The devil we know: is the use of injectable agents for the treatment of MDR-TB justified?


*Médecins Sans Frontières, Khayeltisha; †TB Proof, Cape Town; ‡Division of Medical Microbiology, University of Cape Town, Cape Town, South Africa; §Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa; ¶Stop TB Partnership, Geneva, Switzerland; †Desmond Tutu TB Center, Stellenbosch University, Cape Town, South Africa; **Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts; ††HIV/TB Project, Treatment Action Group, New York, New York; ¶Beth Israel-Deaconess Medical Center, Boston, Massachusetts, USA; §§Centre for International Health, Imperial College, London, UK; ††College of Liberal Arts and Sciences, Wayne State University, Detroit, Michigan, USA

SUMMARY

For decades, second-line injectable agents (IAs) have been the cornerstone of treatment for multidrug-resistant tuberculosis (MDR-TB). Although evidence on the efficacy of IAs is limited, there is an expanding body of evidence on the serious adverse events caused by these drugs. Here, we present the results of a structured literature review of the safety and efficacy of IAs. We review the continued widespread use of these agents in the context of therapeutic alternatives—most notably the newer TB drugs, bedaquiline and delamanid—and from the context of human rights, ethics and patient-centered care. We conclude that there is limited evidence of the efficacy of IAs, clear evidence of the risks of these drugs, and that persons living with MDR-TB should be informed about these risks and provided with access to alternative therapeutic options.

KEY WORDS: drug-resistant TB; MDR-TB; injectable agents; hearing loss; ototoxicity

INJECTABLE AGENTS (IAs) such as kanamycin (KM), amikacin (AMK) and capreomycin (CPM), which are used as second-line drugs in anti-tuberculosis treatment, hold a revered place in the management of multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to at least isoniazid [INH] and rifampin [RMP]), and are recommended by the World Health Organization (WHO) as essential drugs for treatment.1 For decades, IA use has been the mainstay of MDR-TB treatment,2 and resistance to this class of medications is part of the definition of ‘extensively drug-resistant TB’ (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone [FQ] and at least one of the three second-line anti-tuberculosis IAs: CPM, KM, or AMK), a form of TB associated with an exceptionally high rate of morbidity and mortality.3

IAs are, however, among the most problematic medications in use for MDR-TB.4 They are administered intramuscularly for 4–8 months, cause a great deal of pain and distress for patients,5 and are associated with frequent, serious adverse effects.6 Perhaps the most serious problem associated with IAs is permanent hearing loss in as many as 50% of persons receiving them for MDR-TB.7,8 Until recently, no new potent anti-tuberculosis drugs existed as alternatives to IAs.

In the last several years, therapeutic options for the treatment of MDR-TB have increased, and include repurposed drugs such as linezolid (LZD) and clofazimine (CFZ),9 and the newer drugs bedaquiline (BDQ) and delamanid (DLM).10 Although global access to these drugs remains critically inadequate,11 these medications are increasingly being rolled out in programmatic settings. BDQ and DLM are beginning to be used to replace IAs in persons on MDR-TB treatment if there is evidence of baseline or evolving hearing loss or other contraindication to IAs.12 These newer and repurposed drugs could theoretically be used as IA substitutes in the routine treatment of MDR-TB,13 even if there is no hearing loss.

Here we review the evidence for the efficacy and safety of anti-tuberculosis IAs, discuss the logistical challenges of continued use of these medications, and explore alternative therapeutic options. Finally, the continued use of IAs is viewed through the lens of the recently released WHO guidelines on ethical considerations in the treatment of MDR-TB.14

Correspondence to: Jennifer Furin, Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Ave, Boston, MA 02115, USA. e-mail: jenniferfurin@gmail.com


[A version in Spanish of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]
METHODOLOGY

We performed a structured search and synthesis of existing literature on the efficacy, safety and tolerability of IAs; a comprehensive systematic review was not undertaken. We searched the literature using Medline, PubMed, and Ovid databases with the following search terms: ‘tuberculosis’, ‘injectable’, ‘aminoglycoside’, ‘hearing’, ‘adverse events’, ‘side effects’, ‘deafness’, ‘XDR-TB’, ‘pre-XDR-TB’, ‘drug-resistant TB’, and ‘hearing loss’.

WHO guidelines and the evidence used to support these recommendations were also reviewed. We evaluated articles from the reference lists of identified papers, and all authors suggested articles for inclusion. Given that ‘pillar one’ of the WHO’s new End TB strategy is ‘patient-centered care’,15 we also highlighted the experiences of persons who received the IA, with some illustrative stories presented in the Figure (full names and images used with permission).

EVIDENCE OF EFFICACY OF INJECTABLE AGENTS IN THE TREATMENT OF TUBERCULOSIS

Even though IAs have been recommended as core agents for treating MDR-TB for almost 20 years,16 the evidence base for the use of IAs is weak at best. Streptomycin (SM) was first discovered to have inhibitory effects on Mycobacterium tuberculosis bacilli in vitro in 1944,17 and was subsequently found to have a therapeutic effect against TB in guinea pigs, and also possibly in humans.18 With the exception of a small randomized controlled trial (RCT) in the 1940s comparing high-dose SM monotherapy with no treatment,19 other IAs have never been evaluated for the treatment of MDR-TB in an RCT.20

There is limited evidence from prospective observational studies and RCTs to support IA use. The only IA found to have some early bactericidal activity (EBA) was SM at a high—and potentially toxic—dose of 30 mg/kg body weight. The bulk of the evidence supporting the use of IAs comes from three observational cohort studies conducted almost one decade ago. The first was a retrospective cohort analysis comparing 12 patients with FQ-resistant but IA-susceptible MDR-TB in 10 patients who had XDR-TB. Those with IA-susceptible TB had significantly higher rates of culture conversion and treatment success than those with XDR-TB.21 In a second study of 1407 MDR-TB patients, IA-resistant MDR-TB was an independent predictor of poor outcome, whereas retained SM susceptibility was a predictor of treatment success.22 Finally, a retrospective record review of 240 culture isolates from persons with MDR-TB found that resistance to CPM was an independent predictor of mortality, but that resistance to AMK and KM was not associated with worse treatment outcomes.23 A large systematic review and meta-analysis of more than 9000 MDR-TB patients found no differences in outcomes between patients with MDR-TB plus additional resistance to IAs compared with those who had MDR-TB but were susceptible to second-line IAs.24 A summary of the evidence for IA efficacy is shown in Table 1.

