Quality of drug-resistant tuberculosis care: Gaps and solutions

Zarir Udwadia[a], Jennifer Furin[b,*]

[a] Hinduja Hospital, Mumbai, India
[b] Harvard Medical School, Department of Global Health and Social Medicine, 641 Huntington Ave., Boston, MA, 02115, USA

ABSTRACT

Drug-resistant forms of tuberculosis (DR-TB) are a significant cause of global morbidity and mortality and the treatment of DR-TB is characterized by long and toxic regimens that result in low rates of cure. There are few formal studies documenting the quality of DR-TB treatment services provided globally, but the limited data that do exist show there is a quality crisis in the field. This paper reviews current issues impacting quality of care in DR-TB, including within the areas of patient-centeredness, safety, effectiveness and equity. Specific issues affecting DR-TB quality of care include: 1) the use of regimens with limited efficacy, significant toxicity, and high pill burden; 2) standardized treatment without drug susceptibility testing; 3) non-quality assured medications and drug stock outs; 4) lack of access to newer and repurposed drugs; 5) high rates of adverse events coupled with minimal monitoring and management; 6) care provided by multiple providers in the private sector; 7) depression, anxiety, and stress; and 8) stigma and discrimination. The paper discusses potential ways to improve quality in each of these areas and concludes that many of these issues arise from the traditional "public health approach" to TB and will only transformed when a human-rights based approach is put into practice.

1. Introduction

The world is facing a crisis in antimicrobial resistance, and drug-resistant forms of tuberculosis (DR-TB) are one of the significant pathogens in this growing threat to global health [1]. Although insufficient access to diagnosis and treatment for DR-TB remain significant challenges—with only 160,684 of the 558,000 people estimated to become sick with DR-TB each year being diagnosed and only 139,114 (25%) of them started on treatment—poor quality care is rampant in the field [2]. This is reflected in the 65% treatment success rate globally but also in other insidious ways in the DR-TB treatment arena [3]. Patient centeredness—a term that has inserted itself into the vocabulary of the TB field in recent years [4] if not into its actual practices—safety, equity, and effectiveness are all quality domains [5] where there are urgent needs for improvement in DR-TB. Little is known about quality in the routine management of DR-TB, however, for a number of reasons, including the fact that measures of successful treatment are based primarily on bacteriologic outcomes [6].

Three recent "cascade" reviews highlight serious problems with the way DR-TB is diagnosed and treated [7–9] but there is limited literature reporting formal assessments of quality in the treatment of DR-TB. In fact, it is only in the last two decades that the treatment of DR-TB in resource-poor settings has been viewed as a necessary and viable strategy [10]. Prior TB control efforts focused on the prevention of the development of resistance among people who were receiving treatment for drug-susceptible TB, ignoring the fact that most DR-TB occurs via primary transmission [11] and placing the locus of blame square on the shoulders of people living with TB [12]. Even now there is still a tendency to fault people living with the disease for the life-threatening predicament in which they find themselves [13], and this could be one reason why quality of care has been drastically understudied in the field of DR-TB.

2. Experiences and perceptions of quality in DR-TB care

The few studies that have been done on DR-TB and quality show a miserable experience for those individuals who become sick with DR-TB, with a participant in one study summing it up by stating: "I cry every day"[14]. In the absence of formal quality of care assessments, studies on quality of life among persons living with DR-TB become important [15]. A recent mixed-methods study done in India found low quality of life measures among people living with DR-TB, especially in the physical and psychological domains [16]. Other qualitative studies have reported similar low quality experiences for people with DR-TB, including lack of engagement in care, paternalistic attitudes of TB providers, and staffing shortages/absences that greatly compromise DR-

* Corresponding author.
  E-mail address: jennifer_furin@hms.harvard.edu (J. Furin).

TB services [17–20].

