Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study

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Summary

Background **Addition of bedaquiline to treatment for multidrug-resistant tuberculosis was associated with an increased risk of death in a phase 2b clinical trial, resulting in caution from WHO. Following a compassionate access programme and local regulatory approval, the South African National Tuberculosis Programme began widespread use of bedaquiline in March, 2015, especially among patients with extensively drug resistant tuberculosis for whom no other effective treatment options were available. We aimed to compare mortality in patients on standard regimens with that of patients on regimens including bedaquiline.**

Methods **In this retrospective cohort study, we analysed patient data from the South African rifampicin-resistant tuberculosis case register (EDRweb), and identified additional mortality using the national vital statistics register. We excluded patients who started treatment before July 1, 2014, or after March 31, 2016; patients younger than 15 years or older than 75 years; patients without documented rifampicin resistance, and patients with pre-extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with further resistance to a second-line injectable or fluoroquinolone). We compared all-cause mortality between patients who received bedaquiline in treatment regimens and those who did not. Patients who did not receive bedaquiline had kanamycin or capreomycin and moxifloxacin as core medicines in their regimen. We estimated hazard ratios for mortality separately for multidrug-resistant or rifampicin-resistant tuberculosis and extensively drug-resistant tuberculosis and adjusted using propensity score quintile strata for the potential confounders of sex, age, HIV and antiretroviral therapy status, history of prior tuberculosis, valid identification number, and year and province of treatment.**

Findings **24 014 tuberculosis cases were registered in the EDRweb between July 1, 2014, and March 31, 2016. Of these, 19 617 patients initiated treatment and met our analysis eligibility criteria. A bedaquiline-containing regimen was given to 743 (4·0%) of 18 542 patients with multidrug-resistant or rifampicin-resistant tuberculosis and 273 (25·4%) of 1075 patients with extensively drug-resistant tuberculosis. Among 1016 patients who received bedaquiline, 128 deaths (12·6%) were reported, and there were 4612 deaths (24·8%) among 18 601 patients on the standard regimens. Bedaquiline was associated with a reduction in the risk of all-cause mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis (hazard ratio [HR] 0·35, 95% CI 0·28–0·46) and extensively drug-resistant tuberculosis (0·26, 0·18–0·38) compared with standard regimens.**

Interpretation **Our retrospective cohort analysis of routinely reported data in the context of high HIV and extensively drug-resistant tuberculosis prevalence showed that bedaquiline-based treatment regimens were associated with a large reduction in mortality in patients with drug-resistant tuberculosis, compared with the standard regimen.**

Funding **None.**

Introduction

In 2016, there were 600 000 cases of rifampicin-resistant tuberculosis globally, and an estimated 190 000 people died from multidrug-resistant tuberculosis.[1] Rifampicin-resistant tuberculosis can be rifampicin mono-resistant, multidrug-resistant (that is, resistant to both rifampicin and isoniazid), extensively drug-resistant (that is, multidrug-resistant plus at least resistance to fluoroquinolones and second-line injectable drugs), or pre-extensively drug-resistant (that is, multidrug-resistant plus resistance to either a fluoroquinolone or a second-line injectable drug).[2] Rifampicin-resistant tuberculosis requires 9–24 months of treatment using second-line antituberculosis drugs and is associated with high mortality.[3,4] Across all countries reporting to WHO, among patients initiating tuberculosis treatment only 54% of patients with multidrug-resistant or rifampicin-resistant tuberculosis and 30% of patients with extensively drug-resistant tuberculosis (2014 cohort) were successfully treated.[1]

Bedaquiline is a diarylquinoline that inhibits mycobacterial ATP synthase.[5] As of June, 2017, at least 89 countries reported using bedaquiline for treatment of rifampicin-resistant tuberculosis.[1] Stage 1 phase 2b clinical trial results showed an increase, from 9 to 48%, in the proportion of patients with multidrug-resistant

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Research in context

Evidence before this study

In 2014, only 54% of patients initiating treatment for multidrug-resistant or rifampicin-resistant tuberculosis had successful outcomes. In South Africa, about 20% of such patients die during the standard long-course 18–24 months of second-line treatment. Patients with multidrug-resistant or rifampicin-resistant tuberculosis who are co-infected with HIV and those with resistance to second-line injectable drugs and fluoroquinolones, including those with extensively drug-resistant tuberculosis, are 2–3 times more likely to die compared with people who are HIV-negative and those without second-line injectible or fluoroquinolone resistance. Results from phase 2b clinical trials of bedaquiline (TMC207-C208) showed significant benefit in terms of the proportion of patients who culture converted, time to culture conversion, and proportion of patients achieving cure when bedaquiline was added to the standard multidrug-resistant tuberculosis treatment. However, more deaths occurred in the bedaquiline plus background regimen arm compared with the standard multidrug-resistant tuberculosis treatment arm (10 of 79 patients *vs* 2 of 81 patients). The deaths in the bedaquiline arm were not attributed to bedaquiline by the investigators, but the significant increased risk of mortality led to a black box warning attached to the 2012 US Food and Drug Administration bedaquiline approval. WHO bedaquiline guidelines (2013 and 2017 revision) were also cautious, recommending bedaquiline only when an effective treatment regimen could not be constructed with other WHO-recommended drugs.

