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Implementation of latent tuberculosis screening in HIV care centres: evaluation in a low tuberculosis incidence setting

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SUMMARY

The screening and treatment of latent tuberculosis infection (LTBI) to prevent active tuberculosis (TB) is recommended by the WHO in all HIV-infected patients. The aim of this study was to evaluate its implementation within Belgium's HIV care. A multiple-choice questionnaire was sent to 55 physicians working in the country's AIDS reference centres. Response rate reached 62%. Only 20% screened all their HIV-infected patients for LTBI. Screening methods used and their interpretation vary from one physician to another. The main barriers to the implementation of LTBI screening and treatment, as perceived by the participants, are lack of sensitivity of screening tools, risks associated with polypharmacy and toxicity of treatment. The poor coverage of LTBI screening reported here and the inconsistency in methods used raises concern. However, this was not unexpected as, in low-TB incidence countries, who, when and how to screen for LTBI remains unclear and published guidelines show important disparities. Recently, a targeted approach in which only HIV-infected patients at highest risk of TB are screened has been suggested. Such a strategy would limit unnecessary exposure to LTBI treatment. This methodology was approved by 80% of the participants and could therefore achieve greater coverage. Its clinical validation is still pending.

Key words: HIV/AIDS, prevention, screening programme, tuberculosis (TB).

INTRODUCTION

In 2012, 8·6 million incident cases of active tuberculosis (TB) were reported worldwide, 1·1 million cases occurred in HIV-infected patients and 320 000 deaths from HIV-associated TB were recorded [1]. HIV-infected patients have a 20–30% greater risk of developing TB compared to non-infected subjects and TB remains one of the principal causes of HIV-associated deaths.

To address the co-epidemics of HIV and TB, various prevention strategies are promoted by the World Health Organization (WHO) including the 'Three I's for HIV/TB': Intensified case finding, Isoniazid preventive therapy (IPT) and TB Infection control [2]. IPT generally implies 6–12 months' treatment by isoniazid monotherapy to treat latent tuberculosis infection (LTBI), the asymptomatic phase of *Mycobacterium tuberculosis* infection that frequently precedes active TB.

The available screening tools for LTBI are the tuberculin skin test (TST) and, more recently, two

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interferon-gamma release assays (IGRAs), the QuantiFERON®-TB Gold-IT (QFT-GIT; Cellestis, Australia) and the T-SPOT.TB® (Oxford Immunotec, UK). Evaluating these tools is complicated by the absence of a gold standard for the diagnosis of LTBI. However, using various methods (concurrent testing with the different tools and comparing results, using clinical risk factors of exposure to *M. tuberculosis* as a surrogate for LTBI, using active TB as a surrogate for LTBI or longitudinal follow-up to document development of active TB), the calculated sensitivity of all three tools is about 80% in HIV-uninfected patients [3]. As these LTBI screening tools are immunologically based tests exploiting T-cell responses, their sensitivities are decreased when used in HIV-infected patients, particularly in subjects with advanced disease [4–6]. The sensitivity estimates of TST, QFT-GIT and T-SPOT.TB in HIV-infected subjects are 71%, 61%, and 72%, respectively [5, 7]. Nevertheless, according to a 2010 Cochrane review, the treatment of LTBI in HIV-infected patients with a positive TST reduces the incidence of active TB by 62% [8].

Despite an increase in the number of HIV-treatment centres implementing LTBI screening and IPT in their standard practice, the WHO believes that the current coverage remains insufficient. Indeed, low rates of LTBI testing and treating are still being reported, in both low and high TB-incidence countries [9–11]. According to the WHO, 50% of patients newly enrolled in HIV care and screened for TB are likely to be eligible for IPT [1]. By contrast, scepticism with regards to systematic screening of all HIV-infected patients has emerged. At the 14th European AIDS Conference (Brussels, October 2013), both Dr Pozniak from London and Dr Maniewsky from Brussels suggested in their oral presentations that screening for LTBI in countries of low TB incidence should only target the patients at highest risk of developing TB (http://www.eacs-conference2013.com). Dr Pozniak presented the British HIV Association (BHIVA) guidelines that recommend using a risk assessment algorithm based on country of origin, blood CD4+ T-cell count and length of time on antiretroviral therapy to identify these high risk patients [12]. More radically, Dr Maniewsky suggested screening only patients from TB-endemic countries with a nadir (lowest-ever) CD4+ T-cell count <200 cells/mm^3. This strategy is based on a retrospective study of 1140 HIV-infected patients entering the Brussels St Pierre cohort between 2005 and 2012, and showing that of the 42 patients that would develop TB during follow-up, 83% were of African origin and 60% had a nadir CD4 T-cell count <200 cells/mm^3 [13].

