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STATE OF THE ART

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

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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]

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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 ototoxicity. 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]

Ototoxicity

Ototoxicity 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 rates[36] 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

Figure Personal experiences with hearing loss during treatment for MDR-TB*

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 losing my mind and 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.[39] 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.[40] 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.[41] 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.[42] 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.[76] Other risk factors for ototoxicity may include infection with the human immunodeficiency virus,[77] older age[51] and persons exposed to a high level of noise in their home or work environment, most notably persons working in mines.[78] 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.[34]

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.[9] 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.[79] 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.[48] 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.[51]

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.[80] 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.[81] However, recent data from the WHO Vigibase show that hearing loss from IA use in persons with MDR-TB is grossly under-reported.[82] 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,[83] 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,[84] 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.[67] More recently, there has been interest in the use of high-dose aspirin[85] or *N*-acetylcysteine[86] 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[87]—and the further increase in the already large pill burden of persons being treated for MDR-TB.[88] 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.[89] Hearing loss is the third most common cause of years lost to disability globally.[90] 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

Table 1 Studies that have examined the efficacy of injectable agents for DR-TB

First author	Year of study	Design	Sample size	Results
Ahuja[20]	2012	Meta-analysis of 32 observational studies	9153 people with MDR-TB assessed	No association between use of any injectable agent and the probability of treatment success
Althomsons[25]	2012	Meta-analysis of data from the national TB surveillance system (USA)	1179 people with MDR-TB assessed	Among persons with MDR-TB, additional resistance to injectable agents was a statistically significant predictor of mortality and poor treatment outcomes ($P < 0.005$, risk ratio not calculated in study)
Bastos[26]	2014	Meta-analysis of data from 31 previously published studies of people with MDR- or XDR-TB	8955 people with XDR- or MDR-TB assessed	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)
British Medical Research Council[27]	1948	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	107 participants with TB enrolled	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
Chan[21]	2009	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	This was a subanalysis in which 22 people with TB were assessed	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 ($n = 10$)
Donald[28]	2002	EBA study on SM in humans with pulmonary TB	63 participants randomized; 43 included in the analysis	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
Donald[29]	2001	EBA study of AMK in humans with pulmonary TB	7 participants	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)
Falzon[24]	2013	Meta-analysis of data from persons with MDR-TB from 26 centers	6724 people with MDR-TB assessed	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)
Goerghiou[30]	2017	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	451 clinical isolates sequenced and analyzed	Presence of *rrs* 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)
Kim[22]	2010	Meta-analysis of patient data after 5–8 years of follow-up	1407 people with MDR- or XDR-TB assessed	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; $P = 0.048$) SM resistance was independently associated with a worse treatment outcome
Migliori[23]	2008	Meta-analysis of data from people with MDR- and XDR-TB with definitive treatment outcomes	288 people with MDR- or XDR-TB included for review	Resistance to CPM yielded a higher proportion of failure and death than CPM-susceptible cases (OR 3.51) Unfavorable outcomes were similar in persons with DR-TB 1) susceptible or 2) resistant to KM or AMK (respectively $P = 0.31$ and $P = 0.78$) Resistance to more than one injectable agent increased the chance of an unfavorable outcome (OR 2.66; $P = 0.024$)

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.

