Isoniazid-associated Hepatitis and Antiretroviral Drugs during Tuberculosis Prophylaxis in HIV-infected Adults in Botswana

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***Rationale*: Little is known about the incidence of isoniazid-associated hepatitis in HIV-infected Africans who receive both isoniazid preventive therapy (IPT) and antiretroviral therapy (ART).**

***Objectives*: To assess the rate of and risk factors for isoniazid (INH)-associated hepatitis in persons living with HIV (PLWH) during IPT.**

***Methods*: PLWH recruited for a clinical trial received 6 months of open-label, daily, self-administered INH at public health clinics. At screening PLWH were excluded if they had any cough, weight loss, night sweats, or other illness. Alcohol abuse was defined as meeting any CAGE criterion. INH-associated hepatitis (INH-hepatitis) was defined as having either alanine or aspartate aminotransferase greater than 5.0 times the upper limit of normal regardless of symptoms when INH was not excluded as the cause.**

***Measurements and Main Results*: Of 1,995 PLWH enrolled between 2004 and 2006, 1,762 adhered to at least 4 months of IPT and were analyzed. Nineteen (1.1%) developed hepatitis probably or possibly associated with INH including one death at month 6; 14 of 19 (74%) occurred in months 1–3. Antiretroviral therapy (ART) was received by 480 participants but was not statistically associated with INH-hepatitis (relative risk [RR], 1.56; 95% confidence intervals [CI], 0.62–3.9); those receiving nevirapine had a higher rate (2.0%) than those receiving efavirenz (0.9%; $P = 0.34$). Although alcohol use did not reach significance (RR, 1.42; 95% CI, 0.57–3.51), meeting at least one CAGE criterion approached statistical significance (RR, 2.37; 95% CI, 0.96–5.84). Neither age greater than 35 years nor the presence of hepatitis B virus core antibody was associated with INH-hepatitis.**

***Conclusions*: The observed rates of INH-hepatitis were similar to published data. Six months of IPT, which is recommended by the World Health Organization, was relatively safe in this, the largest cohort of African PLWH.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00164281).

Keywords: HIV infection; isoniazid; hepatitis; viral hepatitis; antiretroviral therapy

Tuberculosis (TB) is a major cause of morbidity and mortality among persons living with HIV (PLWH) in countries where TB is endemic (1). In Botswana, which suffers from one of the highest rates of TB in the world (2), TB was identified as the most common cause of death (38%) in PLWH (3). Isoniazid preventive therapy (IPT) has been demonstrated to prevent TB in PLWH with an efficacy of up to 62% (4). These important findings led Botswana's Ministry of Health to roll out a nationwide IPT Program for PLWH in 2004 (5). Since 1994, and now with renewed intensity, the World Health Organization (Geneva, Switzerland) and the International Union against Tuberculosis and Lung Disease (Paris, France) have recommended African countries to adopt IPT for the prevention of TB in PLWH (6, 7). As hepatitis is a well-established adverse effect of isoniazid (INH) (8), vigilance for INH-associated hepatitis is necessary as larger numbers of PLWH receive the therapy.

Although TB prevention is necessary in TB-endemic countries, the urgent requirement to reduce AIDS deaths has resulted in a steady increase in the provision of antiretroviral therapy to PLWH in Africa (9). Botswana has led Africa in the implementation of an antiretroviral therapy (ART) program that has reached 90–95% of its target population (10). Hepatitis is also a well-known adverse effect of antiretroviral therapy, particularly of nevirapine- and ritonavir-boosted protease inhibitors (11). Nevirapine is part of the ART regimen for women of child-bearing age in Botswana, efavirenz is the nonnucleoside reverse transcriptase inhibitor (NNRTI) of choice for others, and ritonavir-boosted protease inhibitors have become increasingly available.

An additional concern for hepatitis among PLWH in Africa is widespread chronic hepatitis virus coinfection, particularly hepatitis B virus (HBV), with some countries reporting hepatitis B surface antigen (HBsAg) prevalence rates as high as 26% in PLWH (12). Furthermore, alcohol, a common substance of abuse among PLWH in Africa (13) and a risk factor for HIV infection in Botswana (14), is another potential source of hepatic injury.

In the initial phase of a double-blind, placebo-controlled, 36-month trial for TB prevention, we provided 6 months of open-label INH to 1,995 HIV-infected participants as recommended

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

International guidelines on the concomitant use of isoniazid tuberculosis prophylaxis (IPT) and antiretroviral therapy (ART) are vague. Little is known about the incidence of isoniazid-associated hepatitis in HIV-infected Africans who receive both IPT and ART.

