



LTBI treatment in subjects with autoimmune diseases and T-cell interferon-gamma responses

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**CENTRAL SERVICE TO EVALUATE THE INFECTIOUS DISEASES RISK IN
PATIENTS CANDIDATES TO TNF-ALPHA BLOCKERS**

SAFETY TEAM

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SCREENING FOR LATENT TUBERCULOSIS INFECTION

- Collection clinical and pharmacological history
- Identification of TB risk factors of exposure, infection and progression
- Tuberculin skin test (TST) (5 UI PPD – Biocine, Chiron, Italy)
- QuantiFERON-TB Gold In Tube (Cellestis, Australia)
- Chest x-ray

QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases

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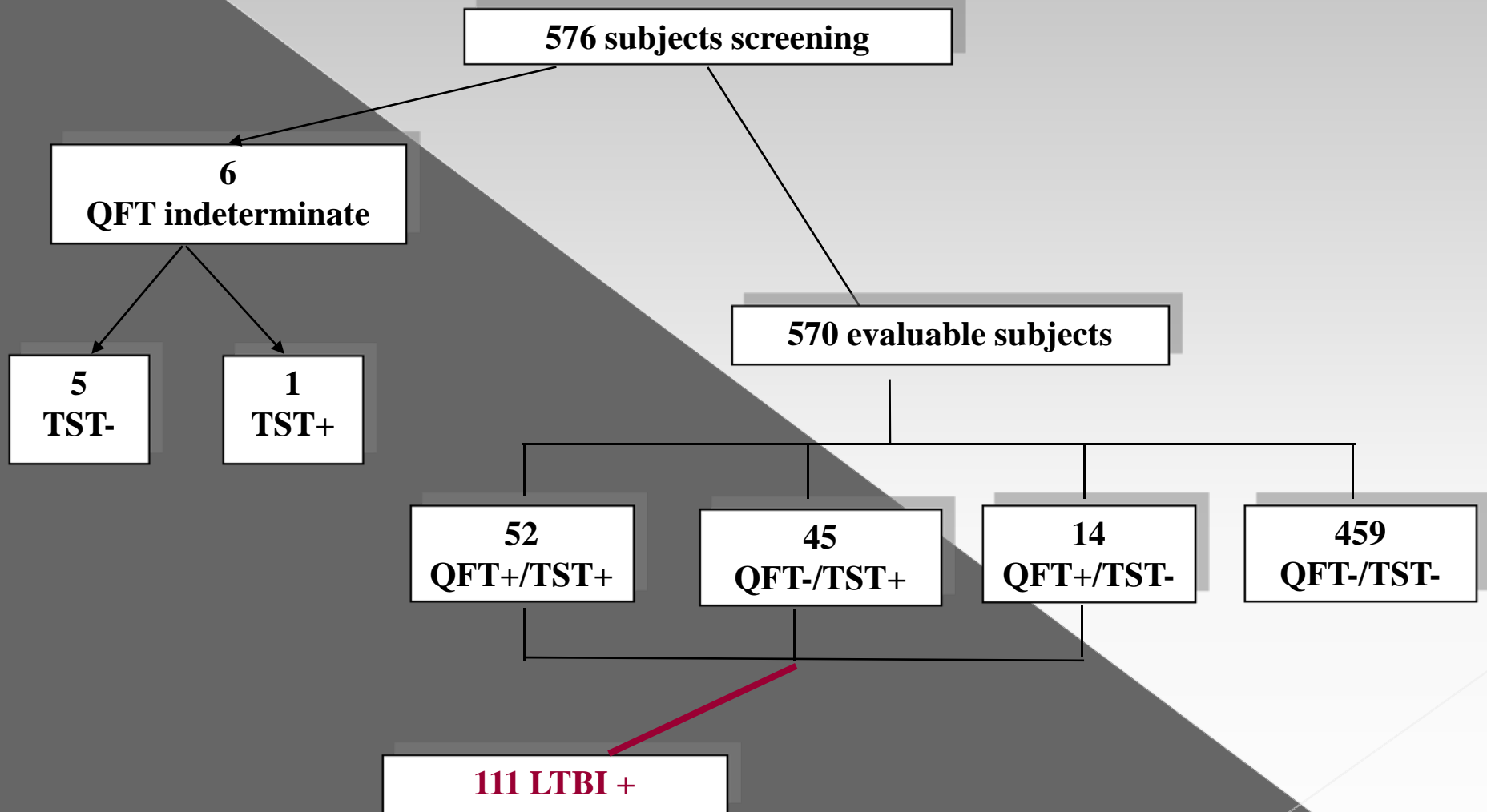
Subjects screened for LTBI: 393

