**ONLINE SUPPLEMENT**

# LONG TERM BEDAQUILINE-RELATED TREATMENT OUTCOMES IN PATIENTS WITH EXTENSIVELY DRUG RESISTANT TUBERCULOSIS FROM SOUTH AFRICA

Olatunde Olayanju[1], Jason Limberis[1] Aliasgar Esmail[1], Suzette Oelofse[1], Phindile Gina[1], Elize Pietersen[1], Mohammed Fadul[1], Rob Warren[2], Keertan Dheda[1]

Affiliation: [1]Lung Infection and Immunity Unit, Division of Pulmonology, Department of Medicine, University of Cape Town, South Africa. [2]DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, US/SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Departments of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

Correspondence: Keertan Dheda, Lung Infection and Immunity Unit, Division of Pulmonology, Department of Medicine University of Cape Town.H46.41 Old Main Builiding, Groote Schuur Hospital, Observatory,7925 South Africa.

E-mail: keertan.dheda@uct.ac.za

Table S1: Grading of adverse events severity[1]

| | |
|---|---|
| Grade 0 | No Adverse events |
| Grade 1 | Mild adverse event, requiring no intervention |
| Grade 2 | Moderate adverse event requiring either changing the dose or frequency of the offending drug, or prescribing another drug to manage the adverse event |
| Grade 3 | Severe adverse event, enough to stop the offending drug |
| Grade 4 | Life threatening or disabling adverse event |
| Grade 5 | Death resulting from the adverse event |

[1]Grading was done according to the modified American National Institute of Health common terminology of criteria for adverse events

Table S2: Treatment-related outcome definitions applied, as adapted from the 2013 WHO revised definitions and reporting framework for TB guidelines, and the core research definitions for drug-resistant TB clinical trials recommended by Furin *et al* [1, 2].

| **Treatment outcome** | | **Definition** |
|---|---|---|
| Favourable outcome | Cured | Treatment completed, as recommended by the National TB programme, without evidence of failure or an unfavourable outcome as defined below. Three or more consecutive negative sputum cultures, taken at least 30 days apart, after the intensive phase (up to 12 months from the initiation of treatment), or a participant's last two culture results at the end of treatment are negative. |
| | Completed treatment | Treatment completed, as recommended by the National TB programme, without evidence of failure or an unfavourable outcome, however no record of three or more consecutive negative sputum cultures, taken at least 30 days apart, after the intensive phase (up to 12 months from the initiation of treatment), or a participant's last two culture results at the end of treatment are not recorded as negative. |
| Unfavourable outcome | Treatment failure | Treatment terminated (stopping of two or more drugs), or the need for permanent regimen change of at least two anti-TB drugs (stoppage of or the change one drug in the case of linezolid or bedaquiline) because of one or more of the following: i) lack of sputum culture conversion, or culture reversion after initial conversion, or culture positivity after month 6 [1], (ii) drug-related adverse events (AEs), (iii) evidence of additional acquired drug resistance precluding the composition of a regimen of at least 4 likely effective drugs.<br><br>(In the case culture positivity during or after month 6, only 1 positive culture is deemed to be sufficient when considered in the context of other biomarkers including weight, radiological disease extent, symptoms etc, based on the core research definitions for drug-resistant TB clinical trials recommended by Furin *et al* [1].) |
| | Died while on treatment | A patient who died for any reason while on any TB treatment, or within 7 days of termination of treatment. For post treatment time-specific outcome all-cause mortality will be used. Death superseded any treatment outcome at a specific time point. |
| | Recurrence (relapse or re-infection) | Two or more consecutive positive sputum cultures, at least 7 to 30 days apart, subsequent to the outcome of 'Cure' or 'Treatment Complete'. Genotyping is required to distinguish relapse from re-infection. |
| | Defaulted | A patient who interrupted treatment for 2, or more, consecutive months and who did not restart treatment but remained hospitalised or traceable in the community. |
| | Loss to follow up | A patient who interrupted treatment for 2, or more, consecutive months and who did not restart treatment but remains untraceable despite intensive and best efforts to find or track down the patient. |
| Indeterminate | Ongoing treatment | A patient for whom no treatment outcome can be assigned due to ongoing treatment in accordance with the National TB programme. |

Table S3: Univariate Cox proportional hazard model for risk of death for all the XDR-TB patients (n=272).

| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| Age at XDR-TB diagnosis (years) | 1.00 (0.99,1.02) | 0.51 |
| Weight <50 | 1.68 (1.22,2.32) | 0.002 |
| Duration of TB treatment (days) | 0.98 (0.98,0.98) | <0.001 |
| Gender (male) | 0.93 (0.67,1.29) | 0.66 |
| Median number of days of admission | 1.00 (1.00,1.00) | 0.03 |
| Median number of anti-TB drugs received | 0.92 (0.83,1.03) | 0.14 |
| *HIV Infected | 1.17 (0.85,1.61) | 0.35 |
| Previous TB treatment | 1.60 (1.04,2.44) | 0.03 |
| Amikacin | 2.37 (0.58,9.59) | 0.23 |
| Capreomycin | 3.51 (2.09,5.91) | <0.001 |
| Kanamycin | 1.80 (1.30,2.50) | <0.001 |
| [a]Any aminoglycosides | 4.96 (2.60,9.44) | <0.001 |
| PAS | 0.35 (0.19,0.68) | 0.002 |
| Moxifloxacin | 0.91 (0.66,1.26) | 0.57 |
| Levofloxacin | 0.17 (0.09,0.33) | <0.001 |
| [b]Third generation quinolones | 0.46 (0.33,0.64) | <0.001 |
| Clofazimine | 0.36 (0.25,0.51) | <0.001 |
| Linezolid | 0.15 (0.07,0.34) | <0.001 |
| Bedaquiline | 0.17 (0.09,0.32) | <0.001 |
| Ethionamide | 4.33 (2.34,8.03) | <0.001 |
| Amoxycillin | 0.94 (0.46,1.92) | 0.86 |
| Age at XDR-TB diagnosis (years) | 1.00 (0.99,1.02) | 0.51 |

*One patient refused HIV testing, n=271; [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S4: Univariate Cox proportional hazard model for risk of death for HIV-infected patients in both groups (n=134).

| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| Age at XDR-TB diagnosis (Years) | 1.00 (0.97,1.03) | 0.87 |
| Gender (Male) | 0.89 (0.56,1.41) | 0.61 |
| Weight <50kg at admission | 1.65 (1.04,2.62) | 0.03 |
| Previous TB treatment | 1.44 (0.77,2.68) | 0.25 |
| On ARV treatment | 0.65 (0.28,1.50) | 0.31 |
| *Median CD4 count <200 cells/µl at admission | 1.14 (0.72,1.81) | 0.58 |
| Median number of anti-TB drugs received | 0.94 (0.79,1.11) | 0.47 |
| Median number of days of admission | 1.00 (1.00,1.00) | 0.01 |
| Median duration of TB treatment (in days) | 0.98 (0.98,0.98) | <0.001 |
| Bedaquiline | 0.20 (0.08,0.45) | <0.001 |
| Clofazimine | 0.31 (0.19,0.50) | <0.001 |
| Linezolid | 0.19 (0.08,0.47) | <0.001 |
| Capreomycin | 3.42 (1.70,6.89) | <0.001 |
| Kanamycin | 2.32 (1.46,3.68) | <0.001 |
| Amikacin | 1.64 (0.23,11.85) | 0.62 |
| [a]Any aminoglycosides | 4.10 (1.87,8.97) | <0.001 |
| Levofloxacin | 0.21 (0.09,0.48) | <0.001 |
| Moxifloxacin | 1.02 (0.64,1.62) | 0.93 |
| [b]3rd Generation fluoroquinolones | 0.45 (0.28,0.73) | <0.001 |
| PAS | 0.34 (0.14,0.85) | 0.02 |
| Ethionamide | 4.34 (1.87,10.04) | <0.001 |
| Amoxycillin | 1.43 (0.45,4.56) | 0.54 |

*2 patients did not have CD4 count done at admission (n=132); [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S5: Multivariate Cox proportional hazard model for risk of death in both groups excluding colinear variables; A) all the XDR-TB patients (n=271), B) HIV-infected patients (n=132). Univariate analyses are shown in supplementary Tables S3 and S4 for the whole cohort and the HIV-infected subgroups respectively.

| **Variables** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| **I)** All the XDR-TB patients (n=271) | | |
| Weight <50kg at admission | 1.96 (1.38,2.77) | <0.001 |
| Gender (male) | 1.06 (0.76,1.49) | 0.72 |
| [A]HIV-infected | 1.49 (1.05,2.11) | 0.03 |
| Previous TB treatment | 1.08 (0.69,1.67) | 0.74 |
| Number of anti-TB drugs received | 0.83 (0.72,0.96) | 0.01 |
| [B]Bedaquiline | 0.14 (0.06,0.30) | <0.001 |
| Clofazamine | 0.80 (0.47,1.37) | 0.42 |
| [C]Third generation fluoroquinolones | 1.10 (0.68,1.76) | 0.70 |
| **II)** HIV-infected patients (n=132) | | |
| Weight <50kg at admission | 1.86 (1.13,3.08) | 0.02 |
| Gender (male) | 0.72 (0.43,1.20) | 0.21 |
| Number of anti-TB drugs received | 0.86 (0.66,1.12) | 0.26 |
| [D]Any aminoglycoside | 0.05 (0.00,0.58) | 0.02 |
| On ARV treatment | 1.29 (0.49,3.38) | 0.6 |
| [E]CD4 count <200 cell/µl | 1.53 (0.92,2.54) | 0.11 |
| [B]Bedaquiline | 0.01 (0.00,0.16) | <0.001 |
| Clofazamine | 0.63 (0.3,1.33) | 0.23 |
| Kanamycin | 1.50 (0.88,2.55) | 0.14 |
| Previous TB treatment | 1.21 (0.61,2.38) | 0.58 |

