Contribution of different oxazolidinones to the efficacy of novel regimens containing bedaquiline and pretomanid in murine models of TB

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Unmet need in TB treatment

- A short-course oral regimen that
  - is active against virtually all circulating strains of DR-TB
  - is safe and well-tolerated
  - has no serious drug-drug interactions
  - produces cure rates at least comparable to the first-line regimen for drug susceptible TB
  - prevents selection of mutants resistant to component drugs

Background

- The novel combo of bedaquiline+pretomanid (JPa) plus sutezolid (U) has sterilizing activity superior to the 1st-line regimen (RHZ) in BALB/c mice
- As linezolid (L) & tedizolid (T) are marketed agents, and AZD 5847 is in Phase II, these oxies warrant evaluation in this combo.
- Further study of these combos in C3HeB/FeJ mice which, unlike BALB/c mice, develop caseous lesions will be useful to confirm their efficacy.

R Tasneen et al, AAC 2015; 59:129

Oxazolidinone plasma AUC in BALB/c mice (JHU) and humans, with reference to MIC vs. *M. tb*

Drug	Species	Dose	$AUC_{0\text{-}24h}$ (μg-h/ml)	MIC* (μg/ml)
Linezolid	Mouse	100 mpk	244	0.5-1.0
	Human	*1200 mg*	*215-294*	
Sutezolid	Mouse	50 mpk	3.36	≤ 0.06-0.25
	Mouse (M1)	50 mpk	31.9	0.5
	Human	*1200 mg*	*7.13*	
	Human (M1)	*1200 mpk*	*36.8*	
Tedizolid	Mouse	10 mpk	40.4	0.25
		20 mpk	77.7	
	Human	*200 mg*	*22-26*	
AZD 5847	Mouse	125 mpk	160-190	0.5-1.0
	Human	*800 mg bid*	*180.2*	

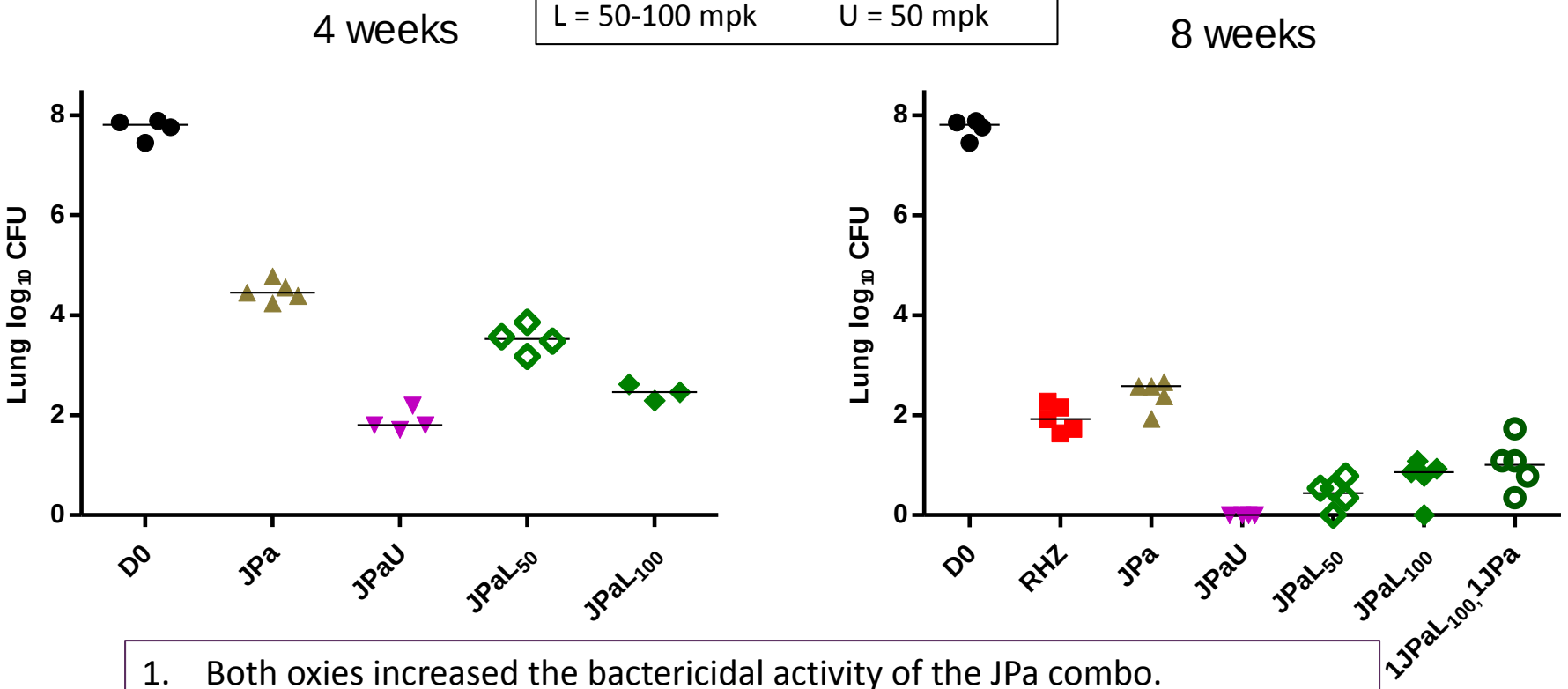
*MIC_{50}, geometric mean or median values from the literature

