Preventing pellagra during isoniazid preventive treatment

See **Articles** page e705

An estimated 1·7 billion people globally are latently infected with *Mycobacterium tuberculosis*.[1] Latent *M tuberculosis* infection is defined by WHO as a state of persistent immune response to *M tuberculosis* antigens with no clinical evidence of active disease. During their lifetime, up to 10% of people with latent *M tuberculosis* infection are at risk of progressing to active tuberculosis disease.[1] In 2018, the UN General Assembly End TB targets included the specific goal to give tuberculosis preventive treatment for all people with latent *M tuberculosis* infection.[2] Proactively screening for and treating this huge reservoir needs to be addressed if the UN End TB targets are to be achieved by 2050. Several treatment regimens to eradicate latent *M tuberculosis* infection are recommended by WHO, which reduce the risk of reactivating the disease by at least 60%.[3] Giving daily isoniazid preventive treatment (IPT) to immunocompromised people; pregnant or lactating women; and people living with HIV, malnutrition, diabetes, chronic liver disease, or renal failure with latent *M tuberculosis* infection can prevent progression to active tuberculosis disease and save lives. In countries with a high burden of tuberculosis and HIV, the tuberculosis drug isoniazid is part of the management of people living with HIV taking highly active antiretroviral therapy (HAART).[3]

Since the discovery of isoniazid 70 years ago, peripheral neuropathy is a well-documented side-effect that can be prevented by co-administration of vitamin B6 (pyridoxine). However, intermittent clinical reports of an association of isoniazid use with non-vitamin-B6-related severe dermatitis, changes in cognitive, affective, and behavioural states, dementia, and psychosis due life-threatening pellagra, have not attracted global attention.[4-8] Thus, the diagnosis of pellagra is often overlooked clinically, especially in people living with HIV taking HAART. Ever since WHO recommended fortification of food with vitamin supplements, only sporadic cases of pellagra have been reported,[6-8] which are associated with tuberculosis therapy in people living with HIV or malabsorption disorders, and in populations in sub-Saharan Africa that rely on unfortified maize as their primary food source.

Over the past few years, clinical observations in Malawi showed an increasing number of pellagra cases in people living with HIV taking IPT. However, there have been no specific data from clinical trials or epidemiological risk analyses of the association between isoniazid use and pellagra in people living with HIV. To fill this important gap, Scott Nabity and colleagues,[9] in this issue of *The Lancet Global Health*, fill this knowledge gap and publish findings from the first ever, large, controlled, epidemiological risk analysis between isoniazid use and dermatologist-confirmed pellagra. Their data show that isoniazid given to people living with HIV in an HIV-endemic setting does have an independent association with the development of pellagra. Importantly, their data show that stopping isoniazid, and adding treatment with multi-B vitamins for 30 days, resolved the rash and other symptoms of pellagra. Given additional stressors of concomitant food shortages, undernutrition, and lactation, pellagra might manifest within a few weeks of isoniazid therapy and the diagnosis can easily be overlooked or delayed. Nabity and colleagues suggest that targeted food supplementation and fortification efforts for people living with HIV starting isoniazid-containing regimens, particularly for those facing food insecurity and lactating women, might be effective in pellagra prevention. Although these findings are important, there are several limitations to the study; key questions remain and need answering before the findings can be included in WHO IPT management guidelines. First, controlling for many covariates might cause imprecise risk estimates. Nearly all of the people living with HIV enrolled in the study were on isoniazid prophylaxis (159 [81%] of 197). As such, further studies across different geographical regions, using adequate numbers of people living with HIV who are not on isoniazid prophylaxis as a comparator group, might provide definitive data for the true independent contribution of HIV. Second, the study was restricted to Malawi only, where other risk factors for pellagra are present. Thus, their findings might not be applicable to other geographical regions. Third, the resulting co-linearity and interpretation of the independent epidemiological association between HIV status and pellagra is not defined accurately. Fourth, B complex vitamins were used instead of niacin to treat pellagra due to the high cost, and pyridoxine

For the **WHO food fortification strategy** see https://www.who.int/publications/i/item/WHO-NHD-00.10

dose was empirically increased to 50 mg twice a day for 12 weeks. This strategy, together with the cost-effectiveness of coadministration of B complex vitamins with isoniazid compared with individual vitamin B6 and vitamin B3, needs to be evaluated further. Fifth, community engagement, education, and counselling, especially for the stigma of pellagra rash, should be part of future studies.

It is now an opportune time to re-evaluate single-drug isoniazid therapy for latent *M tuberculosis* infection and focus discussions on non-isoniazid containing regimens for people living with HIV. Using short-course rifamycin-based regimens for latent *M tuberculosis* infection might help avoid some of the unintended side-effects of isoniazid treatment, including pellagra. Furthermore, the issue of isoniazid prophylaxis for latent *M tuberculosis* infection in people living with HIV comes at an crucial time in Europe, where the current armed conflict in Ukraine has generated more than 6 million refugees and displaced populations who are particularly susceptible to developing active tuberculosis and will require careful management of latent *M tuberculosis* infection and all other clinical forms of tuberculosis.[10,11] Ukraine has the highest rates of tuberculosis and HIV co-infection, multidrug-resistant tuberculosis, and latent drug-resistant *M tuberculosis* infection in Europe.[1] While we await further evidence for updating the WHO guidelines on preventing pellagra in people living with HIV on IPT, given the nutritional and other risk factors refugees face for re-activating the *M tuberculosis* infection, and for developing pellagra and other nutritional deficiency states, proactive screening in all refugees for all forms of tuberculosis and supplementing their diets empirically with B complex vitamins would be prudent and important.

For more on **refugees from Ukraine** see http://data2.unhcr.org/en/situations/ukraine

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