What This Study Adds to the Field

The observed 1.1% rate of severe isoniazid-associated hepatitis was similar to rates in HIV-uninfected populations. Although IPT was relatively safe and ART did not significantly increase the risk of drug-related hepatitis, in practice, if a delay in ART initiation is medically appropriate, it is preferable to complete IPT before initiation of ART; if the two therapies are combined, sequential initiation would facilitate attribution of drug-related toxicity.

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by Botswana's Ministry of Health. Within the context of the trial, we estimated the rate of INH-associated hepatitis, and examined its potential association with use of ART, viral hepatitis, and alcohol use. This article is the first evaluation of hepatitis in a large cohort of African PLWH in the public health setting receiving IPT, many of whom concomitantly received ART. Some of the results of this analysis have been previously presented in the form of an abstract of a paper presented at the 40th Union World Conference on Lung Health.

METHODS

Participant Enrollment, Baseline Tests, Study Drugs

Nonpregnant HIV-infected adults between the ages of 18 and 70 years, who were free from cough, fever, clinical AIDS, or respiratory illness or lymphadenopathy on physical examination, were enrolled at eight local health clinics in the cities of Gaborone and Francistown between 2004 and 2006. PLWH having any CD4 lymphocyte count were included. Exclusion criteria measured at screening included serum aspartate aminotransferase (AST) greater than 85 international units (IU)/L or alanine aminotransferase (ALT) greater than 103 IU/L ($\geq$2.5 times the upper limit of normal [ULN]), or total bilirubin greater than 39 μmol/L ($\geq$1.5 times ULN). Although not required for IPT eligibility, tuberculin skin tests were performed with 5 tuberculin units of RT23 tuberculin (Statens Serum Institut, Copenhagen, Denmark) and were read by study nurses at 48–72 hours. A reading of 5 mm or more was considered positive.

At enrollment, as per Botswana national guidelines, we provided 100-mg INH tablets to be taken daily (self-administered) at a dose of 300 mg for weight ranging from 30 to 49 kg and at 400 mg for weight of or exceeding 50 kg. Participants also received 25 mg of pyridoxine daily. In late 2005 the national guidelines changed and beginning January 1, 2006, all study participants were provided 300 mg of INH daily. Body mass index was calculated to determine underweight (<18.5 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity ($\geq$30.0 kg/m^2).

ART and co-trimoxazole for HIV-related opportunistic infections were provided through the government program to participants with CD4 lymphocyte counts less than 200 cells/mm^3 (CD4 <200). Before initiating ART, government clinics routinely drew blood to measure AST, ALT, and total bilirubin.

Clinical and Laboratory Follow-Up

Two weeks after enrollment, we measured serum AST, ALT, and total bilirubin. All participants returned monthly to receive INH and pyridoxine, at which time nurses inquired after their health. Every 3 months they were asked about fatigue, yellow eyes, nausea, vomiting, abdominal pain, itchy skin, and numbness or tingling in their hands or feet. Participants were instructed to stop study medication if they developed jaundice or any of these symptoms and to return for an evaluation. Having these symptoms prompted a repeat measurement of serum AST, ALT, and total bilirubin.

Adverse Events

For all severe adverse events (AEs), study physicians were asked whether INH might be the cause. The attribution scale was as follows: unrelated, the AE was clearly not related to the drug; unlikely, the AE was doubtfully related to the drug; possible, the AE might have been related to the drug; probable, the AE was likely related to the drug; definite, the AE was clearly related to the drug. An Endpoints Committee consisting of four external physicians well experienced in the care of HIV-infected patients with TB reviewed the study physicians' attributions and made final judgments on attribution of the AEs to INH.

Using aminotransferase or total bilirubin values, hepatitis was graded from 1 to 5 as per the *Common Terminology Criteria for Adverse Events* (Cancer Therapy Evaluation Program, version 3.0) (15), with severe INH-associated hepatitis (Table 1) defined as grade 3 or more (AST or ALT > five times the upper limit of normal; INH-hepatitis) with or without symptoms and at least possibly attributed to INH. INH was stopped with no rechallenge if a participant had grade 3 or higher hepatitis.

Viral Hepatitis and Alcohol Use

If participants developed transaminase elevations of grade 2 or higher they were tested for serological evidence of both hepatitis B and hepatitis C virus (HCV) infection. To detect HCV infection, we used either MEIA (AxSYM HCV 3.0; Abbott Diagnostic Division, Wiesbaden, Germany) or anti-HCV version 4.0 VK 47/48 (Murex Biotech, Kyalami, South Africa). To test for hepatitis B surface antigen (sAg), anti-HBV surface antibody (sAb), and anti-HBV core antibody (cAb), we used HBsAg Determine strips (Abbott Diagnostics, Tokyo, Japan) or Murex version 3.0 GE 34/36 (Abbott, Dartford, UK), and the sAb and cAb Architect anti-HBs reagent kit 7C18 (Abbott Diagnostic Division). Subsequently other participants who did not develop at least grade 2 transaminase elevations (control subjects) were randomly selected to test for evidence of HBV or HCV infection, and a case–control analysis was performed to determine whether viral hepatitis was associated with INH-hepatitis.

