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Editorial

Adherence and Acquired Drug-Resistance in Tuberculosis: Wisdom Stood on its Head

Drug-resistant tuberculosis is an important public health problem.[1] Erratic adherence to anti-tuberculosis treatment often results in treatment failure and is widely considered to be the driving force behind the emergence of drug-resistance in previously treated patients. "Drugs do not work in patients who do not take them," once said by C. Everett Koop, the former (1982-89) US Surgeon General.[2] It is a statement that rings true — perhaps universally across disease paradigms. We know for sure that it is particularly true for the diseases, such as human immunodeficiency virus (HIV) infection where empirical evidence shows that even minor degrees of non-adherence lead to sub-optimal treatment outcomes.[3,4] The same belief applies to the treatment of tuberculosis (TB) as well.

Mitchison propounded four mechanistic principles that explain the emergence of acquired drug-resistance as a result of non-adherence to treatment.[5] Simultaneously, Lipsitch and Levin[6] described a mathematical model that predicted that non-adherence and heterogeneity of susceptibility are important determinants of acquired drug-resistance in TB. Many of us might even think that the assertion that poor adherence results in drug-resistance does not need empirical verification. Indeed, it seems to be an obvious fact. But, things do not remain the same for long in science. Once a while someone appears on the scene declaring that it is the earth that revolves around the sun, not the other way around. In that sense, the Copernicus seems to have arrived in the field of TB.

Recently, Gumbo and Colleagues at the University of Texas Southwestern Medical Center reported that the emergence of drug-resistance in TB is the result of pharmacokinetic variability among patients rather than non-adherence.[7] They used a novel *in vitro* pharmacodynamic model, the hollow fiber system, to study the effect of varying levels of non-adherence on bactericidal and sterilising activities of TB treatment. And, to everyone's surprise, they reported that missing up to 60% of daily doses made no difference to ultimate treatment success as well as the emergence of acquired drug-resistance.[7] They did not stop with that; of late, they have come up with empirical evidence to show that fast acetylators of isoniazid have a significantly higher risk of treatment failure and acquired drug-resistance despite supervised drug administration.[8] The later findings do not exonerate non-adherence as the cause of drug-resistance; instead, they draw our attention to inter-patient variation in bio-availability, a hitherto overlooked factor.

Do these findings from hollow fiber system count as solid evidence that necessitates a change in our clinical practice — perhaps not. First, notwithstanding its technological sophistication, the hollow fiber system is still an oversimplified replica of the anatomic and functional complexity of the *in vivo* lesions encountered in TB. Particularly, there are two important attributes that are missing in a hollow fiber system but are likely to play a role *in vivo* — *(i)* immune-mediated clearance of *Mycobacterium tuberculosis* is an important determinant of treatment success and acquired drug-resistance (absence of this factor, however, would not hamper the ability of a hollow fiber system to detect treatment failure); and *(ii)* spatial heterogeneity in drug distribution within the clinical lesions is another potentially important factor. Emerging body of evidence suggests a pivotal role for drug gradients in acquired drug-resistance.[9,10] Another relevant issue that was not addressed by Gumbo and colleagues in their experiments, as pointed out by Dartois, is the interaction of non-adherence and poor bio-availability.[11]

How do these findings apply to our national programme that employs thrice-weekly directly observed treatment in the intensive phase? Even though thrice-weekly dosing was not evaluated by Gumbo, the findings indirectly vindicate the stand that the therapeutic efficacy of thrice-weekly dosing would not be compromised.[7] Moreover, the higher dose of isoniazid (600 mg thrice-weekly) used in the programme should act as a buffer against failure in rapid acetylators. However, as emphasised by Gumbo, thrice-weekly administration is like treading on the edge, and anything less than 100% adherence in such a situation would prove to be sub-optimal.[7] This underscores the vital importance of adherence in the national programme.

How could one explain the diametrically opposite conclusions by Lipsitch and Gumbo on the effect of non-adherence? I believe, the basic reason probably lies in the way non-adherence was modelled. Lipsitch and Levin included in their model what is called a 'thermostat' non-adherence, i.e., the patient is assumed to completely stop taking drugs following initial clinical improvement and restart treatment only after the bacillary population increases to the pre-treatment level, which is possibly far from reality.[6] On the contrary, the work by Gumbo and Colleagues is commendable for the fact that they evaluated the effect of different patterns of non-adherence including a random forgetting pattern similar to erratic non-adherence. In the final analysis, given the fact that the questions being addressed cannot be easily answered

by clinical trials, the hollow fiber system experiments by Gumbo and Colleagues assume greater significance. Certainly, it is a work to be read closely and ruminated over.

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