Population implications of the use of bedaquiline in people with extensively drug-resistant tuberculosis: are fears of resistance justified?

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Global rollout of the new antituberculosis drug bedaquiline has been slow, in part reflecting concerns about spread of bedaquiline resistance. Acquired resistance to bedaquiline is especially likely in patients with extensively drug-resistant (XDR) tuberculosis. However, the very high mortality rates of patients with XDR not receiving bedaquiline, and promising cohort study results, suggest these patients also have greatest need for the drug. In this Personal View, we argue that resistance concerns should not forestall use of bedaquiline in patients with XDR tuberculosis. Our position in favour of increased access to bedaquiline for these patients is based on three arguments. First, the use of drug combinations that include bedaquiline might prevent spread of XDR disease to others in the community. Second, until new combination regimens of novel drugs for XDR tuberculosis become available, patients with XDR disease and their infected contacts will face equivalent outcomes if bedaquiline is either not provided because of policy, or not effective because of resistance. Finally, because resistance to bedaquiline and other antituberculosis drugs is caused by mutations within a single bacterial chromosome, use of bedaquiline in patients with XDR tuberculosis will not substantially increase the risk of bedaquiline resistance in patients with drug-susceptible or multidrug-resistant (non-XDR) tuberculosis strains.

Introduction

Tuberculosis is once again the leading infectious cause of death worldwide.[1] Treatment and prevention strategies rely on identification of active cases and provision of effective antibiotic treatment. Antibiotic resistance has been documented globally, and is increasingly identified as a serious threat to tuberculosis control.[2,3] Since the initial recognition of patients infected with extensively drug-resistant (XDR) tuberculosis (resistant to the first-line drugs rifampicin and isoniazid, as well as at least one fluoroquinolone and one second-line injectable drug), patients with XDR disease have been identified in 117 countries.[1] Treatment outcomes for this form of tuberculosis are very poor, with success achieved in less than 40% of patients.[4,5] Patients who have not responded to therapy for XDR tuberculosis might be sent home while still infectious to await their probable death, leading some clinicians to suggest the reintroduction of sanatoria.[6]

Discovery of new antituberculosis drugs could provide a beacon of hope for patients with XDR disease. One such drug, bedaquiline, has been approved by several stringent regulatory authorities and has been recommended for treatment of multidrug-resistant (MDR) tuberculosis by WHO since 2013.[7] In this Personal View, we provide a brief summary of the potential effect of bedaquiline use for individual patients with XDR disease. We then discuss the potential population effect on the spread of disease and resistance in the community when using bedaquiline in these patients. Many of the population arguments presented here in favour of bedaquiline use also apply to other novel agents, such as delamanid, and provide strong support for investigation of new drug combinations, for example, bedaquiline and delamanid, or the novel regimen of bedaquiline, pretomanid, and linezolid, which

is being explored in the Nix-TB trial (NCT02333799).[8] However, we focus on bedaquiline in particular (and in combination with an optimised background regimen) on the basis of its accessibility and the urgent need for improved treatment options for patients with XDR tuberculosis.

Individual effect of bedaquiline

Clinical trials[9,10] of bedaquiline for MDR tuberculosis (resistant to isoniazid and rifampicin) and pre-XDR tuberculosis (resistant to isoniazid, rifampicin, and at least one fluoroquinolone or second-line injectable drug) have shown significantly faster times to culture conversion for patients receiving bedaquiline in combination with an optimised background regimen, compared with an optimised background regimen alone. Cohort studies[11–14] of patients with MDR, pre-XDR, and XDR tuberculosis receiving bedaquiline in addition to optimised background regimens have shown success rates of 62–96%. These findings are consistent with studies[4,15] showing associations between the number of effective drugs in older MDR and XDR tuberculosis regimens and improved treatment outcomes, including declines in treatment failure, death, and acquired resistance.

