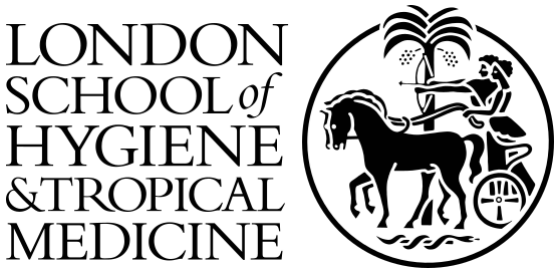

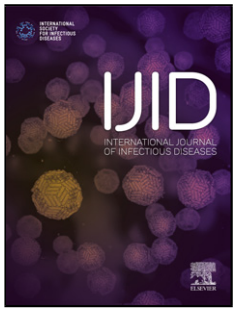

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PII: S1201-9712(19)30199-7
DOI: https://doi.org/10.1016/j.ijid.2019.04.028
Reference: IJID 3599

To appear in: *International Journal of Infectious Diseases*

Received date: 21 March 2019
Revised date: 25 April 2019
Accepted date: 26 April 2019

Please cite this article as: Olayanju O, Esmail A, Limberis J, Gina P, Dheda K, LINEZOLID INTERRUPTION IN PATIENTS WITH FLUOROQUINOLONE-RESISTANT TUBERCULOSIS RECEIVING A BEDAQUILINE-BASED TREATMENT REGIMEN, *International Journal of Infectious Diseases* (2019), https://doi.org/10.1016/j.ijid.2019.04.028

LINEZOLID INTERRUPTION IN PATIENTS WITH FLUOROQUINOLONE-RESISTANT TUBERCULOSIS RECEIVING A BEDAQUILINE-BASED TREATMENT REGIMEN

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Highlights:

- Linezolid interruption occurred in one-third of patients on bedaquiline therapy
- Anaemia and peripheral neuropathy are the most commonly reported adverse events
- System-specific toxicities occurred at predictable time frames following treatment
- HIV co-infection and high bacteria load predispose to linezolid interruption
- Linezolid interruption does not predispose to having unfavourable treatment outcome

Abstract

Background

Treatment outcomes of extensively drug-resistant tuberculosis (XDR-TB) patients are sub-optimal and treatment options remain limited. Linezolid is associated with improved outcomes but also substantial toxicity, and details about the relationship between these are lacking from resource-poor HIV-endemic settings.

Methods

We prospectively followed up 63 South African XDR-TB patients (58.7% HIV-infected; median CD4 131 cells/µl) between 2014 and 2018. The frequency and severity of linezolid-associated adverse events and the impact on treatment outcomes were compared between linezolid interrupters and non-interrupters.

Results

Twenty-two patients (34.9%) discontinued or underwent dose reduction due to presumed linezolid-associated toxicity. Anaemia (77.3% *versus* 7.3%; p<0.001), peripheral neuropathy (63.6% *versus* 14.6%; p=0.003), and optic neuritis (18.2% *versus* 9.8%; p=0.34) occurred more frequently in linezolid interrupters than in non-interrupters. Anaemia, peripheral neuropathy, and optic neuritis occurred at a median of 5, 18 and 23 weeks, respectively, after treatment initiation. Linezolid interruption was not associated with unfavourable outcomes but was strongly associated with HIV co-infection (aHR 4.831 (1.526- 15.297); p=0.007) and bacterial load (culture days to positivity; aHR=0.824 (0.732- 0.927); p=0.001).

Conclusion

Linezolid-related treatment interruption is common, is strongly associated with HIV co-infection, and system-specific toxicity occurs within predictable time frames. These data inform the clinical management of patients with drug resistant TB.

Keywords: Drug-resistant tuberculosis, Linezolid, Bedaquiline, Outcome, Treatment interruption