The aim of this questionnaire-based study is to assess the use of LTBI screening and treatment in the various HIV care centres across Belgium, identify barriers to its implementation, if present, and investigate the clinician's point of view about selective screening based on individual risk of TB.

METHODS

Study setting

The study is set in Belgium, a western European country with a low global TB incidence. According to the Belgian Registry of Tuberculosis, 987 cases were reported in 2012, that is 8·9 cases/100 000 inhabitants [14]. Non-negligible incidences are, however, recorded in its largest cities (up to 27·4 cases/100 000 inhabitants) as a result of significant immigration from Sub-Saharan Africa, Northern Africa and Eastern Europe. In 2012, of the declared TB cases, 43 (4·4%) were infected with HIV of which 32 (74·4%) originated from a country bearing a high TB prevalence [14].

At least 20 000 subjects are living with HIV in the country and the number of new HIV infections diagnosed per year is among the highest in Europe (1227 cases reported in 2012, which is 11·2 cases/100 000 inhabitants). In total, 13 335 HIV-infected subjects were in care in 2012. The core of HIV care is organized into nine AIDS reference centres (ARCs) distributed across Belgium and collaborating with several satellite centres (SCs) [15, 16].

Population and methods

The target group, identified by the Belgium Research on AIDS and HIV Consortium (BREACH), was made up of the infectious disease specialists working in Belgium's ARC or SCs. These physicians care for about 70% of the country's HIV-infected patients. In February 2014, a questionnaire was sent electronically to all members of this target group (55 physicians; 44 working in ARCs and 11 in SCs). Once completed, the questionnaires were returned via email to the investigator. The investigator was not blinded to the identity of the surveyed physicians. Up to three reminders were sent to non-responders.

Questionnaire

The questionnaire was made-up of 14 multiple-choice questions. A complete version can be found in the

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Supplementary online Appendix. Briefly, the first series of questions addressed the clinician's experience (number of years working as an HIV infection specialist, size of HIV-infected practice population, estimated incidence of TB in their practice). The second series of questions inquired on the implementation of LTBI screening and treatment of HIV-infected patients in their practice and, if applicable, their choice of screening method and their interpretation of results. The last series of questions focused on the clinician's opinion about the systematic screening of LTBI in all HIV-infected patients and the barriers to its implementation.

Statistics

Descriptive statistics were used to calculate the overall response rate and response frequencies for each question. For the latter, the questions incorrectly completed (several responses given when a single answer was requested; unanswered questions; answered questions when not applicable) were disregarded. The relationship between categorical variables was calculated with either Fisher's exact test ($n < 5$) or χ^2 test ($n \geqslant 5$) using GraphPad Prism v. 6 software (GraphPad Software, USA; www.graphpad.com).

Ethics

The study protocol (P2013/354) was approved by the Ethics Committee Erasme Hospital (aggregation no. OM021).

RESULTS

Out of the 55 infectious disease specialists invited to participate, 34 (62%) completed the questionnaire. For each centre, at least two physicians participated and the response rate per centre varied between 25% and 100% (67% for ARCs and 63% for SCs). One responder/questionnaire was excluded from the analysis as the answers given were incoherent (the participant declared not screening his HIV-infected patients for LTBI but detailed his method of screening). As detailed later, one question (no. 13), was particularly problematical with regards to errors in completion. Other questions for which instructions were not correctly followed were no. 6 (by four participants), no. 5 (by three participants), no. 7B (by one participant), and no. 10 (by one participant). One respondent omitted question no. 8.

