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Short communication: **Antituberculosis drug-induced hepatotoxicity is unexpectedly low in HIV-infected pulmonary tuberculosis patients in Malawi**

A. Tostmann[1], M. J. Boeree[1], A. D. Harries[2], D. Sauvageot[3], H. T. Banda[4] and E. E. Zijlstra[4]

1 *Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre and University Lung Centre Dekkerswald, Nijmegen, The Netherlands*
2 *HIV Unit, Ministry of Health, Lilongwe, Malawi*
3 *INSERM Unit 330, Bordeaux, France*
4 *Department of Medicine, College of Medicine, Blantyre, Malawi*

Summary The proportion of patients with antituberculosis drug-induced hepatotoxicity (ATDH) was unexpectedly low during a trial on cotrimoxazole prophylaxis in Malawian HIV-positive pulmonary tuberculosis patients. About 2% of the patients developed grade 2 or 3 hepatotoxicity during tuberculosis (TB) treatment, according to WHO definitions. Data on ATDH in sub-Saharan Africa are limited. Although the numbers are not very strong, our trial and other papers suggest that ATDH is uncommon in this region. These findings are encouraging in that hepatotoxicity may cause less problem than expected, especially in the light of combined HIV/TB treatment, where drug toxicity is a major cause of treatment interruption.

keywords Adverse effects, Drug-induced liver disease, Tuberculosis treatment, *Mycobacterium tuberculosis*, HIV

Treatment adherence is crucial for curing patients with active tuberculosis (TB). Adverse effects of TB treatment significantly contribute to non-adherence, which has its consequences for TB control. Antituberculosis drug-induced hepatotoxicity (ATDH) is a serious adverse effect, which causes substantial morbidity and mortality, complicating TB treatment. The incidence of ATDH has been variably reported as between 2% and 11% (Dossing *et al.* 1996; Schaberg *et al.* 1996; Yee *et al.* 2003; Fernandez-Villar *et al.* 2004). This rate depends on the investigators' definition of hepatotoxicity as well as the population studied. Most studies on ATDH are performed in Europe, Southeast Asia and northern America. Data on ATDH in sub-Saharan Africa are limited. This is probably due to the fact that transaminases are not measured routinely and hepatotoxicity is often diagnosed clinically by the occurrence of jaundice.

We report the proportion of antituberculosis drug-induced hepatotoxicity cases observed in a randomised clinical trial on cotrimoxazole (CTX) prophylaxis in 579 Malawian HIV-positive adult tuberculosis patients. They were treated for smear-positive pulmonary TB with an 8-month regimen of $1SHRZ/1S_3H_3R_3Z_3/6HE$ (see Box 1 for explanation) plus daily CTX at a dose of 480 or 960 mg (Boeree *et al.* 2005). None received antiretroviral treatment. They were followed-up every 4 weeks until the end of TB treatment and aminotransferase levels [aspartate aminotransferase (ASAT) and alanine aminotranferase (ALAT)] were measured at enrolment and at months 2, 5 and 8.

During TB treatment, five patients (1.3%) developed grade 2 hepatotoxicity and three patients (0.9%) developed grade 3 hepatotoxicity according to WHO definitions (WHO 1992). No grade 4 hepatotoxicity was observed in this cohort. Table 1 shows the number of patients with hepatotoxicity at different time points during the study. Patients with grade 1 toxicity were still at risk for toxicity on subsequent measurements.

In this study, ALAT >50 u/l at inclusion and male gender were associated independently with ATDH (Table 2). In multivariate analysis, both ALAT >50 u/l at inclusion and male gender tend to be associated with ATDH [adjusted hazard ratios 2.18 (95%CI 0.93–5.07) and 1.58 (95%CI 0.99–2.53) respectively], although at borderline statistical significance. Whether hepatotoxicity was related to alcohol use, HIV infection or concomitant use of other hepatotoxic drugs cannot be concluded from our data. Due to the small numbers, grade 1 toxicity was included in these analyses.

