Alladi Mohan
Srinivas Bollineni
Sri Venkateswara Institute of Medical Sciences
Division of Pulmonary and Critical Care Medicine
Department of Medicine
Tirupati, Andhra Pradesh, India
e-mail: alladimohan@rediffmail.com

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In reply. Obstructive sleep apnoea in Asia: an open mind for an evolving field

We note the above correspondence[1] on our review article published in the January 2007 issue of the *Journal*.[2] Our article aimed to provide an overview of obstructive sleep apnoea (OSA) regarding the salient aspects of epidemiology, risk factors, morbidity and clinical management in Asia in relation to the international scene, rather than to discuss all publications on OSA emanating from Asia.

An open mind can easily appreciate that, notwithstanding the era of the internet, the publication process still has its timeline. At the time of writing, we cited available data on a prevalence rate of 7.5% for obstructive sleep apnoea syndrome (OSAS) in a cohort of middle-aged (30–65 years), urban men in Bombay, India.[3] Subsequent to our submission, another study from India was published,[4] as cited in the above correspondence, reporting an OSAS prevalence of 4.96% and 2.03% in middle-aged (30–60 years) men and women, respectively, from a semi-urban community in Delhi. Both studies identified obesity as an important risk factor. Other data pertinent to our scope of review, on the use of screening questionnaires prior to polysomnography and metabolic parameters in OSA in an Indian cohort, were published in late 2006 or early 2007. With escalating interest in sleep disordered breathing, a regular stream of work is expected in the medical literature, and for this very reason the review serves to raise awareness and inspire the reader to actively pursue this constantly evolving field.

B. Lam
D. C. L. Lam
Mary S. M Ip
University Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Hong Kong SAR, China
e-mail: msmip@hku.hk

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What is the best strategy for treating TB-HIV co-infected patients with HAART and rifampicin without saquinavir?

Tuberculosis is a very complex disease when associated with HIV, and many aspects should be considered, especially concerning the concomitant treatment of both diseases.

Few options are available in current guidelines for treating tuberculosis and AIDS with rifampicin-containing HAART regimens, and few studies in the literature assess the efficacy and safety of the combination of these drugs.

In Brazil, because we have a policy of free distribution of antiretrovirals and anti-tuberculosis drugs, we also require HAART regimens for salvage therapy. We currently have no other HAART combination in our guidelines (excluding ritonavir-saquinavir) that is recommended for treating AIDS patients who fail on nevirapine or efavirenz. This is why we are so concerned about the prohibition of saquinavir as advised by Roche Laboratories.[1]

Dr Gray pointed out in our last discussion[1] that the once-daily regimen[2] (1200 mg saquinavir) lacked efficacy. This is true, but the point is, why was a higher dose of saquinavir not toxic in this study? Why was

the high proportion of hepatotoxicity observed only in the study that used a 500 mg tablet?

Dr Gray also mentioned that in the clinical/pharmacokinetics study conducted by our group,[3] a high proportion of dropouts occurred due to intolerance and that this was probably observed because the study was conducted with HAART-naïve patients, in whom we introduced two protease inhibitors (ritonavir 400 mg and saquinavir 400 mg). Our conclusion was that the association of two protease inhibitors should be kept back for salvage therapy, and that other, simpler regimens could be used as first-line treatment for HAART-naïve patients.

Based on the above information we can at this point conclude the following:

- The evidence available is not adequate to associate saquinavir with hepatotoxicity, as this was observed in only one study. No other investigation has been performed to clarify this suspicion, and no other paper has shown the same result.
- New combinations are being recommended based on a single study of healthy volunteers[4] using a high dose of ritonavir, although no trial has been performed in TB-HIV patients to evaluate the safety of this combination (lopinavir 400 and ritonavir 400) in real life. This approach was used in 2000 to put ritonavir and saquinavir in all guidelines, and the same rationale is being used today. We can imagine that the risk of hepatotoxicity and other adverse events may be similar to that of ritonavir 400 mg and saquinavir 400 mg.

In conclusion, the fact that there is very little money available to perform clinical trials in TB-HIV may be the main reason why we do not have enough information about our concerns. This lack of information obliges health care professionals to make their own decisions regarding the treatment of TB-HIV patients and we, researchers in countries where there is a significant TB-HIV problem, should accept the challenge of seeking new strategies and discussing the available data to help others to choose the best treatment options.

Thiago S. Torres
Valéria C. Rolla
Instituto de Pesquisa Clínica Evandro Chagas
Fundação Oswaldo Cruz
Clinical Research
Rio de Janeiro, RJ, Brazil
e-mail: ttorres@ipec.fiocruz.br

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False-positive tuberculin reactions due to non-tuberculous mycobacterial infections

In a laudable attempt to quantify the effect of non-tuberculous mycobacterial (NTM) infections on the tuberculin skin test (TST) response, Farhat et al. analysed data from studies that compared TST reactions with reactions to simultaneously administered antigens of NTM.[1] They estimated the rate of false-positive TSTs as the number of TST reactions of 10–14 mm that were ⩾1 mm smaller than the NTM reaction per 100 positive NTM reactions (defined as ⩾5 mm). This rate was averaged over a limited number of studies from which these data were available, and then applied to a corrected prevalence of positive NTM infections in a larger set of studies to estimate the absolute prevalence of false-positive TSTs in various regions of the world. These effects were remarkably small, ranging from 0.1% to 2.3% only.

There are reasons to question the validity of this method. First, standardisation of NTM antigens for their bioequivalence is generally done in guinea pigs, but generalisability to humans is doubtful.[2] The only studies in humans to show that the relative size of TST versus NTM reactions predicts development of tuberculosis (and thereby reflects latent tuberculosis versus NTM infection) compared 5 TU PPD-S with a defined set of antigens.[3] However, various combinations of tuberculins and NTM antigens were used in the studies reviewed, and for these there are few data to support that any particular difference in reaction size to the NTM antigen versus the tuberculin reflects the infecting species.

Second, the minimum average false positivity rate derived from the smaller set of studies (2.0%) is strongly determined by the low rates in one very large US study. (The maximum average false positivity rate, based on a set of studies in which these US studies were not included, was 2.7%, but 5.3% when recalculated from the data presented in Table 8.[1]) The use of this average assumes that there is only random variation across these studies with respect to the false positivity rate or, more precisely, to the association between responsiveness to a particular antigen and the proportion of positive TSTs due to cross-reactions. However, the tuberculin RT23 used in many of the studies reviewed has broader cross-reactivity with NTM than has PPD-S, probably due to differences in the antigenic