A) One patient refused testing; B) 53 of the 68 (77.9%) patients who received bedaquiline also received linezolid; C) 3rd generation fluoroquinolones = moxifloxacin and levofloxacin; D) Any aminoglycoside = amikacin, capreomycin and kanamycin. E) 2 patients did not have CD4 count done at admission (n=132).

**Secondary analyses using treatment outcome (rather than survival) as the dependant outcome variable, mirroring the analyses shown in the main manuscript.**

Definitions

Favourable outcome = cured or completed treatment.

Unfavourable outcome = treatment failed, lost to follow-up, defaulted, died.

Table S6: Univariate Cox proportional hazard model for risk of unfavourable treatment outcome for all the XDR-TB patients (n=270).

| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| Age at XDR-TB diagnosis (years) | 1.00 (0.99,1.02) | 0.51 |
| Weight <50 | 1.47 (1.11,1.95) | 0.01 |
| Duration of TB treatment (days) | 0.98 (0.98,0.98) | <0.001 |
| Gender (male) | 1.05 (0.79,1.39) | 0.74 |
| Median number of days of admission | 1.00 (1.00,1.00) | 0.02 |
| Median number of anti-TB drugs received | 0.94 (0.86,1.03) | 0.21 |
| *HIV Infected | 1.07 (0.80,1.41) | 0.66 |
| Previous TB treatment | 1.41 (0.99,2.00) | 0.06 |
| Amikacin | 2.06 (0.51,8.33) | 0.31 |
| Capreomycin | 2.57 (1.70,3.86) | <0.001 |
| Kanamycin | 1.59 (1.20,2.11) | <0.001 |
| [a]Any aminoglycoside | 3.15 (1.97,5.02) | <0.001 |
| PAS | 0.40 (0.22,0.73) | 0.003 |
| Moxifloxacin | 0.96 (0.72,1.27) | 0.76 |
| Levofloxacin | 0.32 (0.20,0.49) | <0.001 |
| [b]Third generation quinolones | 0.58 (0.44,0.77) | <0.001 |
| Clofazimine | 0.49 (0.37,0.66) | <0.001 |
| Linezolid | 0.30 (0.18,0.51) | <0.001 |
| Bedaquiline | 0.31 (0.20,0.48) | <0.001 |
| Ethionamide | 2.96 (1.87,4.66) | <0.001 |
| Amoxycillin | 1.15 (0.66,2.03) | 0.62 |

*one patient refused HIV testing, n=269; [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S7: Univariate Cox proportional hazard model for risk of unfavourable treatment outcome in HIV-infected patients from both groups (n=133).

| **Variable** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| Age at XDR-TB diagnosis (Years) | 1.00 (0.97,1.02) | 0.79 |
| Gender (Male) | 1.00 (0.66,1.51) | 0.99 |
| Weight <50kg at admission | 1.75 (1.15,2.66) | 0.008 |
| Previous TB treatment | 1.34 (0.78,2.30) | 0.30 |
| On ARV treatment | 0.94 (0.41,2.20) | 0.89 |
| *Median CD4 count <200 cells/µl at admission | 1.10 (0.72,1.67) | 0.66 |
| Median number of anti-TB drugs received | 0.91 (0.78,1.07) | 0.24 |
| Median number of days of admission | 1.00 (1.00,1.00) | <0.001 |
| Median duration of TB treatment (in days) | 0.98 (0.97,0.98) | <0.001 |
| Bedaquiline | 0.30 (0.16,0.57) | <0.001 |
| Clofazimine | 0.38 (0.25,0.59) | <0.001 |
| Linezolid | 0.28 (0.14,0.57) | <0.001 |
| Capreomycin | 2.42 (1.36,4.31) | <0.001 |
| Kanamycin | 1.94 (1.27,2.96) | <0.001 |
| Amikacin | 1.47 (0.20,10.63) | 0.70 |
| [a]Any aminoglycoside | 2.85 (1.54,5.26) | <0.001 |
| Levofloxacin | 0.32 (0.17,0.60) | <0.001 |
| Moxifloxacin | 1.02 (0.67,1.54) | 0.93 |
| [b]3rd Generation fluoroquinolones | 0.54 (0.35,0.83) | 0.004 |
| PAS | 0.35 (0.15,0.80) | 0.01 |
| Ethionamide | 3.18 (1.64,6.17) | <0.001 |
| Amoxycillin | 1.68 (0.61,4.61) | 0.31 |

*2 patients did not have CD4 count done at admission (n=131); [a]amikacin, capreomycin and/or kanamycin; [b]moxifloxacin or levofloxacin.

