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Preventing TB in people with HIV – no more excuses

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In 2014 tuberculosis eclipsed HIV as the leading infectious killer on earth and it remains the foremost cause of death for people with HIV infection. The risk of tuberculosis doubles after HIV is acquired, skyrockets inversely with falling CD4 counts, and remains substantially elevated even after immune reconstitution with antiretroviral therapy (ART). From the earliest days of the HIV epidemic it was evident that preventive therapy with isoniazid, a cheap, widely available, well-tolerated drug that has been around for >60 years, was protective against tuberculosis in people with HIV infection, and the World Health Organization (WHO) recommended its use as a personal health measure (i.e., not as a programmatic imperative) in 1993. (1, 2) Over the past 20 years numerous clinical trials and observational cohort studies have demonstrated the effectiveness of isoniazid preventive therapy (IPT) in preventing tuberculosis in people with HIV infection in the absence of ART in settings as diverse as Haiti, the United States, Brazil, Uganda, and Zambia. (3) Ten years ago cohort data from Brazil showed that IPT had additional benefit to ART, with individuals receiving both interventions having a 76% reduction in tuberculosis incidence, greater than with either treatment alone. (4) In 2008 the WHO elevated its guidance to recommend IPT as a public health priority for people with HIV in high-burden settings. (5)

Despite the abundant evidence for the efficacy of IPT, global recommendations for its routine use, and the continuing toll that tuberculosis exacts from people with HIV, the uptake of preventive therapy has been scandalously low. The WHO reported in 2016 that fewer than 1 million individuals with HIV infection were treated with IPT, a tiny fraction of the more than 30 million people who should receive it. (6) Excuses for not providing IPT at an individual and programmatic level have included unfounded fears of the emergence of drug resistance, concern about ruling out active tuberculosis, uncertainty about the durability of protection, lack of ironclad proof of a survival benefit, and the need to prioritize delivery of ART. While there is no doubt that ART is essential and it reduces the risk of tuberculosis (7), a cluster-randomized trial in Brazil found that programmatic implementation of IPT in HIV clinics providing ART resulted in an additional 31% reduction in tuberculosis or death at a population level. (8)

In this issue of *Lancet Global Health*, Anani Badje and colleagues publish the long term follow up data from the TEMPRANO study, a randomized, factorial design trial testing the impact of IPT and/or early ART for individuals with HIV infection and CD4 counts <800 cells/mm^3 but above the threshold for initiating treatment during the trial, prior to universal

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ART being endorsed. (9) The initial results of TEMPRANO found that IPT and early ART each reduced the risk of developing a serious HIV event, a large proportion of which were tuberculosis, and that receiving both IPT and early ART provided the best protection from disease. The post-trial phase doubles the duration of observation and shows that 6 months of IPT given early in the course of HIV infection provides a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART over an average of 4.9 years of follow up. These remarkable results furnish the first evidence from an individually randomized trial that IPT prolongs survival, and are noteworthy for several reasons. First, IPT in TEMPRANO was given to individuals with high CD4 counts, yet the survival benefit persisted over ~5 years with no sign of waning. Second, the benefit was seen both in participants with and without positive results on an interferon-gamma release assays, supporting a policy of treating all patients and foregoing tests for latent tuberculosis. Third, when adjusted for baseline covariates associated with risk of tuberculosis, such as CD4 count and hemoglobin, the survival benefit was unchanged. Finally, and most importantly, the effect was independent of ART but those who received ART as well as IPT had additional benefit. By the end of the study 89% of all participants had received ART, but survival was still better for those who received IPT in addition.

The TEMPRANO long term follow up should put an end to the malign neglect of clinicians, HIV treatment programs, policy makers, funders, and global agencies who have failed to take serious and concerted steps to provide IPT people to receiving HIV care. A celebrated analysis in 2008 estimated that AIDS denialism under President Thabo Mbeki in South Africa resulted in 330,000 preventable deaths from delays in making ART available. (10) Using the TEMPRANO results, a simple back of the envelope estimate of AIDS mortality since the WHO recommended programmatic use of IPT in 2008 suggests that at several million deaths could have been averted if IPT had been rolled out worldwide. This shameful figure should motivate the global HIV community to accelerate current feeble efforts to provide tuberculosis preventive therapy to all HIV-infected people living in high-burden settings. If a new ART regimen were shown, like IPT in TEMPRANO, to reduce mortality by 37%, the demand for immediate access from clinicians, programs, international agencies, and the advocacy community would be deafening. The faint whispers for IPT must be amplified and action must be taken to reduce deaths from such an eminently preventable disease.

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