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TITLE: Balancing access to BPaLM regimens and risk of resistance

AUTHORS: Annelies Van Rie¹, Timothy Walker^{2,3}, Bouke de Jong⁴, Praharshinie Rupasinghe⁴, Emmanuel Rivière¹, Véronique Dartois⁵, Lindsay Sonnenkalb⁶, Diana Machado⁷, Sebastien Gagneux^{8,9}, Philip Supply¹⁰, Viola Dreyer⁶, Stefan Niemann^{6,11}, Galo Goig^{8,9}, Conor Meehan¹², Elisa Tagliani¹³, Daniela Maria Cirillo¹³

AFFILIATIONS

¹Tuberculosis Omics Research Consortium, Family Medicine and Population Health, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

²Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

³Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine Research Building, University of Oxford, Oxford, UK

⁴Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium

⁵Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ, USA

⁶Molecular and Experimental Mycobacteriology, Research Center Borstel, Parkallee 1-40 23845 Borstel, Germany

⁷Laboratório de Micobactérias, Unidade de Microbiologia Médica, Global Health and Tropical Medicine, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Portugal

⁸Swiss Tropical and Public Health Institute, Allschwil, Switzerland

⁹University of Basel, Basel, Switzerland

¹⁰Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, U1019 - UMR 8204 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille, France

¹¹German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Reims, Borstel, Germany

¹²Department of Biosciences, Nottingham Trent University, Nottingham, UK

¹³Emerging 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 effectiveness 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). Praharsinie 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 *ddn88** 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 fluoroquinolone resistant TB 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 temporarily 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 (8).

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, some things can be done now. The COVID pandemic has boosted the global next generation sequencing (NGS) infrastructure which should be harnessed to predict resistance, guide rescue treatment in case of resistance or toxicity, and reduce knowledge gaps on resistance-associated mutations. Patients for whom treatment does not appear to be effective should have samples assessed by DST at reference centres. As we move forwards, rapid diagnostic tests, including targeted NGS, will be important. Data presented by Philip Supply and Viola Dreyer suggests that targeted NGS can detect resistance directly from (smear positive) sputa (9) and maybe from stool samples (10). These need validation and 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 demand that every new drug is developed alongside a companion diagnostic that will ensure the longevity of new regimens well into the future.

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