Introduction

The increasing prevalence of multidrug resistant tuberculosis (XDR-TB) has become a serious public health problem (Dheda et al., 2017). MDR-TB is defined as *M. tuberculosis* resistant to isoniazid and rifampicin, the two most important TB drugs. Treatment outcomes for MDR-TB are poor and treatment options are limited. . Extensively drug resistant (XDR-TB) is defined as MDR-TB with further resistant to a fluoroquinolone and a second line injectable drug. Although injectables are no longer frontline treatment for MDR-TB, in this manuscript we have retained the term XDR-TB and it was the definition used for the duration of the study.Linezolid, usually together with bedaquiline, is now widely used to treat XDR-TB and fluoroquinolone-resistant TB and is associated with improved culture conversion and survival (Borisov et al., 2017; Guglielmetti et al., 2017; Myungsun Lee et al., 2012; Olayanju et al., 2018; Sotgiu et al., 2012; Tang et al., 2015). However, linezolid has substantial toxicity and is associated with significant myelosuppression, peripheral neuropathy and optic neuropathy (Cox & Ford, 2012; Myungsun Lee et al., 2012; Sotgiu et al., 2012). Thus, toxicity often leads to interruption of linezolid (stopping the drug for a variable period of time or reducing the dose) in 30 to 60% of patients (Cox & Ford, 2012; M. Lee et al., 2012).

However, details about the specific relationship between the duration of linezolid treatment and system-specific toxicity, impact of treatment interruption on outcomes, and effect of HIV co-infection are lacking. Moreover, there are very limited data about linezolid toxicity from TB and HIV endemic settings. To address this knowledge gap, we determined the frequency of linezolid-associated toxicity, the temporal relationship between linezolid initiation and system-specific drug toxicity, and the effect of linezolid interruption (dose reduction or discontinuation) on treatment outcomes of XDR-TB patients receiving a bedaquiline-based regimen.

Methods

Participants

We prospectively followed up 63 patients with culture-confirmed XDR-TB between April 2014 and April 2018. All patients received a bedaquiline-based treatment regimen containing linezolid as one of the major components. The patients were admitted to Brooklyn Chest Hospital, Cape Town, the XDR-TB treatment centre in the Western Cape province of South Africa. Patients' treatment was directly observed by trained health care workers during hospitalisation and after discharge to outpatient treatment centres. Data were captured by a trained researcher; relevant information obtained included demographics, clinical details, medications received and adverse events. Patients were classified as linezolid interrupters (dose reduction or discontinuation) or non-interrupters, and we performed a comparative analysis of linezolid interrupters and non-interrupters to expressly interrogate whether this interruption adversely impact outcomes, and its potential association with HIV co-infection. Ethical approval was obtained from University of Cape Town human research ethics committee.

Diagnosis and medications received

All the patients had culture isolates with *M. tuberculosis* strains resistant to isoniazid, rifampicin, ofloxacin and a second line injectable anti-TB drug, and met XDR-TB diagnosis criteria (WHO, 2006). They all received a treatment regimen based on a backbone of Linezolid and bedaquiline. Linezolid was administered at 600mg daily for one year and bedaquiline at 400mg daily for two weeks, and then 200mg three times weekly for 22 weeks. The other drugs common to most of the patients were clofazimine, levofloxacin, pyrazinamide (PZA) and para-amino salicylic acid (PAS).

Adverse events profiling

Adverse events were actively reported by trained health care workers using a standardised case report form and were graded according to the modified American National Institute of Health Common Terminology of Criteria for Adverse Events. Grades 0 means no adverse events; grade 1 means mild adverse event, requiring no intervention; grade 2 means 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 means severe adverse event, enough to stop the offending drug; grade 4 means life threatening or disabling adverse event; grade 5 means death resulting from the adverse event (Trotti et al., 2003).

Outcomes

Treatment outcomes were assigned according to an adapted version of the 2013 world health organisation definitions and reporting frameworks for TB and, the core research definitions for drug-resistant TB clinical trials recommended by Furin *et al* (Furin et al., 2016; WHO, 2013). Patients were said to have achieved a favourable outcome if they were cured or completed treatment; other treatment outcomes: deceased, lost to follow-up and treatment failure, were considered to be unfavourable.

Statistical analysis

The effect of linezolid interruption was determined by comparative analysis of demographics, clinical characteristics and treatment outcomes. Qualitative and quantitative variables were reported in percentages and median (interquartile range; IQR). Quantitative and qualitative variables were compared using Mann-Whitney U and chi-square or Fisher's exact tests respectively. Univariate cox proportional hazard model was used to estimate the relationship between independent variables (demographic and clinical characteristics), and selected outcome variables (mortality, the development of linezolid associated adverse events, linezolid interruption, culture conversion and unfavourable outcome). Multivariate models

included variables that were significantly associated with outcomes and pre-selected variables. A p-value of <0.05 was taken as statistically significant. Kaplan-Meier curves for the probability of survival was estimated considering the duration between the day of treatment initiation and follow-up censor date. Comparison between strata (HIV-infected vs HIV non-infected, linezolid treatment greater than three months vs linezolid treatment less than three months) was made using log-rank test. Statistical analysis was done using SPSS (Version 25).

