Precision medicine for drug-resistant tuberculosis in high-burden countries: is individualised treatment desirable and feasible?

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Treatment for drug-resistant tuberculosis is largely delivered through standardised, empirical combination regimens in low-resource, high-burden settings. However, individualised treatment, guided by detailed drug susceptibility testing, probably results in improved individual outcomes and is the standard of care in well-resourced settings. Driven by the urgent need to scale up treatment provision, new tuberculosis drugs, incorporated into standardised regimens, are being tested. Although standardised regimens are expected to improve access to treatment in high-burden settings, they are also likely to contribute to the emergence of resistance, even with good clinical management. We argue that a balance is required between the need to improve treatment access and the imperative to minimise resistance amplification and provide the highest standard of care, through a precision medicine approach. In tuberculosis, as in other diseases, we should aim to reduce the entrenched inequalities that manifest as different standards of care in different settings.

Lancet Infect Dis 2018

Published Online
March 13, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30104-X

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Introduction

The recommended programmatic treatment of tuberculosis in high-burden countries has, until recently, been based on treatment of the so-called average patient, with a one-size-fits-all approach. However, the concept of precision medicine, treatment strategies that take individual variability into account—although not new—is now receiving increased attention.[1] This attention is partly due to an increasing capacity to create and use large-scale biological databases, particularly of genomic sequence data. Although the potential for precision medicine to improve the health of people in low-income settings has been questioned,[2] the increasing use of communication technology, even in the poorest settings, offers opportunities to improve data collection and individual medical care.[3]

One of the most obvious examples of how precision medicine might be effectively applied in tuberculosis treatment is in the creation of individualised treatment regimens for patients with drug-resistant tuberculosis, based on the detailed characterisation of the resistance profile of the bacterium. In this Personal View, we describe how a precision medicine approach might be used to improve the treatment of drug-resistant tuberculosis, and contrast this with the benefits associated with a standardised treatment approach, which allows greater treatment scale-up and reflects the realities of settings with a high burden of drug-resistant tuberculosis. We argue that a balance is required between these two potentially conflicting approaches, but seeking the highest quality of care in all settings should be an ethical imperative for treatment of drug-resistant tuberculosis.

Background

Drug-resistant tuberculosis is recognised as a substantial threat to the efforts to reach the targets set out by WHO in their End Tuberculosis Strategy.[4] Although an estimated 580 000 cases of tuberculosis with resistance to rifampicin emerge each year, only 125 000 patients are diagnosed and started on recommended second-line treatment regimens.[5] Among the 30 countries with a high burden of multidrug-resistant (MDR) tuberculosis (tuberculosis resistant to rifampicin and isoniazid), encompassing 87% of the global burden, all but Russia are classified as low-income or middle-income countries.[5,6]

Treatment regimens for drug-resistant tuberculosis have primarily been constructed on the basis of observational data, with little clinical trial evidence, and include a range of older tuberculosis drugs and newer drugs repurposed for treatment of tuberculosis.[7,8] Treatment is lengthy, often associated with debilitating side-effects, and only results in a cure for approximately 50% of patients under programmatic conditions.[5] Most patients with rifampicin-resistant tuberculosis (including MDR tuberculosis) who are fortunate enough to receive treatment are treated with standardised regimens. Treatment can be adjusted if patients are affected by drug toxicity or intolerance to second-line drugs, or if second-line drug susceptibility testing (DST) is available and shows further resistance, such as extensively drug-resistant (XDR) tuberculosis (MDR tuberculosis with additional resistance to second-line injectable drugs and fluoroquinolones) or pre-XDR tuberculosis (MDR tuberculosis with resistance to either injectable drugs or fluoroquinolones).