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

First author	Year of study	Study country	Patients with ototoxicity *n* (%)	Age range years	Patients known to be HIV-infected *n* (%)
Baghaei[43]	2006–2009	Iran	8–14 (10.0–17.5)	14–81	4 (5.0)
Bloss[44]	2000–2004	Latvia	195 (19.0)	13–83	32 (3.1)
Burgos[45]	1982–2000	USA	2 (4.2)	22–78	11 (22.9)
Chan[46]	1984–1998	USA	39 (19.0)	2–85	NS
Codecasa[47]	2001–2003	Italy	1 (2.6)	43.6 (17.3)*	2 (5.3)
de Jager[48]	1995–2000	The Netherlands	11 (18.0)	10–83	NS
Dheda[49]	2002–2008	South Africa	10 (6)	⩾16	82/174 (47.1)
Drobac[50]	1999–2003	Peru	2 (6.7)	2–14	2/38 (5.3)
Duggal[51]	2000–2006	India	12 (18.8)	17–65	NS
Furin[52]	1996–1998	Peru	4 (6.7)	12–60	1 (1.7)
Geerligs[53]	1985–1998	The Netherlands	0–6* (0–15)	10–82	0
Ghafar[54]	May–August 2010	South Africa	12 (48)	7 months–16.6 years	12 (40)
Goble[2]	1973–1983	USA	13 (7.6)	17–79	NS
Isaakidis[55]	2007–2011	India	5 (8.6)	11–61	58 (100)
Jacob[56]	2002–2007	Belgium	11 (50.0)	21–76	1/21 (4.8)
Joseph[57]	2006–2007	India	1 (2.6)	⩾18	†
Karagoz[58]	1995–2000	Turkey	24 (22.0)	16–65	0
Keal[6]	2006–2011	UK	5 (27.8)	10–80	1 (5.6)
Kennedy[40]	2004–2009	Ireland	8 (61.5)	24–82	1/7 (14.3)
Keshavjee[59]	2000–2004	Russia	78 (12.8)	XDR-TB: 33.9 ± 11.1† MDR-TB: 35.9 ± 11.3†	5 (0.8)
Kim[60]	1996–2005	Republic of Korea	8 (3.8)	13–91	†
Leimane[61]	2000	Latvia	58 (28.4)	17–78	1/197 (0.5)
Malla[62]	2005–2006	Nepal	12 (9.6)	33.6 ± 12.5†	NS
Masjedi[63]	2002–2006	Iran	20 (46.5)	15–83	0
Modongo[64]	2006–2012	Botswana	270 (62)	⩾15	288 (66%)
Nathanson[65]	1998–2002	Multiple sites	98 (12.0)	NS	NS
Palmero[66]	1996–1999	Argentina	5 (6.8)	<16 excluded 36.0 ± 13.0†	‡
Peloquin[67]	1991–1998	USA	32–28* (36.8–32.2)	19–79	NS
Sagwa[68]	2004–2014		206 (58%)	36.4 (11.7)	164 (46)
Shin[7]	2000–2002	Russia	38 (15.6)	17–65	NS
Sturdy[69]	2004–2009	UK	9 (18.0)	34.6 ± 12.8†	5 (10)
Tahaoğlu[70]	1992–1999	Turkey	45 (28.5)	15–68	‡
Telzak[71]	1991–1994	USA	1 (5.9)	<25: 2 ⩾25: 23	‡
Törün[8]	1992–2004	Turkey	110 (41.8)	14–68	‡
Tupasi[72]	1999–2002	Philippines	22 (18.8)	15–24: 11 ⩾25: 90	Unable to test HIV status
Uffredi[73]	1998–1999	France	2 (4.4)	17–77	9 (20)
van Deun[74]	1997–2007	Bangladesh	19 (4.4)	<25: 108 >25: 319	Not tested
Yew[75]	1990–1997	Hong Kong	9 (14.3)	12–77	0

* 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.

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

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,[98] 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[99] (and renewing this recommendation in 2017),[100] and DLM in 2014,[101] and with recent recommendations for repurposed TB drugs such as CFZ and LZD, the cruel yet oft-repeated saying 'better deaf than dead' is both outdated and irrelevant.[102]

LZD is an antibiotic that has been demonstrated in two RCTs[103,104] and in observational studies to increase culture conversion and treatment success in drug-resistant TB.[105] 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.[106] 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.[107,108] Both have also been shown in animal models to have the potential to substantially shorten treatment,[109,110] 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.[111]

One reason why there has been hesitation in recommending that DLM or BDQ 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.[112] 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.[113,116] To date, more than 8000 individuals have received BDQ globally as part of programmatic management of drug-resistant TB.[115] 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.[116] In that cohort, 50 of the 91 participants 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.[117] 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.[118] More recent programmatic data from the South African Electronic Drug-Resistant Tuberculosis Register suggest 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.[100]

