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Authors' reply

We thank Drs Byrnes and Edwards for their comments regarding our paper[1] and would certainly agree that the diagnosis of persistent bacterial bronchitis/persistent bacterial endobronchial infection can be difficult to make. However, without recognition that the condition exists, the diagnosis cannot be made. In our earlier letter (***see page 921***) we highlight the difficulties in reaching a correct diagnosis in a child with a chronic cough due to the limited repertoire of responses shown by the lungs when inflamed.[2] Failure to identify children with persistent endobronchial infection results in a huge burden of unnecessary morbidity due to the disease and due to inappropriate treatment. In a significant proportion it probably leads to bronchiectasis, although this may take decades. Our experience is that persistent endobronchial infection in children is curable, irrespective of the CT appearance, providing there is not a significant ongoing underlying problem such as cystic fibrosis or severe immunodeficiency. Bronchiectasis is not a diagnosis; rather, it is represents a radiological finding at one end of the spectrum from normality through minor peribronchial wall thickening and patchy non-specific changes. We have major concerns regarding the use of CT scans by those who do not understand the natural history of the disease. We have seen a number of patients who were noted to have significant quantities of secretions on bronchoscopy and a heavy growth of one or two organisms in the lavage fluid who were then largely left untreated because the CT scan did not show bronchiectasis.

The letter from Drs Byrnes and Edwards highlights the problem of using a non-specific term such as ''chronic bronchitis''. This is why we and Anne Chang's group[3] have deliberately adopted the terms ''persistent bacterial bronchitis/persistent bacterial endobronchial infection'' which highlight the fact that this is persistent endobronchial bacterial infection and is quite distinct from adult ''chronic bronchitis'' associated with cigarette smoke. Many adult patients with chronic obstructive pulmonary disease (COPD) are plagued by recurrent/persistent bacterial endobronchial infection with the same organisms we see in children but this, as in the children, is a secondary phenomenon resulting from impaired mucocilary clearance. These patients have two ongoing pathologies—one (COPD) predisposing to acquisition of the second (persistent endobronchial bacterial infection). We would go further and speculate that the continuing symptoms and decline in lung function in a significant proportion of ex-smokers is due to ongoing inflammation secondary to persistent endobronchial bacterial infection.

As noted above, we believe that persistent endobronchial bacterial infection is not a primary diagnosis but represents colonisation secondary to impaired clearance of the airways. This may be due to cystic fibrosis or an immunodeficiency but, most commonly, is secondary to a ''hit and run'' insult such as a significant viral lower respiratory tract infection or—much less commonly these days—pertussis. Other causes of impaired clearance such as mucus plugging in asthma, tracheomalacia or even pulmonary vascular congestion with congenital heart disease may allow *Haemophilus influenzae* in particular to colonise the lower airways.

Finally, we would wish to clarify some of the misconceptions in the letter by Drs Byrnes and Edwards. We did not say that bronchiectasis frequently resolves in those with immunodeficiency but mention that it has been reported. Patients did not take up to six courses of prolonged antibiotics to improve. This was the time taken to affect a cure and a few will take longer. As previously noted, in the vast majority of cases the cough resolves within 10–14 days on high-dose antibiotics and failure to show a dramatic response calls the diagnosis into question. However, a small minority do take longer and occasionally do not clear even with 2 weeks of intravenous antibiotics, but have subsequently cleared with nebulised colistin which is active against *Haemophilus*. Our approach is based on the belief that the lack of a cough suggests that there is no active inflammation and that, under these conditions, the airways are healing themselves. When the typical cough returns, we aim to treat it aggressively and early until the condition resolves. We believe the main focus of research should be in how to identify the condition early in order to prevent the need for long and, in some cases, recurrent courses of antibiotics once the infection has been present for months or years.

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HIV-related TB and adverse drug events

Breen and coworkers[1] showed that, in the era of effective antiretroviral therapy, discontinuation of anti-tuberculosis (TB) treatment occurred with a similar frequency in HIV-infected and HIV-uninfected individuals despite a greater rate of serious (grade III/IV) adverse events among HIV-infected individuals.

