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Latent tuberculosis infection screening in persons newly-diagnosed with HIV infection in Italy: A multicentre study promoted by the Italian Society of Infectious and Tropical Diseases

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ABSTRACT

Background: The Italian Society of Infectious and Tropical Diseases performed a survey on the application of guidelines for the management of persons living with HIV (PLWH), to evaluate current practice and the yield of screening for latent tuberculosis infection (LTBI) in newly-diagnosed PLWH; in addition, the offer of preventive therapy to LTBI individuals and the completion rate were analysed.
Materials and methods: Newly-diagnosed PLWH in nine centres were evaluated retrospectively (2016/2017) using binary and multinomial logistic regression to identify factors associated with LTBI diagnostic screening and QuantiFERON (QFT) results.
Results: Of 801 patients evaluated, 774 were studied after excluding active TB. LTBI tests were performed in 65.5%. Prescription of an LTBI test was associated with being foreign-born (odds ratio (OR) 3.19, $p < 0.001$), older (for 10-year increments, OR 1.22, $p = 0.034$), and having a CD4 count <100 cells/mm^3 vs ≥500 cells/mm^3 (OR 2.30, $p = 0.044$). LTBI was diagnosed in 6.5% of 495 patients evaluated by QFT. Positive results were associated with being foreign-born (relative risk ratio (RRR) 30.82, $p < 0.001$), older (for 10-year increments, RRR 1.78, $p = 0.003$), and having a high CD4 count (for 100 cells/mm^3 increments, RRR 1.26, $p < 0.003$). Sixteen LTBI individuals started TB preventive therapy and eight completed it.

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Conclusions: LTBI screening is inconsistently performed in newly-diagnosed PLWH. Furthermore, TB preventive therapy is not offered to all LTBI individuals and compliance is poor.

Introduction

HIV infection is a well-known risk factor for progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB) (WHO, 2019). In 2018, the World Health Organization (WHO) estimated 860 000 TB cases worldwide with 251 000 deaths from TB among HIV-infected persons; this population is defined hereafter as 'persons living with HIV' (PLWH) (WHO, 2019). Therefore, international guidelines for the management of HIV infection recommend screening for LTBI diagnosis and treatment in individuals newly diagnosed with HIV infection (WHO, 2019), or at least once in HIV-infected individuals (Migliori et al., 2018), or in selected groups of patients identified as at higher risk of developing active TB, as in the British guidelines (BHIVA, 2018). The treatment of LTBI is known to reduce the risk of developing TB by 60% when using therapy for up to 6 months (isoniazid (INH) monotherapy for 6 months or rifampicin (RIF) monotherapy for 4 months or the combination of RIF and INH for 3 months), or by up to 90% using INH monotherapy for 9 months (Fox et al., 2017), and the clinical benefit is higher among those testing positive in a screening test (WHO, 2019).

In spite of the existing recommendations, there is evidence that even in resource-rich countries, a significant proportion of PLWH are not screened for LTBI diagnosis (WHO, 2019; Evenblij et al., 2016; Wyndham-Thomas et al., 2016). This may be due to the low accuracy of LTBI tests to predict the development of active TB (Diel et al., 2011; Petruccioli et al., 2016a; Goletti et al., 2018a; Goletti et al., 2018b), to the awareness of the reduction in TB risk in those on combined antiretroviral therapy (cART) (Girardi et al., 2004; Girardi et al., 2012), and to the lack of availability of LTBI tests in clinical centres (CDC, 2011; Web site, 2018).

Current Italian guidelines recommend screening for LTBI diagnosis by tuberculin skin test (TST) or interferon gamma release assay (IGRA), either T-SPOT.TB or QuantiFERON (QFT) (Italian Ministry of Health, 2017). A study conducted in Italy in 2001 (Antonucci et al., 2001) after the first national guidelines on the diagnosis and treatment of HIV infection recommended TST screening for newly-diagnosed HIV individuals, reported a sub-optimal implementation of those recommendations. In particular, out of 1705 patients studied, 103 were identified as eligible for preventive therapy. However, this could not be proposed for 20 (five were eventually diagnosed with active TB and 15 had contraindications to therapy); among the remaining 83, only 40 individuals agreed to start preventive therapy and 29 completed a full-course regimen. Since then, it appears that no further update on this issue has been reported.