Encouragingly, the arrival of new tuberculosis drugs, bedaquiline and delamanid, has raised the prospect of much improved treatment for drug-resistant tuberculosis.[9] These drugs have primarily been recommended by WHO for patients with extensive drug resistance who require individualised drug regimens, on the basis of DST and previous use of tuberculosis drugs.[10,11] Several clinical trials[12] are in progress with the goal of incorporating the new drugs into shorter, more effective, and more tolerable treatment regimens for all patients with drug-resistant tuberculosis. These trials aim to test a

	Risks	Benefits
Standardised treatment	• Increased risk of resistance amplification with potentially suboptimal regimens, with subsequent transmission of acquired resistance • Treatment with potentially ineffective, toxic drugs for specific individuals • Poorer treatment outcomes at the individual patient level	• Simplified approach to disease management, with less reliance on specialist knowledge • Treatment provision at lower health system levels, with simplified drug management and lower costs • Facilities programmatic treatment scale-up, with potential for greater effect at population level
Individual treatment	• Increased complexity in regimen formulation (requiring specialist knowledge) potentially contributing to poorer access to treatment • Increased delays to treatment initiation and pretreatment loss to follow-up	• Reduced risk of resistance amplification • Lower risk of unnecessary drug toxicity and more rapid clinical improvement with effective treatment (better risk–benefits ratio), potentially reducing risk of loss to follow-up during treatment • Improved treatment outcomes for individual patients

Figure: **Contrasting potential risks and benefits for standardised and individualised treatment of drug-resistant tuberculosis**

range of different standard drug combinations that would cover a wide range of drug resistance profiles and minimise reliance on detailed DST at the individual level.

By contrast with the standardised approach used in high-burden countries, in many low-burden, high-resource settings, patients with drug-resistant tuberculosis have access to the full range of new, repurposed, and existing tuberculosis drugs, and they receive regimens that are individualised according to results of sensitivity tests for a large array of drugs. This difference in treatment approaches raises questions as to the desirability and feasibility of individualised treatment for all patients with drug-resistant tuberculosis (figure).

Recommendations and use of standardised treatment in high-burden settings

WHO recommends that treatment regimens for rifampicin-resistant or MDR tuberculosis, lasting 18 months or longer, could be either standardised or individualised, and be designed to include the minimum number of second-line drugs considered to be effective.[8] In 2016, WHO produced a conditional recommendation on the use of a shorter drug-resistant tuberculosis regimen lasting 9–12 months, which is largely standardised.[13] Probable effectiveness of drugs can be estimated at a population level by use of drug resistance surveillance data, which can inform the design of a standardised regimen for patients in a particular setting.

Traditionally, DST has been slow because it relies on culturing *Mycobacterium tuberculosis* and phenotypic resistance testing (comparing growth in the presence and absence of antibiotic). Genotypic DST (detecting bacterial chromosomal mutations that confer resistance), using tests such as the Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA, USA) and line probe assays, offers the opportunity for quicker diagnosis, but commercially available tests are restricted in terms of the number of resistance-conferring mutations that can be identified. Rapid treatment initiation after early detection of rifampicin-resistant tuberculosis (often used as a proxy marker for further drug resistance) is increasingly emphasised as a way to avert pretreatment mortality and reduce further transmission.[14,15] As a result, standardised treatment regimens are often started on the basis of phenotypic or genotypic resistance to one or two key drugs. These regimens might be suboptimal in many patients with second-line drug resistance, and might require adjustment after additional DST results become available, to maintain an adequate regimen with at least five effective drugs.[5,8] However, for most patients, standardised regimens are continued throughout treatment, because only 36% of patients with rifampicin-resistant or MDR tuberculosis globally receive DST for second-line drugs.[5]

Risks associated with standardised treatment approaches

One of the main objectives of tuberculosis treatment combinations is to minimise acquisition of resistance during therapy, or the amplification of resistance.[16] Historically, resistance has emerged to all tuberculosis drugs in widespread use, with subsequent transmission of these resistant strains.[17–19] Resistance is most likely to emerge when patients are treated with an inadequate regimen, including only one or two active drugs.[20,21]

During treatment of MDR tuberculosis, with baseline resistance to three or more second-line drugs, the risk of developing XDR tuberculosis was 44%.[22] Although resistance to new drugs is likely to be low, increased use of repurposed drugs, such as linezolid, for the treatment of tuberculosis has resulted in the emergence of linezolid resistance.[23] Even within countries, the presence of second-line resistance varies substantially across different settings,[24] suggesting that a standardised MDR tuberculosis regimen that is effective in one setting might not be as effective throughout the country. Without knowledge of resistance to key drugs at the individual level, standardised regimens will inevitably result in resistance amplification, including resistance to new drugs, even with prudent clinical management and programme oversight.