Addition of a linezolid (L) or sutezolid (U) increases the bactericidal activity of bedaquiline+pretomanid (JPa) in BALB/c mice

Doses tested

J = 25 mpk Pa = 100 mpk

L = 50-100 mpk U = 50 mpk



1. Both oxies increased the bactericidal activity of the JPa combo.
2. The JPaOxie combos were superior to RHZ at 8 wks.
3. U was superior to L at either dose.
4. Halving the L dose or duration did not significantly affect results at 8 weeks.

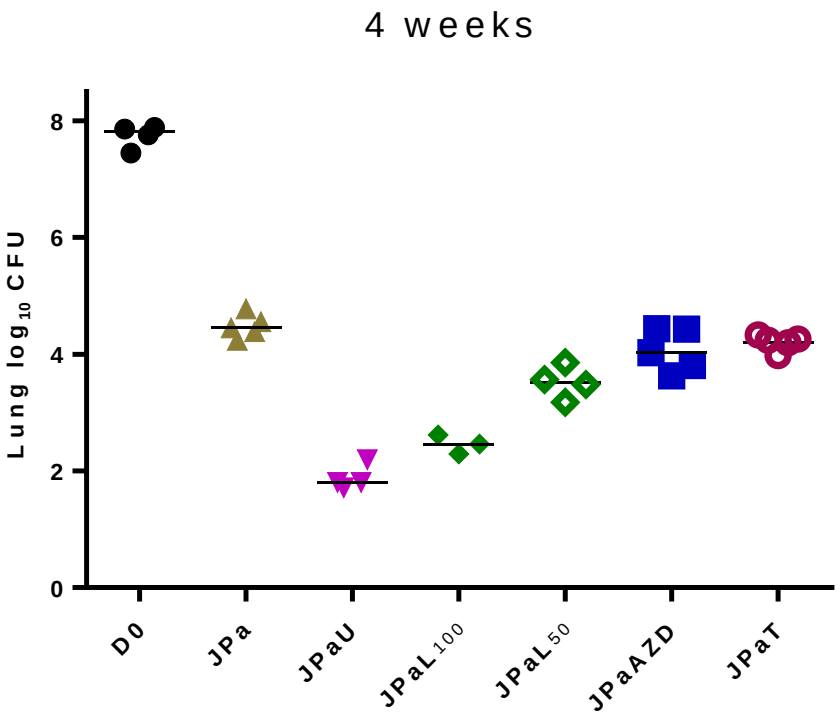
Addition of a linezolid (L) or sutezolid (U) increases the sterilizing activity of bedaquiline+pretomanid (JPa) in BALB/c mice