Added value of this study

Since March 2015, bedaquiline has been used within the South African National Tuberculosis Programme for all patients for whom an effective regimen could not be constructed (ie, those with second-line drug resistance or toxicity to the standard regimen). In our study, we analysed the South African drug-resistant tuberculosis case register from July 1, 2014, and March 31, 2016, and 18 601 patients who initiated drug-resistant tuberculosis regimens without bedaquiline were compared to 1016 patients who initiated bedaquiline-containing regimens. We used propensity score strata to adjust for potential confounders. In this cohort, bedaquiline was associated with a 3 times reduction in the adjusted hazard ratio for mortality. Results from our large cohort treated under the state tuberculosis programme and in a population with high prevalence of HIV and second-line drug resistance provided evidence that bedaquiline is associated with reduced rather than increased mortality in drug-resistant tuberculosis.

Implications of all the available evidence

Initial recommendations for bedaquiline weighed the benefits of the increased rate of culture conversion and cure against the unexplained higher risk of mortality observed in randomised controlled trials. However, given the evidence from our study that patients receiving bedaquiline are not at increased mortality risk, this risk evaluation could change. As bedaquiline was associated with increased culture conversion and cure in clinical trials and with decreased mortality in our large observational cohort, clinicians and policy makers should re-evaluate the practice and guidance of only using bedaquiline in drug-resistant tuberculosis treatment when there are no other options.

tuberculosis who converted to a negative sputum culture at 8 weeks when bedaquiline was added to a standard multidrug-resistant tuberculosis regimen, with no significant increase in the frequency or severity of adverse drug reactions.[6] However, the final outcomes at 120 weeks for stage 2 of the same phase 2b trial showed a statistically significant imbalance in mortality in the two treatment arms, with ten deaths occurring in the 79 patients exposed to bedaquiline (12·7%) and two deaths (2·5%) in the 79 patients in the placebo arm (p=0·02).[7] None of the deaths in the bedaquiline arm were attributed to bedaquiline by the investigators. Nonetheless, interim WHO guidelines recommended use of bedaquiline in rifampicin-resistant tuberculosis only when there is second-line drug resistance, the patient is not eligible for the standard treatment for rifampicin-resistant tuberculosis, or when there are no other treatment options.[8,9] Similarly, because of the reported increased risk of mortality,[7] regulatory approval in the USA included a black box warning[10] to only use bedaquiline when an effective treatment regimen cannot otherwise be provided.[11]

WHO categorised South Africa as a country with a high burden of tuberculosis, HIV tuberculosis, and multidrug-resistant tuberculosis in its 2017 global report.[1] 19 073 laboratory-confirmed multidrug-resistant or rifampicin-resistant tuberculosis cases were diagnosed and 967 extensively drug-resistant cases were diagnosed in 2016. Similar to global reporting, 54% (n=11 111) of the 2014 multidrug-resistant or rifampicin-resistant tuberculosis cohort in South Africa were successfully treated. Short-term mortality is highest in patients with extensively drug-resistant tuberculosis, compared with other forms of tuberculosis—42% of the 2014 South African cohort died during extensively drug-resistant tuberculosis treatment.[1] Long-term survival for extensively drug-resistant tuberculosis is even poorer—in one South African cohort study, 73% had died within 5 years of initiating treatment.[12]

In January, 2013, the South African National Tuberculosis Programme, with the support of non-governmental and academic partners, established the Bedaquiline Clinical Access Programme so that patients with pre-extensively drug-resistant tuberculosis and extensively drug-resistant tuberculosis at specialised public health facilities in South Africa could receive bedaquiline.[13] Early results of the South African Bedaquiline Clinical Access Programme cohort showed high amounts of culture conversion and encouraging outcomes, including survival.[14] In

October, 2014, the South African Medicines Control Council regulatory authority approved the use of bedaquiline for treatment of multidrug-resistant and rifampicin-resistant tuberculosis. Starting in March, 2015, the South African National Tuberculosis Programme began the process of rolling out bedaquiline as an additional drug to strengthen the existing regimens for rifampicin-resistant tuberculosis.

In our study, we analysed survival from routinely reported data from the South African National Tuberculosis Programme to establish the hazard ratio (HR) for mortality for patients who received bedaquiline compared with patients who received regimens that did not include bedaquiline in public sector health-care facilities in South Africa.

