Measuring the Early Impact on Transmission of New Treatment Regimens for Drug Resistant Tuberculosis

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ABSTRACT

Rationale: Most multidrug and extensively-drug resistant tuberculosis (MDR- and XDR-TB) occurs due to transmission of unsuspected or ineffectively treated DR-TB. Recently, results from the NiX-TB study in South Africa demonstrated durable cure at 6 months in 89% of XDR-TB patients. The duration of treatment needed to stop person to person spread of DR-TB is not known, but is critical to the potential for ambulatory management. Using the human-guinea pig (H-GP) transmission model, Riley showed almost immediate transmission cessation of drug susceptible TB in response to effective treatment, and we showed similar findings, retrospectively, for MDR-TB. We sought to evaluate the impact of novel DR-TB regimens including NiX-TB on transmission using the H-GP transmission model.

Methods: We admitted smear positive DR-TB patients to the H-GP facility and measured baseline infectivity by exhausting ward air to one of two GP exposure rooms (Control), each containing 90 GPs. In Experiment 1, (presented at ATS, 2017) patients were initiated on an optimized DR-TB regimen including bedaquiline (BDQ) and linezolid (LZD) based on the South African national guidelines at that time. In Experiment 2, patients were initiated on the NiX-TB regimen, consisting of BDQ, high dose LZD and pretomanid. During the initial 72 hours of treatment, no ward air was exhausted to either animal room. After 72 hours, ward air was exhausted to the second GP exposure room (Intervention). Infectiousness, over an average of 8 patient-days per participant (observation window) before and after starting DR-TB treatment in the same patients, was compared by performing tuberculin skin tests (TST) in GPs at baseline and 6 weeks following the end of the exposure.

Results: In Experiment 1 (see Figure), pre-treatment, five DR-TB patients infected 24 of 90 (26.7%) GPs (Control). Post-treatment (72 hours after drug initiation), the same patients (minus one who was withdrawn) infected 25 of 90 (27.8%) GPs (Intervention) (p = 1.00). In Experiment 2 (see Figure), pre-treatment, nine DR-TB patients infected 40 of 90 (44.4%) GPs (Control). Post-treatment (72 hours after drug initiation), the same patients infected 0 of 90 (0%) GPs (Intervention) (p < 0.0001). are pending.

Conclusions: South African DR-TB drug regimens that included BDQ and standard dose LZD *did not* decrease DR-TB transmission to GPs during the observation window. In contrast, transmission was rapidly and completely inhibited in patients treated with the NiX-TB regimen. That is, patients *did not transmit* DR-TB to GPs during the observation window, *suggesting an early and profound impact on transmission.*

BACKGROUND

Since the classic human-to-guinea (H-GP) pig transmission experiments of Riley and colleagues in Baltimore 60 years ago, effective treatment has been known to stop *M. tuberculosis (Mtb)* transmission almost immediately – well before 2-weeks of treatment, or sputum smear and culture conversion at about 2-months.[1] Epidemiological observations confirmed the rapid impact of effective treatment *Mtb* on spread.[2] Retrospective observations at the South African Airborne Infection Research (AIR) Facility indicate that patients with multidrug-resistant tuberculosis (MDR-TB), like drug susceptible TB, become rapidly non-infectious soon (less than 72 hours) after starting effective anti-TB therapy.[3,4] These data supported the ambulatory treatment of DS and DR TB. However, at ATS 2017, we presented H-GP evidence that patients in South Africa with MDR-TB treatment failure (some with XDR-TB) continued to transmit after bedaquiline (BDQ) and linezolid (LZD) were added for 11 days (data shown here as Experiment 1). We sought to test the rapid effects on transmission of the "NIX-TB" regimen – an entirely oral regimen shown in a recent treatment trial to result in clinical cure in 6-mos, and rapid sputum smear and culture conversion. The results have important implications for the safety of community-based treatment and the ability of certain drugs or regimens to interrupt the largely unknown mechanisms of transmission.