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.[119] 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.[120] Nonetheless, the cautious use of both of these agents has been recommended, including monthly electrocardiography (ECG) monitoring while the drugs are being administered.[121] 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 sutezolid (from the same class as LZD) are in the pipeline.[122] 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.[123] 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.[124] 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.[125] 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.[126] 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'. They also state that persons with MDR-TB must be 'given information about the risks and benefits of treatment' and that treatment be 'accessible, acceptable, affordable and appropriate'.[14] 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.[127] 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).[128] 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.[129] However, a recent perspective suggests that if given with an optimized background regimen (underscoring the need for universal drug susceptibility testing), the risk of developing resistance is minor.[130] 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.[131]

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.[132] 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.[133] 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.[134] The necessity of the IA as a core part of MDR-TB regimens in other population groups should similarly be scrutinized.

Table 3 Comparison between injectable agents, BDQ and DLM

	Injectable agent	BDQ	DLM
Efficacy	EBA trials—only SM has EBA at a high dose of 30 mg/kg[19] Observational cohorts with no clear evidence of benefit[20] No RCT No ongoing RCTs	EBA trials show efficacy (late)[107] Observational cohorts with evidence of benefit[113,116] Phase-IIB RCT data show improved outcomes[114] Phase-III trial underway[123]	EBA trials show efficacy[108] Observational cohorts with evidence of benefit[101] Phase-IIB RCT data showed improved outcomes[111] Phase-III trial has completed enrollment[123]
Adverse events reported in >5% of patients receiving the drug that are causally linked to the agent	Hearing loss in ⩽61.5% of patients[40] Vestibular toxicity in ⩽9%[31] Renal toxicity and electrolyte abnormalities in ⩽12%[33] Injection site reactions/ abscesses[39]	QTc prolongation >500 msec in 3.9% Hepatitis in 5%[114]	QTc prolongation >500 msec in 2.3%[111]
Logistical considerations	Daily interaction with health care providers required Biohazard and universal precautions required Monthly monitoring for hearing loss required[9]	Monthly monitoring of ECG required[9]	Monthly monitoring of ECG required[9]
Long-term impact	Permanent impact on ability to perform activities of daily living and employment[36] Deafness has been associated with an increased risk of being a victim of physical violence, depression[91]	Arrhythmia, if it occurs, could be fatal	Arrhythmia, if it occurs, could be fatal

BDQ = bedaquiline; DLM = delamanid; EBA = early bactericidal activity; SM = streptomycin; QTc = corrected QT interval; ECG = electrocardiogram; RCT= randomized controlled trial.

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.

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References

1 World Health Organization. WHO treatment guidelines for drug resistant tuberculosis: 2016 update. WHO/HTM/TB/ 2016.04. Geneva, Switzerland: WHO, 2016.

