injectable products for 2013–14. If large purchasers who once offered the option of jet injection[15] switch procurement to a newly labelled Afluria—to consolidate inventory to a single product permitting either needle or jet-injected delivery—other manufacturers might perceive pressure to pursue similar label changes to retain customers unwilling to vaccinate in the off-label grey zone.

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I was a CDC official (1980–2010) and provided technical oversight of research and development contracts with jet injector manufacturers; I am an unpaid adviser to PATH's initiative on jet injection.

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Preventive treatment for tuberculosis in people with HIV

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Isoniazid

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See Articles page 682

Research on prevention of tuberculosis in people with HIV is an active specialty, with varying and often contradictory results from clinical trials. A systematic review[1] of ten trials showed that treatment of latent tuberculosis infection in people with HIV not on antiretroviral treatment lowered the risk of tuberculosis by a weighted average of 62% in people who had a positive tuberculin skin test, 11% with a negative test, and 38% overall. However, the studies were heterogeneous in terms of duration of isoniazid preventive therapy and follow-up, with varying degrees of efficacy. Although WHO recommends the use of isoniazid preventive therapy (along with intensified case finding and infection control) in people with HIV to reduce incidence of tuberculosis, evidence about its benefit in individuals on antiretroviral treatment is scarce.[2]

A growing body of evidence has recently challenged the notion that *Mycobacterium tuberculosis* infection exists only as a bimodal distribution of latent infection and active tuberculosis.[3] Some imaging studies have noted metabolically active lesions in people with latent infection, suggesting that latency can be a dynamic process.[4] Latency probably represents a state in which the host is able to control the infection but not completely eradicate bacteria. Although host immunity plays a major part in infection control and containment, findings of studies investigating the genome of *M tuberculosis* have shown that differences between strains might contribute to virulence and outcome of infection.[5]

As described in *The Lancet*, Molebogeng Rangaka and colleagues[6] did a pragmatic randomised, double-blind, placebo-controlled trial to assess the effect of 12 months of isoniazid treatment in 1329 adults with HIV established on or newly starting antiretroviral therapy, in Khayelitsha, South Africa. The researchers noted that isoniazid preventive therapy reduced the incidence of tuberculosis by 37% overall (hazard ratio [HR] 0·63,

95% CI 0·41–0·94), with a non-significant increase in liver enzyme abnormalities, compared with placebo. Furthermore, isoniazid preventive therapy was effective both in individuals who were positive and negative for tuberculin skin test or interferon gamma release assay. This finding is in contrast with the BOTUSA study[7] in which the main effect of treatment was recorded in individuals who were positive for tuberculin skin test (72% reduction of tuberculosis) who received isoniazid for 36 months.

Because most cases of tuberculosis in people with HIV living in endemic countries are probably due to new infection or reinfection, isoniazid might not only treat latent infection, but also prevent or cure early infections. Results of a cohort study[8] done in the pre-antiretroviral era in south India showed similar incidence rates of tuberculosis in people with HIV who tested positive and those who tested negative for tuberculin skin test. Further, the sensitivity of the test to detect latent tuberculosis infection was low in this setting.[9] The implication of these findings is that isoniazid preventive therapy should be recommended to all people starting antiretroviral therapy, irrespective of tuberculin skin test or interferon gamma release assay status, at least in settings with moderate or high tuberculosis burden.

The greatest benefit from isoniazid preventive therapy in Rangaka and colleagues' study[6] seemed to be in the first year, a finding consistent with other studies. The optimum duration of treatment has not been established and probably depends on many factors, including the immune status of the individual, prevalence of other risk factors, and local tuberculosis epidemiology. The researchers reported no effect on all-cause mortality (HR 0·72, 95% CI 0·34–1·34).[6] Isoniazid preventive therapy did not increase the chance of development of multidrug-resistant tuberculosis. With a 12-month regimen, the number needed to harm was four times higher than the number needed to treat to prevent a case of tuberculosis (100 *vs* 25). Although the benefits of isoniazid preventive therapy probably outweigh the risks in most settings with high tuberculosis burden, individuals would need to be properly screened, and those with the highest risk of adverse events excluded—eg, chronic alcoholics, people co-infected with hepatitis B or C, and those with peripheral neuropathy. Moreover, regular follow-up and monitoring of patients on isoniazid preventive therapy is essential and often difficult in situations in which patients do not visit the clinic every month.

