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6-year follow-up of 522 HIV-positive individuals screened for *Mycobacterium tuberculosis* infection in Denmark

To the Editor:

We report the result of a 6-year follow-up study among 522 HIV-positive patients showing a positive predictive value (PPV) of 7% (two out of 28) and a negative predictive value (NPV) of 100% (478 out of 478) for developing active tuberculosis (TB) using the QuantiFERON-TB Gold In-Tube test (QFT-IT).

Denmark is a low TB incidence country with an annual incidence rate of six cases per 100 000 persons and a HIV prevalence of 70 cases per 100 000 persons [1]. Among HIV-positive patients registered in the Danish HIV Cohort, comprising all known HIV-positive individuals in Denmark, the incidence rate of TB was as high as 8.2 cases per 1000 person-years [2]. The rate was highest before and within the first 6 months of antiretroviral treatment (ART) and among patients with known TB risk factors.

HIV is a well-known risk factor for developing active TB, increasing the risk >20-fold compared to HIV-uninfected individuals [3–5]. In Eastern Europe the risk of death in HIV patients co-infected with TB is especially high [6].

Isoniazide preventive treatment (IPT) has shown to be effective in preventing reactivation of TB in HIV positive individuals [7–9], and the treatment has been recommended by the World Health Organization and the US Centers for Disease Control and Prevention [10].

In order to prevent further spread of the disease and prevent infection, IPT of HIV-positive individuals is now recommended in high-burden regions, independently of tuberculin skin test or interferon-gamma release assay results [10].

In Denmark, screening and treatment of latent TB infection is only recommended in individuals with recent TB exposure and candidates of tumour necrosis factor (TNF)-α inhibitor treatment, but no specific guidelines exist for HIV-positive individuals.

The objective of this study was to estimate the predictive value of the QFT-IT among HIV-positive individuals in Denmark. The study is a follow-up study of a cohort of 590 HIV-positive individuals screened for latent TB infection in 2004–2005 [11].

We conducted a prospective cohort study at the outpatient clinic at Copenhagen University Hospital (Hvidovre, Denmark) to determine the risk of developing active TB. In the outpatient clinic we followed 1122 HIV-positive individuals who attended three to four annual visits. QFT-IT screening was routinely offered in the period between December 2004 and May 2005, and the result of this screening has been reported previously [11]. Initially, 590 HIV-positive individuals were screened with the QFT-IT test. Information on patient status (still attending the clinic, dead or lost to follow-up) at December 31, 2010 was obtained for each patient *via* the hospital patient registry using the Civil Registration System (CRS). Patients referred to other hospitals in Denmark but who were still alive were included. Information on TB diagnosis was derived from the Danish National TB register.

TB is a mandatory notifiable disease in Denmark and all incident cases diagnosed by a medical doctor are recorded in the Danish National TB register. The CRS provides all citizens in Denmark with a unique personal identifier, which can be used to trace a person through all public registries. For the present study all incident TB cases recorded among the study participants were retrieved from the Danish National TB register between the date of recruitment and December 31, 2010. Additional information on ethnicity, death or emigration was obtained from the CRS. Data including sex, ethnic origin, HIV status and CD4 cell counts for all 1122 HIV-positive individuals seen in the outpatient clinic were derived from the Danish HIV Cohort [12] and the local hospital registry. HIV-positive patients were grouped into Caucasian and non-Caucasian, where persons born in Africa, Asia or Latin America were defined as non-Caucasian.

Between 2004 and 2005, patients were tested with the QFT-IT as previously described [11], and all QFT-IT-positive individuals were screened for signs and symptoms of active TB. None of the QFT-IT-positive patients were offered chemoprophylactic TB treatment. One patient, who developed active TB within

30 days of the QFT-IT test, was excluded from the analysis because he was considered to have active TB at the time of testing. The study was notified to the Danish Data Protection Agency (Jr.nr.2005-41-5520).

Out of 1122 HIV-positive individuals registered in the outpatient clinic, 590 (52%) accepted QFT-IT testing. 68 patients were either lost to follow-up due to emigration or died during the study period and were excluded from analysis. None of the 68 patients had been registered with TB in the Danish National TB register during the time after screening. Thus, complete follow-up data for 522 (88.5%) of the screened HIV patients were available.

The study participants were representative of the patients seen in our outpatient clinic with regards to sex, ethnicity, HIV status, CD4 count and ART (table 1). In the study cohort of 522 individuals, 412 (79%) were Caucasian and 110 (21%) were non-Caucasian. This distribution is comparable to all 1122 HIV individuals seen in our outpatient clinic where 878 (78%) were Caucasian and 244 (22%) were non-Caucasian.