Table 1. *Characteristics of the study participants and their practice*

	Number (total = 33)	Percentage (%)
Place of main practice		
AIDS reference centre	26	79
Satellite centre	7	21
Number of years working in the HIV field		
<5	7	21
5–10	7	21
>10	19	58
Estimated number of HIV-infected patients in practice		
<50	7	21
50–100	2	6
>100	24	73
Estimated incidence of active tuberculosis per year in HIV-infected patients followed		
0–1	15	45
2–5	11	33
>5	7	21

Table 1 gives the characteristics of the responders and their practice. Briefly, the majority of clinicians interviewed are working in ARCs rather than SCs, most have a practice with >100 HIV-infected patients per year and have more than 10 years' experience in the field. Twenty-one per cent of the participating physicians estimate that the incidence of TB in their practice is above five cases per year.

Table 2 details the different LTBI screening practices applied by the participants. Use of LTBI screening and the method chosen are described as well as the physicians' approach with regards to: repetition of screening, exclusion of TB in those with positive LTBI screen, management in case of close contact with an infectious case of TB and prescription of LTBI treatment. TST and an approach adapted to CD4+ T-cell count are the two most frequently used LTBI screening methods, while combination of TST and IGRA is being used by only four participants. Of these, two consider an LTBI screen as positive if either of the two tests are positive, one requires a positive result for both tests to consider the screening as positive and the last uses a two-step strategy (IGRA only if TST negative). While the study was underpowered to show statistical significance of small differences, there was a trend towards testing with TST only and testing adapted to CD4+ count in physicians with more experience, more patients with HIV, and fewer patients with TB (Table 3).

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Table 2. *LTBI screening practices in Belgium's AIDS reference centres and satellite centres*

	Number	Percentage (%)
Use of LTBI screening ($N = 30$)*		
No	3	10
Yes, always	6	20
Yes, if *M. tuberculosis* exposure risk factors	9	30
Yes, in close contact cases	6	20
Other	6	20
LTBI screening methods applied ($N = 29$)		
TST only	7	24
IGRA only	2	7
TST and IGRA	4	14
Adapted to $CD4^+$ T-cell count	6	21
Other	7	24
N.a.†	3	10
Repetition of LTBI screening during follow-up ($N = 32$)		
Yes	8	25
No	21	66
N.a.	3	9
Exclusion of TB by chest X-ray in asymptomatic patients with positive LTBI screen ($N = 33$)		
Yes, always‡	25	76
Yes, in certain circumstances‡	4	12
No	1	3
N.a.	3	9
Prescription of LTBI treatment after close contact with an infectious TB case ($N = 33$)		
Yes, always	4	12
Only if LTBI screening positive	10	30
Dependent of patient's immune-deficiency	17	52
Other	2	6
Prescription of LTBI treatment when positive screen ($N = 32$)		
Yes, always	14	44
Yes, in certain circumstances	17	53
No	1	3

IGRA, Interferon-gamma release assay; LTBI, latent tuberculosis infection; TB, active tuberculosis; TST, tuberculin skin test.
* *N*, represents the effective number of questionnaires taken into account for each question. The variation of *N* is explained by the exclusion of those inadequately answered.
† N.a., Not applicable: screening of LTBI not performed.
‡ Among those excluding TB ($n = 29$), 20 (69%) participants do not use sputum analysis if the chest X-ray is normal. None use lipoarabinomannan to exclude TB either for lack of availability ($n = 20$, 69%) or alternative reasons ($n = 9$, 31%).

Overall, four (12%) participants believed that all HIV-infected patients should be screened for LTBI whilst 26 (79%) participants believed in selective screening targeted to those at highest risk of TB. A further two participants gave positive answers for both the proposed methods. A single doctor did not believe in LTBI screening of HIV-infected patients, regardless of the strategy applied. No significant relationship was found between being in favour of selective screening and the general characteristics of the participants, as shown in Table 4.