Individual perceptions of quality of care among persons living with DR-TB are driven by multiple factors [21]. Some of these can be attributed to the treatment regimens themselves and include pill burden, routine use of injectable agents, adverse events, and a lengthy duration of therapy [22]. The treatment for DR-TB is highly problematic. Boasting a global "success rate" of around 65%, the regimens given to people living with DR-TB are complex [23]. The most commonly used regimens consist of a total of five to seven different drugs given for a period of 9 to 24 months [24]. Most problematic among these agents is the daily injection that, until recently, formed the core of most DR-TB regimens, even though there was limited scientific evidence to support the use of this category of drugs and that they are associated with permanent hearing loss in as many as one of three people who receive them [25]. Recently, the WHO updated its recommendations on the routine use of injectable agents, stating that only one of these drugs (amikacin) should only be used when there are no other treatment options and then only if there is demonstrated susceptibility to it and formal hearing assessments can be done [26]. In spite of this, many programs are continuing to use these medications and have no plans to phase them out of treatment regimens anytime in the near future, in part because they are relatively cheap.

Although significant attention has been paid to the damages associated with the injectable drugs, the oral medications that are used for treating DR-TB also lead to poor quality experiences among people with the disease. In the WHO-recommended shorter DR-TB treatment regimen, a total of 13 tablets must be taken daily just for the DR-TB regimen [27]. In addition to this, the pills are associated with multiple adverse events ranging from nausea/vomiting and skin discoloration to hypothyroidism and renal failure [28]. As many as 80% of people on treatment for DR-TB experience an adverse event during treatment, and access to monitoring for and management of these side effects is limited [29]. In fact, the lack of rigorously applied standards to evaluate and treat adverse events for people with DR-TB is one of the most glaring gaps in the provision of quality DR-TB care [30]. Also of concern is the limited counseling and treatment literacy support provided to people during their treatment, with many patients reporting that they were never informed about the possibility of side effects or offered treatment alternatives [31].

Others have to do with the experience of undergoing DR-TB treatment and include psychological distress, economic hardship, and the stigma and discrimination faced by people living with DR-TB, often at the hands of medical providers themselves. The experiential treatment journey of a person who is diagnosed with DR-TB is treacherous at best [32]. High rates of depression and anxiety have been reported among persons undergoing treatment for DR-TB, and while some of this may be due to circumstances faced prior to the DR-TB diagnosis, a substantial proportion of people report worsening of mental health during the first several months of treatment [33]. These mental health issues may be associated with worse TB treatment outcomes and require management by multi-disciplinary teams consisting of counselors, social workers, and psychiatric/psychologic specialists [34]. The important roles of patient empowerment and the support provided by people who are DR-TB survivors and activists via official and unofficial support forums must also be underlined [35].

Some of the mental health challenges faced by people living with RR-TB is due to the discrimination such individuals face, including the loss of jobs, homes, and family support [36]. Of great concern, there is evidence showing that such discrimination may frequently occur at the hands of health care providers themselves [37]. This discrimination is often internalized and can increase feelings and shame and guilt leading to a worsening of mental well-being [38]. Exacerbating many of these issues is the rampant poverty that is both associated with and caused by DR-TB itself [39]. Studies show that even though TB services are technically provided "free of charge", many individuals are driven deep into an economic crisis from which they and their families cannot

emerge [40]. Multiple studies have shown that relieving these burdens can result in improved treatment outcomes [41,42]. The first target of the "End TB" strategy is to eliminate catastrophic costs for people living with TB by 2020 [43], but the international community has remained ill-equipped to address the socioeconomic needs of people with TB and will fail to achieve this bellwether target.

3. Effectiveness and equity in DR-TB care

Not only is the experience of people undergoing treatment for DR-TB of poor quality, but there are also issues regarding whether or not individuals are receiving the highest quality of care for DR-TB as well—that is the performance of DR-TB health services in the quality domains of effectiveness and equity. The global approach to TB has historically been one of "control" where there has been an emphasis on "public health" often at the detriment to individual people living with TB [44]. When programmatic management DR-TB was finally—if somewhat reluctantly—embraced, the approaches to care put forth did not focus on providing quality services. Rather, they advocated for two standards of care for people living with DR-TB, depending on the income levels of the countries and programs within which are was provided. In low resource settings, treatment recommendations eschewed the use of drug-susceptibility testing and personalized medicine that are considered the gold standard of care in wealthy countries, opting instead for standardized approaches to all patients, regardless of their individual human needs [45].