METHODS

Exp. 1. Add BDQ/LZN to a failed MDR-TB regimen
We selectively admitted 5 *Mtb*, mostly smear positive patients, potentially bedaquiline suitable, to the AIR facility and measured baseline infectivity for an average of 8 days, by exhausting ward air to one of two guinea pig exposure chambers (Control), each containing 90 Hartley guinea pigs. Once bedaquiline suitability was confirmed, and pre-treatment clinical evaluation completed, patients were initiated on standard South African treatment, including bedaquiline and linezolid, amongst others.

During the initial 72 hours of treatment, no ward air was exhausted to either animal room. After 72 hours, ward air was exhausted to the second guinea pig exposure chamber (Intervention) for an average of 8 days. Infectiousness during exposure before and after starting MDR/XDR treatment in the same patients, was compared by Guinea Pig tuberculin skin test (TST, 100 TU) induration, 6 weeks following the end of exposure. Note that one patient was withdrawn early, during the baseline infectivity period and subsequently passed, not contributing to guinea pig exposure during BDQ/LZD treatment. Note: indications for BDQ/LZD treatment includes high level INH resistance.

Exp 2. Treat failed MDR/XDR treatment pts with NIX-TB.
In a second experiment, we selectively admitted 9 *Mtb* patients who met criteria for the NIX clinical trial (but were not in the trial) to receive Pa 200 mg qd, Ldz 1200 mg qd, and Bdq 400 mg qd. The same experimental design was used to achieve similar 40 patient-day exposures for the 90 pre- and 90 on-treatment guinea pigs. The same 72 hrs of treatment without exposure was used to allow for drug exposure.

EXPERIMENTAL DESIGN

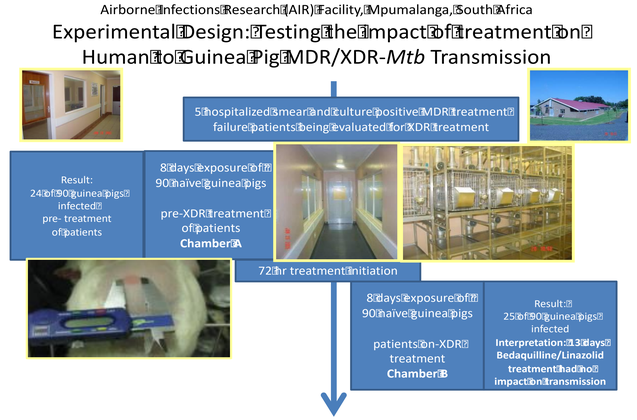
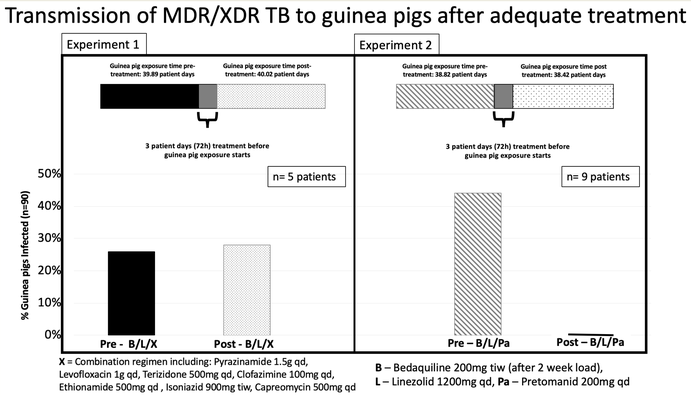


Fig 1 The same protocol was used for both experiments. Patients were admitted to the AIR facility to establish baseline, pre-treatment infectiousness for 90 guinea pigs in exposure chamber A (approximately 40 patient-days). Then, for 3 days GP exposure was stopped and all patients were started on treatment. Then, exposure of 90 GPs in chamber B started as treatment continued for another 40 patient-days. **Outcomes: GP TST reactions of 6 mm or more were considered positive indicating infection (transmission).**

