

SUPPORTING INFORMATION

Variation in missed doses and reasons for discontinuation of anti-tuberculosis drugs during hospital treatment for drug-resistant tuberculosis in South Africa

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Data Files (See separate .csv files):

- Supplement for Publication – General study data.csv
- Supplement for Publication – Medication count data.csv
- Supplement for Publication – Completion per Hospitalization.csv
- Supplement for Publication – Hospitalization data.csv
- Supplement for Publication – PAS model.csv
- Supplement for Publication – Reason for discontinuation.csv

S1 Table. Standardized Treatment Regimens. Recommended standardized regimens during study period, including duration, for treatment of MDR-TB and XDR-TB according to South African Department of Health policy guidelines, 2011. Patients with previous exposure to second-line anti-tuberculosis drugs required individualized treatment regimens. Drugs that differ between MDR-TB and XDR-TB treatment regimens are bolded.

Treatment phase	Duration	Drugs included in treatment regimen	
		MDR-TB regimen	XDR-TB regimen
Intensive phase	6 months	Kanamycin or Amikacin Moxifloxacin Ethionamide Terizidone Pyrazinamide	Capreomycin Moxifloxacin Ethionamide Terizidone Pyrazinamide PAS Clofazimine
Continuation phase	≥18 months after TB culture conversion	Moxifloxacin Ethionamide Terizidone Pyrazinamide	Moxifloxacin Ethionamide Terizidone Pyrazinamide PAS Clofazimine
Additional second-line drugs to consider		Ethambutol Levofloxacin Prothionamide Cycloserine Clofazimine Amoxicillin-clavulanate Clarithromycin Azithromycin Linezolid Thioacetazone Imipenem Isoniazid (high dose)	
Other drugs post 2011 Guidelines		Bedaquiline Delamanid Pretomanid	

S2 Table. Comparison of hospital-based doses received of anti-tuberculosis drugs based on primary analysis and a sensitivity analysis in which we added the remainder of the intended treatment duration to the doses prescribed for drugs that were discontinued due to adverse events.

Drugs included in treatment regimen ^a	All Regimens			Sensitivity Analysis		
	Total doses received (n)	Total doses prescribed (n)	Total Doses received (%)	Total doses received (n)	Total doses prescribed (n)	Total Doses received (%)
Amikacin	606	739	82	606	986	61.5
Capreomycin	33,320	40,521	82.2	33,320	44,120	75.5
PAS	94,308	113,618	83	94,308	114,294	82.5
Kanamycin	11,211	13,370	83.9	11,211	14,719	76.2
Rifampicin	87	99	87.9	87	99	87.9
Augmentin	22,973	25,868	88.8	22,973	26,042	88.2
Clarithromycin	16,648	18,615	89.4	16,648	18,749	88.8
Streptomycin ^a	194	216	89.8	194	216	89.8
Amoxicillin	14,318	15,922	89.9	14,318	15,922	89.9
Azithromycin	489	538	90.9	489	538	90.9
Dapsone	6,242	6,806	91.7	6,242	7,540	82.8
Ethionamide	58,396	63,271	92.3	58,396	66,990	87.2
Ofloxacin	34,190	36,979	92.5	34,190	37,036	92.3
Clofazimine	22,706	24,508	92.6	22,706	24,702	91.9
Isoniazid ^b	30,609	33,033	92.7	30,609	34,073	89.8
Ethambutol	55,522	59,635	93.1	55,522	61,534	93
Terizidone	65,253	70,101	93.1	65,253	70,497	92.6
Moxifloxacin	32,687	35,055	93.2	32,687	35,132	93
Rifafour ^a	1,005	1,076	93.4	1,005	1,106	90.1
Pyrazinamide	69,908	74,706	93.6	69,908	75,604	92.5
Levofloxacin	1,315	1,402	93.8	1,315	1,402	93.8

Delamanid	185	192	96.4	185	192	96.4
Linezolid	517	531	97.4	517	531	97.4
Bedaquiline	350	339	103.2	350	339	103.2

^a Some treatment regimens included anti-TB drugs recommended for DS-TB or non-WHO recommended DR-TB drugs

^b Dose corresponding to high-dose isoniazid prescription

- 1 **S3 Table. Other Reasons for discontinuation of Drugs.** Expanded categories of “Other reasons” (Table 3, main paper) drug-
- 2 resistant tuberculosis patients discontinuation of anti-tuberculosis drugs while hospitalized

