Isoniazid-Associated Hepatitis in Adults Infected With HIV Receiving 36 Months of Isoniazid Prophylaxis in Botswana

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BACKGROUND: The World Health Organization recommends 36 months of isoniazid preventive therapy (36IPT) for adults infected with HIV living in TB-endemic countries. We determined the rates and risk factors for isoniazid-associated hepatitis with the use of 36IPT.

METHODS: One thousand six adults infected with HIV received 36IPT during a pragmatic randomized trial set in Botswana public health clinics providing HIV care. Enrollment exclusion criteria included jaundice or elevations of serum transaminases (ESTs) > 2.5-fold the upper limit of normal (ULN). Participants with any $CD4^+$ lymphocyte count were eligible and received antiretroviral therapy (ART) when $CD4^+ < 200$ cells/μL. 36IPT was stopped for severe hepatitis (more than fivefold ULN EST) but not for moderate hepatitis (2.5-fold to fivefold ULN EST).

RESULTS: Pharmacy refill records showed 2,237 person-years of isoniazid receipt; 48% of participants initiated ART by 36 months. A total of 1.9% (19 of 1,006) of participants were diagnosed with severe hepatitis; three had jaundice and two of these developed hepatic encephalopathy. Another 3.1% (31 of 1,006) of participants experienced moderate hepatitis. Thirty-eight percent (19 of 50) of participants with moderate to severe hepatitis concomitantly received ART. Forty percent (20 of 50) of moderate to severe cases occurred within the first 2 months of IPT and during this period were not associated with receipt of ART at baseline (hazard ratio, 1.49; 95% CI, 0.20-11.1; $P = .70$).

CONCLUSIONS: Adults infected with HIV receiving 36IPT did not have an increased incidence of moderate to severe hepatitis or hepatic encephalopathy compared with published reports among people infected with HIV, people not infected with HIV in trials or public health programs. Compared with participants not receiving ART, the risk of moderate to severe hepatitis was not increased by ART.

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ABBREVIATIONS: ART = antiretroviral therapy; HBcAb = anti-hepatitis B virus core antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IPT = isoniazid preventive therapy; IQR = interquartile range; ULN = upper limit of normal; WHO = World Health Organization

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Although recommended by the Word Health Organization (WHO), 6 months of isoniazid preventive therapy (IPT) for the treatment of latent TB infection in people infected with HIV does not have a durable effect in TB-endemic settings. Prior to the availability of antiretroviral therapy (ART), researchers in Uganda and Zambia conducted follow-on studies after 6-month IPT trials among adults infected with HIV. They reported that within 6 to 18 months after IPT cessation, TB incidence among participants in IPT arms reached levels observed in their respective placebo arms.[1,2] Since the advent of ART provision to people infected with HIV living in TB-endemic settings, it has become increasingly evident that ART alone inadequately prevents TB.[3,4]

A two-arm, randomized, double-blind, placebo-controlled clinical trial conducted in a public health setting in Botswana, a country where ART is freely available to people living with HIV, showed that compared with receipt of 6 months of IPT, adults infected with HIV receiving 36 months of IPT experienced a 43% reduction in their hazard of TB.[5] Moreover, the trial found that participants in the 36-month arm who had a positive tuberculin skin test at enrollment experienced a 73% decline in TB incidence compared with their 6-month counterparts. In 2011, the WHO recommended up to 36 months of IPT in TB-endemic settings even when ART is provided.[6] Hepatic toxicities associated with ART are not negligible, and the addition of isoniazid to triple therapy regimens requires closer monitoring, particularly in such settings where chronic viral hepatitis is common.

Surveillance of US programs for the treatment of latent TB infection has shown that for every 1,000 people initiating IPT there was one hepatitis death or the need for liver transplantation.[7,8] We previously reported that the rates of severe hepatitis in the Botswana IPT cohort, whether biochemical (1.5%), symptomatic (0.4%), or resulting in hepatic encephalopathy (0.1%), were similar to published reports about people infected with HIV and people not infected with HIV.[5,9-11] Rates of severe hepatitis in the 6-month and 36-month arms were 1.6% and 1.9%, respectively.