SAFETY OF SECOND-LINE INJECTABLE AGENTS FOR TREATING TUBERCULOSIS

Adverse events associated with use of injectable agents

In contrast to the limited evidence for the efficacy of second-line IAs, there is a large body of evidence documenting the adverse events associated with these medications. These adverse events include nephrotoxicity, electrolyte abnormalities, pain/injury at the injection site and, importantly, vestibular toxicity and otoxicity. The latter is the most worrying adverse event, as hearing loss is usually permanent. Nephrotoxicity and electrolyte abnormalities are common (studies from persons receiving aminoglycosides for indications other than TB have reported rates of nephrotoxicity of up to 50% depending on age and comorbidities)31 and, although usually reversible, can be life-threatening. In most settings with high rates of MDR-TB, monitoring of electrolytes and access to renal replacement therapy is extremely limited.32 Irreversible vestibular toxicity has also been reported.33

Otoxicity

Otoxicity occurs because anti-tuberculosis IAs selectively destroy cochlear hair cells—starting with the hair cells responsible for hearing at higher frequencies, and progressing to lower frequencies as the damage worsens. Hearing loss can be progressive—even after discontinuation of the IA—and because it starts with loss of hearing at frequencies higher than those for human speech, it may be missed without rigorous audiology monitoring.34 What is alarming is that hearing loss may also develop after a single dose of the IA (although this is relatively uncommon).35 Hearing loss is usually permanent. Devastatingly, hearing aids and cochlear implants are not available in most settings with high MDR-TB rates36 and, even if available, they are far inferior to normal hearing as they do not replicate the full spectrum of human hearing, irrespective of the physical and financial costs they involve.

Hearing loss associated with the use of IAs for the treatment of TB has been reported since the early 1950s with SM,37 and with KM since 1964.38 It has also been reported in most cohorts of MDR-TB patients treated with second-line IAs. A recent review of hearing loss among MDR-TB patients found that
Ntokozo Nkosi, Mpumalanga:
I was diagnosed with MDR-TB in May 2014, about which I didn’t know much back then. I started my treatment on 13 May 2014. It wasn’t easy because of the side effects I got from the treatment. I was injected 6 days a week (Monday–Saturday) for 6 months. During my treatment period, I lost my hearing. It started with the right ear. Both ears were affected by July—just 2 months after I started treatment. I felt so lost and isolated because I couldn’t communicate with my family. I preferred to be alone, that way I felt like I was coping. Meanwhile I was dying inside because all my dreams and the fun I used to have with my loved ones were shattered. I try to cope but it is not easy. I feel like I am missing out a lot in life. I’ve just learned to live with my deafness, but it affects me when I am with people because it is not easy to communicate with them. I am happy that I am alive and I got cured from the MDR-TB, but I just feel they should change this treatment because we will end up with the whole country being deaf due to MDR-TB. I finished my treatment in 2015 and now I am trying to build my life back.

Thabile Shabangu, Mpumalanga:
I was diagnosed with MDR-TB in December 2014 and admitted to hospital to start my medication. I was so scared because I didn’t even know how to take lots of pills and I had to take injections daily. The injections led to my hearing loss in March 2015. During that time, I had already been discharged from hospital and took my injections at one of the local clinics. I felt a funny sound in my ears, so I went to the nearest hospital where I was admitted again. They continued the injections even though I reported that I heard a buzzing sound and birds in my ears. I was very sad because I stopped being able to hear speech. Then eventually I could not hear anything anymore, only the loud funny sound. I felt I was going crazy. They told me in hospital I was supposed to choose between death and deafness so I had to continue with the injections and medications with lots of side effects. I lost my hearing completely on Good Friday in April 2015. I have tried a hearing aid but it doesn’t work for me so I am living with my deafness. It is very hard to live with a loud sound like birds non-stop in your ears. I wish the loud sound would just go away and I can live in quietness once and for all. It is very bad to live with hearing loss.

Mamello Evelyn Moilwa, Lesotho:
January 2014: the month I will never forget in my entire life. I had been in hospital for only 4 months taking MDR-TB treatment when one morning I woke up and I heard a weird noise in my ears. It was exactly the same as the noise made by the air ventilator. I got out of bed to get some fresh air away from the ventilator, hoping to refresh my ears so the noise can go away but it was too late, nothing changed. Later on that day one of the nurses tried speaking to me but I could not comprehend the language. She had to repeat one phrase for many times but to no avail, it was like she was murmuring and I had to read her lips to understand what she was saying. During the pre-treatment counselling, I was warned about all the possible side effects of the treatment and one of them included hearing loss. I still remember that the very first thing I did before taking my first dose of the treatment was to pray and I recall one of the verses I prayed: “Dear Lord, I know I have strength to endure every single pain I am facing throughout this painful journey but I lack courage and strength to sustain just one thing, that of hearing loss, I pray that you let that pass me by”. But my prayers were not good enough I guess.

