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Human rights: finding the right balance for rifampicin-resistant TB treatment

Dear Editor,

We read with interest the recent article by Cox et al.[1] which claimed that the use of second-line injectable drugs (SLID) for the treatment of rifampicin-resistant TB (RR-TB) violates human rights. The authors encourage national TB programmes (NTPs) to modify all-oral regimens.[1] However, in order to protect the right of our patients to safe treatment with proven efficacy we advocate the use of evidence-based approaches. Until solid evidence for safe alternatives to SLIDs is available, NTPs should be free to choose the RR-TB treatment regimen that best benefits their patients.

In 2012, we withdrew from a meta-analysis recommending a minimum of 8 months of SLID use in a long regimen,[2] because of the almost certain ototoxicity that would result. SLID use in the short treatment regimen (STR) had always been limited to the recommended minimum, but a cohort with kanamycin for only 2 months showed significantly higher failure and relapse outcomes with acquired fluoroquinolone (FQ) resistance.[3] The STR could be further shortened by switching to gatifloxacin, which has a higher sterilising activity (Table).[4] The STR was highly effective at the national level in all settings with a low prevalence of initial FQ resistance and when standardised approaches were used for RR-TB treatment.[4] Except for the initial resistance to FQ, and possibly SLID, resistance to other drugs in the regimen had limited impact.[4] Also, other WHO exclusion criteria such as extensive disease,[5] contradict published evidence, which indicates a lack of understanding of how the STR works, through the concerted action of drugs, rather than the number of effective drugs. Several studies have reported that 4 months of SLIDs, which are crucial for long-term effectiveness, resulted in the avoidance of acquired FQ resistance as long as high-dose gatifloxacin was used.[3,6] Even the weaker moxifloxacin-based STR was proven to be non-inferior to longer regimens in a clinical trial,[4] while in routine care superior results were recorded due to significantly lower loss to follow-up. The 2018 meta-analysis, which concluded that SLID had "no or little effect", overlooked its essential contribution to the outcome, i.e., the aversion of failure through acquired resistance to the core drug.[7] As described earlier, there is ample evidence for this key activity of SLIDs.[3,8]

The "State of the Art" article by Cox et al. presents preliminary and (presumably) non-peer-reviewed results from clinical trials and the South Africa NTP guidelines, together with a few references on the effect of individual drugs, but no results of standard regimens and no data on acquired resistance to core drugs.[1] The development of the current 6-month rifampicin-based, first-line regimen showed that constructing a robust regimen requires combining drugs based on their specific activities,[9] to achieve complementary action. Whether new drugs can effectively take the role of the SLID in the STR remains unknown. The delayed onset of bactericidal activity for bedaquiline poses a risk for acquisition of resistance, first to the FQ and then to itself.[8] Linezolid does not have the same protective effect and causes potentially more harm than SLID.[8] It can, however, provide an alternative to SLID if any hearing loss is detected.

To recommend in a "State of the Art" article that modifications to a proven, highly effective RR-TB regimen should be rolled out as soon as possible could have dire consequences, for the patient and for the community. Countries that switch to an all-oral STR, despite the excellent results obtained with the SLID-containing STR, are likely to find a deterioration in the results. All-oral RR-TB treatment regimens are most welcome once solid evidence that the regimens are more efficacious and safer in all respects is available. Meanwhile, experts have the responsibility to avoid creating a new type of incurable TB, which would truly harm the rights of future generations of RR-TB patients.

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Table Comparative studies on shorter RR-TB treatment regimens

First author, year	Study regimen*	Control*	Setting	Study type	Descriptive outcomes (study regimen vs. control)†	Conclusion†
Van Deun, 2019[6]	GFX-based STR [4(+)KmCfz GfxHEmbHHZPth/5GfxHEmb ZCfz]	MFX or LVX-based STR	Bangladesh, Cameroon, Niger	Cohort study	Bacteriological effectiveness: 97.5% (954/978) vs. 95.1% (525/552); Acquired FQ resistance: 0% (0/858) vs. 1.4% (6/427)	GFX-based STR: higher bacteriological effectiveness and lower acquired FQ resistance
Decroo, 2020[3]	2SLID-containing/GFX-based STR [2KmCfzGfxHEmbHHZPth/ 2(+)CfzGfxHEmbHHZPth]	4(+)SLID-containing/GFX-based STR [4(+)KmCfzGfxHEmbHH ZPth/5GfxHEmbZCfz]	Bangladesh	Before-after cohort study	Bacteriological effectiveness: 90.4% (47/52) vs. 97.2% (717/738); Acquired FQ resistance: 4.5% (2/44) vs. 0% (0/639)	2 months of SLID in the STR: lower bacteriological effectiveness and greater acquired FQ resistance
Nunn, 2019[4]	MFX-based STR [4(+)CfzMfxH EmbHHZPth/5MfxHEmbZCfz]	Local long regimen	South Africa, Ethiopia, Mongolia, Viet Nam	Randomised clinical trial	78.8% (193/245) vs. 79.8% (99/124) success (trial endpoint) 81.0% vs. 82.3% programmatic success 84.2% vs. 83.1% success at 2.5 years, corrected for retreatment outcomes	MFX-based STR is non-inferior to locally used long regimens
Philips, 2020[10]						

* (4+) = The standard duration of the intensive phase was 4 months, but was extended until smear-negative.
† Programmatic effectiveness: relapse-free cure vs. either treatment failure, relapse, mortality, or loss to follow-up; Bacteriological effectiveness: relapse-free cure vs. either treatment failure or relapse (mortality and lost to follow-up excluded).
RR-TB = rifampicin-resistant TB; GFX = gatifloxacin; STR = shorter (RR-TB) treatment regimen; Km = kanamycin; Cfz = clofazimine; H = high-dose; Emb = ethambutol; H = isoniazid; Z = pyrazinamide; Pth = prothionamide; MFX = moxifloxacin; LVX = levofloxacin; FQ = fluoroquinolone; SLID = second-line injectable drugs.

References

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Reply to: "Human rights: finding the right balance for rifampicin-resistant TB treatment"

Dear Editor,

In their Correspondence[1] regarding our manuscript on all-oral, shorter regimens for the treatment of people living with rifampicin-resistant TB (RR-TB),[2] Van Deun and colleagues advocate for the use of injectable-containing regimens. We agree with the authors that having additional data from randomized clinical trials would bolster the evidence base for all-oral shorter regimens. However, observational data, such as that cited in our review,[3] can also play a crucial role. Indeed, the authors themselves acknowledge the value of such data in citing numerous observational studies to support their arguments. The injectable-containing shorter regimen the authors refer to was designed and rolled out globally based on focused observational studies.[4] This was because trial data were not available until 2019, 3 years after the WHO recommended the regimen based, in part, on their Guideline Development Group review of these observational studies. In addition, the cited trial compared the injectable-containing regimen to an outdated control arm (based on WHO recommendations from 2011).

When considering the use of an individual medication or treatment regimen for RR-TB, several issues must be considered, including efficacy, safety and