Box 1 Tuberculosis treatment regimens

H, isoniazid; R, rifampin; Z, pyrazinamide; E, ethambutol; S, streptomycin.

The regular-size number refers to the number of months this regimen is used, the subscript number refers to how many times per week a drug is taken. For example: 1SHRZ/$1S_3H_3R_3Z_3$/6HE = one month of daily streptomycin, isoniazid, rifampin and pyrazinamide, followed by 1 month of the same four drugs three times a week, followed by 6 months of daily isoniazid and ethambutol.

Table 1 Patients with hepatotoxicity during tuberculosis treatment

	Month 2	Month 5	Month 8
No. of patients still followed	526	478	437
No. of patients measured	446 (84.8%)	376 (78.7%)	333 (76.2%)
No hepatotoxicity (ALAT<50 U/l)	410	336	302
Grade 1*	35 (7.8%)	35 (9.3%)	29 (8.7%)
Grade 2	1 (0.2%)	4 (1.1%)	–
Grade 3	–	1 (0.3%)	2 (0.6%)
Grade 4	–	–	–

ALAT = alanine aminotransferase.
*WHO definition of drug-induced hepatotoxicity.
Grade 1 (mild): <2.5 × the upper limit of normal (ULN) (ALAT 51–125 U/l).
Grade 2 (mild): 2.6–5 × the ULN (ALAT 126–250 U/l).
Grade 3 (moderate): 5–10 × the ULN (ALAT 251–500 U/l).
Grade 4 (severe): >10 × the ULN (ALAT >500 U/l).

Eighty-five patients (14.7%) died during TB treatment, 44 (7.6%) were lost to follow-up and the trial was stopped in 13 patients (2.2%) upon their request (Figure 1). Most deaths were because of TB ($n = 22$), diarrhoea ($n = 19$) and meningitis ($n = 11$); the other causes are summarised in the original paper of Boeree *et al.* (2005).

Patients who died or were withdrawn from the trial were more likely to have an ALAT level of >50 u/l at inclusion (9.3%) than patients who remained followed-up until the end of treatment [2.9% ($P = 0.02$)]. Therefore, these patients were possibly more at risk for ATDH, which could give an underestimation of ATDH in our trial (Fernandez-Villar *et al.* 2004).

The inclusion criteria for the trial are summarised in the original paper. The most relevant inclusion criterion in our study is HIV infection, as this is a risk factor for ATDH (Yee *et al.* 2003). Four patients were excluded because of 'jaundice or liver problems'. Regarding the low number, we did not expect this to affect the generalisability of our findings. A total of 80 patients were ineligible according to the exclusion criteria, mostly because of having received TB drugs for more than 8 days. We assume that these criteria were not related to (risk factors for) ATDH.

Table 2 Baseline characteristics according to hepatotoxicity status and univariate analysis among 464 patients with liver function information at 2, 5 and/or 8 months (*Cox proportional hazards model*)

	Hepatotoxicity* %, (*n*/*N*)	Hazard ratio (CI 95%)
Sex		
Female	15.1% (36/239)	*Ref**
Male	23.6% (53/225)	1.71 (1.12–2.62)
CTX prophylaxis		
CTX 480 mg	19.1% (42/220)	*Ref*
CTX 960 mg	19.3% (47/244)	1.02 (0.67–1.55)
Age		
15–24	17.2% (17/99)	*Ref*
25–34	18.2% (39/214)	1.08 (0.61–1.91)
35–44	22.1% (25/113)	1.32 (0.71–2.44)
>45	21.6% (8/37)	1.28 (0.55–2.97)
CD4-count		
0–99	20.7% (25/121)	*Ref*
100–199	17.3% (22/127)	0.78 (0.44–1.39)
200–349	19.6% (20/102)	0.93 (0.52–1.68)
>350	19.6% (18/92)	0.91 (0.50–1.68)
Hepatotoxicity at inclusion*		
No	18.4% (82/446)	*Ref*
Yes	35.3% (6/17)	2.23 (0.97–5.10)

ALAT, alanine aminotransferase; CTX, cotrimoxazole; CI 95%, 95% confidence interval; Ref, reference value.
*Hepatotoxicity is defined as grade 1 or higher.