Therefore, the primary aim of this survey was to evaluate current practice and the yield of screening for LTBI diagnosis in persons newly-diagnosed with HIV infection in Italy. The secondary objectives were to evaluate whether preventive therapy was offered to those diagnosed with LTBI and its completion rate.

Materials and methods

Study design

The protocol of this multicentre retrospective observational study was developed by an ad hoc group of the Italian Society for Infectious and Tropical Disease (SIMIT). The survey was sent to the infectious diseases centres in Italy. Among them, nine centres, all located in public hospitals and/or public universities, volunteered to participate. Six centres were in northern Italy and three in central Italy. These centres account for the diagnosis and cure of at least 10% of persons newly-diagnosed with HIV infection in Italy, based on the 2018 national report (Istituto Superiore di Sanità, 2019), showing 3673 and 3561 new diagnoses in 2016 and 2017, respectively.

Persons newly-diagnosed with HIV infection in participating centres were enrolled retrospectively from January 2016 to December 2017. All recruited patients were naïve to cART, by definition. For each patient, the following information was collected: sex, age, country of birth, HIV transmission category, hepatitis B virus (HBV) serology and antigen detection (HBsAg/Ab) and hepatitis C virus (HCV) serology, first CD4 cell count, first HIV viremia, AIDS diagnosis, TB diagnosis, chest X-rays, LTBI diagnosis, and preventive therapy uptake.

For the purposes of this analysis, it was considered that the screening for LTBI diagnosis was performed when the result of a TST or of an IGRA (QFT-Gold In Tube or QFT-Plus; Qiagen, Hilden, Germany) was available within 6 months from the first HIV-positive test and before starting cART. In the text, the acronym 'QFT' is used to indicate either IGRA test, unless specified otherwise.

Statistical analysis

The median and interquartile range (IQR) was calculated for continuous measures. The Chi-square test or Fisher's exact test was used for categorical variables. The Kruskal–Wallis test was used for comparisons among several groups. Univariable and multivariable binary logistic regression were used to identify factors associated with screening for LTBI diagnosis, reporting the odds ratio (OR), 95% confidence interval (CI), and *p*-value. Univariable and multivariable multinomial logistic regression analyses were used to identify factors associated with positive and with indeterminate QuantiFERON results, assuming negative results as the reference category, reporting the relative risk ratio (RRR), 95% CI, and *p*-value. Multivariable models included variables with a *p*-value less than 0.2 in the univariable analysis together with sex, age, and born in Italy. A *p*-value less than 0.05 was considered significant. The data analysis was performed using Stata Statistical Software Release 15, 2017 (StataCorp LLC, College Station, TX, USA).

Results

Population characteristics of the newly-diagnosed HIV-infected patients who underwent screening for LTBI diagnosis

A total of 801 newly-diagnosed PLWH coming from nine centres in Italy located in the north and centre of the country were evaluated. Active TB was diagnosed in 27 individuals (3.4%) (Figure 1). Excluding those with active TB, 774 individuals remained eligible for screening for an LTBI diagnosis (Table 1). The median age of these patients was 38 years (IQR 30–47 years); 71.8% were born in Italy, 52.1% were men who have sex with men (MSM), and 16.8% had an AIDS diagnosis. The median CD4 count was 319 cells/mm^3 (IQR 133–540 cells/mm^3) and the median HIV RNA was 4.9 $\log_{10}$ copies/ml (IQR 4.2–5.4 $\log_{10}$ copies/ml) (Table 1).

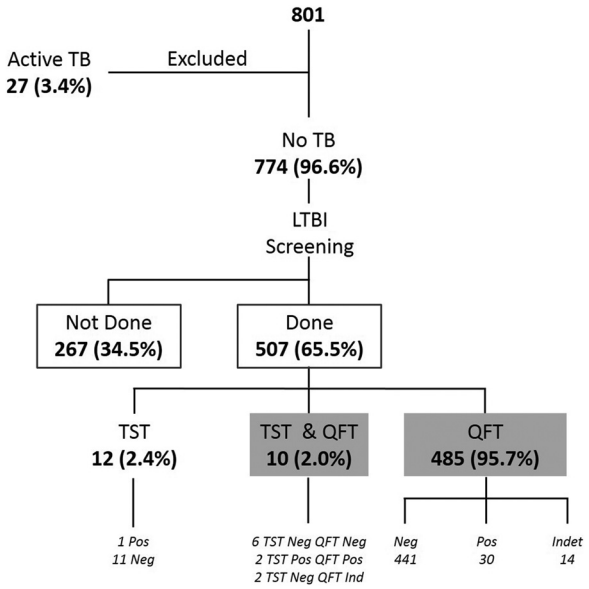

Figure 1. Flow chart of enrolled newly HIV diagnosed patients in 9 Italian centres (2016–2017).