Finally, participants were asked to identify the three main barriers to the implementation of LTBI screening and treatment for this population using a selection of seven items. This question was the most incorrectly completed with only 20 respondents properly selecting three answers while five respondents only identified two, seven respondents identified only one and one respondent identified four. The most frequently chosen barriers in the 20 correctly completed questionnaires were lack of sensitivity of screening tools (chosen by 15 participants), polypharmacy (chosen by 13) and toxicity of treatment (chosen by 13). Lack of specificity of screening tools, risk of emergence of *M. tuberculosis* resistance and alternative reasons to those proposed were selected less frequently (chosen by eight, six and five participants, respectively). None selected lack of efficacy of LTBI treatment. Of note,

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Table 3. *Correlation between participant characteristics and applied LTBI screening method*

	TST only	TST & IGRA	Adapted to CD4+*	Other	*P* value (χ^2)
Place of main practice					
ARC	6	2	4	16	n.a.†
SC	1	0	0	4	
Number of years working in the HIV field					
⩽10	2	2	2	5	0·68
>10	5	2	4	4	
Estimated number of HIV-infected patients in practice					
⩽100	2	2	1	4	0·62
>100	5	2	5	5	
Estimated number of TB cases per year among HIV-infected patients followed					
⩽1	4	2	5	6	0·68
>1	3	2	1	3	

ARC, AIDS reference centre; IGRA, Interferon-gamma release assay; LTBI, latent tuberculosis infection; n.a., not applicable; SC, satellite centre; TB, active tuberculosis; TST, tuberculin skin test.
* Latent tuberculosis screening strategy adapted to CD4+ T-cell count.
† χ^2 analysis not calculated as certain subgroups have numbers <1.

Table 4. *The relationship between participant characteristics and opinion on LTBI screening strategy*

	In favour of selective LTBI screening*	Not in favour of selective LTBI screening	*P* value (Fisher's test)
Place of main practice			
ARC	23	3	0·28
SC	5	2	
Number of years working in the HIV field			
⩽10	13	1	0·37
>10	15	4	
Estimated number of HIV-infected patients in practice			
⩽100	8	1	1·00
>100	20	4	
Estimated number of TB cases per year among HIV-infected patients followed			
⩽1	12	3	0·64
>1	16	2	

ARC, AIDS reference centre; LTBI, latent tuberculosis infection; SC, satellite centre; TB, active tuberculosis.
* Selective LTBI screening = screening only in HIV-infected patients at highest risk of active tuberculosis.

the barriers remain in the same order of frequency when taking into account the choices of the participants wrongly selecting one, two or four answers.

DISCUSSION

This questionnaire-based survey on LTBI screening in HIV-infected patients reveals important heterogeneity in the strategies applied by the different infectious disease specialists working in Belgian's ARCs and SCs. If the choice of screening method varied, a large majority agreed upon the need for selective screening targeted at the patients with highest risk of TB. The most frequently identified barriers to the implementation of LTBI screening and treatment, as perceived by the participants, were lack of sensitivity of the available screening tools, risk associated with polypharmacy and the toxicity of LTBI treatment.

The limits of this study include a moderate response rate and the absence of data to characterize non-responders. The frequency of incorrectly completed questions and a non-negligible selection of the item 'other' among the suggested answers may reflect a lack of clarity and completeness of the multiple-choice questionnaire. Furthermore, only doctors working in ARCs and SCs were solicited whereas an estimated 30% of HIV-infected patients in Belgium attend alternative medical services. Nevertheless, despite these

weaknesses, the study clearly underlines the inconsistency of LTBI screening in Belgium's HIV care.