2 Goble M, Iseman M D, Madsen L A, Waite D, Ackerson L, Horsburgh C R, Jr. Treatment of 171 patients with pulmonary

tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993; 328: 527–532.
3 Gandhi N R, Moll A, Sturm A W, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368: 1575–1580.
4 Garcia-Prats A J, Donald P R, Hesseling A C, et al. Second-line anti-tuberculosis drugs in children: a commissioned review for the World Health Organization 19th expert committee on the selection and use of essential medicines. Geneva, Switzerland: World Health Organization, 2013. http://www.who.int/entity/selection_medicines/committees/expert/19/applications/TB_624_C_R.pdf Accessed July 2017.
5 Shringarpure K S, Isaakidis P, Sagili KD, Baxi R K, Das M, Daftary A. 'When treatment is more challenging than the disease': a qualitative study of MDR-TB patient retention. PLOS ONE 2016; 11: e0150849.
6 Keal J L, Khachi H, Hanzaree E, White V L C. Treatment of multidrug resistant tuberculosis: where are the guidelines for monitoring? Thorax 2011; 66: A91. [Abstract P56]
7 Shin S S, Pasechnikov A D, Gelmanova I Y, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis 2007; 11: 1314–1320.
8 Torun T, Gungor G, Ozmen I, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9: 1373–1377.
9 World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of multidrug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, Switzerland: WHO, 2014.
10 Furin J, Brigden G, Lessem E, Rich M, Vaughan L, Lynch S. Global progress and challenges in the implementation of new medications for the treatment of multidrug-resistant tuberculosis. Emerg Infect Dis 2016; 22. doi: 10.3201/eid2203.151430.
11 Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. Int J Tuberc Lung Dis 2016; 20: 177–186.
12 South African Department of Health. Introduction of new drugs and drug regimens for the management of drug-resistant tuberculosis in South Africa. Pretoria, South Africa: DoH, 2015.
13 Guglielmetti L, Hewison C, Avaliani Z, et al. Examples of bedaquiline introduction for the management of multidrug-resistant tuberculosis in five countries. Int J Tuberc Lung Dis 2017; 21: 167–174.
14 World Health Organization. Ethics guidance for the implementation of the End TB Strategy. WHO/HTM/TB/2017.07. Geneva, Switzerland: WHO, 2017. http://www.who.int/tb/publications/2017/ethics-guidance/en/. Accessed July 2017.
15 World Health Organization. Implementing the End TB Strategy: the essentials. Geneva, Switzerland: WHO, 2015. WHO/HTM/TB/2015.31. http://www.who.int/tb/publications/2015/end_tb_essential.pdf. Accessed July 2017.
16 Zumla A I, Gillespie S H, Hoelscher M. New anti-tuberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis 2014; 14: 327–340.
17 Schatz A, Bugle E, Waksman S A. Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. 1944. Clin Orthop Relat Res 2005; 437: 3–6.
18 Sims E. A case of tuberculous meningitis treated with streptomycin without success. Med J Aust 1947; 2: 12.
