

## ART and tuberculosis: the final nail in nevirapine's coffin?

Tuberculosis is the most common indication for initiation of antiretroviral therapy (ART) in low-resource settings. Incidence of tuberculosis in patients with HIV/AIDS receiving ART is much higher than in the general population, even for patients who respond to treatment and whose CD4 cell counts increase to the normal range.<sup>1</sup> Therefore treatment of both diseases is frequently necessary. However, concomitant administration of antituberculosis treatment and ART is associated with drug interactions, mediated largely by the inducing effect of rifampicin, and shared drug toxicity. Few controlled studies have compared different ART regimens in patients with tuberculosis, and thus the report by Maryline Bonnet and colleagues in *The Lancet Infectious Diseases* of the CARINEMO study,<sup>2</sup> a randomised comparison of nevirapine-based ART with efavirenz-based ART in participants with tuberculosis, is welcome.

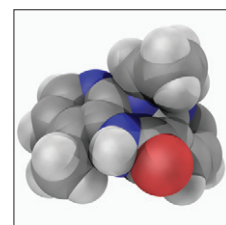
Either efavirenz or nevirapine is recommended in first-line ART regimens in low-resource settings. A meta-analysis of seven randomised controlled trials of previously untreated patients without tuberculosis reported that efavirenz and nevirapine (at the standard dose of 200 mg every 12 h) had much the same efficacy and rates of discontinuation.<sup>3</sup> However, drug interaction studies in patients on ART and treatment for tuberculosis show that efavirenz concentrations are minimally affected by ART co-treatment, whereas nevirapine concentrations are significantly reduced.<sup>4</sup> The inducing effect of rifampicin is of particular concern during the nevirapine lead-in low-dose period, resulting in concentrations of less than the recommended therapeutic range in most patients in a Malawian study.<sup>5</sup> Efavirenz is thus preferred in patients with tuberculosis, but nevirapine is more widely used than efavirenz in low-income countries because of its lower cost and its safety in pregnancy. In some countries efavirenz is not available.

Two randomised controlled trials have assessed the efficacy of efavirenz and nevirapine in patients on antituberculosis treatment. A Thai study<sup>6</sup> reported much the same efficacy of the two drugs, but lacked power to detect non-inferiority. An Indian study<sup>7</sup> was stopped early because of the inferior efficacy of nevirapine, but patients in this study were dosed once per day, which has been associated with worse outcomes than the standard twice-daily dose.<sup>3</sup>

The need for an adequately powered randomised trial of efavirenz and nevirapine was met by the CARINEMO study<sup>2</sup> in 570 participants starting ART in Mozambique, who had been treated for tuberculosis for less than 4 weeks. ART was started when CD4 counts reached less than 250 cells per  $\mu\text{L}$ . The lead-in dose of nevirapine was omitted. The one-sided 95% CI of the difference in efficacy between efavirenz and nevirapine exceeded the predefined non-inferiority margin of 10% in both the intention-to-treat and per-protocol analyses. Thus, non-inferiority of nevirapine was not shown—that is, nevirapine seemed inferior to efavirenz.

The proportions of participants with rash and significant increases in liver enzymes did not differ between the nevirapine and efavirenz groups, but more patients discontinued in the nevirapine group than in the efavirenz group. The low rate of rashes in the nevirapine group was probably because of the participants' low CD4 cell counts as the risk of nevirapine hypersensitivity reactions increases with increasing CD4 cell count.<sup>8</sup> Omission of the lead-in dose did not seem to increase the risk of hypersensitivity. The low incidence of hepatotoxicity (7% in the nevirapine arm) was noteworthy, because more than 20% of participants were hepatitis B surface antigen positive and all participants were taking three potentially hepatotoxic antituberculosis drugs.

The results of the CARINEMO study will add weight to the already compelling arguments to prefer efavirenz to nevirapine in first-line ART in low-income and middle-income countries. First, the difference in cost between efavirenz and nevirapine is decreasing.<sup>9</sup> Second, a systematic review<sup>10</sup> reported no evidence of increased risk of birth defects after first-trimester exposure to efavirenz, resulting in WHO recommending the use of efavirenz in pregnancy.<sup>9</sup> Third, only efavirenz is available as a single once-daily generic fixed-dose combination tablet, which improves adherence and is easy for public health programmes to deliver. Fourth, the risk of life-threatening toxicity is much higher for nevirapine than for efavirenz.<sup>8</sup> Finally, increasing numbers of patients are starting ART with high CD4 cell counts (which increases the risk of nevirapine hypersensitivity reactions) because ART programmes mature and



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because the CD4 count criterion for ART initiation has increased from 200 cells per  $\mu\text{L}$  to 350 cells per  $\mu\text{L}$  (and is widely expected to increase to 500 cells per  $\mu\text{L}$  in the 2013 WHO recommendations). Nevirapine will still be necessary for patients in whom efavirenz is contraindicated or not tolerated.

**Gary Maartens**

Division of Clinical Pharmacology, Department of Medicine,  
University of Cape Town, Cape Town, South Africa  
gary.maartens@uct.ac.za

I declare that I have no conflicts of interest.

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