Drugs included in treatment regimen	Number of patients who received drug	Cumulative treatment duration (years)	Reasons for discontinuation of anti-TB drug (Number of events per year) ^{a, b}							
			Change of medication prescribed	Treatment continued after discharge	Course of treatment complete	Granted leave ^c	Transfer out	Treatment beyond censor date	Not Categorized ^d	Unknown
Amikacin	20	2.9	2.72	0	1.02	0	0.68	0	0	0.34
Amoxicillin	50	24.2	0	0.33	0.54	0.04	0.04	0	0.04	0.5
Augmentin	77	40.2	0	0.27	0.35	0.02	0.05	0	0.12	0.5
Azithromycin	1	1.6	0	0.62	0	0	0	0	0	0
Bedaquiline	21	6.8	0	1.17	0.88	0	0	0.15	0.15	0.15
Capreomycin	211	145.4	0.08	0.1	0.25	0.06	0.03	0	0.06	0.14
Clarithromycin	55	27.9	0	0.18	0.14	0	0.11	0	0.04	0.65
Clofazimine	114	74.8	0.04	0.43	0	0	0.01	0.03	0.07	0.09
Dapsone	40	19	0	0.47	0.05	0.05	0.05	0	0.11	0.42
Delamanid	3	1.2	0	0.81	1.63	0	0	0	0	0
Ethambutol	221	183.7	0.04	0.58	0.05	0.05	0.07	0	0.03	0.16
Ethionamide	234	191.6	0.05	0.67	0.03	0.03	0.07	0	0.04	0.09
Isoniazid	156	102	0.04	0.51	0.05	0.04	0.06	0.01	0.01	0.15
Kanamycin	137	47.1	0.62	0.93	0.3	0	0.13	0	0.02	0.04
Levofloxacin	15	4.9	1.01	1.01	0	0	0	0.4	0	0.2
Linezolid	18	6.1	0	1.81	0.33	0	0	0.16	0	0
Moxifloxacin	137	107.2	0.08	0.51	0.01	0.01	0.04	0	0.01	0.04
Ofloxacin	153	115.3	0.32	0.75	0	0.07	0.08	0	0.01	0.08

PAS	217	172.5	0.02	0.45	0.02	0.04	0.04	0.01	0.02	0.06
Pyrazinamide	238	230.8	0.02	0.62	0.02	0.03	0.06	0.01	0.02	0.05
Rifafour	6	1.9	1.61	1.07	1.07	0	0.54	0	0	0.54
Rifampicin	2	0.38	0	2.67	2.67	0	2.67	0	0	0
Streptomycin	2	0.61	0	3.29	0	0	0	0	1.65	0
Terizidone	235	213.3	0.02	0.58	0.005	0.04	0.04	0.005	0.02	0.02

3

4 ^a Columns are color scaled from lowest (white) to highest (red)

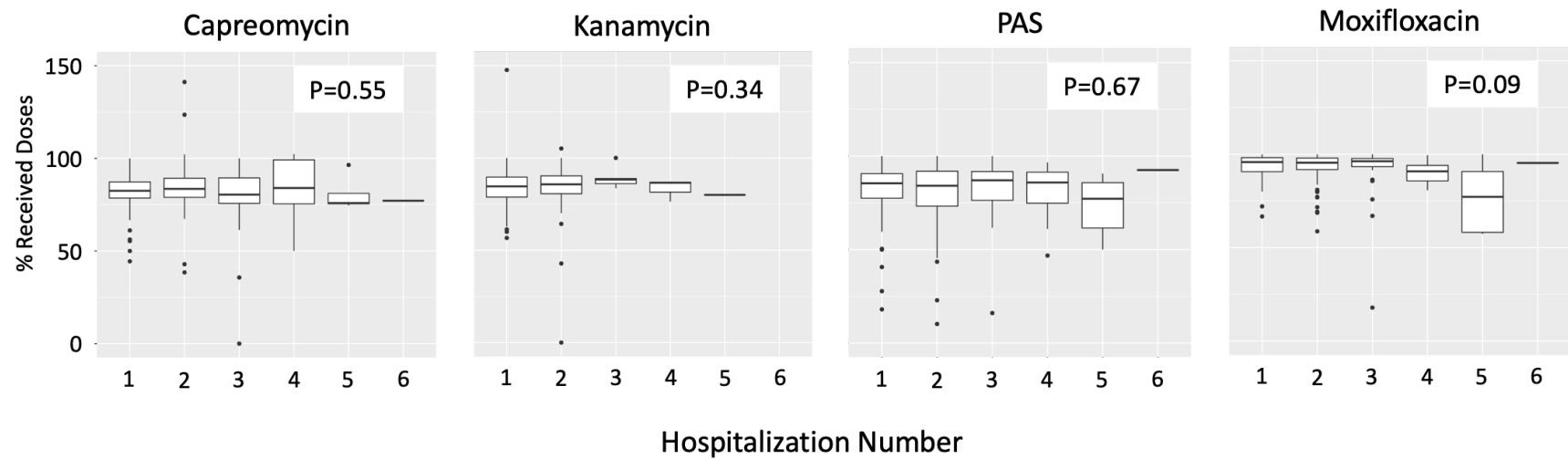
5 ^b Reasons for discontinuation of drugs were reported if patients received anti-TB drugs for ≥ 1 day. Reasons for same day prescription
6 and discontinuation of anti-TB drugs were not reported (e.g., adverse event, death, refusal of treatment).