The past few years have seen promising advances in the treatment of DR-TB with both newer and re-purposed drugs demonstrating both efficacy and safety [46]. In fact, for the first time ever, the World Health Organization has strongly recommended several drugs—including bedaquiline, linezolid, and the fluoroquinolones—based on moderate quality evidence [47]. These medications have not only been associated with improved treatment outcomes in people living with DR-TB but also with lower mortality rates [48]. Access to these medications—along with clofazimine and delamanid—however, is a significant concern. An analysis done comparing estimated need with actual use found that only 15% of persons who would qualify to receive either bedaquiline or delamanid received these medications [49]. While some countries—most notably South Africa—provide bedaquiline to a majority of their patients with DR-TB, others such as India have provided bedaquiline to just over 1600 of the estimated 30,000 people who become sick annually with DRTB [50]. While there are multiple potential barriers to using the newer DR-TB medications, including regulatory delays, diagnostic roadblocks in detecting resistance, complex health-care systems dominated by unregulated private sectors, concerns about side effects and unjustified fears about development of resistance, most of these have been successfully overcome in countries where there is political will to use these life-saving agents [51]. The prevailing policy of "protecting the drug" rather than protecting the patients whose lives depend on speedy access to bedaquiline (BDQ) is to be condemned as a violation of not only the right to health but also the right to benefit from scientific progress [52].

Other factors that significantly affect the quality of care for people with DR-TB are drug stock outs—which occur at alarmingly high rates in some settings—as well as the use of products that have not been quality assured or tested. Many countries use a two-year ordering and forecasting cycle for DR-TB drug procurement which can led to imprecise quantification and both overstocking and under-stocking of medications [53]. Although the Stop TB Partnership's Global Drug Facility is able to provide most countries with second-line drugs that have gone through rigorous evaluation to ensure they meet minimal standards, many countries forego these services to procure through local suppliers [54].

Finally, the locus of DR-TB care and whether it occurs in the public sector, the private sector, or both may have a significant impact on the quality of care received. Many countries with a high burden of DR-TB

Table 1
Barriers and solutions for quality care in DR-TB.

Barrier to quality care	Potential solutions
Limited measures of studies on quality of care in DR-TB	Undertake formal studies in key settings and adopt formal quality measures as part of routine monitoring and evaluation activities undertaken by TB programs.
	Additional work should also focus on quality of life after treatment completion, since some patients have persistent and ongoing health issues caused either by the DR-TB itself or by treatment for the disease.
Poor treatment outcomes seen with current regimen	Improved regimens and treatment approaches linked to access to these clinical advances
Continued use of injectable drugs	Cessation of the injectables except in rare individuals who need them, with tangible consequences for countries, programs, and providers who continue their routine use
High pill burden	Improved regimens and treatment approaches linked to access to these clinical advances
Use of standardized regimens without drug susceptibility testing	Targeted therapy based on drug susceptibility testing to allow for the use of effective drugs and avoidance of ineffective drugs which only cause toxicity.
Use of non-quality assured medications	Procurement of medications for a quality-assured supplier of via the Stop TB Partnership's Global Drug Facility.
Medications stock outs	More frequent forecasting and ordering of medications used to treat DR-TB
Lack of access to newer and repurposed medications, including bedaquiline, delamanid and linezolid	Ensure adequate supplies of these medications are procured and evaluate access to them (i.e. percentage of people needing them who receive them) as part of program monitoring and evaluation.
High rates of adverse events	Improved regimens and treatment approaches linked to access to these clinical advances
Limited access to monitoring and management of adverse events	Basic packages of services offered as an essential part DR-TB care, with reporting on access to these types of support in addition to routine TB program outcomes
	Pharmacovigilance programs must stress quality management of adverse events, with incentives for those who meet them
	Improve treatment literacy for people living with DR-TB and their support networks and utilize counselors, social workers, and peers to provide and ongoing counseling and support throughout care.
Private providers may utilize sub-standard treatment approaches, including persons trained in other types of medical practices (i.e. homeopathy, Ayurvedic medicine)	Train private providers in the optimal treatment of DR-TB and legislate clear roles for different cadres of practitioners (i.e. active case finding, screening, treatment initiation, adverse event monitoring, etc.).
Depression, anxiety and stress of DR-TB treatment	Provide supportive counseling and services as routine DR-TB care.
	Enlist the services of multi-disciplinary teams made up of counselors, social workers, and persons with expertise in psychiatry/psychology.
Discrimination and stigma	Use existing laws and court systems to uphold the rights of people living with DR-TB
Socioeconomic burdens	Implement programs to immediately address the socioeconomic needs of people living with DR-TB, including conditional cash transfers, nutritional support, disability grants, etc.
	Monitor and report on access to these types of support in addition to routine TB program outcomes
Public health approach	Implement a human-rights based approach to TB with accountability mechanisms at all levels

