve culture conversion after 12 months of treatment. Our findings further indicate that treatment of 100 patients with XDR tuberculosis for a further 6 months leads to only an additional two culture conversions at a substantial cost. We also noted that almost 20% of initial converters subsequently reverted, and 90% of patients with net reversion have an unfavourable outcome. These data will be useful for policy makers when defining measures of treatment failure and criteria for withdrawal of treatment.

Overall predictors of survival included net culture conversion and use of clofazamine (also a predictor of culture conversion). The association with use of clofazamine has not previously been described in XDR tuberculosis, but intuitively makes sense because clofazamine is a mycobacteriostatic agent not widely used in treatment regimens for multidrug-resistant tuberculosis in South Africa. A systematic review[33] suggested a potential beneficial effect of clofazamine in XDR tuberculosis and our data suggest that it should be a key drug in any regimen. Interestingly, the mortality benefit was not recorded in patients infected with HIV. This finding could represent type 2 error due to small sample size, although increased mortality with clofazimine has been shown in patients with HIV during treatment of *Mycobacterium avium* complex.[34] Other studies[9,35] showed that moxifloxacin was associated with survival in patients with XDR tuberculosis despite ofloxacin resistance, and minimum inhibitory concentrations for local XDR tuberculosis isolates are often below the achievable serum concentrations of moxifloxacin.[36] However, the fact that we did not show an outcome advantage might be related to the relatively small numbers of patients on moxifloxacin or could be related to the changing susceptibility profile of isolates in South Africa. With continuing treatment and primary spread, the proportion of isolates that are sensitive to moxifloxacin could have decreased substantially.

Our study has several limitations. The initial cohort that we followed up was derived retrospectively and so mortality and unfavourable outcomes have probably been underestimated because of selection bias. Indeed, about 21% of patients with XDR tuberculosis in the original cohort died before starting treatment, most of whom had HIV infection,[9] suggesting that outcomes are worse than recorded in this study. However, the frequency of default was low and our intention was to document the long-term treatment-related outcomes to inform future cost-conscious public health interventions. We did not distinguish between deaths related to tuberculosis and those ascribable to HIV or other medical causes. We assessed only a proportion of isolates for susceptibility testing and did not test for drugs such as cycloserine, because methods for testing of such drugs are unreliable and not well defined. Furthermore, phenotypic testing methods have several limitations,[12] and we therefore resorted to genotypic testing. Our findings apply to patients treated across South Africa where previous multidrug-resistant tuberculosis is common, HIV co-infection is frequent, and empirical capreomycin is used widely. Therefore, our findings might not be applicable to other settings including localised or extended outbreaks, low and intermediate burden settings, and those with a low HIV prevalence including other parts of Africa.

In conclusion, our data suggest that even with a multidrug capreomycin-based regimen and fairly good adherence, long-term treatment outcomes in patients with XDR tuberculosis are poor. These patients also frequently fail treatment and are discharged with positive smear microscopy, and therefore are likely to transmit disease. Collectively, our data underscore the urgent need for testing of new combined regimens for XDR tuberculosis and institute interventions such as community and palliative care facilities to minimise disease spread by patients who fail treatment.[32] At the same time, preventive strategies are important, such as strengthening of the national tuberculosis programme, reductions in the overall burden of disease through HIV control and poverty, and management of overcrowding.

Contributors

KD conceived and designed the study. EP, EMS, BM, XP, AP, MB, ML, PvH, FAS, RW, and KD collected data. EI, ML, and KD analysed data. All authors interpreted data. EP, EI, RW, and KD wrote the first draft of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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