According to the Division of AIDS table for grading the severity of adult and pediatric adverse events (http://rcc.tech-res-intl.com), grade III adverse events are likely to cause inability to perform usual social and functional activities while grade IV adverse events are potentially life-threatening. However, among HIV-infected patients with grade III/IV adverse events in the above study,[1] treatment was interrupted only in a minority of patients, except for those with hepatotoxicity, and no mention was made regarding any modification of treatment regimens. With the retrospective study design, it might be difficult to exclude some degree of subjective bias in symptom reporting/grading/interpretation, especially among HIV-infected individuals, despite the use of a standardised grading scheme.

In contrast with previous studies,[2 3] anti-TB drug-related hepatotoxicity was observed at a similar rate in HIV-infected and HIV-negative patients.[1] Differing abilities to control socio-demographic and clinical profounders—such as malnutrition, alcohol use, drug abuse, hepatitis B/C, anti-retroviral drugs—could account for the difference, especially with the limited sample sizes of these studies.[1 3] In this regard, it is interesting to note that use of rifampin plus pyrazinamide in the treatment of latent TB infection was associated with apparently higher prevalences of hepatotoxicity in clinical trials conducted among HIV-negative subjects[4] than those conducted among HIV-infected individuals.[5] As hepatotoxicity is a major factor leading to interruption of anti-TB treatment,[1] the similar incidence of hepatotoxicity in HIV-infected and HIV-negative patients is perhaps reassuring.

However, while the attending clinicians might be unwilling to interrupt the anti-TB treatment among HIV-infected subjects even in the face of severe vomiting and peripheral neuropathy,[1] patient cooperation could be jeopardised and drug adherence would then be difficult to ensure outside the setting of directly observed therapy. Non-adherence, frequent regimen modifications and treatment interruptions certainly increase the risk of treatment failure and relapse with acquired resistances. With the recent report of highly fatal cases of drug resistant TB among HIV-infected patients,[6] there remains a need for heightened awareness of possible adverse drug events, as well as vigilance in the prevention, detection and management of such events.

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Author's reply

We thank Dr Leung and colleagues for their interest in our data[1] and their insights into the management of individuals with HIV and tuberculosis (TB) co-infection. We agree that, as with any retrospective study, it is possible that some events may have been misclassified despite our best efforts. However, we would be surprised if this were the case for hepatotoxicity, which is measured by objective blood test results, or treatment interruption.

Highly active anti-retroviral therapy (HAART) has radically altered the management of HIV and TB co-infection. Our overall aim was to describe the occurrence of adverse events and treatment interruption in this era. Data drawn from before this may not serve as a valid comparator. We looked carefully for differences according to anti-retroviral usage but none were observed. As highlighted in our discussion, there do exist a number of other factors that are difficult to control and may account for differing results between studies. Our data suggest a role for ethnicity, which might explain the divergent results seen between populations. As Dr Leung mentions, differences in event rates according to HIV infection with rifampicin and pyrazinamide combination are intriguing. It has been postulated that this reflects immune function.[2] We found no evidence for this when we analysed our event rates according to either baseline blood CD4 count or changes in this value at 2 months.

We agree that maintaining patient cooperation and adherence with appropriate drug regimens is vital to outcome for both TB and HIV, especially when the management of both conditions may be complicated by the development of drug resistance. However, in our cohort we observed reassuringly high levels of TB treatment completion and low rates of TB recurrence (regardless of HIV infection), as well as excellent virological responses to HAART.[3]

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Diagnosis of COPD

Shahab *et al* recently reported significant under-diagnosis of chronic obstructive pulmonary disease (COPD) in England.[1] Adults over 35 years were regarded as having airway obstruction (COPD) if the forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio was <0.70. This conforms with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[2] adopted by various organisations, albeit that no data were obtained after bronchodilation. Even the GOLD group acknowledges that there is no evidence that this cut-off point signifies clinically validated airway obstruction and that "the use of this fixed ratio may result in over-diagnosis of COPD in the elderly, especially of mild disease. Using the lower limit of normal (LLN) values for FEV_1/FVC that are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal is one way to minimize the potential misclassification."[2] This statement does justice to science and to authors of predicted values for spirometric indices who carefully defined the LLN for various indices, none of them advocating the use of a fixed cut-off point. In fact, in 45 publications, an overwhelming majority found that the LLN for FEV_1/FVC fell below 0.70 with age.[3]