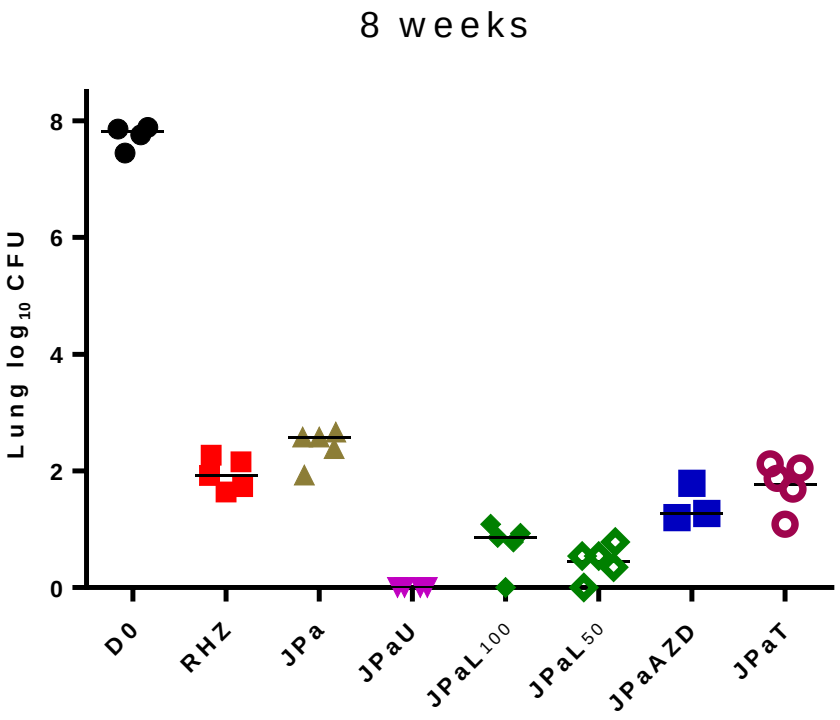
	Proportion relapsing after treatment for:	
Regimen	**2 months**	**3 months**
2RHZ/RH		8/14 **(57%)**
JPa		3/14 **(21%)**
JPaU	1/14 **(7%)**	0/14*† **(0%)**
3JPaL_{100}	6/15 **(40%)**	0/15*† **(0%)**

*p = 0.11 vs. JPa; †p≤ 0.001 vs. RHZ by 1-tailed Fisher exact test

1. JPaU and JPaL were superior to RHZ at 3 months, but JPa was not
2. Limiting the duration of L_{100} to the first month modestly reduced sterilizing activity

AZD 5847 (AZD) and tedizolid (T) increase the activity of JPa in BALB/c mice, but not as much as U or L