Philani Mvelase, Ladysmith, Kwazulu-Natal:
I lost my hearing during the 9th month of treatment, in 2014. It started suddenly one afternoon in my left ear. I didn’t know anything about hearing loss due to the treatment, so I just guessed it was caused by a wound that appeared on the left side of my neck, but the wound healed and by that time both of my ears had a hissing, roaring, buzzing, loud sound. I became totally deaf in my right ear as well. Doctors then told me it was caused by the injections and they said it happens to some people during treatment. Three years later I still have the sound in both ears. Now I do not have money to see an audiologist because it is difficult for me to find a job.

* Full names and photos have been provided by the individuals pictured here with their explicit permission for publication in this article. MDR-TB = multidrug-resistant tuberculosis. This image can be viewed online in color at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000011/art00006.
between 2.6% and 61.5% of persons treated for MDR-TB had documented hearing loss. That review noted that in most observational cohorts of MDR-TB, formal assessments of hearing were not performed, and thus those studies likely underestimated the magnitude of the problem in patients treated with second-line agents. When the hearing of MDR-TB patients was formally tested every 6 weeks regardless of symptoms, more than one in two patients had documented hearing loss, suggesting this is an alarmingly common occurrence. Even in studies on the ‘shortened’ MDR-TB treatment regimen—in which the IA may be given for 4 months—hearing loss was reported in as many as 44% of patients in one cohort. In another cohort treated with the shortened regimen, 13% of patients required hearing aids to manage the hearing loss they suffered, thereby illustrating the severity of the damage caused. A summary of IA-associated ototoxicity is shown in Table 2.

Risk factors for hearing loss
The most important modifiable risk factor is the dose and duration of the IA, as cumulative dose is predictive of hearing loss. Other risk factors for ototoxicity may include infection with the human immunodeficiency virus, older age and persons exposed to a high level of noise in their home or work environment, most notably persons working in mines. It has also been estimated that between 17% and 33% of aminoglycoside-induced ototoxicity may be attributed to mutations in ribosomal-RNA genes, but most of those studies only assessed hearing loss with short-term aminoglycoside use.

Monitoring hearing loss as part of active drug safety monitoring and management
The WHO recommendations for use of second-line IAs include monthly monitoring of serum electrolytes and assessment for ototoxicity. In high-resource settings, serum drug levels may also be closely monitored. Ideally, monitoring for ototoxicity should include otoscopy and tympanometry, followed by audiometry with an audiologist and standardized audiometry equipment or an audiometry booth. For small children, or other persons who cannot understand or cooperate with this type of testing, evaluation using more specialized tests such as oto-acoustic emissions or auditory brainstem-evoked responses may be necessary. This approach requires specialized equipment and trained staff, and may require sedation in the case of young children. These methods of monitoring to detect the early signs of hearing loss are resource-intensive and are therefore not widely available in many settings in which these drugs are being used. In such settings, clinicians rely on self-reporting of hearing loss. Self-reported hearing loss usually indicates that severe damage has already occurred, and relying only on clinical assessment to detect hearing loss misses a significant proportion of patients with more moderate or mild disease.

When IA-associated hearing loss is detected, it is generally irreversible. Actions might be taken to prevent further hearing loss, but little can be done to reverse the damage already caused. As this is a permanent and often disabling adverse event, it is defined as a ‘serious adverse event’. According to WHO recommendations, it should thus be urgently reported as part of drug safety and monitoring. However, recent data from the WHO Vigibase show that hearing loss from IA use in persons with MDR-TB is grossly under-reported. Although careful audiology monitoring of patients being treated with IAs is recommended, often it is not available and, even when implemented appropriately, it does not prevent it (although it may identify hearing loss earlier). Newer mobile technology could be used to expand access to basic audiometric evaluations in all patients using IAs, as it is dangerous for patients not to receive adequate monitoring while taking these medications.

Strategies for mitigating hearing loss
Several strategies have been described to mitigate the toxicity of IAs. Given that hearing loss is related to the cumulative exposure of the IA, some guidelines have advocated administering IAs only three times a week. In a randomized trial of thrice weekly vs. daily treatment with IAs in persons with MDR-TB in which all received the same total weekly IA dose, there was no difference in toxicity. In both of these groups, hearing loss was detected in one out of every three patients treated. More recently, there has been interest in the use of high-dose aspirin or N-acetylcysteine to prevent hearing loss in patients using IAs. Those studies show promise and deserve further evaluation, but data are currently limited, and there are serious concerns about additional adverse events—especially gastritis and increased sputum production—and the further increase in the already large pill burden of persons being treated for MDR-TB. A more promising strategy for avoiding adverse events associated with an IA is to substitute it with an alternative, safer drug that is effective against MDR-TB.

Impact of hearing loss on quality of life
There is ample evidence demonstrating the long-term impact hearing loss can have on the quality of life and the ability of persons with hearing loss to lead productive lives. Hearing loss is the third most common cause of years lost to disability globally. There are multiple consequences of losing one’s hearing that last far beyond the treatment and monitoring performed by TB programs. Persons with hearing loss are more likely to be bullied or physically
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Table 1 Studies that have examined the efficacy of injectable agents for DR-TB