Every 6 months, participants were asked whether they drank alcohol. They were considered alcohol users if they acknowledged use of alcohol within the first year after enrollment. Individuals acknowledging alcohol use were further queried on the basis of CAGE criteria: "Have you ever considered cutting down on your drinking?"; "Do you become angry when your family or friends complain about your drinking?"; "Do you feel guilty about your drinking?"; "Do you sometimes have the shakes in the morning and find that it helps to have a drink?" (16). Although alcohol consumption was not an exclusion criterion for initiating IPT by either the National IPT Program or the clinical trial, PLWH were required to stop alcohol consumption to receive ART from the National ART Program.

Data Analysis

Data were collected using standardized case report forms and double-entered into a Clindex database (Fortress Medical Systems, Minneap-

TABLE 1. INCREASES IN ISONIAZID-ASSOCIATED TRANSAMINASES DURING 6 MONTHS OF ISONIAZID PREVENTIVE THERAPY IN HIV-INFECTED ADULTS BY GRADE

Grade	Transaminase (*IU/L*)	Transaminase Relative to ULN	Number of Participants	Percentage
1	34 < AST ≤ 86, 41 < ALT ≤ 103	>ULN−2.5 × ULN	354*	87
2	86 < AST ≤ 171, 103 < ALT ≤ 206	>2.5–5.0 × ULN	34†	8.4
3‡	171 < AST ≤ 681, 206 < ALT ≤ 821	>5.0–20.0 × ULN	15	3.7
4‡	AST > 681, ALT > 821	>20.0 × ULN	3	0.74
5‡	Death		1	0.25
Total:			407	100.0

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
Note: All grade 1 and most grade 2 increases were detected at the 2-week routine blood draw.
* Five individuals included here had grade 1 increases in total bilirubin (25.7 < total bilirubin ≤ 39 μmol/L) but normal AST and ALT.
† One individual included here had a grade 2 elevation in total bilirubin (39 < total bilirubin ≤ 77 μmol/L) but grade 1 elevations in AST and/or ALT.
‡ Cases of severe isoniazid-associated hepatitis (INH-hepatitis) were defined as symptomatic or asymptomatic individuals with at least grade 3 elevations in transaminases at least possibly attributed to isoniazid.

olis, MN). Using SAS (version 9.1; SAS Institute, Cary, NC), relative risks (RRs) were determined for the cohort analysis and a logistic regression model was developed for the cohort analysis. Odds ratios were determined for the case–control analysis. *P* values of less than 0.05 were considered statistically significant. Two-tailed Fisher's exact test was used in Epi Info 3.5.1 (Centers for Disease Control and Prevention [CDC], Atlanta, GA) to compare rates of hepatitis in several studies and a *P* value of 0.01 was considered significant.

Participants signed witnessed informed consent forms. The protocol was approved by both the Botswana ethics committee and the CDC institutional review board. The trial was registered at www.clinicaltrials.gov (NCT 00164281).

RESULTS

We enrolled 1,995 PLWH, of whom 72% were female. Their median age was 32 years (range, 18–70 yr); 18% were underweight, 17% overweight, and 9% obese. At enrollment 24% were tuberculin skin test positive, 31% had a CD4 count less than 200, and 1.4% were undergoing ART. During the 6-month course of IPT, 516 (26%) of 1,995 participants started ART. The median time after enrollment for ART initiation was 2 months (range, 0–6 mo). ART regimens that participants received were as follows: zidovudine, lamivudine, and nevirapine (50%); zidovudine, lamivudine, and efavirenz (46%); stavudine, lamivudine, and nevirapine (3%); and stavudine, lamivudine, and efavirenz (2%).

Of the 1,995 enrolled, 53 had to discontinue IPT before the end of 6 months of therapy (8 cases of active TB, 20 deaths, 9 severe adverse events other than hepatitis, and 16 others, e.g., moved out of the study area or experienced severe illness). An additional 180 who had insufficient exposure to IPT (i.e., <4 mo) and did not have hepatitis were excluded from the hepatitis analysis. Thus, 1,762 participants were included in the analysis, 95% of whom had 6 months of IPT (range, 4–6 mo).

Excluding the 19 participants with INH-hepatitis (*see below*), 96% (1,666 of 1,743) attended all six visits during the 6-month course of therapy. Of the 1,511 with INH pill counts available for Months 1, 3, and 6, 90% took at least 80% of their tablets. Additional adherence information is provided elsewhere (21).

Alcohol consumption was reported by 34% (597 of 1,762) of participants. The following number of CAGE criteria were reported by these persons: none by 239 (40%), one by 172 (29%), two by 158 (26%), three by 24 (4.0%), and four by 4 (0.7%).