Results

Demographic and clinical characteristics

Sixty-three XDR-TB patients met the diagnostic requirements for this study. Demographic and clinical characteristics are reported in Table 1. The median age at admission was 37 (IQR 30-44) years, and 39 (61.9%) were males. Median weight at admission was 51.8 (IQR 46.0-58.6) kg and patients were on admission for a median of 155 (IQR 102-214) days. 37 (58.7%) patients were HIV-infected, the median CD4 count was 131 (56-257) cells/µl at admission, and all were on antiretroviral therapy. Patients received a median of 8 (7-8) anti-TB drugs with linezolid and bedaquiline being the major components. Drugs used in the regimen are outlined in Table 2. Linezolid interruption due to adverse events occurred in 22 (34.9%) patients during the course of treatment while the remaining 41 (65.1%) completed one year of uninterrupted linezolid therapy. Of the 22 patients who had linezolid interruption, 10 had dosage reduction from 600mg to 300mg daily, while 12 had linezolid discontinued.

Adverse events

A total of 208 adverse events were reported by 57 (90.5%) patients; a median of 3 (IQR 2-5) adverse events were reported in the whole cohort. 33 (52.4%), 45 (71.4%) and 36 (57.1%)

patients reported grade 1, grade 2 and grade 3 adverse events, respectively. No patients had life-threatening adverse events or died from them. Anaemia (31.7%), peripheral neuropathy (31.7%) and body pains (27%) were the most commonly reported adverse events in the whole cohort. Comparison of adverse events between linezolid interrupters and non-interrupters are outlined in Table 3. Anaemia, peripheral neuropathy and optic neuritis developed a median of 5 (IQR 4-10) weeks, 18 (IQR 11-24) weeks and 23 (IQR 21-26) weeks, after linezolid treatment initiation (Online supplement figure S1). In patients who developed anaemia (haemoglobin level< 10g/dl), 62.5% and 87.5% of them had it within eight and twelve weeks of treatment initiation, respectively, with a median of 26.1% (IQR 10.4-36.1) drop in baseline haemoglobin by 12 weeks of treatment. Table 4 shows the cumulative number of patients that developed adverse events with treatment progression. Anaemia ($p<0.001$) and peripheral neuropathy ($p=0.003$) occurred more frequently in linezolid interrupters. Two of these patients received blood transfusion, and two others had nutritional support.

Although we observed no difference in the proportion of HIV-infected patients (89.2%) who reported at least one adverse event compared to the non-infected patients (88.5%), there were more cases of linezolid interruption in HIV-infected patients (40.5%) compared to the non-infected patients (26.9%). Kaplan-Meier estimate also suggested that HIV-infected patients are more likely to have linezolid interruption within 18 months of treatment ($p=0.005$; Figure 1).

Multivariate analysis showed that duration of linezolid treatment is an independent predictor of linezolid interruption in the whole cohort (HR=0.993; $p<0.001$). It also suggested that HIV-infected patients (HR=4.831; $p=0.007$), and patients with higher bacteria load (culture days to positivity; HR=0.824; $p=0.001$) had higher probability of linezolid interruption (Table 5). Kaplan-Meier survival estimate showed no difference in the probability of unfavourable outcome between linezolid interrupters and non-interrupters ($p=0.59$; Online supplementary

Figure S2), it also showed that patients who received linezolid for greater than three months are more likely to survive ($p<0.001$; Figure 2).

Discussion

This is the first prospective study on probable linezolid associated adverse events in XDR-TB patients from a TB/HIV endemic country. Our major findings were that linezolid interruption is common; the adverse events causing linezolid interruption occur at "predictable" time-points; HIV co-infection and bacterial burden are associated with linezolid interruption and linezolid interruption does not affect treatment outcomes.

Our study established that the use of linezolid in treatment regimen for XDR-TB, as recommended by the WHO is associated with several adverse events, especially peripheral neuropathy and anaemia; this is similar to findings from other studies(Agyeman & Ofori-Asenso, 2016; Park et al., 2006; Zhang et al., 2015). Over one third of patients had linezolid interruption in their treatment regimen following the development of an adverse event. Adverse events that were likely due to linezolid toxicity occurred within predictable time frames. The predictability of these events can inform patient care and guide physicians and health care workers in patients management, possibly informing dose adjustment at critical time points in a bid to prevent the occurrence or severity of adverse events.