New standardised regimens on the horizon

There are at least five randomised clinical trials underway or planned that include new drugs in novel combinations for drug-resistant tuberculosis treatment.[12] These trials are predominantly testing standardised drug combinations for the treatment of either MDR or XDR tuberculosis, although some are designed to effectively treat both. Indeed, broad effectiveness against both MDR and XDR tuberculosis is a stated objective of trials done by the Global Alliance for Tuberculosis Drug Development, and trials to be done by Médecins Sans Frontières and Partners in Health.[25,26]

Although it is difficult to estimate the durability of these novel regimens (ie, how long it will take for resistance to emerge and become fixed in a population), some factors might determine the length of time that a standardised

regimen would continue to be effective. These factors include the number of new drug classes in the regimen, reliance on existing drugs, and the total number of drugs. Inclusion of at least two new drug classes in a standardised regimen is likely to substantially reduce the risk of inadvertent monotherapy and resistance amplification. Conversely, the inclusion of only three drugs in a regimen, such as in the Nix-TB trial,[12] might lead to increased risk of resistance amplification if there is undiagnosed resistance to just one of the three drugs.

Benefits of individualised treatment

By contrast with the use of standardised regimens, individualised regimens are designed according to the drug resistance profile of the organism that is infecting an individual and therefore fall into the category of precision medicine. Given the limitations of both phenotypic and available rapid genotypic DST, alternative approaches have been proposed, such as whole genome sequencing, to predict drug susceptibility for a wide range of first-line and second-line tuberculosis drugs.[27–29] In a study done across eight laboratories in Europe and North America,[27] 93% of isolates sequenced within a clinically relevant timeframe produced DST profiles concordant with phenotypic DST results. On the basis of these results, and in an effort to improve treatment outcomes,[30] whole genome sequencing is being implemented to guide treatment for all patients with tuberculosis in the UK.[31] In high-resource settings, such as the UK, most patients receive individualised treatment that is guided by detailed, individual-level DST profiles.[32,33] Reports have suggested treatment success rates greater than 80% with individualised treatment in countries such as the Netherlands, Canada, and South Korea.[34–36] Indeed, there is potential for treatment to be further individualised on the basis of the results of detailed therapeutic drug monitoring in these settings.[37] Individualisation is also often needed because of drug toxicities and drug–drug interactions, particularly when comorbidities, such as HIV infection and diabetes, are present.

In addition to improved treatment outcomes, individualisation reduces the risk of patients receiving poorly tolerated and potentially toxic drugs that are ineffective because of undiagnosed resistance. Available second-line drugs are associated with debilitating and often severe adverse effects,[38,39] which in turn contribute to poor adherence and further resistance generation. Minimising the use of unnecessary drugs and tailoring a regimen according to an individual's drug tolerance is likely to result in decreased permanent disability, such as hearing loss, increased patient acceptability, and improved patient outcomes.

Benefits of simplified, standardised treatment in high-burden settings

Although individualised treatment regimens can be desirable, both for the individual patient (improved outcome, reduced toxicity, and decreased pill burden) and for the community (reduced transmission of strains with amplified resistance), these benefits need to be balanced against programmatic constraints. In high-burden settings, a widespread programmatic use of simplified and potentially shortened regimens is likely to increase access to treatment for the majority of people with tuberculosis, and treatment success among those treated. In countries that treat the largest numbers of patients, treatment success is lower than the global average of 50%.[5] Standardised regimens simplify clinical decision making, pharmacy management, and evaluation of outcomes and therefore simplify programme management at a large scale.