Despite these results, use of bedaquiline for the treatment of MDR and XDR tuberculosis globally is still rare.[16] The slow uptake of bedaquiline is partly explained by concerns of excess mortality, as observed in the treatment arm of a pivotal phase 2b trial.[17] Subsequent observational studies[11–14,18] of patients receiving bedaquiline have shown promising mortality rates compared with historical cohorts, although these analyses are limited by an absence of control groups. Concerns about adverse drug effects are probably less

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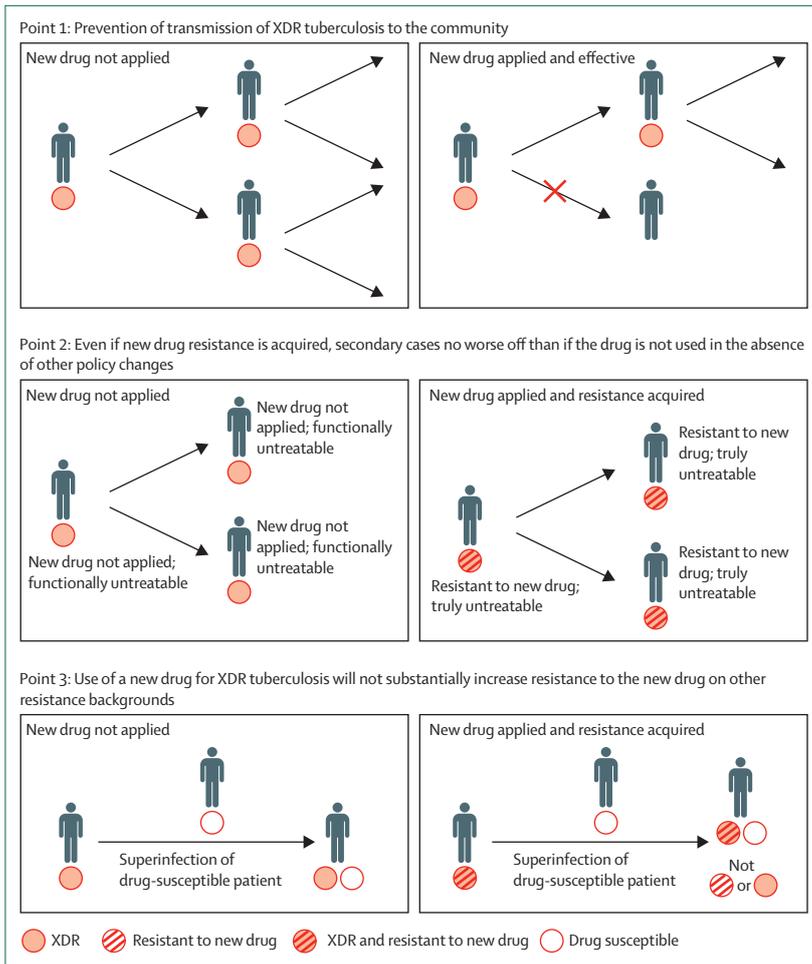agkunkel@gmail.com

Figure: **Arguments in favour of bedaquiline use in patients with XDR tuberculosis**
XDR=extensively drug-resistant.

applicable in patients with XDR disease, who have a very high risk of death from tuberculosis and are therefore most likely to benefit from addition of another effective drug.

Regardless of the potential benefits of bedaquiline at the individual level, several researchers have also expressed concerns about the population effect of introducing bedaquiline for people with XDR tuberculosis or resistance beyond XDR. In particular, researchers have warned that the weak background regimens available to these patients could lead to acquired resistance to bedaquiline and spread of bedaquiline resistance in the community.[19–21] Studies on rates of acquired resistance to bedaquiline are still scarce, particularly in vivo, and have been hampered by the absence of a drug susceptibility test with clinically relevant breakpoints.[7,22,23] Despite this uncertainty, consideration of the epidemiological principles underlying transmission of tuberculosis and drug resistance allows us to draw several conclusions about the possible population-level implications of bedaquiline use in patients with XDR disease.

Population implications

Concerns about acquired resistance to bedaquiline underscore the need to combine new antituberculosis drugs with the strongest possible background regimens for all patients in whom they are used. These concerns additionally suggest a potential benefit of introducing bedaquiline to patients before XDR disease has developed, when the new drug could be best protected by effective companion drugs.[24] However, we find it worrisome that these population-level concerns have also been used to argue for withholding bedaquiline from patients with the most highly resistant tuberculosis, namely those with greatest need for a new drug. In a 2017 court case,[25] the National Institute of Tuberculosis and Respiratory Diseases in India justified the decision not to provide bedaquiline to an 18-year-old patient with resistance beyond XDR, warning that use of bedaquiline with an inadequate background regimen could potentially lead to "catastrophic" consequences in the community.