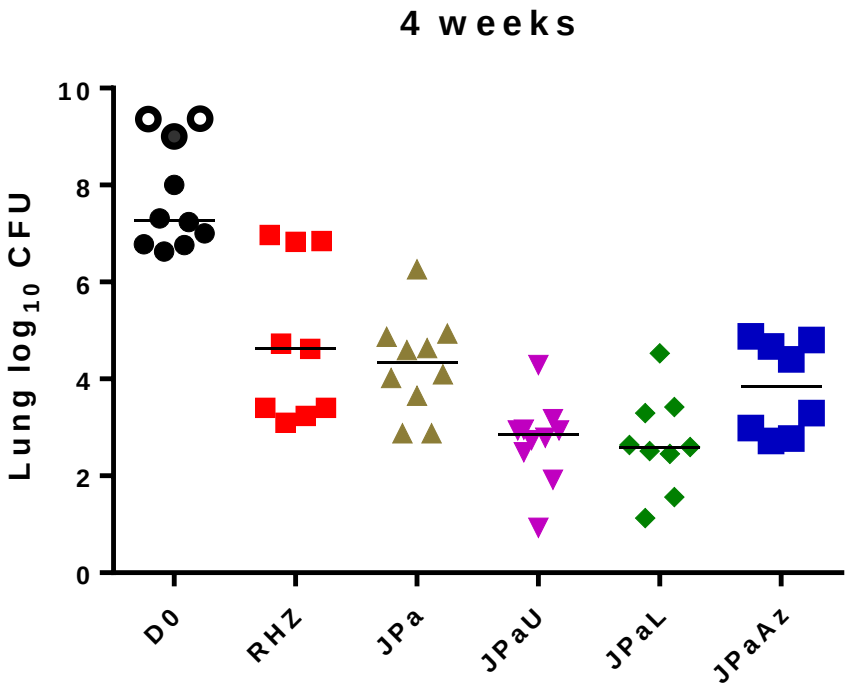


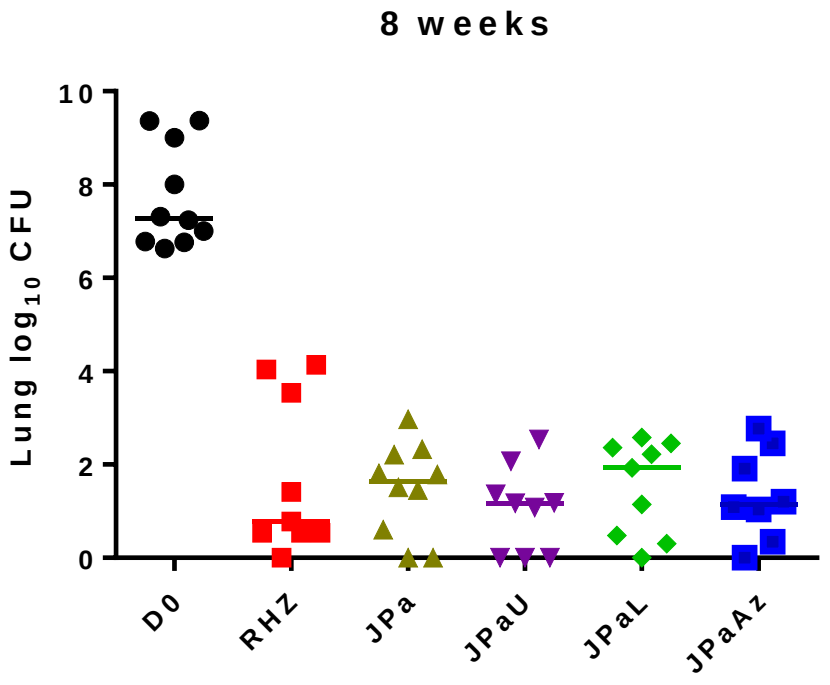
At 4 wks: all oxies add to JPa except T ($p<0.001$ for U, L, RWJ; $p<0.05$ for AZD)

At 8 wks: all oxies add to JPa ($p<0.001$ for U, L, RWJ; $p<0.01$ for AZD; $p<0.05$ for T)

Drug doses (in mpk): U 50; L50-100; AZD 125; T 10 (as pro-drug)

Sutezolid and linezolid increase the bactericidal activity of JPa in C3HeB/FeJ mice

