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 tuberculosis (MtB) transmission almost immediately – well before 2-weeks of treatment, or sputum smear and culture conversion at about 2-months. Epidemiological observations confirmed the rapid impact of effective treatment MtB on spread. 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. These data supported the ambivalence of DST in TB. However, during ART, 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 be 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/LZD to a failed MDR-TB regimen

We selectively administered 5 Mtb, mostly smear positive patients, potentially bedaquiline-suitable, to the AIR facility and measured baseline infectivity by exhausting ward air over an extended observation window (Control), each containing 90 GPs. In Experiment 1, at ATS, 2017, patients were initiated on an optimized MDR-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 level INH resistance. Contributing to guinea pig exposure during BDQ/LZD treatment, nine DR-TB patients were accepted to the study funded by NIAID: RO1AI099603, PI Anton Stoltz, MD, PhD. The same protocol was used for both experiments. Patients were selectively admitted 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 dose South African treatment, including bedaquiline and linezolid, amongst others. During the initial 72 hours of treatment, no ward air was exhausted to either animal chamber. After 72 hours, ward air was exhausted to the second observation exposure chamber (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. Outcomes: GP TST reactions of 6 mm or more were considered positive indicating infection (transmission).

**RESULTS**

Transmission of MDR/XDR TB to guinea pigs after adequate treatment

Table 1 lists the indications for re-treatment in Experiments 1 and 2, and the details of the TB regimen. In experiment 1, treatment 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 initiated on the same NIX-TB 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, 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-DR-TB, 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 transmission and the effects of drugs on those mechanisms.

**REFERENCES**