Proportion of newly-diagnosed HIV-infected patients who underwent screening for LTBI diagnosis

The performance of screening was evaluated in the 774 individuals studied. It was found that a LTBI test (TST or QFT) was performed in only 507 individuals (65.5%) and that one centre did not perform any of these assays (Table 2). The majority, 495 patients, were evaluated by QFT, although two centres did not use this test at all and one centre performed it in less than 5% of the patients (Figure 1; Table 2). HBV and HCV screening are also recommended based on current HIV guidelines (Italian Ministry of Health, 2017; WHO, 2016; EACS, 2019). Therefore, HBV and HCV screening were evaluated among the 774 individuals studied. Considering all centres, HBV serology/HBsAg detection and HCV serology were performed in at least 95.5% of the patients (range 95.5–100%, overall 97.8% and 98.2%, respectively).

Factors associated with LTBI test prescription

Factors associated with the prescription of an LTBI test were analysed. To correctly identify these factors, the two centres in which the test was performed in either 100% or in less than 5% of enrolled individuals were excluded from this analysis (Table 2).

Table 2
Results of the patients without active TB screened for LTBI by centre.

Centre	Screened for LTBI by QFT or TST *n* (%)	Screened for LTBI by QFT *n* (%)
1	101 (88.6)	101 (88.6)
2	4 (8.9)	0
3	32 (100)	32 (100)
4	112 (84.2)	112 (84.2)
5	48 (85.7)	48 (85.7)
6	172 (58.9)	171 (58.6)
7	0	0
8	30 (93.7)	30 (93.7)
9	8 (20.5)	1 (2.6)
Total	507 (65.5)	495 (63.9)

TB, tuberculosis; LTBI, latent tuberculosis infection; TST, tuberculin skin test; QFT, QFT-IT or QFT-Plus (QFT-P).

Among the 711 patients included in this analysis (Table 3), 475 (66.8%) were screened by QFT or TST. By multivariable analysis, also adjusted for centre of enrolment, it was found that the test was more likely to be performed in foreign-born individuals (OR 3.19, $p < 0.001$), in older patients (for 10-year increments, OR 1.22, $p = 0.034$), and in individuals with a CD4 cell count <100 vs ≥500 cells/mm^3 (OR 2.30, $p = 0.044$) (Table 3).

Characteristics of the HIV-infected patients with a positive or indeterminate QFT result

Considering that only a few patients were screened by TST, only those screened by QFT were further analysed. A positive result was found in 32 (6.5%) of the 495 patients evaluated by QFT (Figure 1; Table 4). Among them, four (12.5%) were from a low TB endemic country (<10/100 000 inhabitants; three from Italy and one from Cuba), while eight (25%) were from TB high endemic countries (≥100/100 000 inhabitants) and 20 (62.5%) were from TB intermediate endemic countries (TB incidence ≥11 and <99/100 000 inhabitants and ≥100/100 000 inhabitants) (WHO, 2018; Lonnroth et al., 2015); all had CD4 cell counts higher than 100 cells/mm^3. The majority were male, with the most frequent risk factor for HIV being MSM. None had AIDS, and diagnoses were equally distributed in 2016 and 2017 using either QFT-IT or QFT-P (Table 5). Indeterminate results were found in 3.2% (16/495) of the patients evaluated by QFT (Table 4).

On multivariable analysis, when compared to a negative QFT result, a positive result was significantly associated with being foreign-born (RRR 30.82, $p < 0.001$), older (for 10-year increments, RRR 1.78, $p = 0.003$), and having a CD4 cell count ≥100 cells/mm^3 (for 100 cells/mm^3 increments, RRR 1.26, $p = 0.003$). The indeterminate result was significantly associated only with a low (<100)

Table 1
Demographic and clinical features of 774 patients newly diagnosed with HIV and without active TB, by enrolment centre.