Several methods to reduce linezolid associated adverse events have been proposed. Deliberate reduction in linezolid dosage at specific times in the course of treatment, when adverse events are known to develop may mitigate or outrightly prevent the occurrence of such adverse events (Anger et al., 2010; Zhang et al., 2015). A shorter treatment regimen has also been proposed , following the preparation of suitable protocol, approval by national ethics committee and delivery under WHO recommended standards(WHO, 2018). This was

corroborated by a study suggesting that linezolid cumulative dose and days of exposure play an important role in the development of adverse event (Bolhuis et al., 2015). Therapeutic drug monitoring has been suggested for patients on long-term linezolid treatment, but the cost and the rigours involved make it less feasible; a limited sampling strategy which is cheaper, less time consuming and more feasible has been proposed to individualise linezolid dosing(Alffenaar et al., 2010; Kamp et al., 2017). Recently, a linezolid related adverse events predictive score (LAPS) was developed as a tool for clinicians to assess pre-therapeutic risk of patients to developing those adverse events(Buzelé et al., 2015). LAPS entails assigning scores for certain selected clinical risk factors in patients and grading the summation to predict the development of linezolid associated adverse events.

Yet the effect of linezolid interruption on treatment outcomes remains unclear and has rarely been described in HIV-infected XDR-TB patients from endemic countries. In this study, we explored the relationship between HIV infection and linezolid interruption in patients with drug resistant tuberculosis. We found that HIV co-infection contributed significantly to the occurrence of linezolid interruption. This is in keeping with numerous studies that show higher adverse event rates and consequent drug withdrawal in HIV-infected compared to the un-infected patients (Breen et al., 2006; Mehta et al., 2008; O.S. Michael, 2016). HIV infection also contributed to the development of unfavourable outcome, in this study.

Time to sputum culture positivity in patients has been used over the years as a proxy for disease severity(Dominguez-Castellano et al., 2003; Güler, Ünsal, Dursun, AydIn, & Capan, 2007). In this study, it correlatedsignificantly with linezolid interruption and this may be an indication that patients who are more sick at the commencement of therapy are more likely to have treatment interruption. Attending physician may be required to monitor them more closely and make individualised dosage plan for such patients.

There were a few limitations to this study. All the patients in this study were hospitalised in the designated treatment centre during the course of treatment, thus, selection bias might have affected the findings. However, the programmatic policy at the centre requires all patients to be hospitalised at least in the intensive phase of therapy. Given the small sample size, the study may not have been sufficiently powered to detect the differences between patients who had linezolid interruption and those who did not. This however is arguably one of the linezolid original studies available with the highest number of participants. This study was conducted in a TB/ HIV endemic setting with a very high enrolment on antiretroviral (ARV) therapy; findings may be different in countries with low HIV prevalence or those with low ARV coverage.

In conclusion, linezolid associated system-specific toxicity occurs within predictable time frames and it is commonly associated with treatment interruption This prospective study from a TB endemic country demonstrates that linezolid interruption does not negatively impact treatment outcomes though larger studies are needed to confirm this finding. . These data inform the use of linezolid for DR-TB treatment in TB endemic countries.

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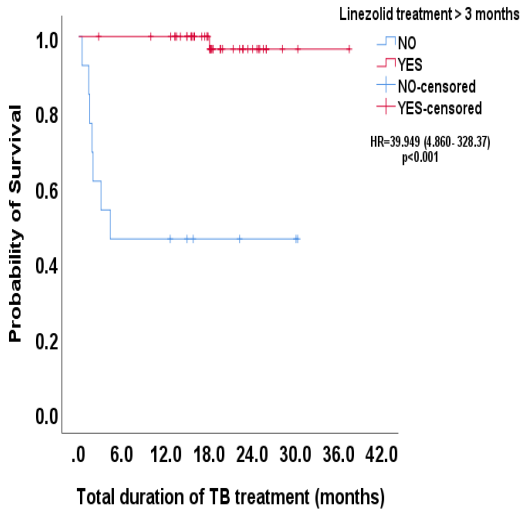