7 ^c Usually 2 weekend days or 2 weeks during festive seasons, as authorized by a physician

8 ^d Not categorize

9 ^d included reasons not otherwise reported (e.g., pregnancy, erroneous administration, conflicting chart details).

10 **S1 Figure. Percent received doses of select anti-TB drugs per hospitalization.** Boxplot of percent doses received per
11 hospitalization of selected core anti-TB regimen drugs with highest overall percent missed doses: capreomycin, kanamycin, and PAS.
12 Moxifloxacin was the only drug with $P<0.25$. Amikacin had substantially fewer prescribed doses during study period.



13

Analysis Code:

Table 1 (STATA):

```
sum Ageatfirstadmission, detail
bysort HIVStatus: sum Ageatfirstadmission, detail
ranksum Ageatfirstadmission, by(HIVStatus)
tab Gender
tab Gender HIVStatus, col row mi chi2
tab race_mod
tab race_mod, nolabel
tab race_mod HIVStatus, col row mi chi2
tab Smokingever
tab Smokingever HIVStatus, col row mi chi2
tab smoke_ever_mod if smoke_ever_mod != 9
tab smoke_ever_mod HIVStatus if smoke_ever_mod != 9, col row mi chi2
tab AnySubstancesever
tab AnySubstancesever HIVStatus, col row mi chi2
tab subs_ever_mod if subs_ever_mod != 9
tab subs_ever_mod HIVStatus if subs_ever_mod != 9, col row mi chi2
sum Weightatfirstadmission, detail
bysort HIVStatus: sum Weightatfirstadmission, detail
ranksum Weightatfirstadmission, by(HIVStatus)
tab edu
tab edu HIVStatus, col row mi chi2
tab hiv_firstadm
tab OnARVsatfirstadmission
sum CD4at1stadm, detail
sum VLat1stadm, detail
```

```

sum VLat1stadm if VLat1stadm != 0, detail
tab CXRat1stadm
tab CXRat1stadm HIVStatus, col row chi2
sum CXRat1stadm if CXRat1stadm != ., detail
bysort HIVStatus: sum CXRat1stadm if CXRat1stadm != ., detail
ranksum CXRat1stadm, by(HIVStatus)
sum disease_scoreat1stadm, detail
bysort HIVStatus: sum disease_scoreat1stadm, detail
ranksum disease_scoreat1stadm, by(HIVStatus)
sum cavity_scoreat1stadm, detail
bysort HIVStatus: sum cavity_scoreat1stadm, detail
ranksum cavity_scoreat1stadm, by(HIVStatus)
tab PriorDSTB
tab PriorDSTB HIVStatus, col row chi2
sum hbat1stadm, detail
bysort HIVStatus: sum hbat1stadm, detail
ranksum hbat1stadm, by(HIVStatus)
sum creatineat1stadm, detail
bysort HIVStatus: sum creatineat1stadm, detail
ranksum creatineat1stadm, by(HIVStatus)
tab ChronicKidneydisease
tab ChronicKidneydisease HIVStatus, col row mi chi2
tab Diabetic
tab Diabetic HIVStatus, col row mi chi2
tab Psychiatricdisorder
tab Psychiatricdisorder HIVStatus, col row mi chi2
tab AdmissionsSingleMultiple
tab AdmissionsSingleMultiple HIVStatus, col row mi chi2

```

```

tab TBdxtat1stadm
tab TBdxtat1stadm HIVStatus, col row mi chi2
tab regimen_total
tab regimen_total HIVStatus, col row mi chi2
tab vital_stat_end
tab vital_stat_end HIVStatus, col row mi chi2

```

Incomplete Treatment:

Percent missed doses = (number of doses missed / number of doses prescribed) x 100

Percent received doses = (number of doses received / number of doses prescribed) x 100

Rate of discontinuation of individual drugs (STATA):

```
gen rate_yrs = n_reason_drug/duration_drug_years
```

Generalized logistic mixed effects model to estimate adjusted odds ratios and 95% confidence intervals of receiving a drug (versus missing a drug) during hospitalization (STATA):

```
meqrlogit recmis i.drug_ultrashort hivstatus || StudyNumber: , or
```

Factors Associated with completion of PAS treatment (R statistical software):

```

mod3<-orm(adher_PAS ~ sex + prevtb + Ageatfirstadmission + hiv_firstadm +
race_mod, data=d, x=TRUE, y=TRUE)
summary(mod3, Ageatfirstadmission=c(20,30))
anova(mod3)

```