Methods

Setting and standard of care

In line with WHO 2011 treatment guidelines,[15] in mid-2016 the standard of care for newly diagnosed multidrug-resistant or rifampicin-resistant tuberculosis treatment in South Africa was to use a standard long-course regimen, unless documented resistance or intolerance to the drugs in the regimen required an individualised regimen.[16,17] Standard multidrug-resistant and rifampicin-resistant tuberculosis treatment is divided into two phases—6 months (intensive phase) of five drugs (kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide) followed by 12–18 months (continuation phase) of four drugs (moxifloxacin, ethionamide, terizidone, and pyrazinamide). Patients with either pre-extensively drug-resistant or extensively drug-resistant tuberculosis are treated with individualised regimens that might include high-dose isoniazid, para-aminosalicylic acid, clofazimine, or capreomycin. Linezolid was also available but with restrictions due to cost and potential toxicity.[18]

In January, 2013, patients with pre-extensively drug-resistant tuberculosis could access bedaquiline under the Bedaquiline Clinical Access Programme at five centralised multidrug-resistant and extensively drug-resistant tuberculosis hospitals in South Africa.[14] Following approval from the national regulatory authority at the end of 2014, in March, 2015, bedaquiline was expanded to more sites nationally. Indications for bedaquiline[16] include rifampicin-resistant patients with resistance to a fluoroquinolone or a second-line injectable drug (pre-extensively drug-resistant or extensively drug-resistant tuberculosis); multidrug-resistant or rifampicin-resistant tuberculosis with both *inhA* and *katG* mutations; and toxicity to drug(s) in the standard multidrug-resistant or rifampicin-resistant tuberculosis regimen. As per la-belling, bedaquiline treatment is for 24 weeks[11] during the intensive phase of second-line tuberculosis treatment. Electrocardiograms are used to monitor QT interval prolongation at baseline and the recommended intervals (every 2 weeks for the first month, then monthly for 5 months). Clinicians report serious adverse events occurring during drug-resistant tuberculosis treatment both through a national pharmacovigilance programme and in the national drug-resistant tuberculosis case register.

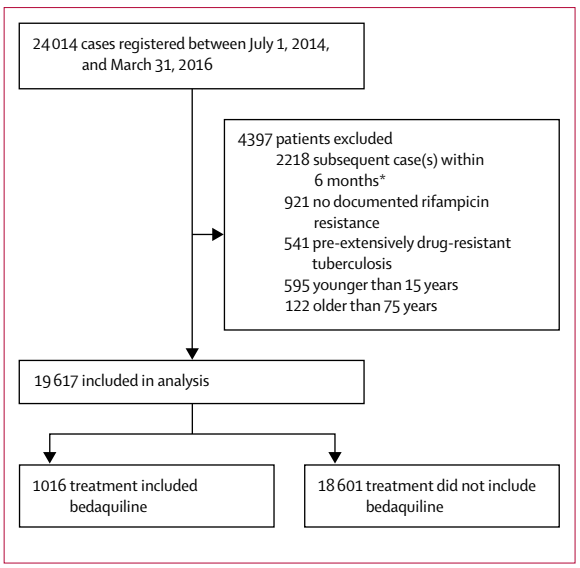

Figure 1: **Study flow chart**
*For time-to-event analyses in which two or more cases had identical South African ID numbers, surname, date of birth, and sex, starting from the 6 months before the analysis period, the initial case record was maintained and subsequent case records excluded.

HIV testing is offered to all patients with tuberculosis and antiretroviral therapy (ART) is initiated after 2–8 weeks in ART-naive HIV-infected patients regardless of CD4 count. Patients with HIV infection are eligible for bedaquiline; appropriate ART regimen switches are made to either lopinavir and ritonavir or nevirapine as clinically indicated if the patient is receiving efavirenz.[11,16]

Data sources

Since 2009, the web-based electronic drug-resistant tuberculosis register (EDRweb) has been used to record cases of drug-resistant tuberculosis and treatment outcomes in the South African National Tuberculosis Programme. Deaths from any cause during drug-resistant tuberculosis treatment are reported within EDRweb as a final treatment outcome. Other EDRweb final treatment outcomes are reported according to standard WHO definitions.[2] We also used data from the South African national vital statistics register, maintained by the Department of Home Affairs, which effectively records more than 80% of all deaths in South Africa.[19–21]

For the **EDRweb** see https://edrweb.net/

Study design and participants

We did a retrospective cohort study of data from patients in the South African rifampicin-resistant tuberculosis case register (EDRweb). We excluded patients starting treatment before July 1, 2014, or after March 31, 2016; patients younger than 15 years or older than 75 years;