Geographical location, centre code		Enrolled patients, *n*	Age, median (IQR) years	Born in Italy, *n* (%)	Risk MSM, *n* (%)	AIDS diagnosis, *n* (%)	CD4 cell count, median (IQR) cells/mm^3	Log_{10} HIV RNA, median (IQR)
North West	1	114	37 (29–47)	75 (65.8)	58 (50.9)	19 (16.7)	298 (116–557)	4.8 (4.2–5.4)
	2	45	36 (28–50)	31 (68.9)	14 (31.1)	7 (15.6)	285 (133–455)	5.0 (4.1–5.4)
Lombardy	3	32	41 (33–55)	18 (56.2)	15 (46.9)	17 (53.1)	102 (39–297)	5.1 (4.7–5.9)
	4	133	40 (30–50)	90 (67.7)	46 (34.6)	30 (22.6)	338 (129–597)	4.8 (4.1–5.3)
North East	5	56	33 (29–45)	34 (60.7)	34 (60.7)	9 (16.1)	376 (98–592)	4.8 (4.3–5.3)
Latium	6	292	36 (29–47)	226 (77.4)	195 (66.8)	25 (8.6)	387 (219–563)	4.9 (4.3–5.4)
	7	31	40 (31–45)	20 (64.5)	8 (25.8)	0	205 (62–332)	4.9 (4.2–5.4)
	8	32	38 (29–49)	30 (93.7)	12 (37.5)	11 (34.4)	252 (73–463)	4.9 (4.4–5.6)
	9	39	40 (32–52)	32 (82.0)	21 (53.8)	12 (30.8)	225 (51–328)	5.1 (4.1–5.7)
Total		774	38 (30–47)	556 (71.8)	403 (52.1)	130 (16.8)	319 (133–540)	4.9 (4.2–5.4)

IQR, interquartile range; MSM, men who have sex with men; TB, tuberculosis. CD4 counts are reported if tested within 90 days from the date of HIV diagnosis, and this was done in 749 patients; HIV RNA is reported if tested within 90 days from the date of HIV diagnosis, and this was done in 745 patients.

Table 3
Characteristics of the patients screened by QuantiFERON or TST among the 711 subjects.

Characteristics	Screening by QFT or TST					
	Total	Done	Binary logistic regression model			
	711	475 (66.8%)	Univariable		Multivariable[a]	
	n (%)	*n* (%)	OR (95% CI)	*p*-Value	aOR (95% CI)	*p*-Value
Sex						
Male	557 (78.3)	365 (76.8)	1		1	
Female	133 (18.7)	91 (19.2)	1.14 (0.76–1.71)	0.527	0.55 (0.28–1.05)	0.070
Transgender	21 (3.0)	19 (4.0)	5.0 (1.15–21.7)	0.032	3.19 (0.65–15.57)	0.152
Age, years						
Median (IQR)	37 (29–47)	38 (30–48)	1.10 (0.96–1.26)	0.179	1.22 (1.01–1.46)	0.034
Born in Italy						
Yes	519 (73.0)	320 (67.4)	1		1	
No	192 (27.0)	155 (32.6)	2.52 (1.7–3.75)	<0.001	3.19 (1.83–5.55)	<0.001
HIV risk						
MSM	380 (53.4)	239 (50.3)	1		1	
Heterosexual	240 (33.8)	165 (34.7)	1.30 (0.92–1.83)	0.137	1.60 (0.88–2.89)	0.122
IDU	20 (2.8)	14 (3.0)	1.38 (0.52–3.66)	0.522	1.16 (0.33–4.01)	0.819
Other/unknown	71 (10.0)	57 (12.0)	2.40 (1.29–4.47)	0.006	1.43 (0.68–3.02)	0.347
CD4[b] T cells/mm^3						
<100	127 (17.9)	97 (20.4)	1.63 (0.99–2.69)	0.057	2.30 (1.02–5.16)	0.044
100–199	82 (11.5)	62 (13.1)	1.56 (0.87–2.79)	0.133	1.98 (0.95–4.13)	0.070
200–499	274 (38.5)	165 (34.7)	0.76 (0.52–1.11)	0.159	1.05 (0.67–1.64)	0.820
≥500	206 (29.0)	137 (28.8)	1		1	
Unknown	22 (3.1)	14 (3.0)	0.88 (0.35–2.20)	0.787	0.94 (0.30–2.94)	0.913
HIV RNA[b] $\log_{10}$						
Median (IQR)	4.9 (4.2–5.4)	4.9 (4.3–5.4)	1.07 (0.91–1.25)	0.410		
AIDS diagnosis[c]						
No	598 (84.1)	388 (81.7)	1		1	
Yes	113 (15.9)	87 (18.3)	1.81 (1.13–2.90)	0.013	1.04 (0.46–2.33)	0.924
Year of HIV diagnosis						
2016	379 (53.3)	244 (51.4)	1		1	
2017	332 (46.7)	231 (48.6)	1.27 (0.92–1.73)	0.142	1.40 (0.95–2.06)	0.085

