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Title:

Host-directed therapies and holistic care for tuberculosis

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Drug resistant TB remains a major threat to global public health security Despite advances in new TB drugs, treatment regimens and rapid diagnostics. There were an estimated half a million new cases of rifampicin-resistant TB of which 78% had multi-drug-resistant TB in 2018 (1). Current WHO treatment recommendations for MDR-TB requires use of a combination of anti-*Mycobacterium tuberculosis* (*Mtb*) drugs, most of which have serious side effects and have to be taken for a period of 6–18 months (1). The risk of *Mtb* developing resistance to these agents is ever present. It has taken over 2 and a half decades to develop three new TB drugs, delamanid, bedaquiline and pretomanid, which have improved treatment regimens for MDR-TB. Resistance to bedaquiline has already been documented and it is only a matter of time before *Mtb* develops resistance to other new drugs.

Whilst TB drug treatment usually achieves microbiological cure, many 'cured' TB patients continue to suffer ill health from permanent lung and other organ damage with long-term functional disability and reduced quality of life (2,3). This arises from excessive and aberrant host immune and inflammatory responses to *Mtb* resulting in extensive tissue destruction (4,5). In addition, most patients with MDR-TB have underlying predisposing and pre-existing host risk factors and other co-morbidities such as diabetes, chronic obstructive pulmonary disease (COPD), and underlying immunosuppression (6). This is compounded by psychological and social issues that may be pre-existing or arise from their MDR-TB diagnosis. Thus, there is an important need to revolutionize MDR-TB management through an integrated, patient-centered approach management for MDR-TB which includes 'precision medicine' and holistic care (7). This should include the unique host-pathogen profile, ensuring optimal TB drug treatment regimens through therapeutic drug monitoring to maximize efficacy and minimize toxicity, enhanced patient support for taking TB drugs, managing co-morbidities, and consideration of any relevant adjunct therapies to curb excessive inflammation and enhance protective immune responses.

Recent technological advances have provided a deeper understanding of inflammatory and immune pathways governing protective or deleterious outcomes, providing novel opportunities to target specific pathways that mediate immune pathology (6,7). Advances in host-directed therapies (HDTs) now provide a range of options as additional adjunct therapy to conventional *Mtb*-targeted TB drug treatment to enhance immune responses or reduce excessive inflammation. A range of HDTS with different mechanisms of action are under consideration from cellular therapy with mesenchymal cells, biologics, and repurposed drugs with HDT potential (5,6, 8). Several biologics and repurposed drugs are safe for use in humans, since they are already licensed and used widely for non-TB indications. These HDTs may act synergistically with TB drugs and could serve as adjuncts to MDR-TB drug regimens, decreasing the duration of treatment and reducing transmissibility. Individual patients are likely to vary in their need for HDTs and calls for a 'precision medicine approach' which is also requires tailoring of individual specific MDR-TB treatment regimen based on the drug resistance profile of the infecting *Mtb* strain (9). The HDT requirement may be highly dependent on the specific disease manifestation and other co-morbidities present.

Ever since 1993, when TB was declared a 'Global emergency', the global community has focused on the causative pathogen *Mtb*. Repeated calls for a more multidisciplinary effort to tackle the critical underlying 'host factors' which underlie poor management outcomes and to consider a comprehensive portfolio of investments for developing a more 'holistic' package of patient-centered care. The use of metformin as HDT to asses impact on both TB treatment and diabetes may have far greater population impact. The global TB clinical trials fraternity, their influence through representation and as reviewers for grant applications, and influence on for-profit industry and funding agencies, seem to be rigidly focused on targeting the pathogen and continue emphasis on new TB drugs. This mindset needs to change drastically towards a more comprehensive portfolio of investments for holistic package of care for MDR-TB patients which targets both *Mtb* and the host (10,11).

As new and more effective drug regimens are being rolled out for DR TB, there now needs to be a major paradigm shift towards a more holistic approach that includes host-directed therapies and precision medicine for management of patients with MDR-TB (**Figure 1).** This needs to be pursued at two levels. First, ensuring that TB is included in the precision medicine revolution, currently enveloping developed countries. This will provide TB patients access to advanced care and will develop the integrated data systems required to deliver state-of-the art TB care. Second, there is an urgent need to develop simplified systems and feasible implementation pathways in resource-limited settings, and to test novel interventions that have high relevance in high TB endemic countries. Holistic care requires a continuous quality improvement approach, identification and treatment of co-morbidities, supportive care, systematic monitoring of long term sequalae and complications, rehabilitation, psychological and community support. In the era of Sustainable Development Goals, and in line with the principles of patient-centred care that is central to the End TB strategy, a multidimensional approach should include social and economic support that reaches the poorest in low-income countries where the burden of TB and MDR-TB is highest (11).

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Figure 1 (for high resolution photo see attached ppt)