Now is the time for shorter all-oral regimens for multidrug-resistant tuberculosis

The newly revised WHO guidelines for multidrug-resistant tuberculosis treatment includes major changes from the previous version, published in 2016.[1] Notably, drugs such as bedaquiline, linezolid, and clofazimine are now strongly recommended for the treatment of multidrug-resistant tuberculosis. At the same time, older drugs, such as injectables, ethionamide, and para-aminosalicyclic acid, have been downgraded due to poor effectiveness and side-effect profiles. These new recommendations, if implemented, are expected to have a huge impact globally, increasing access of patients with multidrug-resistant tuberculosis to more effective and safer drug regimens that avoid debilitating side-effects, such as permanent hearing loss.[2]

Given the new recommendations on the hierarchy of multidrug-resistant tuberculosis drugs, we find it surprising that WHO continues to recommend the shorter "Bangladesh" regimen, which includes several drugs that are low in the current hierarchy of multidrug-resistant tuberculosis drugs (eg, amikacin, ethionamide, and isoniazid). Nowadays, newer and better multidrug-resistant tuberculosis drugs are increasingly available, even in resource-limited settings. In the STREAM trial,[3] the Bangladesh regimen was shown to be non-inferior to a long control regimen that is now considered obsolete. The new WHO guidelines recommend that all patients with multidrug-resistant tuberculosis receive drugs that were not included in the STREAM long control regimen, notably bedaquiline and linezolid. These two drugs were not widely available at the time the trial was done, but they are now known to be highly effective,[4] are considered first-line treatment for multidrug-resistant tuberculosis, and their use has been supported by a retrospective study of South African patients with multidrug-resistant tuberculosis, which revealed that mortality was significantly decreased in those who received bedaquiline.[5] Furthermore, the STREAM trial showed that the Bangladesh regimen had similar toxicity to the injectable-containing control regimen. For example, the frequency of hearing loss (caused by the injectable) was no less frequent than the Bangladesh regimen, despite the total injectable duration being shorter in the latter.

Many new shorter multidrug-resistant tuberculosis regimens are being tested in clinical trials, almost all of them using the new drugs recommended by WHO and eliminating injectables.[6] According to WHO, these new shorter regimens should only be used under operational research conditions pending trial results. We believe that such research should be prospective and longitudinal in nature, supported by external funding, and analysed with a single set of internationally accepted, systematically applied outcome definitions. Ideally, protocols would be harmonised across sites, allowing for data to be pooled easily.[7] If done this way, and rigorously analysed, operational research of new shorter regimens in realistic field conditions can complement the trial experience.

National tuberculosis programmes, starved of scientific advances for so many years, have grown accustomed to a culture of scarcity in which only the cheapest interventions are judged appropriate for implementation in the field, but nowadays the development of new diagnostics and drugs has upended old notions. Now, national tuberculosis programmes must choose between sticking with the obsolete Bangladesh regimen or new, shorter all-oral regimens that are likely to be more effective and safer. The choice is clear: by choosing to implement the new regimens under operational research conditions, national tuberculosis programmes will bring the benefits of scientific advancement to patients who need them and generate important evidence that will benefit other patients worldwide. External funders and experts should enthusiastically support national tuberculosis programmes that roll out the new all-oral multidrug-resistant tuberculosis shorter regimens under operational research conditions.

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