aOR, adjusted odds ratio; CI, confidence interval; IDU, injecting drug user; IQR, interquartile range; MSM, men who have sex with men; OR, odds ratio; QFT, QFT-IT or QFT-Plus (QFT-P); TST, tuberculin skin test. Observations from centres where screening was performed on more than 5% and less than 100% of the enrolled persons were used in this analysis.

[a] All variables with a *p*-value less than 0.2 in the univariable analysis were included in the multivariable model; estimations were also adjusted for centre of enrolment. Age was considered for 10-year increments.

[b] CD4 and RNA were evaluated only if available within 90 days from HIV diagnosis.

[c] AIDS if diagnosed within 90 days from HIV diagnosis.

Table 4
Results of the screening for LTBI done by QFT, by centre.

Centre	QuantiFERON results among 495 patients tested by QFT			
	Negative *n* (%)	Positive *n* (%)	Indeterminate *n* (%)	Total *n* (%)
1	92 (91.1)	5 (4.9)	4 (4.0)	101 (100)
2	–	–	–	–
3	30 (93.7)	1 (3.1)	1 (3.1)	32 (100)
4	104 (92.9)	5 (4.5)	3 (2.7)	112 (100)
5	42 (87.5)	5 (10.4)	1 (2.1)	48 (100)
6	152 (88.9)	16 (9.4)	3 (1.7)	171 (100)
7	–	–	–	–
8	26 (86.7)	0	4 (13.3)	30 (100)
9	1 (100)	0	0	1 (100)
Total	447 (90.3)	32 (6.5)	16 (3.2)	495 (100)

LTBI, latent tuberculosis infection; QFT, QFT-IT or QFT-Plus (QFT-P).

CD4 cell count (for 100 cells/mm^3 increments, RRR 0.11, $p = 0.003$) (Table 6).

Offer of preventive therapy and completion of therapy in individuals with LTBI

Preventive therapy was offered to 19/32 individuals (59.4%) (Figure 2). Among them, 3/19 (15.8%) did not start therapy because of chronic HBV infection or self-declared poor compliance. Among the 16 (84.2%) who started preventive therapy, eight (50%) completed treatment, while of the remaining eight, one had suspected TB lymphadenitis, one was lost to follow-up, and six were poorly compliant.

Preventive therapy was not proposed to 13/32 (40.6%). This was due to transfer from the clinical centre or loss to follow-up (6/13), decision to delay the start of treatment (3/13), HBV co-infection (2/13), cancer (1/13), or an unconfirmed QFT diagnosis after test repetition (1/13).

Discussion

In this multicentre study involving nine Italian HIV centres, it was found that screening for a LTBI diagnosis was performed in approximately 65% of individuals newly-diagnosed with HIV. This screening was more frequently performed among foreign-born individuals, older individuals, and individuals with a low CD4 cell count. LTBI was detected in 6.5% of screened individuals, with a higher risk among foreign-born individuals, older individuals, and individuals with a CD4 cell count higher than 100 cells/mm^3. Indeterminate results were observed in 3.2% of individuals and were associated with a low CD4 cell count. Among LTBI individuals, 60% were offered preventive therapy, 50% started treatment, and 25% completed it.

These results indicate that screening for LTBI diagnosis is not consistently performed in PLWH. Furthermore, TB preventive therapy is not offered to eligible LTBI individuals and compliance with therapy is poor. Therefore, we need to perform an in-depth analysis of the reasons underlying the observed suboptimal prescription of tests and of the criteria for selecting the population to target for LTBI screening, as has already been conducted in other countries (BHIVA, 2018; Evenblij et al., 2016).

Table 5
QFT results and patient characteristics for the 495 patients screened by QFT.