The first element of inconsistency lies in the choice of screening tool and strategy. One probable reason for the disparities observed is the lack of updated national Belgian guidelines on LTBI screening in HIV-infected patients (the 2003 guidelines are currently under revision [17]). In the absence of such guidelines, an evidence-based approach to select the best screening strategy is far from being straightforward for the physician, as no gold standard test for LTBI is available to compare and evaluate the different strategies [18]. Turning to international guidelines is not an ideal option either, as choice of LTBI screening strategy should take into account the local epidemiology of TB and bacille Calmette-Guérin (BCG) vaccination policies. BCG vaccination is important as it may induce false-positive TST results. As a result, the specificity of TST, estimated to be 97% in the non-vaccinated subjects, falls to 60% in BCG-vaccinated persons. Conversely, IGRAs maintain a high specificity (>93%) in BCG-vaccinated subjects and are therefore better tools for this subgroup [3]. In Belgium, the situation is particularly complicated as BCG vaccination is only exceptionally performed but immigrants may be vaccinated in their country of origin prior to their arrival.

Management of people living with HIV in contact with contagious TB cases was also inconsistent among participants. Only four physicians would treat all patients regardless of LTBI screening test results, as is generally recommended [17, 19, 20]. Conversely, 50% of participants would adapt their approach to suit the patient's immune-depression rather than treat all. This may reflect the mistrust of Belgian HIV caretakers with regards to LTBI treatment. It should be noted that in Belgium, TB contact case screening is partially coordinated by two non-profit-making organizations (FARES and VRGT) that work independently from the ARCs. These organizations have no access to the HIV status of the TB contact cases, and rely on self-disclosure of HIV infection. A better integration of HIV clinical care within the public health management of TB should therefore to be considered.

Several studies have already investigated the barriers to the implementation of LTBI screening and treatment in HIV care, but none have focused on high-income countries with low TB incidence [11, 21–24]. In this study, the data about barriers to screening implementation was excluded in a third of the surveys because the survey instructions were not correctly followed (either too many or too few answers given). Of note, the barriers most frequently identified in the excluded questionnaires were the same as those identified in the analysed surveys.

The main barrier identified by the participants was the insufficient sensitivity of screening tools. The inferior sensitivity of LTBI screening tools in HIV-infected subjects, as described earlier, has indeed been established. Moreover, discordant results between TST, QFT-GIT and T-SPOT.TB are prevalent in this population [5, 6, 18]. According to Zwerling *et al.*, the kappa statistic for the agreement between the TST and QFT-GIT is poor (0·26) [25]. The significance of these differences remains unclear although both the subjects that are TST-positive only and the subjects that are IGRA-positive only have been shown to progress to active TB [26]. As a result, most guidelines recommend combining the different screening tools in HIV-infected persons to increase the sensitivity of screening. However, the methods suggested differ between guidelines: TST and IGRA simultaneously [27], sequential testing if first test is negative [20], concurrent TST and IGRA only in patients with CD4+ T-cell count <200 cells/mm^3 [28]. It is therefore unclear for the physician which strategy to adopt. Interestingly, in this study, 25% of the participants declared using TST only. This may be partially explained by the fact that, in Belgium, IGRAs are approximately five times more expensive than TSTs.

An alternative method to increase the sensitivity of screening is its repetition, a method that, according to this study, is not being used in Belgium. The Centers for Disease Control and Prevention (CDC) suggests re-testing for LTBI (if initially negative with CD4+ T-cell count <200 cells/mm^3) once antiretroviral therapy is started and a CD4+ T-cell count >200 cells/mm^3 is obtained [29]. This is based on studies showing conversion of TST after a favourable immune response to antiretroviral therapy [30]. However, the role of repeated IGRAs remains undefined, as issues with unexplained test reversion and conversion have emerged [31]. Future guidelines should detail the necessity (or not) of re-testing, not only after immune reconstitution, but also in patients returning from a prolonged stay in TB-endemic countries as is frequently seen in immigrants visiting friends and relatives.

