TITLE: Implementation of the new BPaLM regimen for rifampicin resistant tuberculosis: balancing access to current patients with the risk of emerging resistance

AUTHORS: Annelies Van Rie[1], Bouke de Jong[2], Sebastien Gagneux[3,4], Véronique Dartois[5], Praharshinie Rupasinghe[2], Lindsay Sonnenkalb[6], Viola Dreyer,[6] Stefan Niemann[6,7], Diana Machado[8], Emmanuel Rivière[1], Galo Goig[3,4], Conor Meehan[9], Timothy Walker[10, 11], Philip Supply[12], Elisa Tagliani[13], Daniela Maria Cirillo[13].

AFFILIATIONS

[1]Tuberculosis Omics Research Consortium, Family Medicine and Population Health, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium
[3]Swiss Tropical and Public Health Institute, Allschwil, Switzerland
[4]University of Basel, Basel, Switzerland
[5]Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ, USA
[6]Molecular and Experimental Mycobacteriology, Research Center Borstel, Parkallee 1-40 23845 Borstel, Germany
[7]German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Reims, Borstel, Germany
[8]Laboratório de Micobactérias, Unidade de Microbiologia Médica, Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Portugal
[9]Department of Biosciences, Nottingham Trent University, Nottingham, UK
[10]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
[11]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine Research Building, University of Oxford, Oxford, UK
[12]Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, U1019 - UMR 8204 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille, France
[13]Emerging Bacterial Pathogens Unit, Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy.

In May 2022, the World Health Organization released a rapid communication stating that "the six-month all-oral BPaLM (bedaquiline, pretomanid, linezolid and moxifloxacin) regimen may be used programmatically for patients (aged ≥15 years) with rifampicin resistant tuberculosis (RR-TB) not yet exposed to bedaquiline, pretomanid and linezolid. In patients with fluoroquinolone resistance, a six-month BPaL (bedaquiline, pretomanid, linezolid) regimen can be used. Drug susceptibility testing (DST) should not delay treatment initiation and DST to fluoroquinolones is strongly encouraged but not required (1)". While near universal eligibility for short all-oral RR-TB treatment is excellent news, data presented at the European Society for Mycobacteriology conference (June 2022) suggest the long term efficacy of these regimens may already be at risk.

First, the efficacy of a drug may vary by *Mycobacterium tuberculosis* (*Mtb*) lineage. Claudio Köser showed an increased pretomanid minimum inhibitory concentration (MIC) distribution for wild type *Mtb* lineage 1 strains compared to strains of other lineages (2). Praharshinie Rupasinghe presented a poster with unpublished data from a multi-country study confirming this finding. Emmanuel Rivière raised the hypothesis of a lineage-dependent MIC distribution for bedaquiline, with a higher proportion of lineage 4 strains with MIC closer to (albeit below) the epidemiological cut-off (3). It is unknown if lineage-dependent differences in MIC distribution are clinically relevant. Second, different drugs penetrate lung lesion at different rates. Véronique Dartois showed experimental data that moxifloxacin, linezolid and pretomanid rapidly penetrate in the caseum, while bedaquiline (even when using a loading dose) only fully reaches mycobacteria in the caseum's center after 2 to 5 weeks of treatment (4). The experimental data presented by Lindsay Sonnenkalb show that bedaquiline exposure at one eighth of a strain's MIC results in acquisition of variants in resistance genes within 20 days of exposure, suggesting that the slowly increasing bedaquiline concentration in the caseum of lung lesions could select for resistance(5). Furthermore, in contrast to moxifloxacin, linezolid and pretomanid, bedaquiline has a long half-life, resulting in prolonged presence in the caseum and potential exposure to a single drug in case of treatment interruption. Third, primary resistance to BPaLM drugs already exists. This was first documented for bedaquiline in 2016 (6, 7). Diana Machado presented the first case report of primary pretomanid resistance due to a *ddn*88* variant in a patient diagnosed in 2008, years before pretomanid and delamanid introduction.