But would the potential population consequences of using bedaquiline in patients with such highly resistant disease truly be catastrophic? We feel that such non-specific language obscures the true potential consequences of using a new drug in patients with the most highly resistant tuberculosis. Although care should be taken to construct the background regimen with greatest likelihood of success, we suggest that the actual risk to the community of the use of new drugs in patients with XDR tuberculosis or resistance beyond XDR might be less than is generally recognised. We base this argument on the following three statements (figure). First, if introduction of a new antituberculosis drug renders a suboptimal background regimen fully or partly effective, a combination treatment regimen that includes this new drug could prevent spread of XDR disease in the community. Second, if the index patient acquires resistance to a new drug, this patient could indeed spread XDR tuberculosis plus resistance to the new drug to the community. In the absence of any additional policy changes, however, these patients would be no worse off than had they been infected with XDR disease without resistance to the new drug and not been eligible for drug access. Finally, because antituberculosis drug resistance is chromosomally mediated, providing a new drug in combination with an optimised background regimen to patients with XDR disease will not substantially increase the prevalence of tuberculosis strains resistant to the new drug but otherwise drug-susceptible or MDR (excluding XDR). Below, we elaborate on these three statements separately.

A crucial feature of tuberculosis control is that effective treatment can render patients non-infectious within days, long before cure or even culture conversion are achieved. This effect has been shown in studies[26,27] of guineapigs exposed to patients with both drug-susceptible and MDR tuberculosis started on effective treatment.

The question of whether a treatment is effective here refers to the ability of a treatment to reduce transmission. Studies have not yet been published on the effect of bedaquiline on transmission of XDR tuberculosis. However, numerous studies[28–30] have shown large differences in transmission between patients with smear-positive, smear-negative, and culture-negative tuberculosis. Clinical trials[9,17] of bedaquiline in combination with optimised background regimens have shown significantly decreased times to sputum culture conversion in patients with MDR and pre-XDR tuberculosis, and cohort studies[11–13] have shown promising time to culture conversion results among patients with XDR disease. As such, it seems likely that bedaquiline would also be at least somewhat effective at reducing transmission of XDR infections.

Such an effect on transmission could have a major impact on the health of patients' families, communities, and health-care workers. Studies[3,31–34] have increasingly shown the importance of transmission as a major driver of XDR tuberculosis epidemics. Patient discharge from hospital after failure of treatment for XDR disease has been linked to clustering of cases and transmission within families.[5,35] Studies[36,37] have also shown increased risk among health-care workers caring for patients with MDR and XDR disease, showing an important potential role for bedaquiline in improving infection control within hospitals.

Multidrug first-line regimens for tuberculosis have drastically reduced the acquisition of resistance compared with early trials of single-drug therapy.[38,39] Single-drug resistance greatly increases the risk of acquiring MDR disease, and additional resistance is a strong predictor of acquired XDR disease among patients with MDR tuberculosis.[4,40] It is therefore probable, and widely recognised, that resistance to new antituberculosis drugs is most likely to be prevented through use of a combination regimen with multiple effective drugs, and physicians should seek to combine bedaquiline with multiple other drugs deemed most likely to be effective whenever possible. Because of the very long half-life of bedaquiline, physicians should also consider extending the duration of companion drugs well past cessation of bedaquiline.[41] Finally, physicians might wish to consider combining bedaquiline with additional novel agents, such as delamanid, if available.

The challenge arises for patients with XDR tuberculosis who, because of setting and resistance patterns, have few effective drug options available besides bedaquiline. In such scenarios, policies such as never adding a single drug to a failing regimen[7] might mean withholding the most promising new drug currently available from the most unwell patients. In fact, patients with XDR disease plus additional resistance are often denied access to bedaquiline because of an absence of sufficient companion drugs.[42] Under such a policy, all patients with these resistance patterns would be considered untreatable, although giving them bedaquiline could substantially increase their chance of cure. If these patients were instead treated with a combination regimen including bedaquiline, their chance of cure would probably increase, and even if they acquired resistance to bedaquiline, they would be no worse off in terms of clinical status than if bedaquiline had never been available to them. One caveat is that resistance to bedaquiline acquired in this manner could also lead to resistance to clofazimine through a common efflux pump mechanism; however, we consider this a minor concern given the stronger existing evidence base for bedaquiline in treatment of MDR and XDR tuberculosis than for clofazimine.[43,44]

The same argument might be made for any secondary cases. Patients with XDR tuberculosis plus resistance to bedaquiline could transmit this resistance pattern to other individuals, thereby spreading untreatable infections. However, under a policy that restricts bedaquiline use in patients with XDR tuberculosis, XDR transmission without bedaquiline resistance would already be spreading infections that are in practice untreatable. Thus, in the absence of other policy changes, introducing bedaquiline would leave both the index patient and all downstream infected patients no worse off than if the drug were not used, even if resistance is acquired.