Out of the 522 individuals with complete follow-up data, 28 (5%) were QFT-IT positive, 478 (91%) were negative and 16 (4%) were indeterminate. Among the 506 individuals with a valid QFT response the QFT was positive in 13.3% (14 out of 105) of the non-Caucasians compared to 3.5% (14 out of 401) of the Caucasians resulting in a three to five times higher odds of a positive QFT-IT test result among non-Caucasians. We found a low proportion of indeterminate results, which could be explained by the fact that 90% of the patients had CD4 cell count >200 cells·uL^{-1} and ~80% were receiving ART.

During the 6 years of follow-up, two (7%) cases of TB were seen among the 28 patients with a positive QFT-IT test. The TB cases were diagnosed 11 and 54 months after QFT-IT testing and both TB patients were male. One patient was of non-Caucasian origin (the Philippines), he had a CD4 cell count of 301 cells·uL^{-1} and no other risk factors. The second patient was of Danish origin with ongoing alcohol and intravenous drug abuse and a CD4 cell count of 530 cells·uL^{-1}. No cases of TB were reported among the 478 QFT-IT-negative patients or among the 16 patients with indeterminate results.

Thus, among the HIV-positive individuals without active TB at the time of screening and with available data at follow-up, the NPV of the QFT-IT was 100% (478 out of 478; 95% CI 99–100) and the PPV was 7% (two out of 28; 95% CI 1–22).

In this study, the number needed to treat with isoniazid to potentially avoid one TB case was 14 (two out of 28) and the number needed to test to identify one QFT-IT-positive individual was 18.6 (28 out of 522).

The strength of this study is the completeness of the data. We had follow-up results for 88.5% of the initial cohort and all patients were followed for a minimum of 6 years. Thus, due to the use of register information, the risk of information bias was minimal. The CRS allows for follow-up of study participants even if they leave the clinic, which also limits loss to follow-up. Furthermore, the personal identifier assures that any TB diagnosis among participants will be registered. The comparability of the study population with the total population of HIV patients in our outpatient clinic minimises the risk of participation bias and may allow us to extrapolate our result to all our patients (table 1).

TABLE 1 Baseline characteristics for the study population and the total HIV population seen in the outpatient clinic

	QFT-IT screened HIV positive	All HIV positive
Subjects n	522	1122
Males	422 (80)	812 (72)
HIV status		
AIDS	123 (22)	230 (15)
ART	435 (83)	858 (76)
CD4 cell count	531	499
0–99 cells·μL^{-1}	9 (2)	19 (3)
100–199 cells·μL^{-1}	25 (5)	37 (6)
200–300 cells·μL^{-1}	48 (9)	69 (10)
>300 cells·μL^{-1}	434 (84)	546 (81)
Caucasian	412 (79)	878 (78)
Non-Caucasian[#]	110 (21)	244 (22)

Data are presented as mean or n (%), unless otherwise stated. There was no statistical significance difference between the two groups. QFT-IT: Quantiferon-TB Gold In-Tube; ART: antiretroviral treatment. [#]: defined as persons born in Africa, Asia or Latin America.

One limitation is the low number of TB cases during the follow-up period, which limits the possibility of calculating measures of association based on TB as outcome parameter. Furthermore, data on larger cohorts should be collected in order to determine the PPV in HIV-positive individuals with low CD4 cell counts.

Although the number of TB cases in this study was small, our finding of a PPV of 7% is similar to that reported from Austria where AICHELBURG *et al.* [13] found a PPV of 8.7%. We can conclude that the QFT-IT test with a NPV of a 100% can be considered a safe test for ruling out risk of TB among immunocompetent HIV-positive individuals in a low endemic country like Denmark. Based on our study and others, there is an increased risk of progressing to TB in QFT-IT-positive HIV-positive individuals that should not be ignored [9].

The evidence to recommend IPT to HIV-positive patients is overwhelming even in the presence of effective antiretroviral treatment [8–10]. This combined effect is shown in high-burden countries, whereas data from low-endemic regions are limited. Being born in a TB high-endemic region is a risk factor for latent TB infection and for developing active TB among HIV-positive individuals in Denmark [2, 11] and other European countries [7]. It is a matter of debate whether screening should be limited to high-risk groups in low-endemic regions. In our study, one of the two cases of active TB was seen in a Danish born male; therefore, we suggest that all HIV-positive individuals should be considered for screening irrespective of the pre-test probability of infection. Testing HIV-positive individuals should be performed with the intension to treat them with IPT.

The cost of one QFT-IT test compared to the total cost of complete HIV care in Denmark is minimal and a discussion of the guidelines is recommended.

In conclusion, the present study shows that QFT-IT screening could be safely used for screening immunocompetent HIV-positive individuals in Denmark to prevent future TB in this group.

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The QFT-IT test can be safely used in HIV-positive patients; consider isoniazid prophylaxis if QFT-IT positive http://ow.ly/vBFOP

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