In the 1995/6 study of a representative sample of the English population, valid spirometric data were obtained in 11 854 men and 13 554 women.[4] Measurements in 6053 non-smoking white people with no reported diagnosis of asthma or respiratory symptoms were used to derive prediction equations for the FEV_1/FVC ratio and its LLN. For an adult woman of 160 cm and a man of 174 cm, the LLN for FEV_1/FVC fell below 0.70 at ages 61 and 48 years, respectively. Using a fixed ratio, airway obstruction will hence be under-diagnosed below those ages and over-diagnosed above those ages.

Using data on 25 408 subjects,[4] we established how often FEV_1/FVC was <0.70 (method A) or below the LLN (method B). Figure 1 illustrates the misclassification rate. We expressed the difference between A and B as a percentage of B. Thus, 0% means equal prevalence, 100% means that the fixed ratio for FEV_1/FVC identified twice as many subjects with airway obstruction as the LLN method (50% false positives), and −80% means that the fixed ratio method failed to identify 8 out of 10 subjects with airway obstruction (80% false negatives). Using the NHANES III database and data from a Dutch population, sample findings were comparable with those in fig 1; the 2001 Health Survey for England data used by Shahab *et al* produced results nearly identical to those in fig 1. The trend in non-smoking men and women with no reported diagnosis of asthma or respiratory symptoms (a healthy reference group) is the same as that in the whole population.

The findings in a healthy reference group illustrate the inappropriateness of using a fixed FEV_1/FVC ratio for establishing airway obstruction. Applying that criterion to the whole population leads to substantial over-diagnosis of airway obstruction in middle-aged and elderly subjects, particularly in men, and unacceptably large under-diagnosis in younger adults. We recommend that organisations like GOLD, the American Thoracic Society, European Respiratory Society, British Thoracic Society and the National Institute for Clinical Excellence—who all recommend an FEV_1/FVC ratio of <0.70 as evidence of airway obstruction—return to evidence-based medicine and revise their guidelines.

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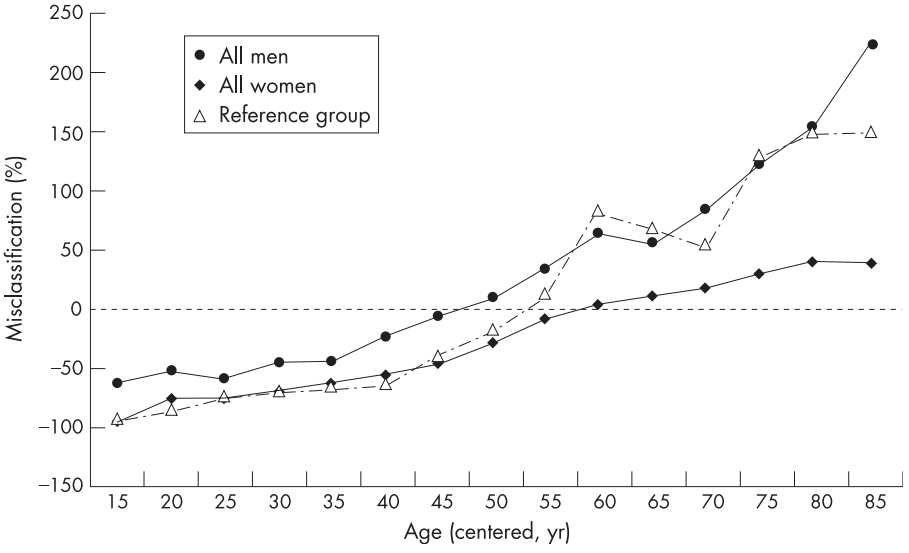

Figure 1 Percentage of subjects with airway obstruction (FEV_1/FVC <lower limit of normal) misclassified using GOLD guidelines (FEV_1/FVC <0.07), as a function of age. Misclassification: negative value = under-diagnosis; positive value = over-diagnosis. Data from 1995/6 Health Survey for England.[4]