Eighty-seven percent of those with transaminase elevations had only a grade 1 increase detected at the routine blood draw 2 weeks after IPT initiation (Table 1). Twenty-nine (85%) of the 34 grade 2 increases were detected at the 2-week blood draw; none of the grade 2 transaminase elevations were symptomatic. One individual was concerned that he had yellow eyes, but he had normal serum bilirubin and normal sclerae on examination.

Nineteen persons had an event meeting the definition of INH-hepatitis, which represents a rate of 1.1% (19 of 1,762) and 74% (14 of 19) within the first 3 months after IPT initiation. Of these cases, one had nausea and emesis before Month 1, two had jaundice during Month 2, one had anorexia and fatigue in Month 2, and one had abdominal pain and malaise at Month 6 (Table 2). One participant died of hepatic encephalopathy in Month 6. Reportedly, she did not consume alcohol or use

TABLE 2. SYMPTOMATIC AND ASYMPTOMATIC CASES OF SEVERE* ISONIAZID-ASSOCIATED HEPATITIS BY MONTH DURING ISONIAZID PREVENTIVE THERAPY

	Month	Grade	Symptoms	Age (*yr*)	Sex	CD4 Count (*cells/mm³*)	ART	Attribution to INH	CPT	Alcohol Use	CAGE	Max. Baseline LFT Grade	Max. 2-wk LFT Grade	HBV Serology Interpretation†
1	0	3	None	41	M	36	No	Possible	No	Yes	3/4	1	3	Incomplete serology
2	0	3	None	43	F	217	No	Possible	No	No	—	0	3	Susceptible
3	0	3	None	27	M	226	No	Possible	No	Yes	2/4	1	2	Natural infection resolved
4	0	3	None	30	F	16	No	Probable	No	No	—	1	3	Not available
5	0	3	None	32	M	194	No	Probable	No	Yes	1/4	0	3	Natural infection resolved
6	0	3	Nausea and vomiting	30	F	472	Yes‡	Probable	No	No	—	0	3	Natural infection resolved
7	1	3	None	34	F	158	No	Probable	No	No	—	1	2	Natural infection resolved
8	1	4	None	41	F	280	Yes‡	Possible	No	Yes	1/4	0	0	Immunized against HBV
9	2	3	Anorexia and nausea	31	F	155	Yes‡	Possible	No	Yes	3/4	0	1	Natural infection resolved
10	2	3	None	33	F	282	No	Probable	No	No	—	0	1	Susceptible
11	2	4	Jaundice	42	M	63	Yes‡	Possible	No	Yes	2/4	1	1	Natural infection resolved
12	2	4	Jaundice	52	F	706	No	Probable	No	No	—	0	0	Natural infection resolved
13	3	3	None	26	F	53	No	Possible§	No	No	—	0	0	Susceptible
14	3	3	None	26	F	178	Yes‡	Possible	Yes	No	—	0	0	Not available
15	4	3	None	37	F	41	Yes‡	Possible	No	Yes	2/4	1	1	Not available
16	4	3	None	30	M	190	Yes‡	Probable	No	Yes	2/4	0	0	Not available
17	5	3	None	47	M	606	No	Possible	No	No	—	0	0	Not available
18	6	3	Abdominal pain and malaise	30	F	225	No	Probable	No	No	—	1	1	Susceptible
19‖	6	5	Jaundice; hepatic encephalopathy	41	F	264	No	Probable	No	No	—	1	0	Not available

Definition of abbreviations: ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; CPT = co-trimoxazole prophylaxis; F = female; HBV = hepatitis B virus; INH = isoniazid; IPT = isoniazid preventive therapy; LFT = liver function tests (AST, ALT, and total bilirubin); M = male; Max. = maximal.

Number of participants with INH-hepatitis (n) = 19.

Maximal grade at baseline (screening) and at routine 2-week blood draw of either aspartate aminotransferase, alanine aminotransferase, or total bilirubin is shown.

* Severe isoniazid-associated hepatitis defined as elevations of grade 3 or higher.

† See Table 4 for serologies corresponding to these interpretations. CAGE, four criteria to determine problem alcohol drinking (*see* text).

‡ Severe hepatitis occurred in seven patients receiving both ART and IPT, with a median of 36 days of combined therapy. The actual days of combined therapy were as follows: 14, 22, 30, 36, 45, 45, and 63 days.

§ This patient was receiving ketoconazole for cryptococcal meningitis at the time of her hepatitis.

‖ This participant died (grade 5).

traditional or other medications. This 41-year-old female complained of icteric sclerae and dark urine. She was advised to stop her INH but did not follow this instruction for several days. At a subsequent hospital visit for a cough she was prescribed paracetamol, after which her mental status deteriorated.