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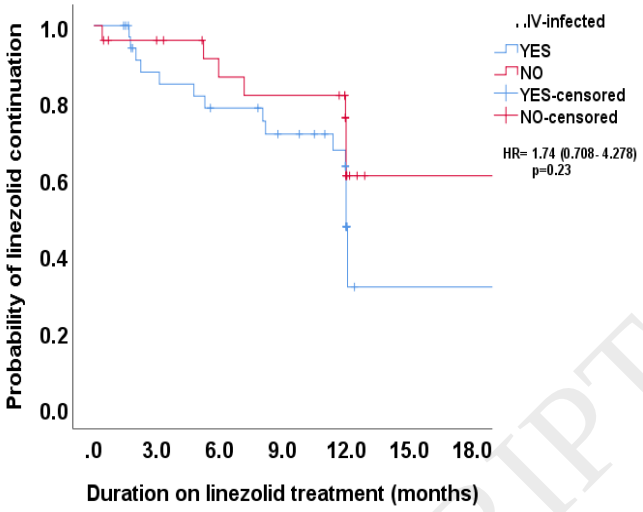

Number at risk

YES	50	50	50	30	12	2	1		1
NO	13	6	6	3	2	2	0		0

Number at risk

YES	15	11	8	6	4	0	0
NO	7	6	4	3	2	0	0

Figure 1 (A): Kaplan-Meier survival estimate for patients who received linezolid for more than 3 months in their treatment regimen and (B) for the probability of linezolid continuation in HIV-infected patient during an 18 months treatment period.

Table 1: Demographic, clinical characteristics and treatment outcomes of XDR-TB patients treated with a linezolid-and bedaquiline-based regimen. Data are reflected as number of persons (%) unless otherwise stated.

Variables	**Patients without linezolid interruption (n=41)**	**Patients with linezolid interruption (dose reduction or discontinuation; n=22)**	**p-values**
Gender (Male)	27 (65.9)	12 (54.5)	0.38
Weight (kg)	53.7(IQR 46.5-60.8)	48.7 (IQR 42.9-54.8)	0.17
Age (years)	36 (IQR 29-44)	38 (IQR 31.5-46.3)	0.36
Admission duration (days)	155 (IQR 106-222)	155 (IQR 107-210)	0.71
Duration of linezolid treatment (days)	365 (IQR 181-366)	231.5 (IQR 151-366)	<0.001
HIV-infected	22 (53.7)	15 (68.2)	0.27
CD4 Count/µl	169 (IQR 55-252)	127 (IQR 56-257)	0.37
Patients with previous TB treatment	21 (51.2)	11 (50)	0.93
Number of anti-TB drugs	8 (7-8)	7 (7-8)	0.31
Favourable outcome (Cured/Completed treatment)	30 (73.2)	15 (68.2)	0.68
Unfavourable outcomes	11 (26.8)	7 (31.8)	

Table 2: Drugs used in the treatment regimens and the number (%) of patients who received them stratified by linezolid interruption

Drug	**Patients without linezolid interruption (n=41)**	**Patients with linezolid interruption (dose reduction or discontinuation; n=22)**	**p-values**
Linezolid	41 (100)	22 (100)	*N/A
Bedaquiline	41 (100)	22 (100)	*N/A
Clofazimine	40 (97.6)	22 (100)	0.46
Ethambutol	15 (36.6)	4 (18.2)	0.13
Ethionamide	11 (26.8)	3 (13.6)	0.23
Isoniazid	12 (29.3)	8 (36.4)	0.56
Levofloxacin	40 (97.6)	21 (95.5)	0.65
Para-aminosalicylic acid	39 (95.1)	21 (95.5)	0.95
Pyrazinamide	40 (97.6)	21 (95.5)	0.65
Terizidone	39 (95.1)	20 (90.9)	0.51
Moxifloxacin	8 (19.5)	2 (9.1)	0.28
Delamanid	5 (12.2)	3 (13.6)	0.87

*N/A= Not applicable

Table 3: Number (%) of patients experiencing adverse events depending on linezolid interruption.