have health systems dominated by private practitioners—a term which encompasses a broad array of providers ranging from those trained in biomedical approaches to DR-TB as well as persons providing alternative forms of medical care, including homeopathy, faith-based healing, and Ayurvedic treatment. India is an example of such a setting, and numerous studies document the heterogeneous nature of TB services provided within such a complex health system. This is not surprising given that 68% of persons who received care in the public sector in India found treatment in the government clinics unacceptable and would prefer to buy their own drugs and access private care [55]. It was long estimated that around 40% of Indian TB patients were treated in the private sector: among persons who have been previously treated for TB—a majority of whom have DR-TB—at least 50% first attempted treatment in the private sector before reaching the Revised National TB Control Program (RNTCP) [56,57]. Even these figures have been shown to be considerable underestimates with data from sales of anti-TB drugs in the private market showing that this market provided 17.79 million patient-months of anti-tuberculosis treatment, almost twice as many as in the public sector, and three times higher than previously assumed [58]. While some studies suggest that care for TB in the private sector is of higher quality than in the public sector [59], persons living with TB often receive sub-standard care from both public and private providers.

With such vast numbers of patients accessing private providers it is crucial to assess and monitor the quality of care these patients receive in this sector. Studies show that such care is sub-optimal, with audit data of prescriptions revealing that only 5 of the 106 respondents could write what could be classified as a good quality prescriptions [60]. The variation in the quality of TB care in urban India has been more recently highlighted in studies using trained standardised patients which found

that only 35% of interactions met minimum quality standards [61]. This number was only 28% when the standard patient was one who was living with DR-TB. An added factor to consider when assessing quality of care in the private sectors is that patients also contact unregulated providers of alternative faiths for advice and treatment of their TB, including homeopaths and Ayurvedic practitioners. Furthermore, pharmacies are often the first point of contact for people with signs and symptoms of TB: standardized patient studies found that pharmacists provided correct management in only 13–62% of interactions with over the counter antibiotics (often a fluoroquinolone) dispensed 16–37% of times [62].

Table 1 summarizes the barriers to receiving quality care among persons living with DR-TB as well as some potential solutions for quality improvement measures.

4. Conclusion

Although there are limited formal studies on quality of care received by persons who have been diagnosed with DR-TB, there appears to be a crisis in the field. Not only are there multiple problems with the qualitative experience of DR-TB treatment but also with the provision of care that meets minimum standards of effectiveness and equity. While global efforts have been mounted to "End TB" within the next decade, almost none of them are focused on measuring or improving the quality of care provided to people living with DR-TB [63]. Without such efforts, however, it is likely that TB will continue to remain one of the world's leading infectious killers and that the dire predictions about the impact DR-TB will have on mortality related to anti-microbial resistance are likely to be realized. While there are many factors associated with the

dismal services provided to people living with DR-TB, perhaps a driving force behind most of them is that aspirations for quality on behalf of people living with the disease seem to have been trumped by desire for simplicity among those who are serving such individuals [64,65]. There is a growing recognition that a human rights-based approach to DR-TB could lead to improvements in the field—as was seen with HIV [66,67]. The TB community seems eager to co-opt the language of human rights and health care: these words, however, must be backed with urgent and concerted actions to ensure all people living with DR-TB receive the highest standard or care, regardless of where they find themselves living when they become sick.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2019.100101.

References

[1] Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. May, 2016. Available at https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Accessed April 20, 2019.