19 Fox W, Sutherland I, Daniels M. A five-year assessment of patients in a controlled trial of streptomycin in pulmonary tuberculosis. Q J Med 1954; 23: 347–366.
20 Ahuja S D, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9153 patients. PLOS Med 2012; 9: e1001300.
21 Chan E, Strand M, Iseman 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; e50–52.
22 Kim D H, Kim H J, Park S K, et al. Treatment outcomes and survival based on drug resistance patterns in multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 113–119.
23 Migliori G B, Lange C, Centis R, et al. TBNET Study Group. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J 2008; 31: 1155–1159.
24 Falzon D, Gandhi N, Migliori G B, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J 2013; 42: 156–168.
25 Althomsons S P, Cegielski J P. Impact of second-line drug resistance on tuberculosis treatment outcomes in the United States: MDR-TB is bad enough. Int J Tuberc Lung Dis 2012; 16: 1331–1334.
26 Bastos M L, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first-and second-line drugs: an individual patient data meta-analysis. Clin Infect Dis 2014; 59: 1364–1374.
27 Medical Research Council Investigation. Streptomycin treatment of pulmonary tuberculosis. Br Med J 1948; 2: 769–782.
28 Donald P, Sirgel F, Venter A, et al. The early bactericidal activity of streptomycin. Int J Tuberc Lung Dis 2002; 6: 693–698.
29 Donald P, Sirgel F, Venter A, et al. The early bactericidal activity of amikacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2001; 5: 533–538.
30 Georghiou S B, Seifert M, Catanzaro D G, Garfein R S, Rodwell T C. Increased tuberculosis patient mortality associated with *Mycobacterium tuberculosis* mutations conferring resistance to second-line anti-tuberculous drugs. J Clin Microbiol 2017; 55: 1928–1937.
31 Oliveira J F, Cipullo J P, Burdmann E A. Aminoglycoside nephrotoxicity. Rev Bras Cir Cardiovasc 2006; 21: 444–452.
32 Kilonzo K G, Jones E S W, Okpechi I G, et al. Disparities in dialysis allocation: An audit from the new South Africa. PLOS ONE 2016; 12: e0176041.
33 Prayle A, Watson A, Fortnum H, et al. Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. Thorax 2010; 65: 654–658.
34 Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des 2007; 13: 119–126.
35 Guthrie O W. Aminoglycoside induced ototoxicity. Toxicology 2008; 249: 91–96.
36 Olusanya B O, Neumann K J, Saunders J E. The global burden of disabling hearing impairment: a call to action. Bull World Health Organ 2014; 92: 367–373.
37 Naismith J T. Deafness with use of dihydrostreptomycin in tuberculous meningitis. Br Med J 1952; 1: 796–798.
38 Degreef I. The ototoxicity of kanamycin: a theoretical and experimental study. Acta Otorhinolaryngolog Belg 1964; 18: 415–427.
39 Seddon J A, Godfrey-Faussett P, Jacobs K, et al. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J 2012; 40: 1277–1286.
40 Kennedy B, O'Connor B, Korn B, Gibbons N, O'Connor T, Keane J. Multi-drug resistant tuberculosis: experiences of two tertiary referral centres. Ir Med J 2011; 104: 182–185.