Table S8: Multivariate Cox proportional hazard model for risk of unfavourable treatment outcome in both groups A) all the XDR-TB patients (n=271), B) HIV-infected patients in the (n=132).

| **Variables** | **Hazard ratio (95% C.I.)** | **p-value** |
|---|---|---|
| **I)** All the XDR-TB patients (n=271) | | |
| Weight <50kg at admission | 1.72 (1.27,2.33) | <0.001 |
| Gender (male) | 1.19 (0.88,1.60) | 0.26 |
| [A]HIV-infected | 1.25 (0.92,1.70) | 0.15 |
| Previous TB treatment | 1.05 (0.72,1.52) | 0.81 |
| Number of anti-TB drugs received | 0.85 (0.76,0.96) | 0.01 |
| [B]Bedaquiline | 0.24 (0.14,0.42) | <0.001 |
| Clofazamine | 0.92 (0.58,1.46) | 0.74 |
| [C]Third generation fluoroquinolones | 1.13 (0.74,1.73) | 0.57 |
| **II)** HIV-infected patients (n=132) | | |
| Weight <50kg at admission | 2.21 (1.39,3.51) | <0.001 |
| Gender (male) | 0.83 (0.52,1.33) | 0.44 |
| Number of anti-TB drugs received | 0.8 (0.63,1.01) | 0.06 |
| [D]Any aminoglycoside | 0.04 (0.00,0.45) | 0.008 |
| On ARV treatment | 1.59 (0.61,4.14) | 0.34 |
| [E]CD4 count <200 cell/µl | 1.37 (0.87,2.17) | 0.17 |
| [B]Bedaquiline | 0.01 (0.00,0.12) | <0.001 |
| Clofazamine | 0.84 (0.44,1.63) | 0.61 |
| Kanamycin | 1.24 (0.75,2.05) | 0.41 |
| Previous TB treatment | 1.26 (0.69,2.31) | 0.46 |

*one patient refused testing; **2 patients did not have CD4 count done at admission (n=132).

Table S9: Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of culture negativity at specific time points to predict A) survival and B) favourable treatment outcome for all patients.

| **A) Survival as dependant variable** | | | | | |
|---|---|---|---|---|---|
| Month | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Number of patients considered |
| 2 | 77.8 | 70.5 | 56 | 86.8 | 166 |
| 3 | 86.4 | 64 | 53.1 | 90.9 | 184 |
| 6 | 98 | 65.7 | 58.5 | 98.5 | 148 |
| 12 | 97.3 | 71.4 | 69.2 | 97.6 | 93 |
| 18 | 97.4 | 62.5 | 80.9 | 93.8 | 63 |
| 24 | 100 | 71.4 | 76.5 | 100 | 27 |
| **B) Favourable treatment outcome as dependant variable** | | | | | |
| 2 | 66.3 | 74.4 | 70.7 | 70.3 | 166 |
| 3 | 78.6 | 77.9 | 80.2 | 76.1 | 184 |
| 6 | 88.5 | 81.4 | 84.1 | 86.4 | 148 |
| 12 | 83.6 | 84.2 | 88.5 | 78 | 93 |
| 18 | 87.8 | 71.4 | 91.5 | 62.5 | 63 |
| 24 | 78.9 | 75 | 88.2 | 60 | 27 |

Table S10: Comparisons of treatment outcomes (A) and survival (B) between the Bdq and non-Bdq treatment groups with patients who died within the first two months following diagnosis excluded.The results show that our conclusions remain unchanged.

| **A) Comparison of Bdq and non-Bdq treatment groups by outcomes** | | | |
|---|---|---|---|
| Variable | BDQ (n=62) | nonBDQ (n=172) | p value |
| Favourable (cured/completed treatment) | 45 (73%) | 27 (15%) | <0.001 |
| Unfavourable outcome (treatment failed, deceased) | 17 (27%) | 151 (85%) | |
| **B) Comparison of Bdq and non-Bdq treatment groups by survival** | | | |
| Variable | BDQ (n=62) | nonBDQ (n=180) | p value |
| Alive | 58 (94%) | 65 (36%) | <0.001 |
| Deceased | 4 (6%) | 115 (63%) | |

**Reference**

1. Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, Andersen J, Davies G, Dheda K, Diacon A *et al*: **Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults**. *Int J Tuberc Lung Dis* 2016, **20**(3):290-294.

2. WHO: **Definitions and reporting framework for tuberculosis,– 2013 revision (updated December 2014)**. 2013.