Letter to the Editors

The effect of cotrimoxazole coadministered with antituberculous drugs on serum transaminases in HIV-infected adults from the Ivory Coast

In March 2000, the World Health Organization (WHO) and UNAIDS recommended that trimethoprim-sulfamethoxazole (cotrimoxazole, SXT) prophylaxis be given in sub-Saharan Africa to HIV-infected adults at WHO clinical stage 2, 3 or 4, and/or with CD4 count under $500/\text{mm}^3$ [1]. In this region, where tuberculosis is the primary cause of HIV-associated mortality, many patients are now likely to receive concurrent administration of antituberculous drugs and SXT under field conditions where liver enzymes will not be monitored. Both antituberculous drugs and SXT may induce hepatotoxicity in HIV-infected patients [2, 3].

From 1996 to 1998, we conducted a placebo-controlled trial (ANRS 059 trial) to assess the ability of SXT (160/800 mg daily) to prevent early severe morbidity in HIV-infected adults in Abidjan [4]. We reviewed available transaminase measurements in 69 (30 and 39 receiving SXT and placebo, respectively) of the 541 patients included in this trial. All 69 had proven active tuberculosis and received the antituberculous drugs, rifampicin, isoniazid for 6 months together with pyrazinamide for 2 months, in association with the trial drug.

In 21 of these 69 patients (SXT 7, placebo 14), antituberculous treatment had been initiated prior to their inclusion in the trial (for a median time of 60 days). In the remaining 48 patients (SXT 23, placebo 25), antituberculous treatment was started after a median follow-up period of 118 days after starting the trial drug. At baseline (defined as the time when trial drug and antituberculous drugs were first given together), the 69 patients had a median age of 31 years, a male : female ratio of 0.77 : 1, and a mean CD4 count of $266/\text{mm}^3$. There was no difference between trial groups in terms of baseline mean age ($P=0.48$), sex ratio ($P=0.64$), mean CD4 count ($P=0.13$), mean time on antituberculous therapy in the 21 patients with prevalent tuberculosis (SXT 56 days, placebo 63 days, $P=0.59$), mean time on the trial drug in the 48 patients with incident tuberculosis (SXT 159 days, placebo 202 days, $P=0.38$), percentage of patients with available baseline transaminases (SXT 70%, placebo 62%, $P=0.46$), and the percentage of patients with baseline transaminases ≥ 2.5 the upper limit of normal (ULN) (SXT 14.3% placebo 12.5%, $P=1.0$).

During the 396 patient-months of follow-up during combined therapy with the trial drug and antituberculous drugs, 233 transaminases measurements were performed, showing repeated normal values in 31 patients (45%), values at least once ≥ 1.25 ULN in 38 (55%) (SXT 22/30 = 73%, placebo 16/39 = 41%, $P=0.007$), at least once ≥ 2.5 ULN in 21 (30%) (SXT 13/30 = 43%, placebo 8/39 = 21%, $P=0.04$), and at least once ≥ 5 ULN in six (9%) (SXT 4/30 = 13%, placebo 2/39 = 5%, $P=0.39$). These abnormal values were not associated with clinical symptoms except in one patient taking SXT who had jaundice and transaminases ≥ 10 ULN. After this patient stopped all drugs, the jaundice resolved and transaminases dropped. Antituberculous drugs were reintroduced without problems, but jaundice, abdominal discomfort and transaminases elevation occurred again after inadvertent rechallenge with SXT, which was then withdrawn completely.

Figure 1 shows the probability of having transaminase activities of 2.5 ULN or less during the coadministration of SXT and antituberculous drugs. Following multivariate analysis, the elevation of transaminases ≥ 2.5 ULN was significantly associated with baseline CD4 count $< 200/\text{mm}^3$ (Hazard Ratio [HR]: 4.87, 95% CI 1.63, 14.60, $P=0.005$) and non significantly associated with SXT treatment (HR: 2.17, 95% CI 0.89, 5.26, $P=0.09$). Using a lower threshold, the elevation of transaminases ≥ 1.25 ULN was significantly associated with both baseline CD4 count $< 200/\text{mm}^3$ (HR: 3.35, 95% CI 1.64–6.84, $P=0.001$) and SXT treatment (HR: 2.27, 95% CI 1.18, 4.36, $P=0.01$).

Comparative data on transaminase measurements in HIV-infected African adults during antituberculous treatment with or without SXT are scarce [5], and given the recent WHO/UNAIDS recommendations [1] many practitioners have already expressed concerns about this topic. The present study contained potential bias because patients were not randomised in the two trial groups at the beginning of the co-treatment with antituberculous drugs and the trial drug, baseline values of transaminases are incomplete, and markers of viral hepatitis, which have been previously shown to be associated with hepatotoxicity of antituberculous therapy in HIV-infected patients [2], are not available. However our data suggest that the combination of SXT with antituberculous drugs has the potential for hepatotoxicity. Mostly this is mild and asymptomatic but there is a potential for rare and severe

Figure 1 Kaplan-Meier estimate of the probability of subjects having transaminase activities of 2.5 ULN or less in 69 HIV-infected adults during antituberculous treatment, and taking trimethoprim-sulfamethoxazole or placebo (Cotrimo-CI ANRS 059 trial, Abidjan, Côte d'Ivoire).

symptomatic complications. In African field conditions where laboratory facilities are limited, prescribers should be aware of this risk in order to stop the drug combination immediately when clinical intolerance is suspected, and to avoid other hepatotoxic drugs during antituberculous treatment in patients taking SXT.

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Eugène Messou,¹ Xavier Anglaret,¹ Dominique Bonard,¹ Henriette Kouabena,² Thérèse N'Dri-Yoman,¹ Mireille Dosso,² François Dabis³ for the Cotrimo-CI ANRS 059 Study Group

¹Programme PAC-CI, Centre Hospitalo-Universitaire de Treichville, Abidjan, Côte d'Ivoire, ²Laboratoire de Biologie, Centre Hospitalo-Universitaire de Yopougon, Abidjan and ³Unité INSERM 330, Université Victor Segalen Bordeaux 2, Bordeaux, France

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Correspondence: Dr Xavier Anglaret, 15 Boulevard du Dr Chantemesse, 43000 Aiguilhe, France. Tel./Fax: [33] 4 71 02 72 20; E-mail: xavan@club-internet.fr

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