Among the 19 cases of INH-hepatitis, 10 patients had possible and 9 had probable attributions to INH. Seven of these 19 individuals were receiving ART when diagnosed with hepatitis; 8 of 19 reported alcohol use and all 8 met at least one CAGE criterion.

In bivariate analysis (Table 3), having a CD4 count less than 200 was associated with INH-hepatitis (RR, 2.80; 95% confidence interval [CI], 1.14–6.84). The rate of INH-hepatitis among PLWH coadministered ART was 1.5% (7 of 480), compared with 0.94% (12 of 1,282) among those not receiving ART. INH-hepatitis occurred 14 to 63 days (median, 36 d) after coadministration of ART with IPT in the seven participants taking both therapies. Receiving ART was not statistically associated with INH-hepatitis. Participants receiving nevirapine (n = 256) had higher rates of INH-hepatitis (2.0%) than those receiving efavirenz (n = 223, 0.9%; $P = 0.34$). Although the use of alcohol was not significantly associated with INH-hepatitis, meeting at least one CAGE criterion approached statistical significance (RR, 2.37; 95% CI, 0.96–5.84). In a multivariate model that included receipt of ART and CD4 count less than 200, CD4 count less than 200 remained significant; however, there was a significant interaction term between these two variables ($P = 0.008$) indicating that ART and not CD4 count less than 200 was the cause of this association. Addition of a CAGE response of at least one, or alcohol use, to the model did not affect the significance of CD4 count less than 200. Age greater than 35 years was nonsignificantly associated with INH-hepatitis (RR, 1.56; 95% CI, 0.64–3.82).

During the course of the trial 708 participants crossed over from the 400-mg maximal dose to the lower 300-mg dose of INH; 445 received the 300-mg dose only and 609 received the 400-mg dose only during the 6 months. The RR of INH-hepatitis among those who only received the 300-mg dose (10 of 445; 2.3%) was 1.5 (95% CI, 0.6, 3.7) compared with those who received only the 400-mg dose (9 of 609; 1.5%).

Thirteen case subjects with INH-hepatitis and 127 control subjects were tested for HBV and HCV (Table 4). None was infected with HCV. Although 39% (55 of 140) were susceptible to HBV, 48% likely had resolved natural infections and an additional 6% had chronic HBV infection (Table 4). None of the case subjects was positive for HBV surface antigen. Other interpretable serological patterns were not significantly different between case and control subjects.

TABLE 3. RISK FACTORS ASSOCIATED WITH SEVERE* ISONIAZID-ASSOCIATED HEPATITIS DURING 6 MONTHS OF ISONIAZID PREVENTIVE THERAPY

	Fraction of Participants with Hepatitis†	RR (95% CI)
Age		
>35 yr	9/645	1.56 (0.64–3.82)
⩽35 yr	10/1,117	1.00
Sex		
Female	13/1,293	0.79 (0.30–2.06)
Male	6/469	1.00
Body mass index		
Underweight‡	2/304	0.63 (0.14–2.72)
Not underweight	15/1,426	1.00
CD4 lymphocyte count		
CD4 < 200 cells/mm³	10/501	2.80 (1.14–6.84)
CD4 ⩾ 200 cells/mm³	9/1,261	1.00
ART§		
Receipt of ART	7/480	1.56 (0.62–3.93)
No receipt of ART	12/1,282	1.00
EFV vs. no ART§		
EFV-based regimens	2/223	0.96 (0.21–4.31)
No ART	12/1,282	1.00
EFV vs. ART not using EFV§		
EFV	2/223	0.46 (0.09–2.35)
ART not using EFV	5/257	1.00
NVP vs. no ART§		
NVP	5/256	2.09 (0.74–5.87)
No ART	12/1,282	1.00
NVP vs. ART not using NVP§		
NVP	5/256	2.19 (0.43–11.2)
ART not using NVP	2/224	1.00
NNRTI vs. not using NNRTI§		
NNRTI	7/479	—
No NNRTI	0/1	
Co-trimoxazole		
Co-trimoxazole use	4/245	1.65 (0.55–4.93)
No co-trimoxazole use	15/1,517	1.00
Alcohol		
Drinks alcohol‖	8/597	1.42 (0.57–3.51)
No alcohol use	11/1,165	1.00
Alcohol dependence		
CAGE ⩾ 1¶	8/358	2.37 (0.96–5.84)
CAGE = 0	11/1,165	1.00

Definition of abbreviations: ART = antiretroviral therapy; CI = confidence interval; EFV = efavirenz; NNRTI = nonnucleoside reverse transcriptase inhibitor; NVP = nevirapine; RR = relative risk.

* Severe isoniazid-associated hepatitis defined as grade 3 or higher.