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of study</th>
<th>Design</th>
<th>Sample size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahuja20</td>
<td>2012</td>
<td>Meta-analysis of 32 observational studies</td>
<td>9153 people with MDR-TB assessed</td>
<td>No association between use of any injectable agent and the probability of treatment success</td>
</tr>
<tr>
<td>Althomsons25</td>
<td>2012</td>
<td>Meta-analysis of data from the national TB surveillance system (USA)</td>
<td>1179 people with MDR-TB assessed</td>
<td>Among persons with MDR-TB, additional resistance to injectable agents was a statistically significant predictor of mortality and poor treatment outcomes ($P &lt; 0.005$, risk ratio not calculated in study)</td>
</tr>
<tr>
<td>Bastos26</td>
<td>2014</td>
<td>Meta-analysis of data from 31 previously published studies of people with MDR- or XDR-TB</td>
<td>8955 people with XDR- or MDR-TB assessed</td>
<td>OR of treatment success compared with treatment failure or death in persons with susceptibility to an injectable agent (compared with resistance): SM 1.8 (1.2–2.7), AMK or KM 1.8 (1.2–2.8), CPM 1.3 (0.8–2.1)</td>
</tr>
<tr>
<td>British Medical Research Council27</td>
<td>1948</td>
<td>RCT: patients randomized to receive SM monotherapy (2 g four times a day for 4 months) or no drug treatment; response was assessed clinically and radiologically</td>
<td>107 participants with TB enrolled</td>
<td>51% of participants in the intervention arm (receiving SM) exhibited radiological improvement compared with only 8% in the control group. Clinical improvement was noted in the SM group compared with the control group in the first few months; however, only 15% of the intervention group was bacteriologically negative after 6 months. Study cautioned against using SM in view of the observed vestibular toxicity</td>
</tr>
<tr>
<td>Chan21</td>
<td>2009</td>
<td>Retrospective cohort study; subanalysis compared long-term treatment outcomes of people with MDR-TB plus SM resistance (susceptible to the three other injectable agents) to people with XDR-TB with resistance to all injectable agents</td>
<td></td>
<td>75% treatment success rate (95%CI 47–91; $P = 0.04$) for persons with MDR-TB and SM resistance only ($n = 12$) compared with 20% success rate (95%CI 6–51; $P = 0.03$) in persons with XDR-TB ($n = 10$)</td>
</tr>
<tr>
<td>Donald28</td>
<td>2002</td>
<td>EBA study on SM in humans with pulmonary TB</td>
<td>63 participants randomized; 43 included in the analysis</td>
<td>Minimal EBA (0.133, $P = 0.0009$) only at 30 mg/kg (doses higher than doses used in clinical practice); no EBA at lower doses</td>
</tr>
<tr>
<td>Donald29</td>
<td>2001</td>
<td>EBA study of AMK in humans with pulmonary TB</td>
<td>7 participants</td>
<td>No significant EBA, 0.041, 0.045 and 0.052 (after 2 days of AMK at 5 mg/kg, 10 mg/kg, 15 mg/kg, respectively)</td>
</tr>
<tr>
<td>Falzon24</td>
<td>2013</td>
<td>Meta-analysis of data from persons with MDR-TB from 26 centers</td>
<td>6724 people with MDR-TB assessed</td>
<td>Compared with treatment failure, relapse and death, treatment success was 64% in persons with MDR-TB only ($n = 4763$), 95%CI 57–72) compared to persons with MDR-TB with resistance to an injectable agent, which was 56% ($n = 1130$, 95%CI 45–66)</td>
</tr>
<tr>
<td>Goergiou30</td>
<td>2017</td>
<td>Observational cohort study in which clinical sputum isolates were analyzed and sequences correlated with clinical details to investigate the relationship between MDR-TB resistance, mutations and mortality</td>
<td>451 clinical isolates sequenced and analyzed</td>
<td>Presence of rs mutation conferring resistance to KM was associated with higher odds of patient mortality (limited study due to lack of follow-up data on 60% of participants)</td>
</tr>
<tr>
<td>Kim22</td>
<td>2010</td>
<td>Meta-analysis of patient data after 5–8 years of follow-up</td>
<td>1407 people with MDR- or XDR-TB assessed</td>
<td>MDR-TB with resistance to an additional injectable agent was a marginal predictor of poor outcome (hazard ratio of resistance to injectable agent 1.57, 95%CI 1.01–2.44; $P = 0.048$)</td>
</tr>
<tr>
<td>Migliori23</td>
<td>2008</td>
<td>Meta-analysis of data from people with MDR- and XDR-TB with definitive treatment outcomes</td>
<td>288 people with MDR- or XDR-TB included for review</td>
<td>SM resistance was independently associated with a worse treatment outcome</td>
</tr>
</tbody>
</table>

DR-TB = drug-resistant TB; MDR-TB = multidrug-resistant TB; TB = tuberculosis; XDR-TB = extensively drug-resistant TB; OR = odds ratio; SM = streptomycin; AMK = amikacin; KM = kanamycin; CPM = capreomycin; RCT = randomized controlled trial; CI = confidence interval; EBA = early bactericidal activity.
assaulted,91 more likely to be depressed and socially isolated,92 and less likely to find work.93 Children are an especially vulnerable population, as the consequences of impaired language and communication skills development can cause severe learning disabilities and problems with psychosocial development.94

LOGISTICAL AND COST CONSIDERATIONS OF INJECTABLE AGENTS

In addition to the resources and logistical requirements for audiometry and monitoring of serum electrolyte and renal function, the daily administration of the IA comes with serious logistical challenges.95 In some settings, injections are given by trained ancillary personnel, but in many other settings a professional nurse must administer the IA.96 This can be time-consuming and may be especially problematic in settings in which there are shortages of health workers. Administering IAs also requires the use of universal precautions and biosafety measures to dispose of used needles and syringes. Furthermore, persons living with MDR-TB often have to travel significant distances to the clinic to receive their daily injections. This can lead to substantial costs, which are frequently further complicated by an inability to work or return to their activities of daily living while taking these medications.97 Given that the WHO End

Table 2  Studies that have examined ototoxicity among patients on treatment for DR-TB (table adapted and updated from References 32 and 38)