Investigators of a recently reported trial[10] of mass screening and treatment for latent tuberculosis reported no significant effect on tuberculosis control in South African gold mines, despite the successful use of isoniazid to prevent tuberculosis during treatment. By contrast, results of a trial done in Brazil[11] showed that training of health-care workers—which increased tuberculosis screening, provision of tuberculin skin tests, and use of isoniazid preventive therapy in HIV clinics—significantly reduced incident tuberculosis and death. Therefore, benefits of isoniazid intervention might be due not only to the effects of isoniazid, but also to effective screening and early diagnosis and treatment of active and subclinical tuberculosis. The use of more sensitive diagnostics is likely to improve the efficacy of this strategy further. Modelling of HIV and tuberculosis co-epidemics suggests that patterns of clustering and tuberculosis transmission within communities lead to heterogeneity in the effectiveness of isoniazid preventive therapy.[12] Therefore, a more nuanced understanding of latent tuberculosis and its outcomes in different risk groups, including people with HIV, is needed so that treatment would have high benefit–risk and benefit–cost ratios.

Future research should focus on simple methods and biomarkers that can identify individuals with HIV for whom preventive therapy is most beneficial, and on the cost-effectiveness of various strategies to reduce the burden of tuberculosis in people with HIV living in different settings.

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I declare that I have no competing interests.

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How to hinder tuberculosis control: five easy steps

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The control of tuberculosis remains an area of interest and concern. Some recent *Lancet* papers bring positive news, albeit with important questions left unanswered. Wang and colleagues' longitudinal study[1] concluded that tuberculosis prevalence in China was reduced by shifting to the recommended approach based on directly observed treatment, short course (DOTS) for tuberculosis diagnosis and treatment, but did not consider that economic progress might have also been a driver. Pietersen and coworkers' cohort study,[2] which reported that 73% of patients with extensively drug-resistant tuberculosis in South Africa died within 5 years of treatment initiation, acknowledged the poor treatment outcomes but did not question whether survival is any better than in the pre-treatment era—better than no treatment at all.[3] A review by Dheda and colleagues[4] aptly highlighted that diverting funding to multidrug-resistant tuberculosis control might destabilise national tuberculosis programmes, using the example of South Africa where multidrug-resistant tuberculosis represents less than 3% of tuberculosis cases but consumes over a third of the national tuberculosis budget.

Difficult decisions about resource allocation clearly need to be made. These should be made on the basis of evidence and long-term strategic goals. A review of studies done by the British Medical Research Council's tuberculosis units between 1946 and 1986 made the striking assertion that, by the late 1980s, we had all the evidence needed to design successful tuberculosis control programmes.[5] Our historical failure to embed research findings into effective policies has meant we have squandered opportunities and resources. We highlight five steps, commonly taken by policy makers, that might be impeding efforts to control tuberculosis (panel).

***Panel:* Five easy steps to impede tuberculosis control efforts**

1 Incentivise national tuberculosis programmes to obscure rather than highlight programmatic challenges
2 Rush to medical or technological solutions rather than systems strengthening
3 Focus on purchasing drugs for multidrug-resistant tuberculosis and ignore essential infrastructure requirements to deliver them effectively
4 Leave the unregulated private sector to incorrectly dispense antimicrobials
5 Start and stop tuberculosis programme funding suddenly

The first step is to incentivise national tuberculosis programmes to obscure, rather than highlight, programmatic challenges. Uniform targets for indicators, such as the tuberculosis treatment success rate (85%), are often set for national tuberculosis programmes. When asked what would happen if treatment success was lower than the target, a programme manager in China candidly told us, "'then I will lose my job". When jobs are at risk if targets are not met, there is little incentive for programmes to highlight challenges posed by patients dropping out during the lengthy tuberculosis treatment course, which is a major cause of the emergence of multidrug-resistant tuberculosis.[6] Moreover, China's reported successes in coverage of DOTS—up to 100% in parts of the country[1]—ignores the fact that access to DOTS facilities is woefully low in some of those same areas.[7] Powerful incentives to report so-called success hide a profoundly challenging implementation issue: China is a large, diverse, and complex country.

International donors might also introduce perverse incentives that affect reporting by national tuberculosis programmes. The Global Fund to Fight AIDS, Tuberculosis and Malaria uses a performance-based funding mechanism to decide which grants to renew, with the stated objective of freeing up committed resources from non-performing grants.[8] In other words, if reports do not