† Participants with grade 1 or 2 transaminase elevations (*see* Table 1) were considered as not having severe INH-hepatitis.

‡ Underweight meant body mass index less than 18.5.

§ In Botswana NNRTIs are used as first-line therapy; only one participant was not undergoing an NNRTI-containing regimen. Among the remaining 479, 223 received an EFV-containing regimen and 256 received an NVP-containing regimen.

‖ "Drinks alcohol" meant acknowledging any alcohol use in the first year of the study.

¶ Meeting one or more CAGE criteria. CAGE criteria include four questions to assess for alcohol dependence.

DISCUSSION

We report the incidence of isoniazid-associated hepatitis in the largest cohort to date of PLWH receiving 6 months of IPT from African public health clinics and among whom 26% also received ART. INH-hepatitis was detected in 1.1% of the cohort, with one death from hepatic encephalopathy. Three-fourths of the cases of INH-hepatitis occurred in the first 3 months of IPT, similar to previous reports (8, 17, 18). Although higher rates of INH-hepatitis occurred among those receiving ART, particularly with nevirapine, and among those with self-reported alcohol abuse, these associations were not statistically significant. Co-trimoxazole use and HBV infection were not associated with INH-hepatitis.

A comparison of our findings with published information on clinical trials and public health programs showed that the rates of biochemical and clinical hepatitis were in the middle of the range (Table 5). We observed a single hepatitis death due to hepatic encephalopathy with probable attribution to INH. Although at the upper range of previous reports, this death rate was not substantially higher. The individual who died received paracetamol after developing jaundice; paracetamol may potentiate INH hepatotoxicity (19).

Although it is difficult to draw firm conclusions about the risk of INH-hepatitis death from a single event, there are several possible reasons why the death rate from INH-hepatitis was as high as observed in our study: (*1*) This study represents the largest clinical trial in PLWH receiving IPT, with 0.1% loss

TABLE 4. SEROLOGIES FOR HEPATITIS B VIRUS AMONG SELECTED HIV-INFECTED ADULTS WITH SEVERE ISONIAZID-ASSOCIATED HEPATITIS AND WITHOUT HEPATITIS

Hepatitis B Virus Serological Pattern	Interpretation	Case Subjects	Control Subjects	Total
sAg^-, sAb^-, cAb^-	Susceptible	4 (31%)	51 (40%)	55 (39%)
sAg^-, sAb^+, cAb^+ or sAg^-, sAb^- cAb^+	Natural infection that resolved*	7 (54%)	60 (47%)	67 (48%)
sAg^-, sAb^+, cAb^-	Immune due to immunization	1 (8%)	7 (6%)	8 (6%)
sAg^+, sAb^-, cAb^+	Chronic infection	0 (0%)	8 (6%)	8 (6%)
Incomplete serology	Other	1 (8%)	1 (1%)	2 (1%)
		13	127	140

Definition of abbreviations: cAb = hepatitis B core antibody; sAb = hepatitis B surface antibody; sAg = hepatitis B surface antigen.
Case subjects, n = 13; control subjects, n = 127.
* Ten to 45% of HIV-infected persons with isolated cAb positivity have detectable hepatitis B virus DNA in their serum (44).

to follow-up; (*2*) we had a high proportion of women of childbearing age—in the largest survey of INH-associated hepatitis deaths, hepatitis deaths among persons aged 20–49 years were fourfold higher in women compared with men (20); (*3*) similar to other clinical trials, participants in our trial had higher completion rates than those in programs (Table 5); furthermore, women in our study were twice as adherent as men (21); (*4*) PLWH in Botswana may have additional risk factors for hepatic disease such as excessive consumption of alcohol and use of traditional medicines.

Repeated blood draws for evidence of hepatitis, as recommended by some researchers, are thought unlikely to be helpful in preventing death from INH-hepatitis (17, 22). Expert opinion is that death from hepatic encephalopathy is avoidable by educating recipients of IPT (23, 24). Therefore, consistent with the existing policy of the Botswana IPT Program, monthly

TABLE 5. RATES OF ISONIAZID-ASSOCIATED BIOCHEMICAL HEPATITIS, CLINICAL HEPATITIS, AND HEPATITIS DEATHS IN PUBLISHED STUDIES AND THE BOTSWANA CLINICAL TRIAL, IN ORDER OF INCREASING RATES