Characteristics	QuantiFERON result			
	Negative (447) *n* (%)	Positive (32) *n* (%)	Indeterminate (16) *n* (%)	Total (495) *n* (%)
Sex				
Male	351(78.5)	18 (56.2)	12 (75.0)	381 (77.0)
Female	81(18.1)	6 (18.8)	4 (25.0)	91 (18.4)
Transgender	15 (3.4)	8 (25.0)	0	23 (4.6)
Age, years				
Median (IQR)	38 (30–48)	37.5 (30–49)	51.5 (43.5–58.5)	39 (30–48)
Born in Italy				
Yes	316 (70.7)	3 (9.4)	15 (93.8)	334 (67.5)
No	131(29.3)	29 (90.6)	1 (6.2)	161 (32.5)
HIV risk				
MSM	229 (51.2)	17 (53.1)	5 (31.2)	251 (50.8)
Heterosexual	148 (33.1)	8 (25.0)	8 (50.0)	164 (33.1)
IDU	13 (2.9)	2 (6.2)	0	15 (3.0)
Other/unknown	57 (12.8)	5 (15.7)	3 (18.8)	65 (13.1)
CD4[a] T cells/mm^3				
<100	93 (20.8)	0	15 (93.8)	108 (21.8)
100–199	56 (12.5)	3 (9.4)	1 (6.2)	60 (12.1)
200–499	162 (36.2)	8 (25.0)	0	170 (34.3)
≥500	116 (26.0)	21(65.6)	0	137 (27.7)
Unknown	20 (4.5)	0	0	20 (4.0)
HIV RNA[a] $\log_{10}$				
Median (IQR)	4.93 (4.34–5.43)	4.3 (3.89–5.06)	5.53 (5.26–5.9)	4.93 (4.3–5.43)
AIDS diagnosis[b]				
No	359 (80.3)	32 (100)	3 (18.8)	394 (79.6)
Yes	88 (19.7)	0	13 (81.2)	101 (20.4)
Year of HIV diagnosis				
2016	233 (52.1)	15 (46.9)	9 (56.2)	257 (51.9)
2017	214 (47.9)	17 (53.1)	7 (43.8)	238 (48.1)
QFT type				
QFT In Tube	276 (61.7)	18 (56.2)	10 (62.5)	304 (61.4)
QFT Plus	171 (38.3)	14 (43.8)	6 (37.5)	191 (38.6)

IDU, injecting drug user; IQR, interquartile range; MSM, men who have sex with men; QFT, QFT-IT or QFT-Plus (QFT-P).
[a] CD4 and RNA evaluated only if available within 90 days from QuantiFERON test.
[b] AIDS if diagnosed within 90 days from HIV test.

In the present study, it was found that LTBI screening among PLWH was performed significantly more frequently in foreign-born individuals coming from high TB incidence countries. This is in agreement with what has been observed in other European countries, such as the Netherlands (Evenblij et al., 2016), Belgium (Wyndham-Thomas et al., 2016), and Switzerland (Elzi et al., 2007), as well as in non-European countries, such as Australia (Doyle et al., 2014). In contrast, a study performed in the United States demonstrated an association between the request for screening for LTBI diagnosis and poverty (Reaves et al., 2017). This is a very interesting issue; however this parameter was not evaluated in our survey. The low implementation of LTBI screening is likely due to the low perception of TB risk in PLWH (Evenblij et al., 2016), and to the awareness of the inaccuracy of LTBI tests, which can give false-negative results in immunosuppressed persons (Goletti et al., 2014; Goletti et al., 2007; Vincenti et al., 2007) and are inadequate to predict progression to disease (Diel et al., 2011; Petruccioli et al., 2016a; Goletti et al., 2018a; Goletti et al., 2018b). The accuracy of LTBI tests improves if a selected population known to have a higher probability to progress to active disease is identified, as recommended in the recent guidelines of the British HIV Association (BHIVA) (BHIVA, 2018). BHIVA recommends testing PLWH for LTBI diagnosis if they come from countries of high and intermediate TB incidence, with particular attention to individuals recently exposed to TB. BHIVA also suggests including PLWH from low-incidence countries in the screening if they have additional TB risk factors. This is a very pragmatic approach and has a high chance of being accepted and followed by HIV specialists.