	Bedaquiline (n=1016)	No bedaquiline (n=18 601)	Total (n=19 617)	p value*
Age, years	38 (30–45)	36 (29–44)	36 (29–44)	<0·0001
Sex	..	..	..	0·015
Male	605 (59·5%)	10 354 (55·7%)	10 959 (55·9%)	..
Female	411 (40·5%)	8247 (44·3%)	8658 (44·1%)	..
Resistance category	..	..	..	<0·0001
Multidrug-resistant or rifampicin-resistant	743 (73·1%)	17 799 (95·7%)	18 542 (94·5%)	..
Extensively drug-resistant	273 (26·9%)	802 (4·3%)	1075 (5·5%)	..
Previous tuberculosis treatment	..	..	..	<0·0001
No reported previous tuberculosis	447 (44·0%)	7168 (38·5%)	7615 (38·8%)	..
History of first-line treatment	392 (38·6%)	10 419 (56·0%)	10 811 (55·1%)	..
History of second-line treatment	177 (17·4%)	1014 (5·5%)	1,191 (6·1%)	..
HIV and ART	..	..	..	<0·0001
HIV-negative	295 (29·0%)	4811 (25·9%)	5106 (26·0%)	..
HIV-positive, on ART	701 (69·0%)	11 729 (63·1%)	12 430 (63·4%)	..
HIV-positive, no or unknown ART	8 (0·8%)	1455 (7·8%)	1463 (7·5%)	..
HIV status unknown	12 (1·2%)	606 (3·3%)	618 (3·2%)	..
Vital statistics	..	..	..	<0·0001
South African ID number for matching	773 (76·1%)	12 562 (67·5%)	13 335 (68·0%)	..
No ID number	243 (23·9%)	6039 (32·5%)	6282 (32·0%)	..
Treatment year	..	..	..	<0·0001
Initiated in 2014	50 (4·9%)	5778 (31·1%)	5828 (29·7%)	..
2015	730 (71·9%)	10 462 (56·2%)	11 192 (57·1%)	..
2016	236 (23·2%)	2361 (12·7%)	2597 (13·2%)	..
Province	..	..	..	<0·0001
Eastern Cape	173 (17·0%)	3320 (17·8%)	3493 (17·8%)	..
Free State	11 (1·1%)	830 (4·5%)	841 (4·3%)	..
Gauteng	163 (16·0%)	2221 (11·9%)	2384 (12·2%)	..
KwaZulu Natal	335 (33·0%)	5571 (30·0%)	5906 (30·1%)	..
Limpopo	7 (0·7%)	692 (3·7%)	699 (3·6%)	..
Mpumalanga	69 (6·8%)	1614 (8·7%)	1683 (8·6%)	..
North West	24 (2·4%)	1109 (6·0%)	1133 (5·8%)	..
Northern Cape	72 (7·1%)	684 (3·7%)	756 (3·9%)	..
Western Cape	162 (15·9%)	2560 (13·8%)	2722 (13·9%)	..

Data are median (IQR) or n (%). ART=antiretroviral therapy. ID=identity. *Calculated using Pearson χ^2 difference of proportions for counts and Wilcoxon rank-sum (Mann-Whitney) for continuous variables.

Table 1: Cohort characteristics

patients without documented rifampicin resistance, and patients with pre-extensively drug-resistant tuberculosis. The study protocol was approved by the Human Research Ethics Committee, Medical, of the University of Witwatersrand (#M150340, March, 2015). The requirement to obtain informed consent for individual patients was waived.

Procedures

We compared mortality between patients who received bedaquiline in their treatment regimen and those who did not. Patients who did not receive bedaquiline had kanamycin or capreomycin and moxifloxacin as core medicines in their regimen.

For our time-to-event analysis, the start date was the date that drug-resistant tuberculosis treatment was initiated. The date of final treatment outcome was used where available. For patients without an outcome, the date of censoring (Nov 30, 2017) was used.

We exported a census of drug-resistant tuberculosis cases registered in EDRweb on Dec 1, 2017. A list of EDRweb patients with valid South African patient identity (ID) numbers was sent to the South African Medical Research Council to match against the vital statistics register to ascertain any additional reports of deaths. Deaths from either source (EDRweb or vital statistics) were combined in the analysis.

For time-to-event analyses in which two or more cases had identical South African ID numbers, surname, date of birth, and sex, starting from the 6 months before the analysis period, the initial case record was maintained and subsequent case records excluded. Remaining case registrations were right censored as of Nov 30, 2017, and all cases had a minimum of 18 months of follow-up.

Outcomes

The primary outcome for analysis was all-cause mortality.

Definitions

We categorised HIV and ART status as HIV-negative, HIV-infected on ART, HIV-infected no ART reported, or HIV status unknown. Characteristics of tuberculosis included whether diagnosed as multidrug-resistant, rifampicin-resistant, or extensively drug-resistant tuberculosis, as well as history of previous first-line or second-line tuberculosis treatment. Characteristics of treatment included province of treatment facility and year initiated. Additionally, we adjusted for whether a valid national patient ID was recorded, as required for matching to the vital statistics register.

Statistical analysis

We estimated Kaplan-Meier survival curves and graphed these separately for patients who received bedaquiline in their treatment regimen and those who did not; we used log-rank tests to assess the equality of the survival functions.

We estimated the propensity score for treatment with bedaquiline using a multivariate logit model[22] inclusive of the above definitions. We used the Hosmer-Lemeshow goodness of fit test for the logit model, and after weighting, we checked the balance of the covariates across treatment and control using the Stata command tebalance. We estimated Cox proportional hazards separately for multidrug-resistant tuberculosis and rifampicin-resistant tuberculosis and extensively drug-resistant tuberculosis and adjusted for the potential confounders of sex, age, HIV and antiretroviral therapy status, history of prior tuberculosis, valid identification number, and year and province of treatment using propensity score quintile strata. We did multivariable Cox proportional hazards

analysis for base case assumptions and sensitivity analyses. Sensitivity analyses included start time set at the date of bedaquiline initiation (if applicable) and was limited to patients who survived at least 8 weeks from initiation. All analyses were done in Stata version 14.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all of the data in the study and final responsibility to submit for publication.

