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Balancing access to BPaLM regimens and risk of resistance

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In May, 2022, WHO released a rapid communication stating that the 6-month all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) "may be used programmatically for patients (aged ≥15 years) with rifampicin-resistant tuberculosis not yet exposed to bedaquiline, pretomanid and linezolid [BPaL]". The rapid communication continued that in patients with fluoroquinolone resistance, a 6-month regimen of BPaL can be used. WHO concluded that "drug-susceptibility testing (DST) should not delay treatment initiation and DST to fluoroquinolones is strongly encouraged but not required".[1] Although near universal eligibility for short, all-oral, rifampicin-resistant tuberculosis treatment is excellent news, data presented at the European Society for Mycobacteriology conference in Bologna, Italy (June, 2022), suggest the long-term effectiveness of these regimens might already be at risk.

First, the efficacy of a drug can vary by *Mycobacterium tuberculosis* lineage. At the conference, Claudio Köser presented the results of a study showing an increased pretomanid minimum inhibitory concentration (MIC) distribution for wild-type *M tuberculosis* lineage 1 strains compared with strains of other lineages.[2] Praharshinie Rupasinghe presented a poster with data from a multicountry study (Rupasinghe P, unpublished) supporting this finding. Emmanuel Rivière raised the hypothesis of a lineage-dependent MIC distribution for bedaquiline, with an increased proportion of lineage 4 strains with MICs closer to—albeit below—the epidemiological cutoff.[3] It is unknown if lineage-dependent differences in MIC distribution are clinically relevant.

Second, different drugs penetrate lung lesions at different rates. Véronique Dartois showed experimental data that moxifloxacin, linezolid, and pretomanid rapidly penetrate the caseum, whereas bedaquiline—even when using a loading dose—only fully reaches mycobacteria in the caseum's centre after 2–5 weeks of treatment.[4] The experimental data presented by Sonnenkalb and colleagues 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 long-lasting presence in the caseum and potential exposure to a single drug in case of treatment interruption. Third, primary resistance to BPaLM drugs already exists. Primary resistance 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.[8]

Taken together, these issues raise questions regarding the robustness of the BPaL regimen for patients now and in the future. Specifically, administration of BPaL to patients with fluoroquinolone-resistant tuberculosis might increase the risk of acquisition of resistance to bedaquiline and linezolid. This risk could 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 might be temporarily exposed to linezolid monotherapy if elevated MICs reduce pretomanid's effectiveness. If compensatory mutations are acquired, resistant strains might then transmit at rates similar to pan-susceptible *M tuberculosis*, as shown by Sébastien Gagneux for rifampicin-resistant lineage 2 strains carrying a *rpoB* S450L and a compensatory *rpoC* mutation. This expands on the previously reported association between compensatory mutations and transmission.[9]

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 empirical (ie,

blinded to DST) use of BPaLM and BPaL regimens could be especially high for rifampicin-resistant tuberculosis caused by lineage 1 strains, estimated to cause 28% of global tuberculosis, mainly in Africa and Asia.

Although there are no easy solutions for this complex issue, some things can be done now. The COVID-19 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 suggest that targeted NGS can detect resistance directly from smear-positive sputum[10] and maybe from stool samples.[11] These diagnostic approaches 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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The growing threat of wild poliovirus 1 and vaccine-derived cases in the COVID-19 era

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The detection of people with paralytic cases of wild poliovirus 1 (WPV1) in two African countries (ie, Malawi in February, 2022, and Mozambique in May, 2022) outside endemic areas of WPV1 transmission (ie, Pakistan and Afghanistan) will become a serious setback if low vaccination coverage and