One of the advantages of the so-called directly observed treatment, short-course strategy (DOTS) recommended by WHO for drug-susceptible tuberculosis, is the capacity for diagnosis and treatment to be delivered at primary care level.[40] Similarly, standardised regimens that can be used for all patients diagnosed with rifampicin-resistant tuberculosis (ie, after the Xpert test), which do not require injections, with minimal side-effects, and simple dosing, could feasibly be administered in primary care settings by less specialised staff. Such a strategy could greatly alter the proportion of patients accessing treatment and, even with conservative improvements in proportional treatment success, would result in effective treatment of a much greater proportion of the total drug-resistant tuberculosis burden, thereby curtailing ongoing transmission.[41] However, although standardised regimens are likely to increase access and improve outcomes in the short term, the risk of resistance amplification threatens these benefits in the long term.

Balancing treatment access and quality of care

The benefits of applying a precision medicine or individualised approach to the patient with drug-resistant tuberculosis should, therefore, be balanced with the need to scale up treatment for the majority of patients who reside in low-resource, high-burden settings. This trade-off is one between practicality and ethical and human rights questions: does the reality of constrained resources and high patient load necessarily imply that different standards of care be used for patients depending on where they live? Or should we strive to implement systems that could deliver the benefits of precision medicine and individualised care to all patients with drug-resistant tuberculosis?

Similar questions were raised in a discussion of the historical double standard in the provision of MDR tuberculosis treatment.[42] Despite the availability of treatment for MDR tuberculosis in high-resource settings, for example, for patients in the well-publicised outbreak in New York in the 1990s,[43] WHO advice was directed more towards prevention of resistance emergence through strengthening treatment for susceptible tuberculosis, rather than specific MDR tuberculosis treatment.[44]

Although factors such as the scarcity of data outlining the extent of the MDR tuberculosis problem, weak health systems, and shortage of human resources capacity could account for this historical approach, the primary consideration is argued to have been the costs associated with MDR tuberculosis treatment.[42] These costs remain several orders of magnitude higher than those for drug-susceptible tuberculosis treatment, ranging from USD$2000–8000 per patient.[5,45] Indeed, cost remains a substantial barrier to scale up of MDR tuberculosis treatment in many settings.[46] Although the recommendation of a shorter treatment regimen is estimated to cost less, at approximately $1000 per patient,[5] these costs are often viewed in the short term, without acknowledging the long-term costs of potential resistance amplification or long-term savings due to reduced transmission.[47]

The right to health is enshrined as a basic human right in article 12 of the International Covenant on Economic, Social, and Cultural Rights.[48] Arguments based on the right to health were used effectively to promote scale-up of access to HIV treatment globally, even in some of the world's poorest countries.[49] Unfortunately, advocacy for MDR tuberculosis treatment has not reached a similar success.[50] The right to health is described in the WHO constitution as "the highest attainable standard of health as a fundamental right of every human being."[51] Although the term attainable suggests that the standard of care might vary according to the resources available in a particular setting, we have long relied on substandard tools and strategies for most patients with tuberculosis. This is a reality that should be continuously challenged.

Panel: **Policy implications and future research in this area**

Key policy implications:

- Precision medicine offers the opportunity to improve treatment of drug-resistant tuberculosis through reduced toxicity and improved outcomes for patients, while reducing the risk of resistance amplification and further transmission at a population level
- Policy makers should aim to progressively reduce inequalities in treatment provision and quality across different settings
- Policies directed at improving access to treatment for drug-resistant tuberculosis need to balance both short-term benefits (such as cost and reduced complexity) and long-term consequences (increased drug resistance)
- Implementation of more individualised treatment for drug-resistant tuberculosis in high-burden settings should aim to avoid a situation in which the disease is only managed by specialists in centralised settings
- Precision medicine for drug-resistant tuberculosis requires a reduction in barriers to accessing new and repurposed drugs, such as costs and regulatory bureaucracy

Implications for future research:

- Operational research projects are required to assess the feasibility and effects of individualised treatment that is guided by detailed drug susceptibility testing in high-burden settings
- Efforts towards operationalising whole genome sequencing for accurate resistance prediction in high-burden settings are important
- Reducing the requirement of initial culture of tuberculosis isolates before whole genome sequencing, is a continued research priority
- Further work to assess associations between genotypic, phenotypic, and clinically relevant resistance would be beneficial