Results

24 014 tuberculosis cases were registered in EDRweb between July 1, 2014 and March 31, 2016 (figure 1). 19 617 patients with multidrug-resistant, rifampicin-resistant, or extensively drug-resistant tuberculosis registered in EDRweb met eligibility criteria and were included in our analyses.

The median age of patients at case registration was 36 years (IQR 29–44). Just over half of patients were male. Most patients were HIV-infected, of whom 12 430 were on ART. 18 542 (94·5%) patients had either multidrug-resistant or rifampicin-resistant tuberculosis, and 1075 (5·5%) had extensively drug-resistant tuberculosis (table 1).

1016 (5·2%) of the 19 617 total patients were reported to have been initiated on bedaquiline during the study period and 18 601 (94·8%) patients received a regimen that did not include bedaquiline. 743 (4·0%) of 18 542 patients with multidrug-resistant or rifampicin-resistant tuberculosis received bedaquiline, and 273 (25·4%) of 1075 patients with extensively drug-resistant tuberculosis were treated with bedaquiline. Among patients with information on a separate bedaquiline start date to the date of treatment initiation with other second-line antituberculosis drugs (n=726), bedaquiline was initiated a median of 58 days (IQR 15–105) after initiation of drug-resistant tuberculosis treatment—for patients with extensively drug-resistant tuberculosis this duration was 37 days (0–90).

As of Nov 30, 2017, 16 293 (83·1%) of the eligible cohort had treatment outcomes reported in EDRweb (table 2). Reported outcomes included 8370 (42·3%) cured or completed treatment, 3175 (16·2%) lost to follow-up, and 763 (3·9%) failing treatment. 4048 (20·6%) of 19 617 patients were reported in EDRweb to have died during rifampicin-resistant tuberculosis treatment (table 2). South African national identity numbers were available for 13 335 (68·0%) patients (table 1). After linking to the vital statistics registry, an additional 692 deaths were ascertained, 296 (42·8%) from patients reported as lost to follow-up in EDRweb. Patients who had received bedaquiline were more likely to have a valid national ID number that matched with the vital statistics register (773 [76·1%] of 1016 *vs* 12 562 [67·5%] of 18 601; Pearson χ^2 difference of proportions p<0·0001) and therefore more likely to have had additional death ascertainment.

	Bedaquiline	No bedaquiline	Total	p value*
Multidrug-resistant or rifampicin-resistant tuberculosis				
All patients with multidrug-resistant or rifampicin-resistant tuberculosis	743	17 799	18 542	..
Deaths (any reported)	88 (11·8%)	4296 (24·1%)	4384 (23·6%)	<0·0001
EDRweb reported outcomes	..	..	..	<0·0001
Cured or completed	366 (49·3%)	7618 (42·8%)	7984 (43·1%)	..
Died (EDRweb)	72 (9·7%)	3667 (20·6%)	3739 (20·2%)	<0·0001
Lost to follow-up	74 (10·0%)	2998 (16·8%)	3072 (16·6%)	..
Still on treatment, no reported final outcome	207 (27·9%)	2906 (16·3%)	3113 (16·8%)	..
Treatment failure	24 (3·2%)	610 (3·4%)	634 (3·4%)	..
Extensively drug-resistant tuberculosis				
All patients with extensively drug-resistant tuberculosis	273	802	1075	..
Died (any reported)	40 (14·7%)	316 (39·4%)	356 (33·1%)	<0·0001
EDRweb reported outcomes	..	..	..	<0·0001
Cured or completed	113 (41·4%)	210 (26·2%)	323 (30·0%)	..
Died (EDRweb)	33 (12·1%)	276 (34·4%)	309 (28·7%)	<0·0001
Lost to follow-up	19 (7·0%)	84 (10·5%)	103 (9·6%)	..
Still on treatment, no reported final outcome	100 (36·6%)	111 (13·8%)	211 (19·6%)	..
Treatment failure	8 (2·9%)	121 (15·1%)	129 (12·0%)	..

*Calculated using Pearson χ^2 difference of proportions, across all outcomes and for Died (EDRweb) *vs* any other outcome.

Table 2: Treatment outcomes

4740 (24·2%) patients had a death reported either in EDRweb or in the vital statistics registry. 128 (12·6%) deaths were reported in 1016 patients who had ever received bedaquiline, and 4612 (24·8%) deaths were reported among 18 601 patients whose treatment regimens did not include bedaquiline (p<0·0001). For patients with extensively drug-resistant tuberculosis, mortality was nearly 3 times higher in patients not receiving bedaquiline; 316 (39·4%) of 802 patients not receiving bedaquiline were reported to have died during the study period, whereas 40 (14·7%) of 273 patients who received bedaquiline were reported to have died. For patients with multidrug-resistant or rifampicin-resistant tuberculosis, 4296 (24%) of 17 799 patients not receiving bedaquiline died and 88 (12%) of 743 patients receiving bedaquiline died.