In addition to the lack of sensitivity of screening, risk associated to polypharmacy and toxicity of regimens were considered by the participants as major

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barriers to LTBI treatment. Nine months' treatment with isoniazid, also known as IPT, is the classical treatment for LTBI in HIV-infected patients. Alternative regimens include isoniazid for 6 months, isoniazid plus rifampicin for 3 months and rifampicin alone for 4 months. Rifamycin-containing regimens are particularly problematical because of pharmacokinetic interactions with several antiretroviral treatments [32]. Furthermore, polypharmacy (generally defined as being on $\geqslant 5$ medications) is a growing issue in HIV-infected patients. This is a result of the increased lifespan and ageing of these patients that are at high-risk of numerous age-associated diseases equally requiring early treatment. Polypharmacy is associated with a decrease in medical adherence, a higher risk of drug-to-drug interactions and an increased incidence of serious adverse events [33]. The main drug-induced toxicity associated with IPT is hepatotoxicity, which occurs in 0·001–0·15% of all treated patients, with increased risks in cases of alcohol consumption and age >35 years [34]. Clinical monitoring is therefore mandatory. Risk of hepatotoxicity does not appear to be greater in HIV-infected patients, although most studies have been made in the the early highly active antiretroviral therapy era with few patients on concomitant combination antiretroviral therapy (cART) [32].

Another feared consequence of IPT, as expressed by eight of the 34 participants, is the development of induced drug-resistance. Studies on the subject have shown no significant increase in isoniazid-resistance following IPT [35, 36]. Risk of resistance may, however, emerge if LTBI treatment is incorrectly prescribed in the presence of active TB, in which mycobacterial load and replication is much higher. As neither TST nor IGRA can differentiate LTBI from TB, exclusion of the latter prior to IPT is essential. In this study, a small number of participating physicians reported not always using chest X-ray to exclude TB in patients with positive LTBI screen. Indeed, the yield of chest X-ray for detection of TB in screening programmes has been recently debated [37]. The WHO currently recommends, in resource-limited countries, a simplified screening algorithm based on the absence of four clinical symptoms (current cough, night sweats, fever, weight loss) to exclude TB, with chest X-ray no longer being mandatory [2]. However this algorithm has a sensitivity of only 79% [38], and should not be applied in high-income countries where access to complementary investigation is unproblematical. Indeed, chest X-ray does not only inform on possible pulmonary TB lesions but can rapidly identify potential contagious cases, thus playing an important role in disease control and prevention.

Increasing the sensitivity of LTBI screening would imply a reduction in its specificity. This may discourage the physicians who fear the adverse effects of IPT from testing for LTBI. One solution is to only screen HIV-infected patients at highest risk of TB and thus limit the number of patients exposed unnecessarily to IPT. In this study, the majority of responding physicians were in favour of this approach, suggesting that this strategy could be better implemented if recommended. Target screening, currently recommended by the 2011 BHIVA guidelines and suggested in the latest European AIDS Clinical Society (EACS) recommendations [39], is indeed an attractive alternative in low-incidence countries. However, its clinical validation is still pending. Moreover, how to identify the HIV-infected patients at highest risk of TB must be clarified and evaluated. In Belgium, if the BHIVA risk assessment algorithm is applied (based on country of origin, blood CD4+ T-cell count, length of time on cART), at least 45% of all subjects with a new diagnosis of HIV infection would require screening as this percentage represents the proportion of subjects with an initial CD4+ T-cell count <350 cells/mm^3, mainly late presenters. By contrast, if limiting screening to subjects from TB-endemic countries that have a nadir CD4+ T-cell count <200 cells/mm^3, as suggested by Maniewski *et al.* [13], fewer than 15% of subjects newly diagnosed with HIV infection in Belgium would be candidates to LTBI screening.

Globally, in low TB-incidence countries, it remains unclear who, when and how to screen for LTBI in HIV-infected patients and discordance between the different available guidelines raises concern. Through this audit on current LTBI screening practices, we hope to have raised awareness in Belgian HIV caregivers with regards to this subject that divides specialists worldwide. An update of the Belgian national guidelines is needed and must address the issues pertinent to a low-incidence, high-resource settings. The Belgian LTBI working group responsible for this update has been informed of the outcome of this study in order to ensure that the actual situation on the ground and opinion of HIV caregivers may be considered. The implementation of new recommendations must be integrated with physician education, follow-up surveys to monitor adherence to the guidelines and a large-scale prospective study to evaluate the screening strategy chosen.

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SUPPLEMENTARY MATERIAL

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DECLARATION OF INTEREST

None.

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