Study	Hepatitis Case Definition or Completion Rate	Persons Starting IPT	Number of Case Subjects	Rate (% or per 100,000)	*P* Value Compared with Botswana Trial
Biochemical hepatitis					
Uganda, trial* (45)	Grade 3 (AST > 5× ULN)†	931	1	0.11%	0.01‡
San Diego County, program (47)	Symptoms + AST > 3× ULN or asymptomatic + AST > 5× ULN	3,788	10	0.26%	<0.001‡
Botswana, trial*§	With or without symptoms, AST/ALT > 5× ULN	1,995	19	0.95%	—
Multicountry, trial* (49)	Grade 4 (>10× ULN)	792	26	3.28%	<0.001‡
U.S. multicity, trial* (48)	Grade 3 (AST > 5× ULN)	260	11	4.20%	<0.001‡
U.S. Air Force, trial (17)	With or without symptoms, AST > 5× ULN	1,000	52‖	5.20%	<0.001‡
Kenya, trial* (46)	AST or ALT > 2× ULN	342	18	5.26%	<0.001‡
Seattle-King County, program (18)	Symptoms only	11,141	NA		—
U.S. multistate, program (8)	Symptoms only	13,838	NA		—
Clinical hepatitis					
Kenya, trial* (46)	Clinical hepatitis or jaundice	342	0	0.00%	0.60
Seattle-King County, program (18)	Symptoms + AST > 5× ULN	11,141	11	0.10%	0.033
Uganda, trial* (45)	Clinical hepatitis†	931	1	0.11%	0.44
San Diego County, program (47)	Symptoms + AST > 5× ULN	3,788	6	0.16%	0.36
Botswana, trial*§	Symptoms + AST/ALT > 5× ULN	1,995	6	0.30%	—
U.S. multicity, trial* (48)	Symptoms, hospitalization	260	1	0.38%	0.57
Multicountry, trial* (49)	Hepatitis ≤ grade 4	792	3	0.38%	0.74
U.S. multistate, program (8)	Symptoms + AST > 7× ULN¶	13,838	57	0.41%	0.46
U.S. Air Force, trial (17)	Symptoms + AST/ALT > 5x ULN	1,000	15‖	1.50%	<0.001‡
Hepatitis deaths					
U.S. multicity, trial* (48)	63% completed therapy	260	0	0	1.00
Kenya, trial* (46)	69% completed therapy	342	0	0	1.00
Multicountry, trial* (49)	69% completed therapy	792	0	0	1.00
Uganda, trial* (45)	87% completed therapy	931	0	0	1.00
U.S. Air Force, trial (17)	88% completed therapy (6 mo)	1,000	0	0	1.00
San Diego County, program (47)	64% completed therapy	3,788	0	0	0.34
Seattle-King County, program (18)	64% completed therapy	11,141	0	0	0.15
Literature search, program (20)	60% completed therapy	1,084,760	177	16	0.28
Botswana, trial*§	89% completed therapy	1,995	1	50	—
U.S. multistate, program (8)	Completion rate unknown	13,838	8	58	1.00

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ART = antiretroviral therapy; IPT = isoniazid preventive therapy; NA = not available; ULN = upper limit of normal.
* Studies that selected exclusively HIV-infected persons. Numbers in parentheses refer to literature references.
† The authors of this article provided additional data that permitted these statistics.
‡ Statistically significant ($P < 0.01$).
§ Rates of clinical hepatitis, biochemical hepatitis, and hepatitis deaths were also determined for participants not receiving ART and with at least 4 months of IPT (n = 1,288) and were 0.93, 0.23, and 78 per 100,000, respectively.
‖ First 6 months of IPT; cases of hepatitis after 6 months excluded.
¶ This article showed AST elevations in Karmen unit strata. The closest stratum available was at 500 Karmen units, which is equivalent to 240 IU/L, which is approximately 7× ULN.

follow-up and patient education about the symptoms of hepatitis are critical. PLWH should be educated to stop the medication and seek medical assistance if they have nausea, vomiting, yellow eyes, dark urine, unexplained fatigue, or abdominal pain.

A statistically nonsignificant 1.6-fold higher risk for INH-hepatitis was observed in the cohort for those concomitantly taking ART and IPT. A South African study of 818 men and 50 women reported no statistically significant association between grade 3 or 4 hepatitis in PLWH receiving IPT and efavirenz-based ART (hazard ratio, 0.83; 95% CI, 0.20–3.4) (25). This is consistent with our finding that participants receiving efavirenz had no increased risk of INH-hepatitis (RR, 0.96; 95% CI, 0.21–4.31). The American Thoracic Society recommends routine serum transaminase monitoring in PLWH receiving both IPT and ART (26). The Botswana national guidelines for ART recommend that ART not be commenced simultaneously with IPT and, unrelated to IPT, that liver enzymes be monitored 2, 4, and 12 weeks after nevirapine initiation and 4 and 12 weeks after efavirenz initiation (27). New international guidelines on concomitant use of ART and IPT are needed. Consideration should also be given to the facts that three-fourths of cases of INH-hepatitis occurred in the first 3 months and that the period with the highest risk of severe nevirapine-hepatitis is the first 6 weeks after nevirapine initiation. Because delay in initiation of ART in persons with low CD4 counts may be hazardous (28) and because IPT is not an urgent intervention, conservative approaches in such persons are justified. Further, initiation of ART and IPT sequentially rather than simultaneously will facilitate attribution of any drug-related toxicities. We suggest that a complete IPT course can reasonably precede ART initiation so long as a 6-month delay in ART initiation is indicated (i.e., a high CD4 count). In persons among whom ART is begun first, IPT should be initiated after stabilization on ART; hepatic enzymes could be monitored according to the schedule used for nevirapine-based ART followed by inquiries about hepatitis symptoms at monthly clinic visits for IPT refills.