[2] World Health Organization. Global tuberculosis report2018. Geneva, Switzerland. 2018. ISBN 978-92-4-156564-6.

[3] Farmer PE. Better and safer treatment for multidrug-resistant tuberculosis. Lancet 2018;09 08(392 (10150)):798–800. PMID: 30215368.

[4] World Health Organization. A patient-centred approach to TB Care. 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/272467/WHO-CDS-TB-2018.13-eng.pdf?ua=1. Accessed February 16, 2019.

[5] Kruk M, Gage A, Arsenault C, et al. High-quality health systems in the Sustainable Development Goals era: time for a revolution. Lancet Global Health 2018:e1196–252.

[6] Reuter A, Furin J. Reducing harm in the treatment of multidrug-resistant tuberculosis. Lancet 2018;09 08(392(10150)):797–8.

[7] Cox V, Cox H, Pai M, et al. Health care gaps in the global burden of drug-resistant tuberculosis. Int J Tuberc Lung Dis 2019;23(2):125–35.

[8] Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N, et al. Constructing care cascades for active tuberculosis: a strategy for program monitoring and identifying gaps in quality of care. PLoS Med 2019;16(2):e1002754.

[9] Naidoo P, Theron G, Rangaka M, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. J Infect Dis 2017;216(S7):S702–13.

[10] Keshavjee S, Farmer PE. History of tuberculosis and drug resistance. N Engl J Med 2013;01 03(368(1)):89–90.

[11] Shah NS, Auld S, Brust J, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Engl J Med 2017;376:243–53.

[12] Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. N Engl J Med 2012;367(September (10)):931–6.

[13] Van Deun A, Tasheen S, Affolabi D, et al. Sputum smear miscroscopy in the Xpert MTB/RIF® era. Int J Tuberc Lung Dis 2019;23(1)http://dx.doi.org/10.5588/ijtld.18.0553.

[14] Isaakidis P, Rangan S, Pradhan A, et al. I cry every day": experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Health 2013;18(9):1128–33.

[15] Guo N, Marra F, Marra CA. Measuring health-related quality of life in tuberculosis: a systematic review. Health Qual Life Outcomes 2009;18:7–14.

[16] Laxmeshwar C, Stewart A, Dalal A, et al. Beyond "cure" and "treatment success": quality of life of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2019;23(1):73–81.

[17] Singla N, Singla R, Fernandes S, Behera D. Post-treatmentsequelae of multi-drug-resistant tuberculosis patients. Ind J Tuberc 2009;56(4):206–12.

[18] Shringarpure KS, Isaakidis P, Sagili KD, Baxi RK, Das M, Daftary A. "When treatment is more challenging than the disease": a qualitative study of MDR-TB patient retention. PLoS One 2016;11(3):e0150849.

[19] Daftary A, Padayatchi N, O'Donnell M. Preferential adherence to antiretroviral therapy over tuberculosis treatment: a qualitative study of drug-resistant tuberculosis/HIV co-infected patients in South Africa. Global Public Health 2014;9(9):1107–16.

[20] Benbaba S, Isaakidis P, Das M, Jadhav S, Reid T, Furin J. Direct observation (DO) for drug-resistant tuberculosis: do we really do? PLoS One 2015;10(12):e0144936.

[21] Oladameji, O., Adeyinka, D., Makola, L., et al. Clients' perceptions of quality of multidrug-resistant tuberculosis treatment and care in resource-limited settings: experiences from Nigeria. 2018. Available at: https://www.intechopen.com/books/mycobacterium-research-and-development/clients-perception-of-quality-of-multidrug-resistant-tuberculosis-treatment-and-care-in-resource-lim. Accessed February 16, 2019.

[22] Ahmad N, Javaid A, Syed Sulaiman SA, Basit A, Afridi AK, Jaber AAS, et al. Effects of multidrug resistant tuberculosis treatment on patients' health related quality of life: results from a follow up study. PLoS One 2016;11(7):e0159560.

[23] Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017 Mar 15. PMID: 28344011.

[24] Dheda K, Chang KC, Guglielmetti L, Furin J, Schaaf HS, Chesov D, Esmail A, Lange C. Clinical management of adults and children with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Microbiol Infect 2017;23(March (3)):131–40.