There is no reference test for the diagnosis of LTBI. The tests currently available assess the presence of an immune response to *Mycobacterium tuberculosis* antigens in vivo (TST) or ex vivo (IGRA). In a large European cohort study with more than 1700 patients with a wide variety of types of immunosuppression, the application of IGRAs among HIV-infected individuals led to a higher number of positive results compared to TST (Sester et al., 2014). This is most likely one of the reasons why the majority of clinicians use IGRAs more frequently than the TST. Additional reasons are related to the wider availability of IGRAs in hospitals compared to TST, and also to the increased acceptability of the blood test by patients (Hirsch-Moverman et al., 2013). It should be noted that in Italy, TB screening was hampered between 2015 and 2016 by an inability to find the TST or the failure to perform IGRAs in the hospitals, which explains the lack of prescription for screening in one centre (Web site, 2018).

Regarding the results, the IGRA allows so-called indeterminate responses to be identified, which are due either to a high interferon gamma (IFN-γ) background concentration in the negative control or a low IFN-γ value in the positive control, alerting the clinician not to exclude LTBI on the basis of the test results. In the present study, a low proportion of indeterminate results were found and these were mainly associated with older age, low CD4 cell counts, and AIDS status. The observed results are in agreement with the literature (Sester et al., 2014).

The proportion of positive responses did not differ when using the old version of QFT-IT in 2017 and the new version of QFT-Plus in 2018. It is known that the new QFT-Plus version has additional peptides specific for CD8 T-cells (Petruccioli et al., 2016b; QIAGEN, 2020) and this may improve the ability to detect LTBI in HIV-infected individuals. However, this study was not designed to evaluate its diagnostic yield.

Table 6
Factors associated with QFT score in the 495 patients screened by QFT.

Characteristics	Multinomial logistic regression model[a]							
	Univariable				Multivariable[b]			
	QFT positive		QFT indeterminate		QFT positive		QFT indeterminate	
	RRR (95% CI)	*p*-Value	RRR (95% CI)	*p*-Value	RRR (95% CI)	*p*-Value	RRR (95% CI)	*p*-Value
Sex								
Male	1		1		1		1	
Female	1.44 (0.56–3.75)	0.451	1.44 (0.45–4.59)	0.534	0.73 (0.25–2.12)	0.558	2.78 (0.66–11.79)	0.166
Transgender	10.40 (3.90–27.72)	<0.001	0 (0)	0.992	1.90 (0.64–5.69)	0.250	0 (0)	0.999
Age, by 10-year increase	0.98 (0.71–1.33)	0.877	2.08 (1.34–3.23)	0.001	1.78 (1.21–2.62)	0.003	1.53 (0.85–2.74)	0.152
Born in Italy								
Yes	1		1		1		1	
No	23.32 (6.98–77.88)	<0.001	0.16 (0.02–1.23)	0.078	30.82 (8.25–115.18)	<0.001	0.15 (0.02–1.41)	0.098
HIV risk								
MSM	1		1					
Heterosexual	0.73 (0.31–1.73)	0.472	2.48 (0.79–7.71)	0.118				
IDU	2.07 (0.43–9.94)	0.363	0 (0)	0.987				
Other/unknown	1.18 (0.42–3.34)	0.753	2.41 (0.56–10.39)	0.238				
CD4[c] T cells/mm^3	1.26 (1.13–1.41)	<0.001	0.09 (0.02–0.37)	0.001	1.26 (1.08–1.46)	0.003	0.11 (0.03–0.48)	0.003
HIV RNA[c] (log_{10} copies/ml)	0.59 (0.41–0.84)	0.003	2.23 (1.26–3.93)	0.006	0.87 (0.53–1.41)	0.570	1.43 (0.58–3.52)	0.434
AIDS diagnosis[d]								
No	1		1		1		1	
Yes	0 (0)	0.986	17.68 (4.93–63.4)	<0.001	0 (0)	0.994	2.26 (0.54–9.53)	0.266
Year of HIV diagnosis								
2016	1		1					
2017	1.23 (0.6–2.53)	0.566	0.85 (0.31–2.31)	0.746				
QFT type								
QFT In Tube	1		1					
QFT In Tube	1.26 (0.61–2.59)	0.538	0.97 (0.35–2.71)	0.951				

CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men; QFT, QFT-IT or QFT-Plus (QFT-P); RRR, relative risk ratio.
[a] In the multinomial logistic model, a negative result was the base outcome, and CD4 for 100 cells/mm^3 increment.
[b] Variables with a *p*-value less than 0.2 in the univariable analysis were included in the multivariable model.
[c] CD4 and RNA evaluated only if available within 90 days from QuantiFERON test.
[d] AIDS if diagnosed within 90 days from HIV test.