41 Kuaban C, Noeske J, Rieder H L, Aït-Khaled N, Abena Foe J L, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015; 19: 517–524.
42 Piubello A, Harouna S H, Souleymane M B, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014; 18: 1188–1194.
43 Baghaei P, Tabarsi P, Dorriz D, et al. Adverse effects of multidrug-resistant tuberculosis treatment with a standardized regimen: a report from Iran. Am J Ther 2011; 18: e29–e34.
44 Bloss E, Kuksa L, Holtz T H, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. Int J Tuberc Lung Dis 2010; 14: 275–281.
45 Burgos M, Gonzalez L C, Paz E A, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis 2005; 40: 968–975.
46 Chan E D, Laurel V, Strand M J, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2004; 169: 1103–1109.
47 Codecasa L R, Ferrara G, Ferrarese M, et al. Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first line drugs. Respir Med 2006; 100: 1566–1572.
48 de Jager P, Van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis 2002; 6: 622–627.
49 Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet 2010; 375: 1798–1807.
50 Drobac P C, Mukherjee J S, Joseph J K, et al. Community-based therapy for children with multidrug-resistant tuberculosis. Pediatrics 2006; 117: 2022–2029.
51 Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord 2007; 7: 5.
52 Furin J J, Mitnick C D, Shin S S, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001; 5: 648–655.
53 Geerligs W A, Van Altena R, De Lange W C M, Van Soolingen D, Van Der Werf T S. Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. Int J Tuberc Lung Dis 2000; 4: 758–764.
54 Ghafari N, Rogers C, Petersen L, Singh S A. The occurrence of auditory dysfunction in children with TB receiving ototoxic medication at a TB hospital in South Africa. Int J Pediatr Otorhinolaryngol 2015; 79: 1101–1105.
55 Isaakidis P, Cox H S, Varghese B, et al. Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. PLOS ONE 2011; 6: e28066.
56 Jacob V, Robert L, Lebrun C, Laethem Y V, Sergysels R. Multidrug-resistant tuberculosis: a review of the 23 cases treated by the Saint-Pierre University Hospital (Brussels). Acta Clinica Belgica 2009; 64: 113–119.
57 Joseph P, Desai V B R, Mohan N S, et al. Outcome of standardized treatment for patients with MDR-TB from Tamilnadu, India. Indian J Med Res 2011; 133: 529–534.
58 Karagoz T, Yazicioglu Mocin O, Pazarli P, et al. The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome. Tuberk Toraks 2009; 57: 383–392.
59 Keshavjee S, Gelmanova I Y, Farmer P E, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008; 372: 1403–1409.
60 Kim H R, Hwang S S, Kim H J, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis 2007; 45: 1290–1295.
61 Leimane V, Riekstina V, Holtz T H, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005; 365: 318–326.
62 Malla P, Kanitz E E, Akhtar M, et al. Ambulatory-based standardized therapy for multi-drug resistant tuberculosis: experience from Nepal, 2005–2006. PLOS ONE 2009; 4: e8313.
63 Masjedi M R, Tabarsi P, Chitsaz E, et al. Outcome of treatment of MDR-TB patients with standardised regimens, Iran, 2002–2006. Int J Tuberc Lung Dis 2008; 12: 750–755.
64 Modongo C, Sobota R S, Kesenogile B, et al. Amikacin concentrations predictive of ototoxicity in multidrug-resistant tuberculosis patients. BMC Infect Dis 2014. 14: 542.
65 Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 2004; 8: 1382–1384.
66 Palmero D J, Ambroggi M, Brea A, et al. Treatment and follow-up of HIV-negative multidrug-resistant tuberculosis patients in an infectious diseases reference hospital, Buenos Aires, Argentina. Int J Tuberc Lung Dis 2004; 8: 778–784.
67 Peloquin C A, Berning S E, Nitta A T, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004; 38: 1538–1544.
68 Sagwa E, Ruswa N, Musasa J P, Mantel-Teeuwisse A K. Adverse events during treatment of drug-resistant tuberculosis: a comparison between patients with or without human immunodeficiency virus co-infection. Drug Saf 2013; 36: 1087–1096.
69 Sturdy A, Goodman A, Jose R J, et al. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. J Antimicrob Chemother 2011; 66: 1815–1820.
70 Tahaoglu K, Torun T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med 2001; 345: 170–174.
71 Telzak E E, Sepkowitz K, Alpert P, et al. Multidrug-resistant tuberculosis in patients without HIV infection. N Engl J Med 1995; 333: 907–911.
72 Tupasi T E, Gupta R, Quelapio M I, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLOS Med 2006; 3: e352.
73 Uffredi M L, Truffot-Pernot C, Dautzenberg B, Renard M, Jarlier V, Robert J. An intervention programme for the management of multidrug-resistant tuberculosis in France. Int J Antimicrob Agents 2007; 29: 434–439.
74 Van Deun A, Maug A K, Salim M A, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.
75 Yew W W, Chan C K, Chau C H, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000; 117: 744–751.
76 Modongo C, Pasipanodya J G, Zetola N M, Williams S M, Sirugo G, Gumbo T. Amikacin concentrations predictive of ototoxicity in multidrug-resistant tuberculosis patients. Antimicrob Agents Chemother 2015; 59: 6337–6343.
77 Harris T, Bardien S, Schaaf H S, et al. Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients. S Afr Med J 2012; 102: 363–366.
78 Brits J, Strauss S, Eloff Z, Becker P J, Swanepoel de W. Hearing profile of gold miners with and without tuberculosis. Occup Environ Med 2012; 69: 243–249.