The low proportion of ATDH in our trial is consistent with the previous studies in sub-Saharan Africa. In a study in former Zaire, TB drugs (2HRZE/4HR) were well tolerated among 446 TB patients. No hepatitis was reported, but increased transaminase-levels were occasionally seen (Perriens *et al.* 1995). In a Ugandan study, only two of 265 HIV-infected subjects (1%) developed hepatotoxicity during treatment of pulmonary TB (2HRZE/6HR) (Johnson *et al.* 2000). The same group reported that hepatitis and transaminase elevations did occur during preventive TB treatment in HIV-positive patients and that 0.8% had transaminase levels >135 u/l (Whalen *et al.* 1997).

These reports suggest that the incidence of ATDH in adults is low in sub-Saharan Africa. This is unexpected, because risk factors such as HIV or hepatitis B and C infection are highly prevalent in this region. There are several possible reasons for this apparently low incidence of ATDH. First, the available studies were not designed to detect ATDH. Cases of mild or transient hepatotoxicity

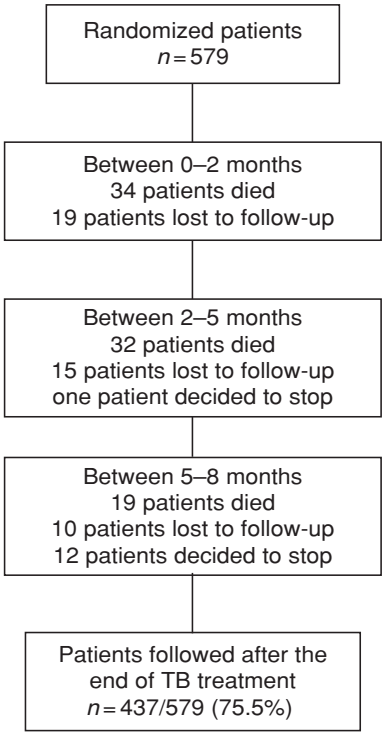

Figure 1 Patient withdrawal during tuberculosis treatment.

may have been missed. In our study, liver function was monitored only four times during TB treatment. Consequently, the incidence of mild ATDH may be underestimated. However, as serious hepatotoxicity would have most probably been detected at the monthly follow-up visits, we do not consider this possible underestimation clinically relevant. Second, patients who were withdrawn from the trial were probably at higher risk of ATDH than patients who remained in the study until the end of treatment. This could result in an underestimation of hepatotoxicity in our trial. Third, there is some evidence that absorption of TB drugs in adults with HIV/AIDS is worse compared with non-HIV-infected patients (Peloquin *et al.* 1996). Although HIV infection is a risk factor for ATDH, this could explain why ATDH is seen less frequently in our HIV-infected population. Possibly, immunosuppresion in patients with advanced AIDS results in fewer side effects during TB treatment. Fourth, ethnic variation causes differences in susceptibility for drug toxicity. Phenotypic variation in human drug metabolism can be attributed to polymorphisms in genes encoding drug-metabolising enzymes. Such polymorphisms may alter enzyme activity and could subsequently increase formation of reactive metabolites(Wilkinson 2005). In the case of isoniazid, toxic metabolites are responsible for its toxicity. Possibly, genetic polymorphisms in drug metabolising enzymes explain the low incidence of ATDH in sub-Saharan populations. On the other hand, in our trial all patients were HIV-positive and were on CTX prophylaxis during TB treatment. Because HIV is a risk factor for ATDH, a higher rate of ATDH would have been expected (Yee *et al.* 2003). Cotrimoxazole can be hepatotoxic, especially in patients with AIDS (Kovacs *et al.* 1984). Therefore, the real incidence of ATDH in patients without concomitant CTX may even be lower.