We note that this argument is dependent on the assumption that treatment policies applied to index cases will also be applied to secondary cases. In some specific instances in which that assumption does not hold, such as when a second new and effective drug is known to be available shortly, secondary cases might be better served by withholding the first drug from index cases until such a change occurs. This might be the case, for example, in countries with access to bedaquiline but awaiting arrival of another new antituberculosis drug, delamanid. There has been great reluctance, however, to use bedaquiline and delamanid in combination.[45] A three-drug regimen of bedaquiline, linezolid, and the novel drug pretomanid has shown promising early results; however, the time at which this combination could become available is unclear, particularly because pretomanid has not yet received regulatory approval.[8,46] In South Africa, combinations of bedaquiline with linezolid, in addition to an optimised background regimen, are being widely applied with promising results.[13,42] Such an approach might provide a balance between the desire to improve future patients' treatment outcomes by combining bedaquiline with other drugs, and the recognition that if physicians wait for entirely novel regimens before providing bedaquiline to patients with XDR tuberculosis, thousands of people will die and the spread of XDR disease will continue.

In addition to regimens for XDR tuberculosis, bedaquiline is also being considered as an element of entirely novel regimens for drug-susceptible and MDR disease.[47] This potential role for bedaquiline might contribute to hesitancy in providing it to patients with XDR disease, in whom it

is not well protected. We argue, however, that use of bedaquiline in patients with XDR tuberculosis would not have a substantial impact on the efficacy of bedaquiline in patients with other background resistance patterns (eg, drug-susceptible or MDR tuberculosis).

The key difference between drug-resistant tuberculosis and many other drug-resistant bacteria is that resistance in tuberculosis is exclusively chromosomally mediated, and not achieved through horizontal gene transfer.[48,49] In other words, the driving mechanism in tuberculosis drug resistance is the occurrence of resistance-conferring mutations within the bacterial chromosome. Because resistance to all drugs is conferred by different mutations on the same chromosome, resistance to the new drug will always occur only in combination with the background on which it was acquired. The bacteria of a patient with XDR disease who acquires resistance to bedaquiline will exhibit mutations causing both extensive drug resistance and bedaquiline resistance together on the same chromosome. Although they might transmit bedaquiline-resistant XDR tuberculosis to other individuals, such patients cannot transmit bedaquiline resistance on any other background, for example, tuberculosis that is resistant to bedaquiline but susceptible to all other drugs.

Therefore, the only way that bedaquiline treatment of patients with XDR disease could lead to bedaquiline resistance in combination with other background resistance patterns is if the patients receiving bedaquiline have heteroresistant infections.[50] For example, a patient harbouring drug-susceptible and XDR tuberculosis strains who receives bedaquiline could potentially develop and spread infection that is resistant to bedaquiline but susceptible to all other drugs. However, this risk will be minor given that bedaquiline is provided with an optimised background regimen that can suppress any less resistant minority strains.

Conclusion

Many clinical trials of novel combination regimens are underway, including regimens containing bedaquiline, delamanid, pretomanid, linezolid, and clofazimine for patients with XDR tuberculosis.[51] The results of these trials are likely to be available years from now, and in the meantime people continue to die from XDR disease. Studies[34,52] suggest XDR tuberculosis transmission might already be a substantial problem in some settings. For the first time in decades, however, there are newly approved single antituberculosis drugs and patients with XDR disease and resistance beyond XDR who do not have time to wait. Though providing bedaquiline to such patients poses other questions beyond those explored here, including issues of clinical management (such as QT monitoring, combination with other QT-prolonging drugs, and changing antiretroviral regimens) and cost-effectiveness, population-level resistance concerns are one of the primary arguments that have so far been used to restrict such patients from receiving bedaquiline.[25,42] We hope that this clarification of the population risks of using bedaquiline, which would also apply to the use of the other novel antituberculosis drug delamanid and other novel combinations, will encourage careful consideration of the risks and benefits of using bedaquiline in such patients, and ultimately support more widespread use in patients with few alternative treatment options.

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