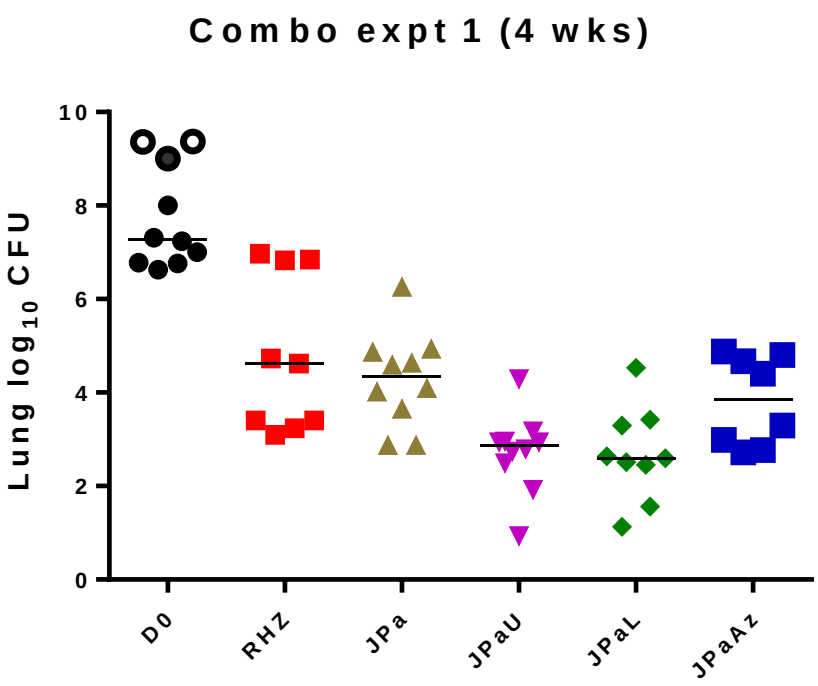


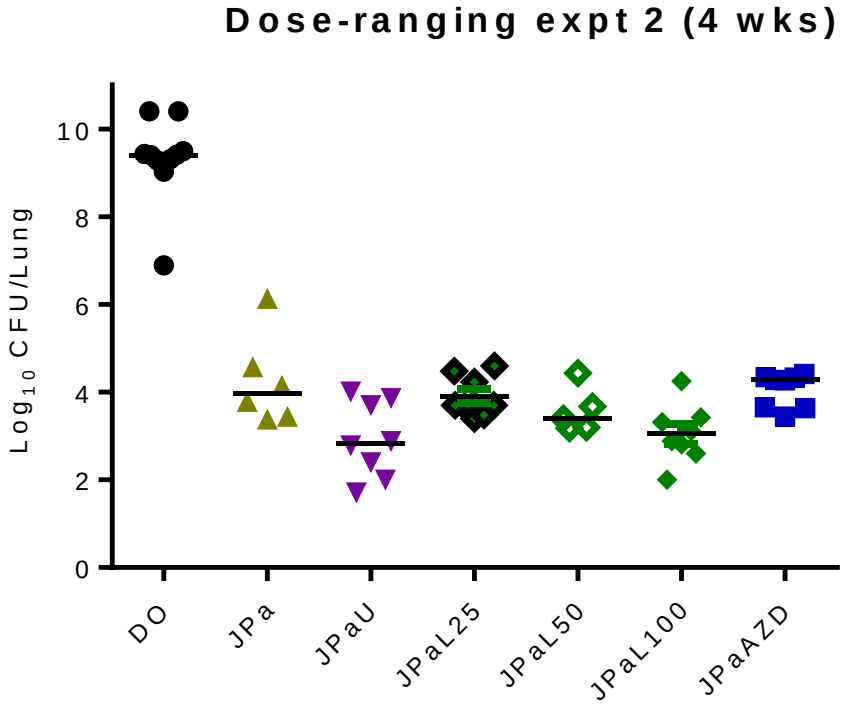


At 4 wks: all oxies but AZD add to JPa ($p<0.01$)