We used Kaplan-Meier survival curves to analyse the association between a treatment regimen including bedaquiline and survival of patients with drug-resistant tuberculosis (figure 2). More than 1 million person-weeks of exposure to a drug-resistant tuberculosis regimen were included in the analysis. The median time on treatment was 85 weeks for all patients (IQR 35–100). For patients with multidrug-resistant or rifampicin-resistant tuberculosis, median survival was 92 weeks (80–102) for those receiving bedaquiline and 85 weeks (34–100) for those not receiving bedaquiline. For patients with extensively drug-resistant tuberculosis, median survival was 96 weeks (85–106) for those receiving bedaquiline

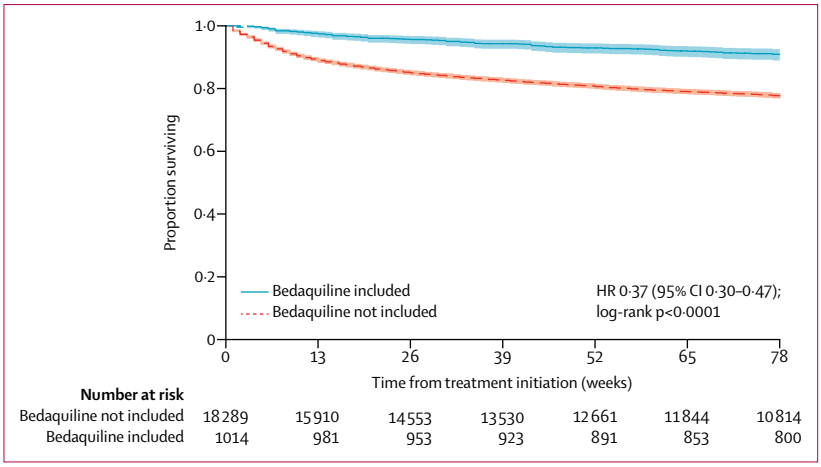

Figure 2: **Kaplan-Meier survival curve, by regimen inclusive of bedaquiline**
The shaded area indicates 95% CI. HR=hazard ratio.

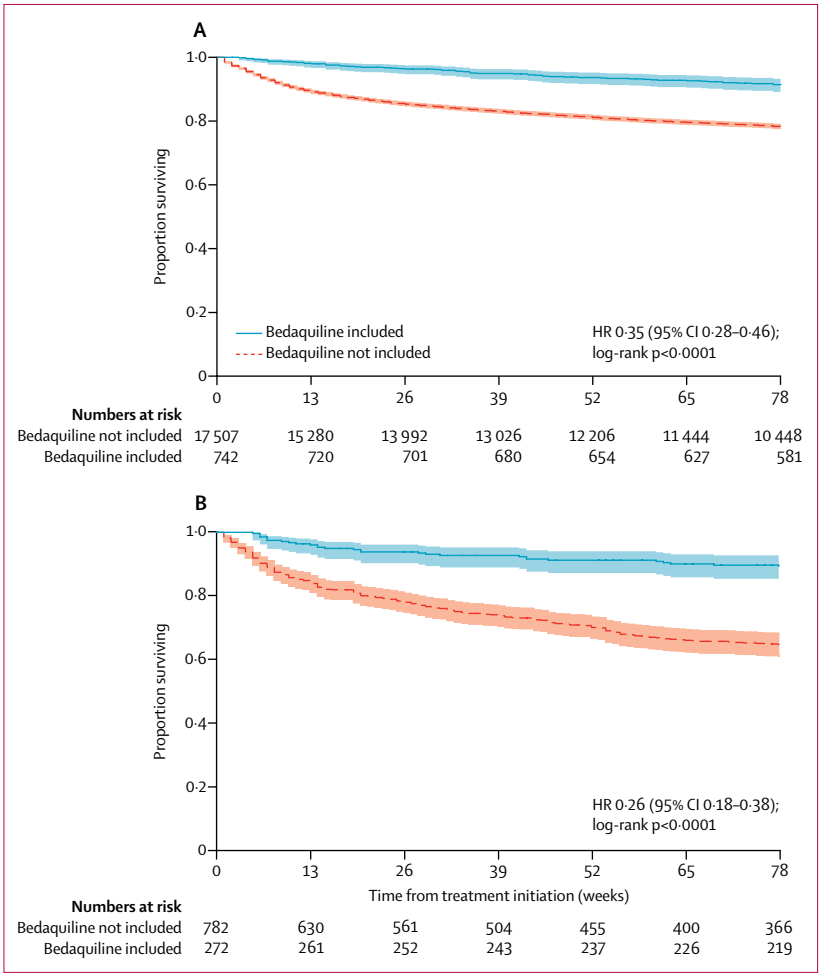

Figure 3: **Kaplan-Meier survival curves for (A) multidrug-resistant or rifampicin-resistant tuberculosis and (B) extensively drug-resistant tuberculosis, by regimen inclusive of bedaquiline**
The shaded area indicates 95% CI. HR=hazard ratio.