It is well established that isoniazid may cause transient elevations in serum transaminases, which typically resolve with the continuation of the drug.[12,13] For this reason, our protocol permitted the continuation of isoniazid when participants experienced nonsevere hepatitis. To better inform clinicians and public health practitioners about the risks of 36-months of IPT, we describe outcomes of moderate and severe hepatitis among participants receiving 36 months of IPT and explore potential risk factors for isoniazid-associated hepatitis such as viral hepatitis and ART during the first 2 months of IPT when the risk of hepatitis was highest.

Materials and Methods

The enrollment process is described in detail elsewhere.[14] Between November 26, 2004, and July 20, 2006, people ≥ 18 years of age infected with HIV and attending eight government clinics were invited to participate in the study. Enrollment exclusion criteria included not being infected with HIV, jaundice, active TB by symptoms or chest radiograph, a history of hepatitis, or elevations in serum transaminases > 2.5-fold the upper limit of normal (ULN). Participants with any $CD4^+$ lymphocyte count were eligible for enrollment. Consistent with both the Government of Botswana and the WHO's recommendations, there was no requirement for tuberculin skin testing prior to IPT initiation. However, we performed tuberculin skin tests; induration ≥ 5 mm was regarded as positive.

On a monthly basis, participants received open-labeled isoniazid for 6 months to be taken daily at a dose of 300 mg for weight 30 to 49 kg and 400 mg for weight ≥ 50 kg, supplemented with 25 mg of vitamin B6. In late 2005, the national guidelines changed, and beginning January 1, 2006, all study participants were provided 300 mg daily.[5] On three occasions approximately 1 year apart and without prior notification, urine samples were collected from 200 randomly selected participants in the 36-month arm and 50 participants in the 6-month arm among those who continued to return to the clinic. These samples were analyzed for isoniazid metabolites using the potassium cyanide-chloramine-T assay of Eidus and Hamilton.[15] ART was offered according to Botswana national guidelines: $CD4^+$ count < 200 cells/μL or WHO clinical stage 3 or 4. Also according to these guidelines, cotrimoxazole prophylaxis was provided for $CD4^+$ count < 200 cells/μL; the dosage was two tablets (trimethoprim/sulfamethoxazole 80/400 mg) taken po once daily or one tablet three times weekly.

Blood draws for serum transaminases and total bilirubin were routinely taken at baseline and 2 weeks after IPT was initiated. Given the pragmatic nature of the trial, regular blood draws for liver function tests were not subsequently scheduled. However blood was drawn for pre-ART screening, if a participant had symptoms concerning for hepatitis, and during a liver safety campaign in 2007 requested by the trial's Data Safety Monitoring Board.

We defined isoniazid-associated hepatitis as elevations in transaminases with or without symptoms that were at least possibly attributed to isoniazid using an attribution scale.[9] Using serum transaminase values, hepatitis was graded from 1 to 5.[16] Elevations in either aspartate or alanine transaminase were used to grade hepatitis: grade 1 (mild) > 1 to 2.5 times the ULN; grade 2 (moderate) ≥ 2.5 to 5.0 times ULN; and ≥ grade 3 (severe) if > 5 times ULN. Participants with mild or moderate hepatitis continued to receive isoniazid; however isoniazid was stopped with no rechallenge if a participant developed severe hepatitis. Attribution of hepatitis to the study drug was decided by study clinicians who were blinded to treatment arm; additionally, severe cases were reviewed by an independent committee of four experienced clinicians who were also masked to treatment arm. The attribution of hepatitis to the study drug was graded as follows: definite ("clearly related"), probable ("likely related"), possible ("may be related"), unlikely, and unrelated.

If participants developed moderate to severe transaminase elevations they were tested for serologic evidence of both hepatitis B virus (HBV)