These findings are an incentive to study ATDH in sub-Saharan Africa. Because of the HIV epidemic, TB rates are increasing in this region. Furthermore, HIV not only increases the burden of tuberculosis in Africa, but also complicates its therapy. Drug interactions and overlapping toxicities are often seen during combined HIV/TB treatment, and drug toxicity has been implicated as a major cause of treatment interruption (Dean *et al.* 2002; Kwara *et al.* 2005). Currently antiretroviral drugs are being introduced on a large scale in sub-Saharan Africa. Our findings are encouraging in that hepatotoxicity due to combined HIV/TB treatment may occur less frequently than expected. However, more studies are needed on hepatotoxicity of combined treatment, in particular, in relation to the degree of immunosuppression as TB can occur at any CD4 level. In addition, more research on the incidence and risk factors for ATDH in Africans may help to prevent serious hepatotoxicity during TB and combined HIV/TB treatment. The prevention of side effects increases treatment adherence and treatment success rates. This will eventually contribute to better TB and HIV control.

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Corresponding Author A. Tostmann, Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, PO Box G101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3610325; Fax: +31 24 3610324; E-mail: A.Tostmann@ulc.umcn.nl

La fréquence d'hépatotoxicité induite par les antituberculeux est inopinément faible chez les patients à tuberculose pulmonaire, infectés par le VIH au Malawi

La proportion de patients avec une hépatotoxicité induite par les antituberculeux était inopinément faible au cours d'une étude sur la prophylaxie au cotrimoxazole chez les patients malawiens à tuberculose (TB) pulmonaire et VIH positifs. Environ 2% des patients ont développé une hépatotoxicité de grade 2 ou 3, selon les définitions de l'OMS, durant le traitement de la tuberculose. Les données sur l'hépatotoxicité induite par les antituberculeux en Afrique subsaharienne sont limitées. Bien que les nombres de cas ne soient pas très élevés, notre étude ainsi que d'autres suggèrent que l'hépatotoxicité induite par les antituberculeux n'est pas courante dans cette région. Ces résultats sont encourageants, l'hépatotoxicité étant peut être un problème moins important que prévu, particulièrement à la lueur du traitement combiné VIH/TB, où la toxicité des médicaments est une cause importante d'interruption du traitement.

mots clés Effets adverses, affection hépatique induite par les medicaments, traitement de la tuberculose, *Mycobactium tuberculosis*, VIH

La hepatotoxicidad inducida por fármacos antituberculosos es inesperadamente baja en pacientes VIH positivos con tuberculosis pulmonar, en Malawi

La proporción de pacientes con hepatotoxicidad inducida por fármacos antituberculosos (HFAT) fue inesperadamente baja durante un ensayo con cotrimoxazol como profilaxis, en pacientes VIH positivos con tuberculosis pulmonar, en Malawi. Alrededor de un 2% los pacientes desarrollaron un hepatotoxicidad grado 2 o 3 durante el tratamiento para la TB, de acuerdo con las definiciones de la OMS. Los datos sobre HFAT en África Subsahariana son limitados. Aunque los números no son muy sólidos, nuestro ensayo clínico y otro artículo publicado sugieren que la HFAT no es común en esta región. Estos hallazgos son alentadores en el sentido de que la hepatotoxicidad puede ser un problema menor de lo esperado, especialmente en un tratamiento suave combinado VIH/TB, en el que la toxicidad por fármacos es la mayor causa de interrupción del tratamiento.

palabras clave Efectos adversos, enfermedad hepática inducida por fármacos, tratamiento tuberculosis, *Mycobacterium tuberculosis*, VIH