and 64 weeks (18–96) for those not receiving bedaquiline. At 78 weeks, mortality for patients with multidrug-resistant, rifampicin-resistant, or extensively drug-resistant tuberculosis on bedaquiline was approximately a third of that for patients not treated with bedaquiline ($p<0·0001$, log-rank test). We also analysed survival separately based on category of resistance (multidrug-resistant and rifampicin-resistant or extensively drug-resistant; figure 3), which showed that the difference in survival was larger for patients with extensively drug-resistant tuberculosis. When plotted on the same graph (figure 4), the 95% CI for the survival curve for patients with extensively drug-resistant tuberculosis who received bedaquiline overlapped with the 95% CI for patients with multidrug-resistant or rifampicin-resistant tuberculosis who received bedaquiline. Patients with extensively drug-resistant tuberculosis receiving bedaquiline had a higher survival curve than did patients with multidrug-resistant or rifampicin-resistant tuberculosis not treated with bedaquiline.

For the 1054 patients with extensively drug-resistant tuberculosis we analysed, treatment with bedaquiline was associated with a 4 times reduction in risk of all-cause mortality (HR 0·26, 95% CI 0·18–0·38) compared with standard regimens. In Cox proportional hazards regression, adjusted using propensity score quintiles, the CI widened (adjusted HR 0·25, 0·07–0·91). Treatment with bedaquiline was associated with a 3 times reduction in risk of mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis in unadjusted regression compared with standard regimens (n=18 249; HR 0·35, 0·28–0·46) and we found similar results in regression adjusted using propensity score quintiles (adjusted HR 0·34, 0·24–0·49).

Sensitivity analysis was repeated using multivariable Cox proportional hazards regression (appendix). Patients with a resistance profile associated with the highest risk of death (patients with extensively drug-resistant tuberculosis) had the greatest decline in risk of death when receiving bedaquiline treatment (extensively drug-resistant tuberculosis adjusted HR 0·35, 95% CI 0·23–0·53) compared with the standard regimen. Bedaquiline was also associated with decreased mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis (adjusted HR 0·37, 0·29–0·48) compared with those who did not receive bedaquiline. For our sensitivity analysis with Cox proportional hazards regression, the regression was re-run using the start date of bedaquiline if reported as separate or different from the start date of any second-line antituberculosis treatment. Thus, for patients receiving bedaquiline, the start date would be later than in the base case analysis and as a result, the length of survival was shortened. This shift had a moderate effect on the estimated adjusted HRs; for patients with multidrug-resistant or rifampicin-resistant tuberculosis, treatment with bedaquiline was associated with adjusted HR 0·53

(0·41–0·70) compared with those who did not receive bedaquiline. In another sensitivity analysis we excluded all early mortality and considered only those patients who survived at least 8 weeks after initiation of drug-resistant tuberculosis treatment. Exclusion of early mortality did not change the direction or statistical significance of the effect (appendix).

Discussion

In our retrospective survival analysis, inclusion of bedaquiline in a drug-resistant tuberculosis treatment regimen was associated with a 3 times reduction in the adjusted HR for mortality in patients with extensively drug-resistant tuberculosis and multidrug-resistant or rifampicin-resistant tuberculosis compared with regimens not containing bedaquiline. Patients with extensively drug-resistant tuberculosis who received bedaquiline had similar mortality to patients with multidrug-resistant or rifampicin-resistant tuberculosis who did not receive bedaquiline.

Phase 2b randomised clinical trial evidence for use of bedaquiline in addition to the standard treatment regimen for multidrug-resistant tuberculosis showed promising efficacy, with higher rates of culture conversion and cure compared with the standard regimen plus placebo. However, there was a significant imbalance in mortality, with 10 deaths (12·7%) occurring in patients exposed to bedaquiline and 2 (2·5%) deaths in the placebo arm.[7] Therefore, interim WHO guidelines recommend use of bedaquiline only in rifampicin-resistant tuberculosis when there is resistance to fluoroquinolones and no other treatment options are available, even while noting that there was a very serious risk of imprecision in the reported mortality estimates and the quality of the evidence was very low.[8,9] An interim cohort analysis of the first 91 patients from the South African Bedaquiline Clinical Access Programme published in 2015 reported 3 deaths (3·3%), few severe adverse events, and high culture conversion among patients with extensively drug-resistant and pre-extensively drug-resistant tuberculosis; however, many patients had 6 months or less follow-up time.[14] At 120 weeks, the open-label trial TMC207-C209 reported 16 (6·9%) deaths in 233 enrolled patients, all of which were considered not related to bedaquiline.[23] Another interim cohort study from a compassionate access program in France (2015) reported that at 6 months, 1 (3%) of 35 patients had died and 28 (97%) of 29 of culture positive patients had culture converted.[24] However, each of these studies were single arm, non-randomised studies, and without a control group the signal of excess mortality from the phase 2b bedaquiline trial could not be confirmed or refuted.