79 American Speech-Language-Hearing Association. Guidelines for audiologic screening (guideline). Rockville, MD, USA: ASHA, 1997.
80 Shean K, Streicher E, Pieterson E, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. PLOS ONE 2013; 8: e63057.
81 World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM): a framework for implementation. WHO/HTM/TB/2015.28. Geneva, Switzerland: WHO, 2015.
82 Sagwa E, Souverein P, Ribiero I, Leufkens H, Mantel-Teeuwisse A. Differences in VigiBase® reporting of aminoglycoside and capreomycin-suspected ototoxicity during tuberculosis treatment. Pharmacoepidemiol Drug Saf 2016; 26: 1–8.
83 Saliba J, Al-Reefi M, Carriere J, et al. Accuracy of mobile-based audiometry in the evaluation of hearing loss in quiet and noisy environments. Otolaryngol Head Neck Surg 2017; 156: 706–711.
84 Huth M E, Ricci A J, Cheng A G. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryngol 2011; 2011: 937861.
85 Chen Y, Huang W-G, Zha D-J, et al. Aspirin attenuates gentamicin ototoxicity: from the laboratory to the clinic. Hear Res 2007; 226: 178–182.
86 Kranzer K, Elamin W F, Cox H, et al. A systematic review and meta-analysis of the efficacy and safety of *N*-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB. Thorax 2015; 70: 1070–1077.
87 Iijima K, Ara N, Abe Y, et al. Association of gastric acid and mucus secretion level with low-dose aspirin-induced gastropathy. Gastroenterol 2012; 47: 150–158.
88 Daftary A, Padayatchi N, O'Donnell M. Preferential adherence to antiretroviral therapy over tuberculosis treatment: a qualitative study of drug-resistant TB/HIV co-infected patients in South Africa. Glob Public Health 2014; 9: 1107–1116.
89 Looi L, Ganten D, McGrath P, Gross M, Griffin G. Hearing loss: a global health issue. Lancet 2015; 385: 943–944.
90 GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545–1602.
91 Kouwenberg M, Rieffe C, Theunissen S C, de Rooij M. Peer victimization experienced by children and adolescents who are deaf or hard of hearing. PLOS ONE 2012; 7: e52174.
92 Tucci D, Merson M H, Wilson B S. A summary of the literature on global hearing impairment: current status and priorities for action. Otol Neurotol 2010; 31: 31–41.
93 Emmett S, Francis H. The socioeconomic impact of hearing loss on adults in the US. Otol Neurotol 2015; 36: 545–550.
94 Seddon J A, Thee S, Jacobs K, et al. Hearing loss in children treated for multidrug-resistant tuberculosis. J Infect 2013; 66: 320–329.
95 Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. Int J Infect Dis 2014; 32: 56–60.
96 Weiss P, Chen W, Cook V J, Johnston J C. Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis. BMC Infect Dis 2014; 14: 333.
97 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: e0144936.
98 World Health Organization. The End TB Strategy. Geneva, Switzerland: WHO, 2017. http://www.who.int/tb/strategy/end-tb/en/. Accessed July 2017.
99 World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim guidance. WHO/HTM/TB/2013.6. Geneva, Switzerland: WHO, 2013.
100 World Health Organization. A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. WHO/HTM/TB/2017.01. Geneva, Switzerland: WHO, 2017. http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/. Accessed July 2017.
101 World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. WHO/HTM/TB2014.23. Geneva, Switzerland: WHO, 2014.
102 Hughes J. Better deaf than dead? Auckland Park, South Africa: Huffington Post, December 2016. http://www.huffingtonpost.co.za/doctors-without-borders/better-deaf-than-dead_a_21621566/ Accessed September 2017.
103 Lee M, Lee J, Carroll M W, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012; 367: 1508–1518.
104 Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015; 45: 161–170.
105 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2012; 16: 447–454.
106 Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J 2012; 40: 1430–1442.
107 Diacon A H, Dawson R, Von Groote-Bidlingmaier F, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. Antimicrob Agents Chemother 2013; 57: 2199–2203.
108 Diacon A H, Dawson R, Hanekom M, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis 2011; 15: 949–954.
109 Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLOS Med 2006; 3: e466.
110 Veziris N, Ibrahim M, Lounis N, Andries K, Jarlier V. Sterilizing activity of second-line regimens containing TMC207 in a murine model of tuberculosis. PLOS ONE 2011; 6: e17556.
111 Gler M T, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug resistant pulmonary tuberculosis. N Engl J Med 2012; 366: 2151–2160.
112 Zumla A, Schito M, Maeurer M. Advancing the portfolio of tuberculosis diagnostics, drugs, biomarkers and vaccines. Lancet Infect Dis 2014; 14: 267–269.
113 Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J 2017; 49: 1601799.
114 Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori G. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J 2016; 47: 394–402.
115 Pai M, Furin J. Tuberculosis innovations mean little if they cannot save lives. eLife 2017; 6: e25956.
116 Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis 2015; 19: 979–985.