At 8 wks: no oxie adds to JPa

JPa + oxies in C3HeB/FeJ mice, 2nd expt



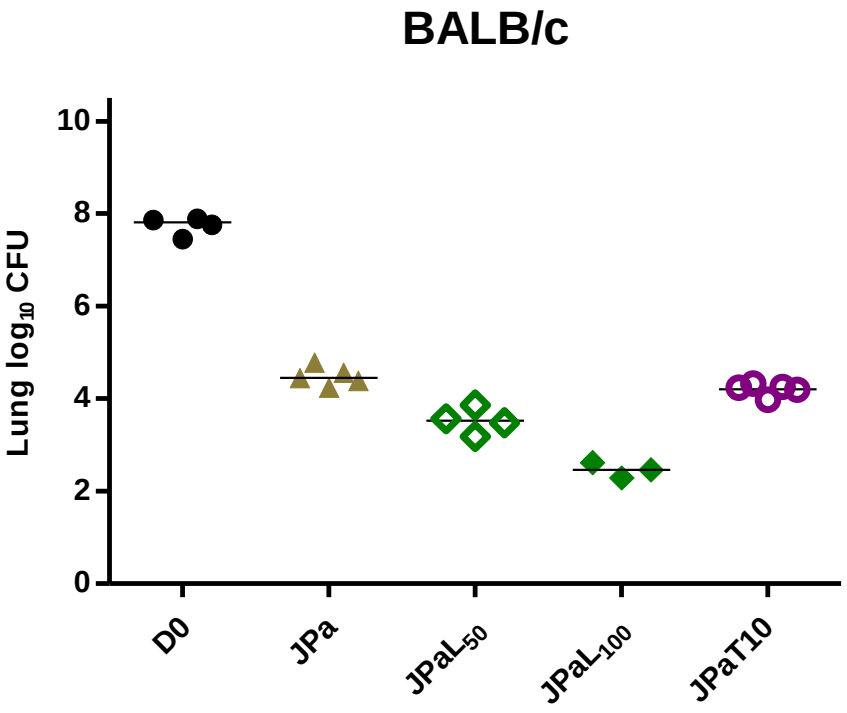


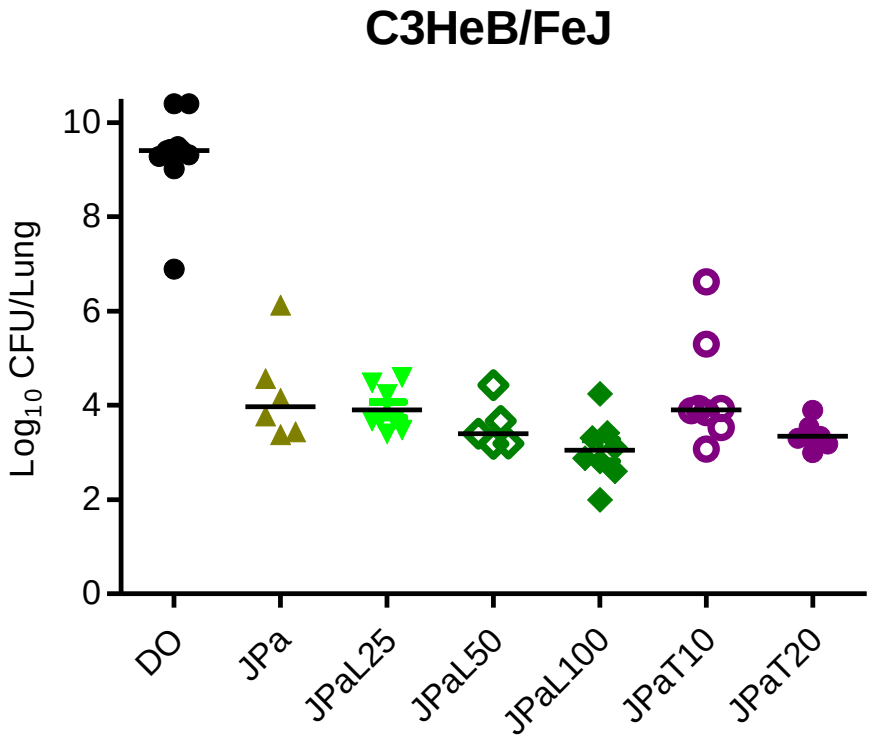
Only U and L100 add to JPa

($p<0.01$ and $p< 0.05$)

1. JPaU and JPaL100 were superior to JPa
2. L had dose-dependent additive effects. At 100 mpk, activity is comparable to U.

Tedizolid also has dose-dependent effects in combination with JPa in C3HeB/FeJ mice

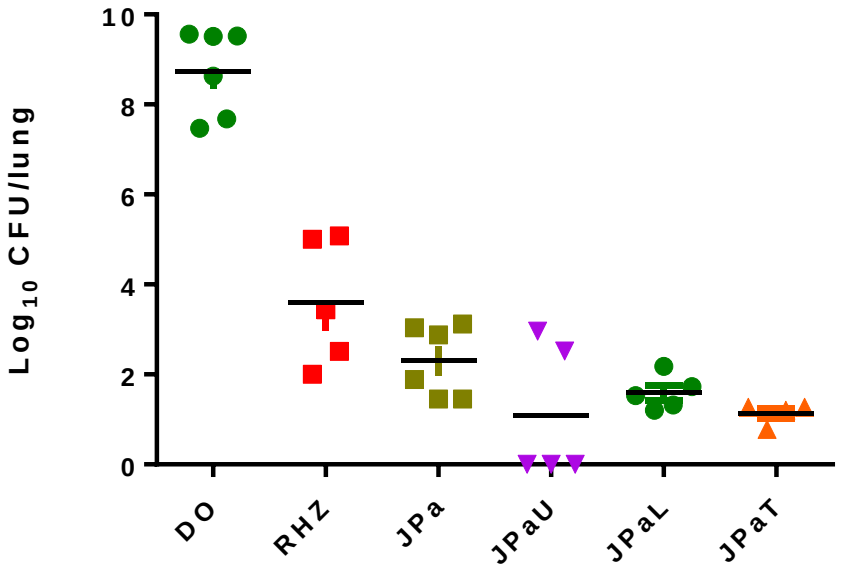




1. JPaT was not statistically superior to JPa alone
2. T at 10 and 20 mpk had effects similar to L at 25 and 50 mpk, respectively

Sterilizing activity of oxazolidinones in combination with JPa in C3HeB/FeJ Mice (Relapse Expt)

Lung CFU counts after 2 months



Doses (in mpk): U (50), L (100), T (20)

