# Bedaquiline or delamanid for rifampin-resistant tuberculosis?

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Almost 50 years after the discovery of rifampin, clinicians and tuberculosis programmes finally have treatment options to offer people with rifampin-resistant tuberculosis, which can improve outcomes and limit toxic effects associated with conventional treatment. Such innovations include the newer drugs bedaquiline and delamanid, repurposed drugs such as linezolid or clofazimine, and shorter regimens.[1] Because of limited availability and resources, many programmes, policy makers, and clinicians have had to choose between using bedaquiline or delamanid, but not both.[2]

No head-to-head comparisons of the two drugs have been done and there exist limited data to inform whether one novel drug is more effective than the other. Increasingly, researchers are exploring the use of both drugs in combination. When used separately, several factors can guide the selection between the two agents in the treatment of rifampin-resistant tuberculosis.[3] In the table, we list the characteristics of bedaquiline and delamanid, and other programmatic and practical considerations, that can inform choice.

Overall, we recommend that countries provide both novel agents available at a programme level because there are individuals who will benefit more with one drug and some who will need both. Having both agents available will ensure that people with rifampin-resistant tuberculosis are offered a novel agent that is most appropriate.

| | Bedaquiline | Delamanid |
|---|---|---|
| Phase 2b study | RCT, multidrug therapy backbone therapy, bedaquiline versus placebo for 24 weeks;[4] results: faster time to culture conversion, higher rates of culture conversion, and higher overall success with bedaquiline[5] | RCT, multidrug therapy backbone therapy, delamanid *vs* placebo for 8 weeks, followed by a washout period, after which all participants offered delamanid for 24 weeks;[6] results comparing delamanid for 8 weeks *vs* 24 weeks: higher rates of treatment conversion, faster time to culture conversion, and higher overall success with 24 weeks |
| Phase 3 study | Results expected in 2020 or later | Topline results expected in quarter 4 of 2017, full results expected early 2018 |
| Programme use | Given to more than 10 000 individuals as of July 1, 2017[7] | Given to almost 700 individuals as of July 1, 2017 |
| Threshold to develop resistance | Higher than delamanid; might have cross-resistance with clofazimine, clinical implications are not clear; naturally occurring resistance in the absence of exposure may occur but is rare | Lower than bedaquiline and similar to isoniazid and pretomanid (PA-824); naturally occurring resistance in the absence of drug exposure might occur |
| Safety issues | Moderate QTc prolongation; hepatotoxicity; phospholipidoisis | Mild to moderate QTc prolongation[8] |
| Use with antiretroviral agents | Cannot be used with efavirenz; can be used with lopinavir/ritonavir, but studies suggest this could result in increased levels of bedaquiline and its metabolites; use with integrase inhibitors preferred; broad field experience, especially in South Africa and Swaziland | Can be used safely with most antiretroviral therapy drugs; limited field experience |
| Other drug–drug interactions | Multiple possible interactions including with buprenorphine, methadone, kanamycin, ketoconazole | Limited interactions |
| Contraindications as per package insert | None | Allergy to metronidazole; albumin <2·8 g/dL; strong inducers of CYP3A4 |
| Special populations | Ongoing PK and safety studies in children aged 5–17 years, field experience in adolescents aged ≥12 years suggests safety (although numbers are small); considered to be safe in pregnancy based on animal data, case reports of use in pregnant women | Completed PK and safety studies in children aged ≥3 years;[9] WHO recommendations for use in children aged ≥6 years;[10] ongoing studies in children aged 0–2 years; considered safe in pregnancy based on animal data, compassionate use programme open to pregnant women |
| Terminal elimination half-life | About 6 months | About 38 h |
| WHO recommendations | Use in patients in whom a four-drug regimen (plus pyrazinamide) cannot be constructed for reasons of resistance or intolerance;[11] use in patients who do not qualify for shortened regimens | Use in patients in whom a four-drug regimen (plus pyrazinamide) cannot be constructed for reasons of resistance or intolerance;[12] use in patients with high risk of poor treatment outcomes |
| Dosing | Requires loading dose of 14 days then is given three times per week | Twice daily dosing recommended (trials assessing daily dosing are underway) |
| Shelf-life | 3 years, no cold chain | 5 years, no cold chain |
| Cost | Currently free for most Global Fund-eligible countries; USD$900–3000 for other low-income and middle income countries | USD$1700 for all Global Fund-eligible countries (which Global Fund funding can cover) |
| Available through Global Drugs Facility | Yes | Yes |
| Registration (as of June, 2017) | USA, Russia, Philippines, Peru, Armenia, India, New Zealand, Hong Kong, Moldova, South Korea, South Africa, Turkmenistan, Uzbekistan, Taiwan, China | EU, Japan, South Korea, Hong Kong |

PK=pharmacokinetic. QTc=corrected QT interval on electrocardiogram. EU=European Union. RCT=randomised controlled trial.

***Table:*** **Summary of clinical evidence, policy, and access considerations for novel agents to treat drug-resistant tuberculosis**

In terms of choosing between the two drugs, we recommend bedaquiline for patients for whom an effective, tolerable regimen can be constructed with only one newer drug. Bedaquiline has been more widely used than delamanid in treatment programmes and is the appropriate choice until phase 3 results are available.

In some instances, delamanid is the preferred novel agent, for example in children younger than 12 years and pregnant women. Although both drugs are presumed safe during pregnancy, the long half-life of bedaquiline could mean that newborn babies will have bedaquiline in their system after birth. Delamanid should also be used in the following groups: people with liver toxicity and those using alcohol, as defined in national protocols; people on efavirenz-based antiretroviral therapy if efavirenz cannot be changed; people on opioid substitution therapy and possibly people on hepatitis C treatment, because of fewer drug interactions than bedaquiline (although there have been no formal studies of either drug in people with hepatitis C); and people at high risk of treatment failure and who need an additional agent added to their standard multidrug-resistant tuberculosis treatment, as per the 2014 WHO recommendations.[12]

Finally, emerging safety data suggest that a combination of bedaquiline and delamanid could be used as part of multidrug backbone therapy for people with limited options.[13] Combination should be considered in people with drug-resistant tuberculosis in whom a four-drug regimen plus pyrazinamide cannot be constructed with only one novel agent; people who received the WHO-recommended shortened regimen without success; people with previous exposure to clofazimine; people with previous exposure to linezolid; and people given multidrug-resistant tuberculosis treatment using conventional regimens without success.

When bedaquiline and delamanid are given in combination, patients should receive a baseline electrocardiogram to assess the corrected QT interval, repeat electrocardiograms every 2 weeks for 12 weeks, then monthly thereafter. Patients should also receive counselling and sign a consent form stating they are aware of the limited experience using these two drugs together, they understand the possible benefits and risks, and they agree to treatment.

In summary, tuberculosis programmes should make both bedaquiline and delamanid available. Although there are no efficacy data to guide the choice of one agent over the other, there are clinical scenarios that favour either bedaquiline or delamanid, and there are some patients who will need both. It is imperative that multiple therapeutic options be available to provide the best possible treatment for people living with this disease.

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