[25] Reuter A, Tisile P, von Delft D, Cox H, Cox V, Ditiu L, Garcia-Prats A, Koenig S, Lessem E, Nathavitharana R, Seddon JA, Stillo J, von Delft A, Furin J. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis. 2017;21(November (11)):1114–26.

[26] World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis: 2018 Update. Pre-final text. Available from: https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf.

[27] World Health Organization. WHO treatment guidelines for drug resistant tuberculosis: 2016 update. Geneva, Switzerland2016.

[28] Keshavjee S, Gelmanova IY, Shin SS, Mishustin SP, Andreev YG, Atwood S, Furin JJ, Miller A. Hepatotoxicity during treatment for multidrug-resistant tuberculosis: occurrence, management and outcome. Int J Tuberc Lung Dis 2012;16(May (5)):596–603. PMID: 22410436.

[29] Satti H, McLaughlin MM, Hedt-Gauthier B, Atwood SS, Omotayo DB, Ntlamelle L, et al. Outcomes of multidrug-resistant tuberculosis treatment with early initiation of antiretroviral therapy for HIV co-infected patients in Lesotho. PLoS One 2012;7(10):e46943.

[30] World Health Organization. Active tuberculosis drug safety monitoring and management (aDSM): framework for implementation. 2015 Available at https://www.who.int/tb/publications/aDSM/en/ Accessed February 16, 2019.

[31] Venkatesan N. Hearing loss: a survivor's perspective. Presentation at the USAID scientific forum on replacing the injectable for drug-resistant tuberculosis. 2018. July 5-6.

[32] Bhattacharya Chakravarty A, Rangan S, Dholakia Y, Rai S, Kamble S, Raste T, et al. Such a long journey: what health seeking pathways of patients with drug resistant tuberculosis in Mumbai tell us. PLoS One 2019;14(1):e0209924.

[33] Sweetland A, Kritski A, Oquendo M, et al. Addressing the tuberculosis-depression syndemic to end the tuberculosis epidemic. Int J Tuberc Lung Dis 2017;21(8):852–61.

[34] Sweetland A, Kritski A, Oquendo M, et al. Addressing the tuberculosis-depression syndemc to end the tuberculosis epidemic. Int J Tuberc Lung Dis 2017;21(8):852–61.

[35] Acha J, Sweetland A, Guerra D, et al. Psychosocial support groups for patients with multidrug-resistant tuberculosis: five years of experience. Global Public Health 2007;2(4):404–17.

[36] Thomas B, Shanmugam P, Malaisamy M, et al. Pyscho-socio-economic issues challenging multidrug-resistant tuberculosis patients: a systematic review. PLoS One 2016;11(1):e0147397.

[37] Loveday M, Hlangu S, Furin J. Healthcare provider discrimination toward pregnant women with rifampin-resistant tuberculosis. Emerg Infect Dis 2019;25(3)https://doi.org/10.3201/eid2503.181571.

[38] Macq J, Solis A, Martinez G, Martiny P. Tackling tuberculosis patients' internalized stigma through patient-centered care: an interventional study in rural Nicaragua. BMC Public Health 2008;8:154. https://doi.org/10.1186/1471-2458-8-154.

[39] Aibana O, Bachmaha M, Krasiuk V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv, Ukraine. BMC Infect Dis 2017;17:129.

[40] Wingfield T, Boccia D, Tovar M, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study. Peru Ruger JP, editor PLoS Med 2014;11(7):e1001675.

[41] Wingfield T, Tovar M, Uff D, et al. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. Bull World Health Organ 2017;95(4):270–80.

[42] Oliosi J, Reis-Santos B, Locatelli R, et al. Effect of the Bosa Familia Programme on the outcome of tuberculosis treatment: a prospective cohort study. Lancet Global Health 2019;7(2). PE219-26.

[43] World Health Organisation. The end TB strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014.

[44] Cox V, Furin J. World Health Organization recommendations for multidrug-resistant tuberculosis: should different standards be applied? Int J Tuberc Lung Dis 2017;12 01(21(12)):1211–3.