Whereas we found that the rate of INH-hepatitis among alcohol drinkers was nonsignificantly higher than among non-drinkers, having at least one positive response to CAGE criteria approached statistical significance with a 2.4-fold increased risk. This finding is consistent with the established literature on the increased risk of INH-hepatitis with daily alcohol use (8). It is possible that some participants did not accurately report their alcohol use, given that self-reporting of alcohol use is fraught with underreporting challenges (29). Furthermore, CAGE criteria have not been validated as indicators for alcohol abuse in Botswana. On the other hand, alcohol abuse is a documented problem in Botswana: in a population-based study, 31% of men and 17% of women met criteria for heavy drinking (30). As the current policy for IPT does not include screening for alcohol use or abuse, it may be advisable to screen and provide a brief intervention (31) for problem drinkers. Other than potentially preventing INH-hepatitis, this measure would benefit individuals with problem drinking through counseling.

Although rates of chronic and resolved HBV infection among those we tested were similar to those found in other studies from Botswana and sub-Saharan Africa (32–35), none of our cases of INH-hepatitis had chronic HBV infection. Some studies have shown that the presence of the HBV e-antigen (36) or surface antigen (37) was a risk factor for hepatitis during anti-TB therapy. We found no evidence of an association between INH-hepatitis and seropositivity for HBsAg or prior HBV infection, but had insufficient power to exclude a moderate relationship and did not assay for the HBV e-antigen.

Although limitations regarding alcohol use, age, and documentation of HBV coinfection are enumerated, a few additional limitations merit comment. We had difficulty in attributing hepatitis to INH; this is a common problem in clinical trials (38). Furthermore, trial clinicians suspected that in addition to greater alcohol abuse, traditional medicines were more commonly in use among participants than the 5.6% who acknowledged using these remedies. Frequent use of traditional medications has been previously reported in southern African PLWH receiving ART (39) and some of these are hepatotoxic (40). We are not able to comment on whether ART regimens without NNRTIs are more or less likely to result in INH-hepatitis with coadministration as there was only one participant undergoing a regimen without an NNRTI. As hepatic enzymes were not routinely measured after the 2-week routine blood draw, it is possible that undetected cases of biochemical hepatitis may have occurred subsequently. Such cases typically resolve through hepatic adaptation without discontinuation of IPT (41) while those that progressed to symptomatic disease were detected in the course of the trial.

It is possible that participants in the clinical trial differed from PLWH seeking IPT from Botswana's National Program as the study drew on catchment areas in two cities that comprise approximately 20% of PLWH seeking IPT throughout the nation. As many PLWH in these cities tend to have migrated from their home villages to seek care, they tend to have more illnesses (O.M., personal observation). In addition, as the trial used intensive counseling of participants as well as incentives, adherence was likely better than what could be achieved in the program, which implies that the rate of INH-hepatitis we report may be higher than what would be observed in the program. On the other hand, drug safety may not be monitored as closely in a program compared with a clinical trial.

Evidence from two retrospective studies that examined the benefit in TB prevention in PLWH receiving ART and IPT indicates that the protection conferred by the combination is additive (42, 43). Although this finding is encouraging, more research on measures to avoid hepatotoxicity from combining these drugs is warranted. In the interim, monitoring of serum transaminases during coadministration of ART and IPT may be performed in accordance with schedules set for specific antiretroviral drugs. Questions about problem drinking should be asked during screening for IPT and patients given prophylaxis with INH should be educated to stop the drug if they develop symptoms. Provision of HBV vaccine to HBV-susceptible PLWH should also be considered to reduce the risk of acute infection.

Conflict of Interest Statement: Z.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. O.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.V. has supervised clinical trials activity for which pharmaceutical firms provided support. The companies included Agouron, Dupont, Pfizer, Hoechst Marion Roussel (before it became Aventis), Merck, and Bayer, as well as Gen Probe and involved paying for PK testing, equipment, or drug supplies. One company (Sanofi Aventis) has provided more than $1 million in support to several trials involving rifapentine. C.D.W. is a full-time employee of Otsuka Pharmaceutical Development and Commercialization. During the course of 1999–2007 C.D.W. was at the U.S. Centers for Disease Control and Prevention. T.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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