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of study</th>
<th>Study country</th>
<th>Patients with ototoxicity n (%)</th>
<th>Age range years</th>
<th>Patients known to be HIV-infected n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baghaei43</td>
<td>2006–2009</td>
<td>Iran</td>
<td>8–14 (10.0–17.5)</td>
<td>14–81</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Bloost8</td>
<td>2000–2004</td>
<td>Latvia</td>
<td>195 (19.0)</td>
<td>13–83</td>
<td>32 (3.1)</td>
</tr>
<tr>
<td>Burgos45</td>
<td>1982–2000</td>
<td>USA</td>
<td>2 (4.2)</td>
<td>22–78</td>
<td>11 (22.9)</td>
</tr>
<tr>
<td>Chan46</td>
<td>1984–1998</td>
<td>USA</td>
<td>39 (19.0)</td>
<td>2–85</td>
<td>NS</td>
</tr>
<tr>
<td>Codescasa47</td>
<td>2001–2003</td>
<td>Italy</td>
<td>1 (2.6)</td>
<td>43.6 (17.3)*</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>de Jager48</td>
<td>1995–2000</td>
<td>The Netherlands</td>
<td>11 (18.0)</td>
<td>10–83</td>
<td>NS</td>
</tr>
<tr>
<td>Dhedda45</td>
<td>2002–2008</td>
<td>South Africa</td>
<td>10 (6)</td>
<td>&gt;16</td>
<td>82/174 (47.1)</td>
</tr>
<tr>
<td>Drobat40</td>
<td>1999–2003</td>
<td>Peru</td>
<td>2 (6.7)</td>
<td>2–14</td>
<td>2/38 (5.3)</td>
</tr>
<tr>
<td>Duggal41</td>
<td>2000–2006</td>
<td>India</td>
<td>12 (18.8)</td>
<td>17–65</td>
<td>NS</td>
</tr>
<tr>
<td>Firun32</td>
<td>1996–1998</td>
<td>Peru</td>
<td>4 (6.7)</td>
<td>12–60</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Geerligs43</td>
<td>1985–1998</td>
<td>The Netherlands</td>
<td>0–6* (0–15)</td>
<td>10–82</td>
<td>0</td>
</tr>
<tr>
<td>Ghafar46</td>
<td>May–August 2010</td>
<td>South Africa</td>
<td>12 (48)</td>
<td>7 months–16 years</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Goble4</td>
<td>1973–1983</td>
<td>USA</td>
<td>13 (7.6)</td>
<td>17–79</td>
<td>NS</td>
</tr>
<tr>
<td>Isaakids55</td>
<td>2007–2011</td>
<td>India</td>
<td>5 (8.6)</td>
<td>11–61</td>
<td>58 (100)</td>
</tr>
<tr>
<td>Jacob56</td>
<td>2002–2007</td>
<td>Belgium</td>
<td>11 (50.0)</td>
<td>21–76</td>
<td>1/21 (4.8)</td>
</tr>
<tr>
<td>Joseph57</td>
<td>2006–2007</td>
<td>India</td>
<td>1 (2.6)</td>
<td>&gt;18</td>
<td>1</td>
</tr>
<tr>
<td>Karagöz58</td>
<td>1995–2000</td>
<td>Turkey</td>
<td>24 (22.0)</td>
<td>16–65</td>
<td>0</td>
</tr>
<tr>
<td>Keal59</td>
<td>2006–2011</td>
<td>UK</td>
<td>5 (27.8)</td>
<td>10–80</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Kennedy40</td>
<td>2004–2009</td>
<td>Ireland</td>
<td>8 (61.5)</td>
<td>24–82</td>
<td>1/71 (14.3)</td>
</tr>
<tr>
<td>Keshavjee59</td>
<td>2000–2004</td>
<td>Russia</td>
<td>78 (12.8)</td>
<td>XDR-TB: 33.9 ± 11.1*</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Kim50</td>
<td>1996–2005</td>
<td>Republic of Korea</td>
<td>8 (3.8)</td>
<td>13–91</td>
<td>1</td>
</tr>
<tr>
<td>Leimane61</td>
<td>2000</td>
<td>Latvia</td>
<td>58 (28.4)</td>
<td>17–78</td>
<td>1/197 (0.5)</td>
</tr>
<tr>
<td>Malik62</td>
<td>2005–2006</td>
<td>Nepal</td>
<td>12 (9.6)</td>
<td>33.6 ± 12.5†</td>
<td>NS</td>
</tr>
<tr>
<td>Masjedi63</td>
<td>2002–2006</td>
<td>Iran</td>
<td>20 (46.5)</td>
<td>15–83</td>
<td>0</td>
</tr>
<tr>
<td>Mbandos64</td>
<td>2006–2012</td>
<td>Botswana</td>
<td>270 (62)</td>
<td>&gt;15</td>
<td>288 (66%)</td>
</tr>
<tr>
<td>Nathanson65</td>
<td>1998–2002</td>
<td>Multiple sites</td>
<td>98 (12.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Palermo66</td>
<td>1996–1999</td>
<td>Argentina</td>
<td>5 (6.8)</td>
<td>&lt;16 excluded</td>
<td>36.0 ± 13.0†</td>
</tr>
<tr>
<td>Pelouquin67</td>
<td>1991–1998</td>
<td>USA</td>
<td>32–28* (36.8–32.2)</td>
<td>19–79</td>
<td>NS</td>
</tr>
<tr>
<td>Sagye68</td>
<td>2004–2014</td>
<td>Russia</td>
<td>206 (58%)</td>
<td>36.4 (11.7)</td>
<td>164 (46)</td>
</tr>
<tr>
<td>Shin69</td>
<td>2000–2002</td>
<td>Russia</td>
<td>38 (15.6)</td>
<td>17–65</td>
<td>NS</td>
</tr>
<tr>
<td>Sturdy69</td>
<td>2004–2009</td>
<td>UK</td>
<td>9 (18.0)</td>
<td>34.6 ± 12.8†</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Tahtaglo70</td>
<td>1992–1999</td>
<td>Turkey</td>
<td>45 (28.5)</td>
<td>15–68</td>
<td>1</td>
</tr>
<tr>
<td>Telbak71</td>
<td>1991–1994</td>
<td>USA</td>
<td>1 (5.9)</td>
<td>&lt;25: 2</td>
<td>1</td>
</tr>
<tr>
<td>Türün8</td>
<td>1992–2004</td>
<td>Turkey</td>
<td>110 (41.8)</td>
<td>14–68</td>
<td>2</td>
</tr>
<tr>
<td>Tupas72</td>
<td>1999–2002</td>
<td>Philippines</td>
<td>22 (18.8)</td>
<td>15–24: 11</td>
<td>2</td>
</tr>
<tr>
<td>Ufriedi73</td>
<td>1998–1999</td>
<td>France</td>
<td>2 (4.4)</td>
<td>&lt;25: 25</td>
<td>0</td>
</tr>
<tr>
<td>van Deun74</td>
<td>1997–2007</td>
<td>Bangladesh</td>
<td>19 (4.4)</td>
<td>&lt;25: 108</td>
<td>Not tested</td>
</tr>
<tr>
<td>Yew75</td>
<td>1990–1997</td>
<td>Hong Kong</td>
<td>9 (14.3)</td>
<td>12–77</td>
<td>0</td>
</tr>
</tbody>
</table>