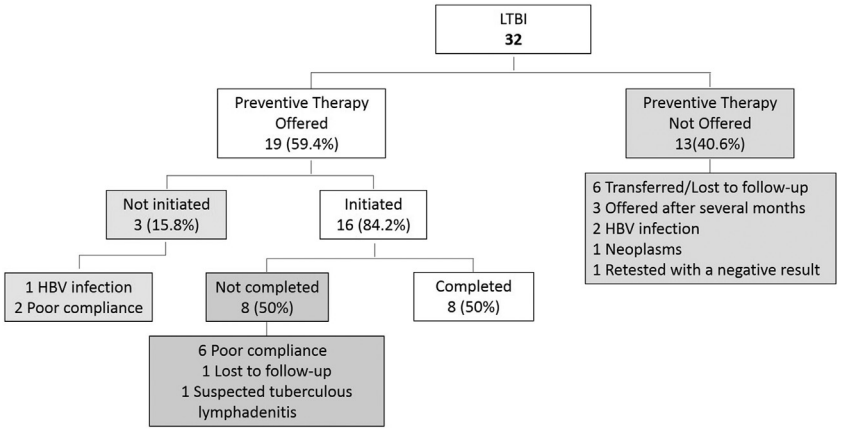

Figure 2. Offer of preventive therapy and completion of therapy in individuals with LTBI.

cART has been shown to reduce the risk of developing TB in PLWH; however, the risk of TB in HIV-infected individuals using cART remains higher than the risk in non-HIV-infected individuals (Lawn et al., 2009; Gupta et al., 2015; Gupta et al., 2012). Therefore, in those who are found to be LTBI-positive, TB preventive therapy should be offered for its beneficial effects in reducing the reactivation of TB also in PLWH on cART (Rangaka et al., 2014), making LTBI screening and treatment a worthwhile strategy also in countries with good access to and uptake of cART. In the present study, TB preventive therapy was offered to only 60% of the eligible patients. This was due mainly to the presence of comorbidities and low patient compliance with the long preventive treatment. New therapeutic options have recently been proposed; in particular, a 1-month regimen of rifapentine plus INH could be very attractive (Swindells et al., 2019). This newly approved regimen could also be useful in increasing the completion rate of LTBI treatment. Indeed, in our cohort, only 25% of those with LTBI completed treatment. This new short regimen could be of added value for clinicians continuing or increasing the screening of newly diagnosed HIV patients for LTBI, considering the possibility of offering a short and effective treatment to those in need.

Interestingly, on evaluating the prescription of other recommended screening tests, such as those for HBV and HCV serology, it was found that these were more frequently performed (in at least 97.8% of PLWH).

Limitations of the study are the retrospective approach used and the partial coverage of the centres caring for PLWH in Italy. However, this is the first multicentre study on the evaluation of LTBI screening

in newly-diagnosed HIV-infected individuals, and it lays the basis to assess the current incidence of LTBI in PLWH in Italy.

In conclusion, this multicentre study found that screening for LTBI diagnosis was performed in only 65.5% of newly-diagnosed HIV-infected patients. LTBI tests were mainly prescribed to foreign-born patients. The majority (87.5%) of LTBI individuals came from countries with a high or intermediate TB incidence. An in-depth analysis of the reasons related to the suboptimal prescription of tests and of the population to target for LTBI screening is envisaged.

Ethical approval

The study was approved by the ethics committee at the coordinating centre (INMI Spallanzani, approval number 13/2018); the participating centres sought further ethical approval according to local regulations. Written informed consent was obtained from all participants. The research was performed in accordance with relevant guidelines/regulations.

Conflict of interest

DG has received consultant fees for public speaking in international meetings by Qiagen and Diasorin. LS has received travel grants from Gilead, Merck, Bristol, and Pfizer, payment for lectures from Merck, Gilead, Bristol, and AbbVie, consulting fees from Angelini SpA, and research funding from Gilead. CM has received grants from AbbVie, Gilead, MSD, ViiV, and Janssen-Cilag. The other authors do not have any conflicts of interest.

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