Variables	**Patients without linezolid interruption (n=41)**	**Patients with linezolid interruption (dose reduction or discontinuation; n=22)**	**p-values**
Peripheral neuropathy	6 (14.6)	14 (63.6)	0.003
Anaemia	3 (7.3)	17 (77.3)	<0.001
Arthralgia	6 (14.6)	5 (22.7)	0.42
Skin reaction	8 (19.5)	8 (36.4)	0.14
Body pains	11 (26.8)	6 (27.3)	0.97
Optic neuritis	4 (9.8)	4 (18.2)	0.34
Dizziness	5 (12.2)	5 (22.7)	0.28
Dyspepsia	2 (4.9)	1 (4.5)	0.95
Nausea	4 (9.8)	5 (22.7)	0.16
Vomiting	7 (17.1)	5 (22.7)	0.59
Epigastric pain	6 (14.6)	5 (22.7)	0.42
Diarrhoea	4 (9.8)	2 (9.1)	0.93
Thyroid dysfunction	3 (7.3)	4 (18.2)	0.19
Psychosis	3 (7.3)	2 (9.1)	0.81

Table 4: Cumulative number (%) of patients that experienced an adverse event (types) with increased treatment duration.

Treatment Duration	**Patients that developed any adverse event (n=22)**	**Patients that developed anaemia (n=16)**	**Patients that developed peripheral neuropathy (n=13)**	**Patients that developed optic neuritis (n=4)**
1 Month	5 (22.7)	5 (31.3)	0 (0)	0 (0)
2 Months	10 (45.5)	10 (62.5)	2 (15.4)	0 (0)
3 Months	15 (68.2)	14 (87.5)	6 (46.2)	0 (0)
4 Months	17 (77.3)	16 (100)	6 (46.2)	0 (0)
5 Months	18 (81.8)	16 (100)	7 (53.8)	1 (25)
6 Months	21 (95.5)	16 (100)	10 (76.9)	3 (75)
9 months	22 (100)	16 (100)	12 (92.3)	4 (100)

Table 5: Univariate and multivariate cox proportional hazard model interrogating factors associated with unfavourable outcome and linezolid interruption.

	Unfavourable outcome (n=18)		Linezolid interruption (n=22)	
Univariate analysis				
Variable	Hazard Ratio (95% C.I.)	p-value	Hazard Ratio (95% C.I.)	p-value
Weight(kg)	0.977 (0.934-1.023)	0.32	0.973 (0.933-1.013)	0.19
Gender (male)	2.655 (1.024-6.889)	0.05	1.790 (0.758-4.229)	0.18
Days hospitalized	0.990 (0.982-0.997)	0.008	0.998(0.994-1.002)	0.38
HIV-infected	1.763 (0.647-4.806)	0.27	1.901 (0.768- 4.779)	0.17
Age (years)	1.011 (0.964-1.060)	0.65	1.025 (0.981-1.071)	0.28
Previous tuberculosis treatment	1.170 (0.706-2.109)	0.51	1.096 (0.719-1.671)	0.67
Levofloxacin/Moxifloxacin treatment	0.045 (0.00- 1266)	0.55	1.162 (0.151- 8.908)	0.89
PZA treatment	3.715 (0.455-30.357)	0.666	2.143 (0.283-16.261)	0.46
Number of TB drugs	0.975 (0.637-1.492)	0.91	0.898 (0.591-1.366)	0.62
Smear grade (baseline)	2.064 (0.902-4.722)	0.09	1.287 (0.762- 2.173)	0.35
[#]Time to culture positivity in days	0.954 (0.890-1.023)	0.19	0.886 (0.818- 0.961)	0.003
Duration on linezolid (days)	0.995 (0.992-0.998)	0.03	0.997 (0.994-1.000)	0.02
Multivariate analysis				
Weight (kg)	1.015 (0.967-1.066)	0.55	0.975 (0.929- 1.024)	0.32
Gender (male)	1.411 (0.473-4.207)	0.54	1.469 (0.513- 4.210)	0.47
Duration on linezolid	0.996 (0.991-1.000)	0.05	0.993 (0.989- 0.997)	<0.001
HIV-infected	2.211 (0.645-7.575)	0.21	4.831 (1.526- 15.297)	0.007
Days hospitalized	0.996 (0.987-1.005)	0.36	N/A*	N/A*
Linezolid interruption	0.981 (0.351-2.744)	0.97	N/A*	N/A*
[#]Time to culture positivity in days	N/A*	N/A*	0.824 (0.732- 0.927)	0.001
Age	N/A*	N/A*	1.093 (1.030- 1.160)	0.003

N/A*=Not applicable, [#]Baseline sputum sample was used