LabCoP EXTENDED ECHO SESSION

Flying blind: the urgent need for rapid detection of bedaquiline-resistant TB

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Bedaquiline (BDQ) resistance

1. **I want to know how to explain the presence of BDQ resistance without rpoB resistance, also for how long BDQ have been introduced in MTB-TB treatment in your country?**

During the presentation, one figure showing a linear regression analysis of correlation of BDQ and fluoroquinolone resistance frequency with the year of strain isolation, additionally stratified by presence or absence of the rpoB Ile491Phe mutation for BDQ, was presented. There we wanted to demonstrate that the BDQ resistance emerged independently from fluoroquinolone resistance, and that the prevalence of BDQ resistance increased over time in strains with and without rpoB Ile491Phe mutation over time. In Mozambique, BDQ was introduced in 2019.

2. **How do you explain decrease prevalence of rpoB I491F but increase prevalence of bdq-r in last years?**

The data presented in slide 17 is preliminary and requires deeper analysis, although we have demonstrated an increment of the average of BDQ resistance from 9% to 19% and a decrease from 4% to 2% of the rpoB Ile491Phe mutation in 2016-2021 and 2022-2024, respectively, further analysis on the relationship of both mutation for the recent data from 2022-2024 is needed.

3. **The rate of resistance for new drugs is really very fast, do you think that new regimens are vulnerable?**

Yes, new TB regimens are potentially vulnerable to resistance, but their success depends on how we implement and monitor their use. Resistance often emerges from inadequate treatment adherence, poor drug supply chains, and lack of robust diagnostics. To protect these new drugs, we need rapid detection by integration of tNGS in national algorithms to track this to stop transmission and strenghten surveillance systems.

4. **Do you have a hypothesis to explain the emergence of BDQ resistance before the implementation of this drug in Mozambique, the cross-resistance relationship with other drugs could explain that evidence?**

One hypothesis can be cross-resistance between clofazimine (CFZ) and BDQ, mainly mediated by mutations in the Rv0678 gene. Another is cross-border migration, for example, with South Africa that have introduced BDQ earlier; but this needs further investigation.

5. **Why introduce new drugs without tools for monitoring?**

That is an important point. Ideally, the introduction of any new TB drug should be accompanied by robust tools for resistance monitoring, to allow to rapidly detect emerging resistance and adjust strategies before resistant strains spread widely. However, in practice, there is often pressure to deploy new drugs early because of the urgent need to improve outcomes in patients with limited treatment options, such as those with MDR/XDR-TB. In these situations, delaying implementation until ideal monitoring systems are in place may leave patients without access to life-saving therapies. The ideal scenario would be a parallel approach, rolling out new drugs while simultaneously investing in and strengthening laboratory capacity for drug resistance surveillance. Without this, we risk losing the effectiveness of these new drugs due to unmonitored resistance, which could undermine global TB control efforts.

6. **Do you perform phenotypic testing for pretomanid?**

Yes, we have been performing phenotypic DST for Pretomanid since April 2025.

7. **And have you seen any Pa-R?**

Pretomanid resistance has been reported to be rare globally. However, rising resistance to companion drugs in some parts of Africa, including Mozambique, raises concerns about the potential emergence of pretomanid resistance as its use expands. We have detected cases of pretomanid resistance, but the data are still being analysed. Continued surveillance and resistance testing are crucial to detect and prevent the spread of resistance.

Sequencing methods

1. **What guided the selection of your sequencing technology?**

The selection of our TB NGS sequencing technology was guided by several key factors. First, the availability of technical assistance locally was critical to ensure capacity building for implementation and sustainability. Second, alignment with our laboratory infrastructure and existing analysis

pipelines and protocols, the ability to generate high-quality data for drug resistance surveillance. Finally, the donor's ability to provide the sequencing equipment, reagents and maintenance played an important role, as it ensured we could deploy the technology without significant procurement delays. Balancing these elements allowed us to choose a platform that met both our technical and programmatic needs.

2. **Could you describe where in the diagnostic algorithm sequencing is placed and what is the TAT?**

We have a plan to initiate the pilot study to include tNGS in the National diagnostic algorithm this year. We will be conducting tNGS for any patient with resistance to Rifampicin and/or Isoniazid, and tNGS will be performed directly from SS+ (at least 1+) and results will be shared with the Clinical Committee for treatment decision. Our target TAT is 7 days.

3. **Could you explain what you mean by genome-based drug-resistance prediction? Do you only use national data, or you also refer to global databases?**

Genome-based DST prediction is related to resistance detection by molecular methods such as Xpert MTB/RIF, Line Probe Assay, target Next Generation Sequencing and Whole genome sequencing. We rely on both national data and international databases like the WHO catalogue to interpret those mutations. This ensures our predictions are accurate and globally contextualized.

4. **What do you think is more appropriate to start a sequencing project? WGS or tNGS?**

Both WGS and tNGS play important roles, but for initiating a sequencing project in a high-burden TB setting, tNGS is generally the more practical choice. It is faster, less demanding in terms of bioinformatics, more cost-effective, and can be performed directly on sputum samples without the need for culture, enabling rapid detection of resistance and timely adjustment of patient treatment. In contrast, WGS offers a much broader view, including insights into strain diversity and transmission patterns. However, it requires more advanced infrastructure, higher technical capacity, and greater bioinformatics expertise, which can be challenging to establish in the early stages of a project.

Pill burden/treatment outcomes

1. **New drugs in Mozambique are gathered in one pill (like RHZE) or they are separated?**

New drugs are separated due to different pharmacokinetics, these drugs have different half-lives, absorption rates, and side effect profiles.

2. **Thanks to the team and congratulations. did you have the opportunity to look at the treatment outcomes of patients with strains harbouring BDQ-R associated mutations? Did you observe association with negative outcomes in BDQ containing regimens?**

So far, our evaluations have focused on laboratory-based surveillance and genomic analysis, and we have not yet conducted systematic patient follow-up to assess treatment outcomes in individuals with strains carrying BDQ resistance-associated mutations. However, we recognize the importance of linking molecular resistance data with clinical outcomes, particularly in the context of BDQ-containing regimens. This type of evaluation is highly relevant and a priority for future studies, as it would provide critical insights to guide treatment decisions and programmatic management.