Taken together, this raises questions regarding the robustness of the BPaL regimen for today's and tomorrow's patients. Specifically, administration of BPaL to patients with a fluoroquinolone resistant *Mtb* may increase the risk of acquisition of resistance to bedaquiline and/or linezolid. This risk may be especially elevated during the first weeks of treatment when the mycobacterial burden is high and bedaquiline is not yet fully distributed into lung lesions. Mycobacteria in the caseum may be temporary exposed to linezolid "monotherapy" if elevated MICs make pretomanid less effective. If compensatory mutations are acquired, resistant strains may then transmit at rates similar to pan susceptible *Mtb*. This was shown by Sébastien Gagneux for rifampicin resistant lineage 2 strains carrying a S450L *rpoB* and a compensatory *rpoC* mutation, expanding on the previously reported association between compensatory mutations and transmission.

These data highlight the need to balance the risks of emergence of resistance to BPaLM drugs with the risks to current patients from not gaining access to BPaLM or BPaL regimens.

The potential risk of empiric (*i.e.*, blinded to DST) use of BPaLM and BPaL regimens may be especially high for RR-TB caused by lineage 1 strains, estimated to cause 28% of global tuberculosis, mainly in India, the Philippines, Africa and Asia.

Although there are no easy solutions for this complex issue, there are some things we can do now. The COVID pandemic has boosted the global next generation sequencing infrastructure which could be harnessed to predict resistance where we currently can, and to improve future catalogues of resistance-associated mutations to overcome current gaps in knowledge. Patients who fail on the new regimens should have samples referred to reference centres for phenotypic DST. As we move forwards, rapid diagnostic tests, including tNGS, will be as important as ever. These need validation and eventual WHO endorsement to facilitate governmental investment and roll-out. We are fortunate to have more new drugs in the pipeline but as a community we should be working towards the end that every new drug is developed alongside a companion diagnostic that will ensure the utility of new regimens well into the future.

REFERENCES

1. World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2022 (WHO/UCN/TB/2022.2). Licence: CC BY-NC-SA 3.0 IGO.
2. Bateson A, Ortiz Canseco J, McHugh TD, Witney AA, Feuerriegel S, Merker M, et al. Ancient and recent differences in the intrinsic susceptibility of Mycobacterium tuberculosis complex to pretomanid. J Antimicrob Chemother. 2022;77(6):1685-93.
3. Rivière E, Verboven L, Dippenaar A, Goossens S, Vos ED, Streicher E, et al. Variants in Bedaquiline-Candidate-Resistance Genes: Prevalence in Bedaquiline-Naive Patients, Effect on MIC, and Association with Mycobacterium tuberculosis Lineage. Antimicrobial Agents and Chemotherapy.0(0):e00322-22.
4. Sarathy JP, Zuccotto F, Hsinpin H, Sandberg L, Via LE, Marriner GA, et al. Prediction of Drug Penetration in Tuberculosis Lesions. ACS Infect Dis. 2016;2(8):552-63.
5. Sonnenkalb L, Carter J, Spitaleri A, Iqbal Z, Hunt M, Malone K, et al. Deciphering Bedaquiline and Clofazimine Resistance in Tuberculosis: An Evolutionary Medicine Approach. bioRxiv. 2021:2021.03.19.436148.
6. Villellas C, Coeck N, Meehan CJ, Lounis N, de Jong B, Rigouts L, et al. Unexpected high prevalence of resistance-associated Rv0678 variants in MDR-TB patients without documented prior use of clofazimine or bedaquiline. J Antimicrob Chemother. 2017;72(3):684-90.
7. Beckert P, Sanchez-Padilla E, Merker M, Dreyer V, Kohl TA, Utpatel C, et al. MDR M. tuberculosis outbreak clone in Eswatini missed by Xpert has elevated bedaquiline resistance dated to the pre-treatment era. Genome Med. 2020;12(1):104.
8. Jouet A, Gaudin C, Badalato N, Allix-Beguec C, Duthoy S, Ferre A, et al. Deep amplicon sequencing for culture-free prediction of susceptibility or resistance to 13 anti-tuberculous drugs. Eur Respir J. 2021;57(3).
9. Sibandze DB, Kay A, Dreyer V, Sikhondze W, Dlamini Q, DiNardo A, et al. Rapid molecular diagnostics of tuberculosis resistance by targeted stool sequencing. Genome Med. 2022;14(1):52.