* Unclear from the article.
† Median and standard deviation presented as age range was unavailable.
‡ HIV-infected patients excluded from the study.
DR-TB = drug-resistant TB; HIV = human immunodeficiency virus; NS = not significant; XDR-TB = extensively drug-resistant tuberculosis; MDR-TB = multidrug-resistant TB.
TB Strategy has set a goal of zero suffering and the elimination of catastrophic costs for persons with drug-resistant TB by the year 2020. Continued reliance on IAs should be questioned based on their contribution to both patient and health system costs.

**THERAPEUTIC OPTIONS FOR THE REPLACEMENT OF INJECTABLE AGENTS**

*Newer and repurposed drugs*

As recently as 2012, there were limited options for the treatment of MDR-TB, and the ongoing use of IAs was not questioned because there were no viable alternatives. With the WHO recommending BDQ for the treatment of MDR-TB in 2013 (and renewing this recommendation in 2017), and DLM in 2014, and with recent recommendations for repurposed TB drugs such as CFZ and LZD, the cruel yet oft-repeated saying ‘better deaf than dead’ is repurposed for drug-resistant TB by the year 2020, continued elimination of catastrophic costs for persons with TB. Median survival times for drug-resistant TB in 2013 reached 50% of the birth cohort.100,101 And with recent recommendations for the efficacy and safety of BDQ, more recent programmatic evidence demonstrating the efficacy of these drugs—especially BDQ—even in populations of patients with extremely poor treatment outcomes and where the background TB regimen does not include an IA, is highly likely.102,103,104

**LZD as an antibiotic that has been demonstrated in two RCTs** and in observational studies to increase culture conversion and treatment success in drug-resistant TB. However, the toxicity profile of LZD—which includes myelosuppression, optic neuritis, and neuropathy—limits its use and makes it a non-ideal routine alternative to IAs. CFZ has also moved up the WHO MDR-TB drug-classification scale, and is a critical component of the shortened MDR-TB regimen. This medication could be considered for drug substitution for IAs in persons who are not on a shortened regimen. Both the newer TB drugs, BDQ and DLM, demonstrate significant EBA, unlike IAs. Both have also been shown in animal models to have the potential to substantially shorten treatment, whereas IAs seem to have limited sterilizing activity. Both BDQ and DLM have been shown to be effective in accelerating sputum conversion in MDR-TB and improving treatment success in Phase-IIB RCTs.

One reason why there has been hesitation in recommending that IAs be used to substitute for IAs is that in the drug trials these agents were added to an optimized background regimen that often included an IA. The possibility that the observed therapeutic effect may be because of synergy between the IA and DLM or BDQ cannot be completely discounted, but there is an increasing pool of observational evidence demonstrating the efficacy of these drugs—especially BDQ—even in populations of patients with extremely poor treatment outcomes and where the background TB regimen does not include an IA. To date, more than 8000 individuals have received BDQ globally as part of programmatic management of drug-resistant TB. Retrospective cohort data from South Africa indicate that 76% of patients who received BDQ experienced culture conversion or remained sputum culture-negative at 6 months. In that cohort, 50% of the 91 patients had resistance to the IA, and all had XDR- or pre-XDR-TB (defined as MDR-TB with additional resistance to either a FQ or a second-line IA, but not both). Those results are particularly striking when compared with the 56% culture conversion reported at 6 months among the 2012 National Tuberculosis Program MDR-TB-only cohort. In that cohort, all of the MDR-TB patients had strains susceptible to IAs and received treatment with an IA and no BDQ. Pooled observational data from other contexts have shown even better results for the efficacy and safety of BDQ. More recent programmatic evidence from the South African Electronic Drug-Resistant Tuberculosis Register suggests that BDQ treatment was associated with a substantial reduction in mortality (adjusted hazard ratio 0.50, 95% confidence interval 0.41–0.61) in patients with MDR-TB. This reduction in mortality was irrespective of resistance profile or history of previous TB.