Mortality for patients on bedaquiline in our study (12·6%) is similar to previous reports. This 12·6% is notable in comparison to tuberculosis patients in the same public health system, with high rates of HIV co-infection and high rates of second-line drug resistance, in which 24·1–39·4% of patients with multidrug-resistant, rifampicin-resistant, or extensively drug-resistant tuberculosis that did not receive bedaquiline died during the 18–24 months of drug-resistant tuberculosis treatment. By contrast, the phase 2b TMC207-C208 trial in which the placebo arm reported 2·5% mortality had restricted enrolment of those with second-line resistance or use of ARVs—only 19 (14%) of the 132 patients in the study were HIV-infected.[7] Additionally, although our analysis is still interim and not all patients included have completed treatment, all patients were followed for at least 18 months from initiation.

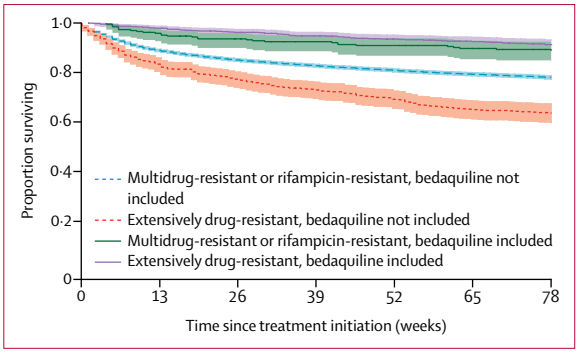

Figure 4: **Kaplan-Meier survival curves, by regimen inclusive of bedaquiline and drug resistance**
The shaded area indicates 95% CI.

Our study was a retrospective analysis using routinely collected data in the national drug-resistant tuberculosis case register. There were many potential confounders that were not or cannot be measured and therefore could lead to bias in the estimates. The sickest patients who were at highest risk of mortality might not have been offered bedaquiline treatment or might have died before initiation of bedaquiline, introducing survival bias. In sensitivity analyses, the associated reduction in mortality associated with bedaquiline was attenuated but still significant, even when the start date of the analysis was taken from the start of bedaquiline treatment rather than any second-line tuberculosis regimen.

See Online for appendix

Conversely, as a new drug, clinicians might have been more careful in the follow-up and management of bedaquiline-treated patients, leading to improved survival or may have been more careful to report every death leading to decreased estimates of survival. Thus, the direction of potential bias is uncertain. The ascertainment of deaths from the national vital statistics register could help to moderate the clinician-related bias. The exclusion of subsequent cases (when a patient failed treatment or was lost to follow-up, but later returned and a new case was initiated) within 6 months of the analysis period was designed to limit survival bias when the start date was from a previous case of drug-resistant tuberculosis, for example, when a patient with multidrug-resistant or rifampicin-resistant tuberculosis survived for 6 months, was determined to be a treatment

failure, and was then initiated on extensively drug-resistant tuberculosis treatment inclusive of bedaquiline. Additionally, use of propensity scores helped to balance the baseline characteristics for patients, their tuberculosis diagnosis, and tuberculosis treatment across the two observed arms, to limit bias, and improve estimation of the effect of bedaquiline treatment.

Multiple clinical trials of bedaquiline are underway, including among patients with extensively drug-resistant tuberculosis, children and adolescents, and in combination with delamanid. While waiting for these clinical trials to report, recommendations for multidrug-resistant and rifampicin-resistant treatment prioritise injection-based regimens,[25] the evidence for which are also based on programmatic and observational reporting.[26] The matching of the EDRweb data and vital statistics register, and the large dataset in which bedaquiline was added to treatment in programmatic conditions among very sick patients with high prevalence of HIV and extremely drug-resistant tuberculosis, suggests that although the limitations of the analysis might add to the uncertainty of the precision of the estimate, the association of bedaquiline with some form of reduction in mortality compared to standard regimens is robust.

In our retrospective cohort analysis of patients with cases registered by the South African National Tuberculosis Programme, treatment with bedaquiline was associated with a 3 times reduction in mortality for patients with multidrug-resistant or rifampicin-resistant tuberculosis and an even larger reduction in mortality for patients with extensively drug-resistant tuberculosis. Our results justify consideration for revised recommendations from WHO and wider use of bedaquiline in multidrug-resistant, rifampicin-resistant, and extensively drug-resistant tuberculosis treatment.

Contributors

KS, NN, GMa, GMe, and FC conceived and designed the analysis. NN, GMa, GMe, IM, NI, JH, HF, XP, RR, JtR, and FC interpreted the findings and provided crucial revisions of the manuscript. KS did the statistical analysis and drafted the manuscript. All authors approved the final version for publication.

Declaration of interests

We declare no competing interests.

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