RESULTS



SUBJECTS

Experiment 1					Experiment 2		
PT #	Line Probe algorithm	TB treatment Bedaquiline 400mg bd for 2 weeks then 400 q.d.			PT #	Line Probe / Reason for starting NIX	TB treatment
1/01	katGmut1; inhA	• PZA 1,5g, • Levofloxacin 1g, • Teridizone 500mg, • Linezolid 600mg, • Clofazamine 100mg • Bedaquiline 400mg			2/01	Newly diagnosed Rif Resistant GeneXpert Not yet on treatment	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
1/02	katGmut1; inhAmut1; rpoBmut3	• PZA 1,5g, • Levofloxacin 1g, • Terivalidin 500mg, • Ethonamide 500mg, • INH 900mg x3xw, • Capreomycin 500mg • Linezolid 600mg, • Bedaquiline 400mg			2/02	KatG 2016; treated Oct-Dec 2016 1+ pos Not yet on treatment	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
1/03	katGmut1; inhA; inhAWT2; rpoBmut1; katGWT, katG	• PZA 1,5g • Levofloxacin 1g • Terivalidin 500mg • Linezolid 600mg • Ethambutol 800mg • Linezolid 600mg, • Bedaquiline 400mg			2/03	Newly diagnosed Rif resistant GeneXpert Hearing loss; Not yet on treatment	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
1/04	katGmut1; inhA; inhAWT2; rpoBmut1; katG	• PZA 1,5g • Levofloxacin 1g • Clofazamine 100mg • Terivalidin 500mg • Linezolid 600mg • Bedaquiline 400mg			2/04	Rif resistant GeneXpert Pre-XDR AFB 3+" Not yet on treatment	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
1/05	Rifampicin resistant	• PZA 1,5g • Terivalidin 500mg • Levofloxacin 1g • Clofazamine 100mg • Ethonamide 500mg • Capreomycin 750mg • Linezolid 600mg • Bedaquiline 400mg			2/05	Rif resistant Pre-XDR AFB 3+ (2 May); AFB 2+	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
					2/06	Rif resistant GeneXpert XDR-TB	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
					2/07	Hearing loss MDR, Rif resist GeneXpert	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
					2/08	Rif resistant GeneXpert Failing MDR treatment AFB+	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.
					2/09	Rif resistant GeneXpert AFB+++	• Pretomanid 200mg q.d. • Linezolid 1200mg q.d. • Bedaquiline 400mg q.d.

Table 1 lists the indications for re-treatment in Experiments 1 and 2, and the details of TB treatment. In experiment 1, retreatment was the addition of BDQ/LZD to whatever other drugs were believed to be still susceptible or had not been previously used, as per RSA MOH protocol. For experiment 2, patients were all started on the same NIX-TB oral regimen.

CONCLUSION & DISCUSSION

South African DR-TB drug regimens that included BDQ and standard dose LZD did not decrease DR-TB transmission to GPs during the observation window. In contrast, transmission was rapidly and completely inhibited in patients treated with the "NiX-TB" regimen. That is, patients did not transmit DR-TB to GPs during the observation window, suggesting an early and profound impact on transmission. Exactly how drug treatment stops transmission well before sputum smear and culture conversion is not known. Some drugs and regimens appear to be better at inhibiting transmission than others. INH, RiF and FQ drugs may account for the rapid effects of treatment on transmission observed in DS and MDR-TB patients. For XDR - B, BDQ and LZD require prolonged treatment to achieve therapeutic levels. Pretomanid and higher-dose linezolid may account for the rapid effect on transmission observed here. Little is known of microbial adaptations to airborne transport and the effects of drugs on those mechanisms.

REFERENCES

1. Riley RL., et al., *Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients.* Am Rev Respir Dis, 1962. **85**: p. 511-25.
2. Rouillion A PS, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. Tubercle, 1976; **57**:275-99.
3. Dharmadhikari, A.S., et al., *Natural infection of guinea pigs exposed to patients with highly drug-resistant tuberculosis.* Tuberculosis; 2011 July ; **91**(4): 329–338.
4. Dharmadhikari, A.S., et al., *Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis.* Int J Tuberc Lung Dis; 2014. **18**(9): p. 1019-25