Another reason for the hesitation in recommending BDQ and DLM as alternatives to the IA is their propensity to prolong the QT interval. A prolonged corrected QT interval (QTc) may be a risk factor for the development of fatal arrhythmias, most notably torsades de pointe. No cases of fatal arrhythmia have been reported in patients receiving either of these agents, and the higher mortality rate seen in the Phase-IIB trial of BDQ was thought unlikely to be attributable to BDQ. Nonetheless, the cautious use of both of these agents has been recommended, including monthly electrocardiography (ECG) monitoring while the drugs are being administered. ECG machines automatically calculate QTc, and thus monthly ECG monitoring may be less resource-intensive and more feasible than monthly audiometry monitoring recommended for the IA. If an elevated QTc interval is noted, the offending agent can be stopped and this effect is completely reversible. Overall, serious adverse events seen with the newer drugs are less frequent and more easily monitored when compared with IAs, and usually reversible.

**Future regimens**

In addition to DLM and BDQ, other new TB drugs such as pretomanid (from the same class as DLM) and suzetozid (from the same class as LZD) are in the pipeline. These new and repurposed drugs are being combined in novel ways in several ongoing RCTs, which are all evaluating treatment regimens that are both IA-free and shorter—with some arms having treatment durations as short as 6 months. Thus far, the preliminary results of the studies such as NIX—6-month treatment with only BDQ/pretomanid and high-dose LZD—show early indicators of treatment success. The preliminary results of many of those studies are expected by 2019–2021 and, with more safety data on BDQ and DLM, it seems highly likely
that IAs will no longer form part of the routine treatment of MDR-TB in the near future. However, while awaiting the definitive results of these RCTs, health providers, policy makers and patients need to make MDR-TB treatment decisions based on current evidence regarding IAs and alternative drug options. Considering the weak evidence for IAs, their toxic side-effect profile, and the presence of efficacious alternative drug options, the risk-benefit of IAs weighs on the side of replacing an IA with DLM or BDQ.

**INJECTABLE AGENTS, ETHICS AND A ‘PATIENT-CENTERED’ APPROACH**

While awaiting further RCT-based evidence on the substitution of the IA with newer anti-tuberculosis drugs, it is imperative to consider not only the clinical risks and benefits of this class of agents, but also the ethics around their continued use. The WHO’s End TB Strategy has as its first pillar ‘integrated, patient-centered TB care and prevention’, which aims to ensure all persons living with TB are engaged in their own care. To further define the meaning of ‘patient-centered care’, in 2017 the WHO released ethical guidelines for implementing the End TB Strategy. Those guidelines reinforce the concept that ‘trust and transparency’ are key to patient-centered care and require that decisions be made by providers and persons living with MDR-TB ‘in an open manner, through a fair process, and that the said decisions are responsive, factual and evidence-based’. However, qualitative data show that the use of IAs is highly problematic for patients, and most are unaware of both the lack of evidence for the efficacy of these agents and the risk of permanent and serious adverse events associated with their use. Patient-centered care in the context of MDR-TB must include providing information to patients on the potential benefits and harms of IAs, as well as of alternative drug choices, and allow active participation in deciding on the most acceptable and appropriate treatment regimen.

Even with more safety and efficacy data on newer agents, there are some in the MDR-TB community who may argue that these newer and possibly more effective drugs should be reserved for persons with particularly high risk of treatment failure (e.g., pre-XDR- or XDR-TB). There is a common belief that widespread roll-out of a new drug such as DLM or BDQ could increase the degree of BDQ or DLM resistance at a population level. However, a recent perspective suggests that if given with an optimized background regimen (underscoreing the need for universal drug susceptibility testing), the risk of developing resistance is minor. The idea that the potential needs of undefined ‘future populations’ should take precedence over the current needs of persons who are suffering from MDR-TB violates multiple ethical principles, including equity, trust, transparency, respect, dignity, and autonomy. These violations are inconsistent with the currently endorsed human rights-based approach to TB.

Table 3 summarizes the evidence on the efficacy, safety, logistics, and ethical justification of IAs compared with those of BDQ and DLM.

**DISCUSSION: SHOULD WE CONTINUE WITH THE DEVIL WE KNOW?**

Before the introduction of newer agents for the treatment of MDR-TB over the past 4 years, there were limited therapeutic options. In this context, providers used the drugs that were available to them, even if there was limited evidence of efficacy and even in the face of demonstrable harm to patients. Historically, IAs have been afforded a distinctive place in the treatment of MDR-TB. However, careful assessment of the evidence of the efficacy of IAs, as described above, shows that in fact there are limited data to support a critical, irreplaceable role of these medications in MDR-TB treatment.

The safety profiles of IAs are worrying, with serious adverse events seen in as many as 61% of those treated with an IA in some studies. This is an alarming statistic, especially given that hearing loss is permanent and has tremendous impact on quality of life and productivity. Furthermore, there is limited access both to monitoring, which could detect hearing loss early, and to interventions such as cochlear implants, which could mitigate the impact of hearing loss on MDR-TB survivors. Moreover, the ongoing use of IAs requires a significant amount of logistical support and likely contributes to the difficulties faced by persons who are unable to return to work, school, or perform other activities of normal life while on treatment. These attributes of IA treatment most certainly contribute to costs incurred by persons living with MDR-TB, and are not compatible with the WHO’s End TB Strategy, which has pledged to eliminate catastrophic costs to MDR-TB patients by 2020. The WHO has also highlighted the ethical duty to address all forms of suffering associated with TB, through appropriate access to care and to the management of adverse drug reactions. The lack of evidence of the benefits of IAs, combined with clear evidence showing their risk, has led some practitioners to call for an end to the unquestioned use of this class of agents, especially as there are several safe and effective options to replace them. In the 2016 guidelines on the treatment of MDR-TB, the WHO noted that children with non-severe disease may be offered IA-free regimens. The necessity of the IA as a core part of MDR-TB regimens in other population groups should similarly be scrutinized.
The WHO’s own ethical guidance on the implementation of the End TB Strategy also calls for increased participation of persons living with MDR-TB in their own treatment decisions. Thus, while some might consider it premature to substitute one of the newer TB drugs for the IA in all regimens, given the lack of high-quality evidence, it is clear that the WHO’s ethical framework for MDR-TB treatment requires that people undergoing treatment for the disease be given information about the efficacy and safety of IAs and possible alternatives to their use, so that they can make an informed decision about whether they choose to receive an injection—or opt for another alternative—in the treatment of their MDR-TB.