Relapses after 3 months of treatment

Regimen	% relapsing	vs. RHZ	vs. JPa
RHZ	91%	NA	NA
JPa	44%	*	NA
JPaU	7%	***	*
JPaL	29%	**	NS
JPaT	14%	***	NS

*p<0.05, **p< 0.01, ***p< 0.001

Relapses after 4.5 months of treatment

Regimen	% relapsing	vs. RHZ	vs. JPa
RHZ	18%	NA	NA
JPa	0%	†	NA
JPaU	0%	†	NS
JPaL	0%	†	NS
JPaT	0%	†	NS

†p=0.07

1. JPaOxie combos reduced the treatment duration by ~1.5 months vs. RHZ
2. Only U added sterilizing activity to the JPa combination in a stat. significant fashion
3. In this 2nd expt in C3HeB/FeJ mice, T20 was at least as potent as L100

Comparative single-dose PK in BALB/c and C3HeB/FeJ mice

Table 1, Pharmacokinetic parameters after single dose oral administration of Sutezolid, Linezolid, and Tedizolid in **BALB**/C mice.

Compound (dose, mg/kg)		t1/2 hr	Tmax hr	Cmax ng/mL	AUC0-24hr hr*ng/mL	AUC0-24hr/Dose hr*ng/mL/mg	Cavg,0-24hr ng/mL
Sutezolid	**Mean**	**2.8**	**0.5**	**1292**	**3359**	**67**	**140**
50	SD	0.5	0.0	707	499		21
Sutezolid M1	**Mean**		**0.5**	**15233**	**31945**	**639**	**1331**
	SD		0.0	7875	5853		244
Linezolid	**Mean**	**3.0**	**0.5**	**81933**	**243547**	**2435**	**10148**
100	SD	2.5	0.0	32240	31577		1316
Tedizolid	**Mean**	**3.0**	**0.7**	**6417**	**40414**	**4041**	**1684**
10	SD	0.4	0.3	624	2942		123
Tedizolid	**Mean**	**3.9**	**0.5**	**11433**	**77698**	**3885**	**3237**
20	SD	1.4	0.0	1665	6107		254

Table 2, Pharmacokinetic parameters after single dose oral administration of Sutezolid, Linezolid, and Tedizolid in Kramnik mice.

Compound dose, mg/kg		t1/2 hr	Tmax hr	Cmax ng/mL	AUC0-24hr hr*ng/mL	AUC0-24hr/Dose hr*ng/mL/mg	Cavg, 0-24hr ng/mL
Sutezolid	**Mean**	**4.3**	**0.5**	**1129**	**2288**	**46**	**95**
50	SD	1.6	0.0	165	464		19
Sutezolid M1	**Mean**		**0.5**	**17325**	**40446**	**809**	**1685**
	SD		0.0	6664	8798		367
Linezolid	**Mean**	**6.7**	**0.9**	**68100**	**401723**	**4017**	**16738**
100	SD	2.8	0.8	22529	66537		2772
Tedizolid	**Mean**	**5.0**	**0.5**	**15575**	**119209**	**5960**	**4967**
20	SD	1.5	0.0	1921	17272		720

Conclusions

- JPa + an oxazolidinone has potential for short-course oral regimens for all forms of TB, justifying evaluation of JPaL in the Nix-TB trial
- Sutezolid was the most active oxie in the combo in BALB/c mice, but was not clearly superior to linezolid, tedizolid in C3HeB/FeJ
- However, the L and T exposures produced in the C3HeB/FeJ relapse expt were higher relative to U than in BALB/c mice, and exceeded the average human exposure at the highest approved doses
- Additional work is needed to confirm whether lower L and T exposures contribute sterilizing activity in C3HeB/FeJ mice
- Relapse results after 6 months of treatment may help to understand if early mortality in JPa-containing groups may have biased the efficacy results in their favor

Acknowledgements

- Colleagues
  - Faculty and staff of the JHU Center for TB Research
  - Matt Zimmerman (Rutgers)
  - Colleagues at the TB Alliance
  - Omar Vandal (Gates Foundation)
  - Anne Lenaerts and colleagues (Colorado St.)
- Funding
  - **Gates Foundation** (OPP1037174 & OPP1066499)
  - **TB Alliance**
  - **NIAID** (R01-AI111992, R01-AI090820)