

ment, and those who are infected but anergic. Two studies have found no evidence of significant benefit from treatment of latent tuberculosis infection (LTBI) in the latter.^{3,4} Three other studies in high TB prevalence countries, in which results of anergy testing were not reported, also failed to show a benefit of treatment among HIV-infected individuals who had negative tuberculin tests.⁵⁻⁷

We do not feel the evidence or other current recommendations^{8,9} support routine provision of LTBI treatment to TST-negative, HIV-infected individuals on the basis of geographic origin alone.

Our second concern relates to the statement that the use of the 2-month pyrazinamide and rifampin regimen for latent tuberculosis is "clearly contraindicated for anyone with underlying liver disease or with isoniazid-related hepatotoxicity." We agree that the use of this regimen should be strictly limited to individuals with a particularly high risk of TB reactivation, such as the HIV-infected, and to those in whom completion of a standard 9-month course of isoniazid would be unlikely. However, in many Canadian settings, a high proportion of patients meeting these criteria have some indication of liver disease from hepatitis C infection, excess alcohol use, or both. The reported experience of serious adverse effects from the US¹⁰ appears to have involved self-administration, variable follow-up and insufficient attention to the high liver disease risk of this selected patient group.

For many years, pyrazinamide and rifampin have been used as part of a 4-drug therapy for active tuberculosis, with manageable toxicity in patients with liver disease. We believe that treatment of LTBI with pyrazinamide and rifampin can be administered to carefully selected patients with hepatitis C or a history of excess alcohol use, with an acceptably low risk, if the following criteria are met: directly observed delivery of each dose, immediate assessment of any clinical symptoms of liver disease and measurement of

transaminase enzymes at baseline and every 2 weeks during therapy.

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[The author responds:]

Stan Houston and colleagues correctly point out the discrepancy be-

tween current Canadian¹ and US² guidelines, with respect to HIV-infected immigrants from high-burden countries. Earlier US guidelines included suggestions that anergic HIV-infected persons be considered potential candidates for treatment of latent TB if they belonged to groups where the expected prevalence of tuberculous infection was 10% or greater.³ More recent research has cast considerable doubt on the use of anergy testing among HIV-infected people.⁴

My purpose in reproducing the Canadian guidelines was to highlight them, rather than to evaluate them. The treatment of latent tuberculosis infection among anergic HIV-infected persons has not been supported by recent investigations — despite the biologic rationale when the prevalence of undiagnosed latent TB is expected to be high. For example, an estimated incidence of 3.0 cases of active TB per 100-person years was found in a cohort of anergic Italian patients with HIV infection — largely injection-drug users.⁵

Several of the articles cited by Houston and colleagues have limited statistical power. In a US multicentre placebo-controlled clinical trial of isoniazid among HIV-infected people with anergy and TB risk factors, substantially fewer cases of active TB occurred than expected in the placebo arm (6 cases in 257 subjects, or 0.9 per person-year), making a significant treatment effect virtually impossible to detect.⁶ This may have reflected concomitant antiretroviral therapy. The Ugandan study cited did not reach target recruitment in the anergic subgroup.⁷ Both studies yielded effect estimates compatible with some benefit of isoniazid (though less than for tuberculin-positive cohorts), but very wide confidence intervals.

These findings are consistent with anergic HIV-infected cohorts including people with and without latent TB. The risk of subsequent active TB must reflect the background prevalence of latent infection, the use of antiretroviral therapy, the impact of competing risks, and the risk of subsequent tuberculous infection. The prevalence of unidenti-

fied latent TB among untreated anergic HIV-infected individuals may be lower than that of the general population, because many would have already developed active TB related to a previous latent infection. I suspect that many practitioners do not ordinarily prescribe isoniazid in this context, although they may occasionally find good reason to do so (for example, a particularly high likelihood of previous exposure, without documentation of specific contacts).

I agree that my statement that the 2-month rifampin-pyrazinamide regimen is "clearly contraindicated for anyone with underlying liver disease or with isoniazid-related hepatotoxicity" was too strong.⁸ This reflected considerable concern about recent reports of liver toxicity,⁹ perhaps related to suboptimal patient selection and supervision, as noted by Houston and colleagues. The key point is that rifampin-pyrazinamide should not ordinarily be prescribed for latent TB when there is substantial risk of hepatotoxicity, except with expert supervision and close monitoring.

I would be particularly hesitant to use this regimen where there is evidence of active ongoing liver disease (as opposed to positive viral serologies or a history of alcohol use). Pyrazinamide is the most likely culprit when liver toxicity does occur.^{10,11} Hence the 4-month rifampin regimen provides a reasonable "short-course" alternative to isoniazid, where feasible.

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Myocardial infarction in South Asians

In their discussion on risk factors and myocardial infarction in South Asians¹ Milan Gupta and colleagues omit some important issues. Lipoprotein (a) and homocysteine levels, reported higher in South Asians² and with multiplicative risk, may partly explain their excess cardiovascular disease (CVD).³ Although not measured in this study, these factors warrant discussion because of risk amplification of conventional risk factors, which has implications for care.

Excess premature CVD (men < 55 years, women < 65 years), a crucial feature of CVD in South Asians, with implications for screening, prevention and treatment, also merits discussion. Recognized across the South Asian diaspora,³ this was previously reported in South Asian men and women admitted with acute myocardial infarctions to a Toronto hospital from 1990-95.^{4,5} The expected 10-year delay in onset of heart

disease in women was reduced for South Asian women to a mean of 4.2 years (median 2.0 years). Premature CVD should thus probably be specifically examined and reported in studies on South Asia.

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[Four of the authors respond:]

We thank Vivian Rambihar for taking an interest in our study¹ and recognize his important contribution to the field of heart disease in South Asian Canadians. Although we agree that novel risk factors such as lipoprotein (a) (Lp[a]) and homocysteine may be implicated in the excess cardiovascular disease noted in South Asian Canadians, this was not the focus of our study. Regarding implications for care, pharmacologic intervention for elevated Lp[a] and/or homocysteine has not yet been shown to affect outcomes. Because our study was a matched case-control comparison, we are unable to comment on the prevalence of premature cardiovascular disease in our study population. However, we have shown in a related study² that South Asian Canadians undergoing coronary angiography are significantly younger than patients of European origin. In that study, South Asian Canadians had more severe angiographic disease in each coronary artery, despite