It is not just the ethical recommendations of the WHO that mandate such options be offered to individuals undergoing treatment for MDR-TB. The technical guidance on the use of BDQ and DLM state that these drugs should be used when there is an inability to build a drug regimen because of resistance or intolerance to other agents. TB providers and programs have traditionally been the ones to determine whether a medication is ‘tolerable’. In this era of patient-centered care, however, persons living with MDR-TB should also have a say in what they consider to be tolerable. Those who decide that they cannot tolerate an IA—or the risks inherent in the use of such agents—should be offered treatment with alternative agents, including BDQ and DLM. With the recent development of new medications for drug-resistant TB, there has been an increased push by the TB community to base MDR-TB treatment decisions on high-quality systematic data. However, until high-quality controlled trial data are available, providers, programs, policy makers and, most importantly, patients, must decide how best to balance emerging data with the limited evidence base underpinning current MDR-TB treatment regimens.

The data presented in this review support the need to reevaluate the current widespread use of IAs in most MDR-TB treatment regimens. The experiences and insights of communities affected by MDR-TB must be prioritized in decision making at national and international levels, and individual patients must be included in shared decision making about their own MDR-TB care. IAs should only be given after persons with MDR-TB are informed of the risks and benefits of the drug as well as the other therapeutic options available to them. Failure to achieve these goals will not only further exacerbate the existing mistrust of communities affected by drug-resistant-TB, they also contravene the ethical and human rights standards set by the WHO for the delivery of high-quality TB care to all.

Conflicts of interest: none declared.

References


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**Table 3** Comparison between injectable agents, BDQ and DLM

<table>
<thead>
<tr>
<th>Injectable agent</th>
<th>BDQ</th>
<th>DLM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>EBA trials—only SM has EBA at a high dose of 30 mg/kg19</td>
<td>EBA trials show efficacy (late)107</td>
</tr>
<tr>
<td></td>
<td>Observational cohorts with no clear evidence of benefit20</td>
<td>Observational cohorts with evidence of benefit113,116</td>
</tr>
<tr>
<td></td>
<td>No ongoing RCTs</td>
<td>Phase-IIB RCT data showed improved outcomes114</td>
</tr>
<tr>
<td></td>
<td>Hearing loss in ≤ 61.5% of patients58</td>
<td>QTc prolongation &gt; 500 msec in 3.9%</td>
</tr>
<tr>
<td></td>
<td>Vestibular toxicity in &lt; 9%31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal toxicity and electrolyte abnormalities in ≤ 12%33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection site reactions6</td>
<td>Monthly monitoring of ECG required9</td>
</tr>
<tr>
<td><strong>Adverse events reported in &gt;5% of patients receiving the drug that are causally linked to the agent</strong></td>
<td>Hearing loss</td>
<td>Arhythmia, if it occurs, could be fatal</td>
</tr>
<tr>
<td><strong>Logistical considerations</strong></td>
<td>Monthly monitoring for hearing loss required9</td>
<td></td>
</tr>
<tr>
<td><strong>Long-term impact</strong></td>
<td>Permanent impact on ability to perform activities of daily living and employment30</td>
<td>Arhythmia, if it occurs, could be fatal</td>
</tr>
</tbody>
</table>
Are injectable agents for MDR-TB justified?

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21 Chan E, Strand M, Isem M. Multidrug-resistant tuberculosis (TB) resistant to fluoroquinolones and streptomycin but susceptible to second-line injection therapy has a better prognosis than extensively drug-resistant TB. Clin Infect Dis 2009; 48; e30–52.


115 Pai M, Furin J. Tuberculosis innovations mean little if they cannot save lives. eLife 2017; 6: e25956.


129 Kirby T. Landmark legal ruling sees Indian girl prescribed bedaquiline for XDR-TB. Lancet Respir Med 2017; 5: 249.


Pendant des décennies, les médicaments injectables de deuxième ligne ont constitué la pierre angulaire du traitement de la tuberculose multirésistante (TB-MDR). Il y a peu d'éléments en faveur de l'efficacité de ces médicaments, mais il y a par contre de plus en plus de preuves de leurs graves effets secondaires. Dans cette revue de pointe, nous présentons les résultats d'une revue de littérature structurée relative à la sécurité et à l'efficacité des médicaments injectables. Nous revoysons la diffusion continue de ces agents en tant qu'alternatives thérapeutiques—plus particulièrement les médicaments TB plus récents, la bedaquiline et le délamanide—et dans le contexte des droits de l’Homme, de l’éthique et des « soins centrés sur le patient ». Nous concluons qu’il y a peu d’arguments en faveur de l’efficacité de ces agents, mais des preuves établies de leurs risques et que les personnes atteintes de TB-MDR devraient être informées de ces risques et avoir accès aux différentes options thérapeutiques.

Are injectable agents for MDR-TB justified?