117 Ndjeka N. Incorporation of bedaquiline in the South African National TB Program. Poster presentation at the 2016 Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA, 22–25 February 2016. Abstract no 754. http://www.croiconference.org/sessions/incorporation-bedaquiline-south-african-national-tb-programme Accessed July 2017.
118 Borisov S E, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J 2017; 49. pii: 1700387.
119 Belard S, Heuvelings C C, Janssen S, Grobusch M P. Bedaquiline for the treatment of drug-resistant tuberculosis. Exp Rev Anti-infective Ther 2015; 13: 535–553.
120 Janssen Pharmaceuticals. TMC207 (bedaquiline) treatment of patients with MDR-TB (NDA 204–384). Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012. Beerse, Belgium: Janssen Pharmaceuticals, 2012.
121 Fox G, Menzies D. A review of the evidence for using bedaquiline (TMC207) to treat multi-drug resistant tuberculosis. Infect Dis Ther 2013; 2: 123–144.
122 Mitnick C D, Rusen I, Bain L J, Horsburgh C R. Issues in design and interpretation of MDR-TB clinical trials: report of the first Global MDR-TB Clinical Trials Landscape Meeting. BMC Proc 2015; 9 (Suppl 8): S1.
123 Resist-TB Research Excellence to Stop TB Resistance. DR-TB Clinical Trials Progress Report. April 2017. http://www.resisttb.org/?page_id=1602 Accessed July 2017.
124 Conradie F, Diacon A H, Everitt D, et al. The NIX-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 13–16 February 2017. Abstract no 80LB. http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb. Accessed July 2017.
125 Horsburgh C R, Rusen I D, Mitnick C D. Optimizing MDR-TB clinical trials: insights from the first global MDR-TB Clinical Trials Landscape Meeting. Int J Tuberc Lung Dis 2016; 20: 1–3.
126 Satta G, McHugh T D, Mountford J, Abubakar I, Lipman M. Managing pulmonary non-tuberculous mycobacterial infection: time for a patient-centered approach. Ann Am Thorac Soc 2014; 11: 117–121.
127 Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. 'I cry every day': experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Health 2013; 18: 1128–1133.
128 Sullivan T, Amor Y. Global introduction of new multidrug-resistant tuberculosis drugs—balancing regulation with urgent patient needs. Emerg Infect Dis 2016; 22: e151228.
129 Kirby T. Landmark legal ruling sees Indian girl prescribed bedaquiline for XDR-TB. Lancet Respir Med 2017; 5: 249.
130 Kunkel A, Furin J, Cohen T. Population implications of the use of bedaquiline in persons with extensively drug-resistant tuberculosis: are fears of resistance justified? Lancet Infect Dis 2017 19 May 2017. http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(17)30299-2.pdf. Accessed July 2017.
131 Citro B, Lyon E, Mankand M, et al. Developing a human rights-based approach to tuberculosis. Health Hum Rights. 2016; 18: 1–8.
132 Fitchett J R, MacPherson P, Corbett E. Implementing the End TB Strategy and the intersection with the sustainable development goals, 2016–2030. Trans R Soc Trop Med Hyg 2016; 110: 145–147.
133 Weld E D, Garcia-Prats A J, Furin J J, Bailey T C, Hesseling A C, Dooley K E. The time has come: sparing injectables in paediatric MDR-TB. Lancet Respir Med 2017 Mar 15. [Epub ahead of print].
134 Falzon D, Schünemann H, Harausz E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J 2017; 49: pii1602308.

RESUME

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 revoyons la diffusion continuelle de ces agents en tant qu'alternatives thérapeutiques—plus particulièrement les médicaments TB plus récents, la bédaquiline 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.

RESUMEN

Durante varios decenios los medicamentos inyectables de segunda línea han representado el pilar del tratamiento de la tuberculosis multirresistente (TB-MDR). Existen pocos datos sobre la eficacia de estos medicamentos, pero cada vez se cuenta con más pruebas de sus efectos adversos graves. En el presente análisis de los resultados más recientes, se presentan las conclusiones de una revisión estructurada de la bibliografía sobre la seguridad y la eficacia de los medicamentos inyectables. Se examinó la utilización generalizada continua de estos medicamentos en el contexto de las opciones terapéuticas, sobre todo de los antituberculosos más recientes como la bedaquilina y el delamanid y desde la perspectiva de los derechos humanos, los principios éticos y la atención 'centrada en el paciente'. Se concluye que existen pocas pruebas de la eficacia de estos medicamentos y una evidencia clara de los riesgos que implica su utilización; es primordial informar a las personas aquejadas de TB-MDR sobre estos riesgos y ofrecer acceso a otras opciones terapéuticas.