In the 'Identification of eligible trials' of the Results section, we stated that a total of 1635 asthma patients were identified from six trials. Kerstjens et al. mention that the sum of the number of tiotropium patients and control patients exceeds the quoted total number of asthma patients. We acknowledge that this was ambiguous, and would like to clarify that of the trials that were finally included, three (Fardon et al, Peters et al, and Kerstjens et al. 2011) were originally designed as cross-over trials. So, although the actual number of patients totalled 1635 (as shown in Table 1), it was natural that the sum of number of patients from each group exceeded 1635, as patients from cross-over trials underwent both interventions.

Finally as Drs Kerstjens and Moroni-Zentraf indicated, we need to highlight that the baseline FEV_1(%) value from Bateman's trial refers to the placebo treatment arm. In addition, we would like to correct the baseline FEV_1(%) for the tiotropium treatment arm as 74.1 ± 16.12.

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HIV screening in tuberculosis patients in the northern region of Portugal

To identify determinants associated with unknown human immunodeficiency virus (HIV) status in tuberculosis (TB) patients in Northern Portugal, we selected all TB cases reported from 2006 to 2012, with no exclusion criteria. We analysed demographic and clinical data for two groups: patients with known and those with unknown HIV status; Northern Portugal was divided into two subgroups, Porto region and Other; co-morbidities were assessed as none and one or more; and addiction comprised alcohol and drug abuse.

Descriptive statistics are expressed as absolute (relative) frequency for categorical variables and mean (± standard deviation) or median (range) for continuous variables. The χ^2 or Fisher tests were used to compare the frequencies of categorical variables; Student's *t*-test or the Mann-Whitney U-test were used to compare means (or medians) from continuous variables between two independent populations.

A logistic regression model was applied to identify differences between the two groups, with a set of predictors that was chosen after the evaluation of their net effect on the response variable. The selection of the best model was based on the likelihood-ratio test, whenever possible, and on the Akaike Information Criterion (AIC) if not. The goodness-of-fit model was assessed by the deviance test while its discrimination ability was given by the area under the ROC curve.

Ethical approval was not necessary as only encrypted information was used.

Of 7683 TB patients notified, 5273 (68%) were male, 3482 (45%) were aged between 30 and 50 years and 7420 (97%) were native born; 879 (11%) had unknown HIV status.

Patients with unknown HIV status were more likely to be aged >50 years (44% vs. 34%, $P < 0.001$), to live outside the Porto region (68% vs. 44%, $P < 0.001$) and to have no co-morbidities (78% vs. 68%, $P < 0.001$) or addictions (83% vs. 75%, $P < 0.001$). Current or past imprisonment (98% vs. 95%, $P < 0.001$), homelessness (97% vs. 93%, $P < 0.001$) and sheltered community accommodation (97% vs. 92%, $P < 0.001$) were more common in the group with known HIV status.

In the fitted logistic regression model, unknown HIV status was positively associated with age >50 years (OR 1.46, 95% confidence interval [CI] 1.17–1.81) and living outside the Porto region (OR 2.77, 95%CI 2.35–3.25). Having one or more co-morbidities (OR 0.72, 95%CI 0.61–0.89) or addictions (alcohol/drug abuse) (OR 0.66, 95%CI 0.48–0.77) was negatively associated with unknown HIV status.

Older people were less likely to have been tested for HIV than younger people, which can be related to a false idea that older people are less at risk. It is well known that preconceived perceptions of risk cause delays in diagnosis, particularly of diseases associated with risk behaviour.[1] In Portugal the proportion of HIV patients aged >50 years has increased over the last 20 years (>20% in 2013), despite the decrease in HIV notifications.[2]

Persons outside Porto region were less likely to have an HIV test result. We cannot exclude access to health care as an explanation for this, as living in rural areas or suburbs has previously been linked to delayed diagnosis in other diseases.[3]

Patients identified as being at high risk, based on social-demographic features, are more likely to undergo HIV screening early on in life.[4] HIV screening tests are less likely to be offered by internists to patients they believe to be at low risk,[5] and risk perception of medical doctors may play an important role in the decision of offering an HIV test to their patients.

Knowing the importance of HIV screening in TB

patients and our epidemiological context with high co-infection rates, efforts are needed to attain maximum HIV testing coverage. Risk perception and access to health care may be barriers to be addressed in Northern Portugal.

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Xpert® MTB/RIF assay sensitivity with different methods of CSF processing for the diagnosis of TB meningitis

A 64-year-old woman born in India was admitted to our hospital with headache and fever of 3 weeks, associated with transient diplopia and dizziness. On examination, the patient was alert with mild neck stiffness and left fourth cranial nerve palsy. Laboratory tests were within normal values (including leucocyte count and C-reactive protein, human immunodeficiency virus negative), except for moderate hyponatraemia. Magnetic resonance imaging of the brain showed a 2 mm cerebellar lesion.

Lumbar puncture showed mononuclear pleocytosis with low glucose concentrations and elevated proteins. No acid-fast direct stain could be performed due to the scarcity of cerebrospinal fluid (CSF). The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) was initially negative for *Mycobacterium tuberculosis* complex using 0.5 ml vortexed CSF. A repeated spinal fluid sample was Xpert-positive, with no rifampicin resistance.

An intensified regimen containing high-dose rifampicin, moxifloxacin, isoniazid and pyrazinamide was started, together with dexamethasone. The following day, the patient developed comatose mental status related to hydrocephalus, requiring placement of a lumbar drainage device. A large volume of CSF (30 ml) was sent for repeated investigations, as detailed below. After the drainage and initiation of treatment, progressive improvement in neurological status was observed. The patient's outcome was good, with no neurological sequelae. Cultures were positive for susceptible *M. tuberculosis*.

The performance of the Xpert assay was assessed by evaluating four aliquots of CSF treated differently before polymerase chain reaction (PCR), as follows: aliquot 1, 0.5 ml CSF without vortexing and without centrifugation; aliquot 2, 0.5 ml CSF with vortexing and without centrifugation; aliquot 3, a 0.5 ml pellet obtained by centrifugation of 1 ml CSF for 10 min at 3500 × *g* followed by vortexing; and aliquot 4, 0.5 ml supernatant obtained by centrifugation at the above conditions. The PCR results are summarised in the Table.

The quantitative PCR data showed that vortexing CSF before PCR seemed not to affect the sensitivity of the assay. However, when PCR was performed on the CSF pellet (aliquot 3) rather than on the supernatant (aliquot 4), a difference was observed in that only the pellet sample was positive, and the threshold cycles were lower than for the non-centrifuged CSF aliquots (1 and 2), thus further improving the sensitivity of the assay.

TB meningitis remains a difficult diagnosis, and improvements in the sensitivity of diagnostic tools, allowing rapid confirmation of the diagnosis, are still needed. Sole reliance on a false-negative test result may delay treatment initiation. Several studies have examined the accuracy of the Xpert assay on CSF, showing that while specificity is consistently very high, sensitivity values are heterogeneous and depend on sample size, tuberculosis (TB) prevalence and the test used as gold standard.[1–4] As a consequence, the World Health Organization (WHO) has endorsed