[45] Shakow A, Admay C, Nicholson T, Keshavjee S. Double Standards in global health: medicine, human rights law and multidrug-resistant TB treatment policy. Health Hum Rights J 2016;18(1):85–101.

[46] Zumla AI, Gillespie SH, Hoelscher M. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis 2014;14(4):327–40. https://doi.org/10.1016/S1473-3099(13)70328-1.

[47] World Health Organization. Rapid communication: key changes to the treatment of multidrug- and rifampin-resistant tuberculosis. 2018 Available at http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf Accessed November 9, 2018.

[48] Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018. Published online July 6 http://dx.doi.org/10.1016/S2213-2600(18)30235-2.

[49] Cox V, Brigden G, Crespo RH, Lessem E, Lynch S, Rich ML, Waning B, Furin J. Global programmatic use of bedaquiline and delamanid for the treatment of

multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2018;22(April (4)):407–12.

[50] Drug-resistant tuberculosis scale-up treatment action team. Quarterly update, August, 2018. Available athttp://drtb-stat.org/. Accessed March 3, 2018.

[51] Reuter A, Furin J. Bedaquiline use in South Africa reveals a lifesaving policy in action. Lancet Respir Med 2018(July). PMID: 30001995.

[52] Frick M, Henry I, Lessem E. Falling short of the rights to health and scientific progress: inadequate TB drug research and access. Health Hum Rights 2016;18(1):9–24.

[53] Matiru R, Ryan T. The global drug facility: a unique, holistic and pioneering approach to drug procurement and management. Bull World Health Organ 2007;85(5):348–53.

[54] Arinaminpathy N, Cordier-Lassalle T, Vijay A, Dye C. The global drug facility and its role in the market for tuberculosis drugs. Lancet 2013;382(9901):1373–9.

[55] Pinto LM, Udwadia ZF. Private patient perceptions about a public programme: what do private Indian TB patients really feel about directly observed treatment? BMC Public Health 2010;10:357.

[56] Sachdeva KS, Kumar A, Dewan P, Kumar A, Satyanarayana S. New vision for revised National Tuberculosis Control Programme (RNTCP): universal access - "reaching the unreached". Indian J Med Res 2012;135:690–4.

[57] Satyanarayana S, Nair SA, Chadha SS, Shivshankar R, Sharma G, Yadav S, et al. From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. PLoS One 2011;6:e24160.

[58] Arinaminpathy N, Batra D, Khaprade S, Vualnam T, Maheshwari N, Sharma L, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. Lancet Infect Dis 2016.

[59] Satyanarayana S, Subbaraman R, Shete P, et al. Quality of tuberculosis care in India: a systematic review. Int J Tuberc Lung Dis 2015;19(7):751–63.

[60] Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? PLoS One 2010;5:e12023.

[61] Kwan A, Daniels B, Saria V, Satyanarayana S, Subbaraman R, McDowell A, et al. Variations in the quality of tuberculosis care in urban India: a cross sectional, standardised patient study in two cities. PLoS Med 2018:1002653.

[62] Miller R, Das J, Pai M. Quality of tuberculosis care by Indian pharmacies: mystery clients offer new insights. J Clin Tuberc Other Mycobact Dis 2018;10:6–8.

[63] Zumla A, Petersen E. The historic and unprecedented United Nations General Assembly high-level meeting on tuberculosis—'Unite to End TB': an urgent global response to a global epidemic. Int J Infect Dis 2018;75:118–20.

[64] Acquah R, Furin J. Universal regimens or universal access to drug susceptibility testing for tuberculosis. Lancet Infect Dis 2019https://doi.org/10/1016/S1473-3099(18)30742-4.

[65] Wallis R, Cohen T, Menzies N, Churchyard G. Pan-tuberculosis regimens: an argument for. Lancet Respir Med 2018;6(4):239–40.

[66] Citro B, Lyon E, Mankad M, et al. Developing a human rights-based approach to tuberculosis. Health Hum Rights 2016;18(1):1–8.

[67] Daftary A, Frick M, Venkatesan N, Pai M. Fighting TB stigma: we need to apply lessons learned from HIV activism. BMJ Glob Health 2017;2:e000515.