Antimicrobial resistance is a global problem

Resistance to tuberculosis drugs is part of the wider, global problem of antimicrobial resistance that is increasingly gaining substantial public and political attention.[52] 700 000 deaths each year are estimated to result from antimicrobial resistance, with predictions that this number might increase to a staggering 10 million lives lost by 2050.[53] However, more individuals are estimated to die from insufficient access to effective antimicrobials than from resistant disease.[54]

Strategies to respond to the need for improved access to effective antimicrobials and to the increasing threat of resistance include substantial increases in funding for research of new drugs.[55] For tuberculosis, however, funding for new drug research does not meet global targets and decreased in 2015, compared with previous years.[56] The lack of attention to tuberculosis was also highlighted when *M tuberculosis* was not included in a list of bacteria for which new drugs are urgently needed.[57] Although access to bedaquiline and delamanid has been met with much excitement, these drugs are the first new tuberculosis drugs to reach the market in more than 40 years and access remains insufficient in most high-burden settings.[58] The increasing global attention to antimicrobial stewardship, defined as a coordinated programme that promotes the appropriate use of antibiotics to improve patient outcomes, reduce resistance, and decrease the spread of infections caused by resistant organisms, is a timely reminder to apply these principles to MDR tuberculosis treatment. Use of standardised regimens that risk poor outcomes for patients, amplification of resistance, and transmission of highly resistant strains is poor stewardship of the few antibiotics that we have available to treat this disease.

Conclusions

Access to effective diagnosis and treatment has remained unattainable for the majority of the 580 000 individuals that are estimated to develop drug-resistant tuberculosis each year. For the few who receive treatment, the treatment course is lengthy, arduous, and associated with considerable side-effects, often resulting in permanent disability. Additionally, patients are generally poorly supported throughout this lengthy treatment, and those among the half that are cured can be left socially isolated and suffering catastrophic economic costs.[59] In this context, the scale-up of simplified, standardised, and more patient-centred treatment could provide tangible benefits and should be an urgent priority.

However, we would argue that universal access to standardised treatment is a minimum requirement. Countries should aim to fulfil their responsibilities to progressively achieve the right to the highest attainable standard of health through increased individualisation.

 Published online March 13, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30104-X

This effort should not divert resources away from providing universal access to care, but should seek to enhance the quality of care in an iterative manner. In this context, implementation of the recommended shorter MDR tuberculosis treatment regimen (with existing drugs) could be used to increase access where needed, but might be considered a temporary measure in settings that have the health system capacity to provide more individualised care.

Ultimately, a range of evolving strategies across different settings, and designed according to disease burden, drug-resistance profile, and health system capacity are likely to be required (panel). These strategies can incorporate individualisation to varying degrees, for example, by allocating patients to one of several standardised regimens. Individualisation can be done based on key decision points according to more detailed patient-level DST, with the overall aim to achieve cure with a minimum of drug-related harm. Although there might be no right or wrong approaches, considerations of equity and provision of the highest standard of care that can be attained for each setting should be at the forefront of decision making.

To drive innovation and reduce the risk of entrenched inequalities, one approach would be to encourage the funding and support of pragmatic pilot programmes providing fully individualised high-quality treatment for drug-resistant tuberculosis at scale, in high-burden settings. Such programmes would be both a means to learn what works and what does not, and catalysts to drive quality improvement in settings beyond the pilot stages. Ultimately, our aim should be to strike a balance between maximising the chances of cure for the individual through precision medicine, providing universal access to effective treatment, and minimising the risk of further resistance development.

Contributors

All authors contributed to the conceptualisation and writing of this manuscript.

Declaration of interests

HC reports grants from the Swiss/South Africa Joint Research Programme (SSAJRP), outside the submitted work. MPN reports grants from the Foundation for Innovative New Diagnostics, outside the submitted work. JH and JB declare no competing interests.

Acknowledgements

HC, JB, and MPN acknowledge support from the Medical Research Council of the UK (Grant ref: MR/N015924/1) to study delivery of care for drug-resistant tuberculosis. This UK-funded award is part of the EDCTP2 programme supported by the European Union. HC is supported by a fellowship from the Wellcome Trust (No. 099818/Z/12/Z).

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