Test considered	Estimated rate % (95% CI)
Only TST positive	18.8 (14.9–22.7)
Only QFT-GIT positive	13.2 (9.8–16.5)
QFT-GIT and TST positive	9.9 (6.9–12.8)
QFT-GIT among TST positive	9.9 (6.9–12.8)
At least one positive test	22.1 (18–26.2)

A strategy of simultaneous TST and QFT testing in populations with a low prevalence of BCG vaccination should maximise the sensitivity for LTBI diagnosis

SCREENED POPULATION

MAY 2006 – DECEMBER 2008



AIM OF STUDY

To assess the effect of LTBI treatment on T-cell IFN- γ response to *Mycobacterium tuberculosis*-specific antigens in subjects with autoimmune diseases



METHODS

We tested the subjects by QFT-GIT at baseline (T0), at the end of Latent TB treatment (T1) and three-six months after the end of treatment (EOT) (T2).

Latent TB therapy : rifampin+isoniazid for three months

STUDIED POPULATION

15 No treated

111 LTBI +

96 treated

79
T0-T1

48
T0-T1-T2
8 s after EOT
(T0-T1-T2)

35
QFT
+/TST +

19
QFT
+/TST +

11
QFT
+/TST -

9
QFT
+/TST -

33
QFT -/TST
+

20
QFT -/TST
+

STUDIED POPULATION

	LTBI	T0-T1 LTBI	T0-T1-T2 LTBI
➤ Number of subjects	111	79	48
➤ Female	55.8%	59.5%	58.3%
➤ BCG vaccinated	10 (9%)	9(11.4%)	5(10.4%)
➤ Birth/residence			
> Low prevalence of TB	100 (90.1%)	70(88.6%)	44(91.7%)
> High prevalence of TB	11 (9.9%)	9(11.4%)	4(8.3%)
➤ Median age	56 years	54 years	54 years
➤ Diagnosis			
> Rheumatoid arthritis	55 (49.6%)	41(51.9%)	23(47.9%)
> Psoriatic arthritis	29 (26%)	20(25.3%)	16(33.3%)
> Ankilosing spondylitis	16 (14.4%)	13(16.5%)	6(12.5%)
> Others	11 (10%)	5(6%)	3(6.3%)
➤ Therapy			
> No therapy	24(21.6%)	17(21.5%)	9(18.8%)
> Therapy including TNFa inhibitors	17(15.3%)	11(13.9%)	5(10.4%)
> Therapy DMARDs and/or Steroids	70(63.1%)	51(64.6%)	34(70.8%)

QFT conversion

baseline IFN- γ < 0.35 IU/ml and follow-up IFN- γ \geq 0.35 IU/ml
(i.e., a negative to positive change, as recommended by the CDC)

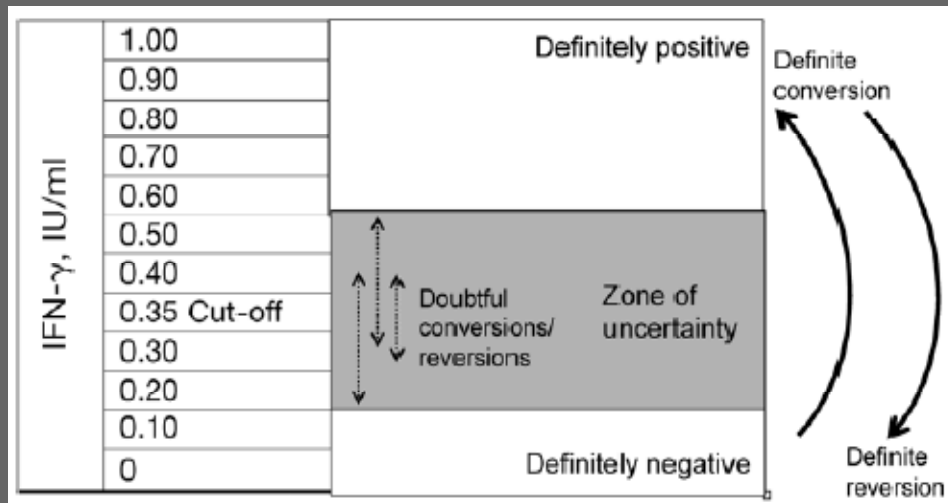
QFT reversion

baseline IFN- γ \geq 0.35 and follow-up IFN- γ < 0.35 IU/ml

T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India

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Uncertainty zone
0.20-0.50 IU/ml



True conversion/reversion

QFT results pre- and post-LTBI therapy

using two different cut-off criteria for QFT result interpretation

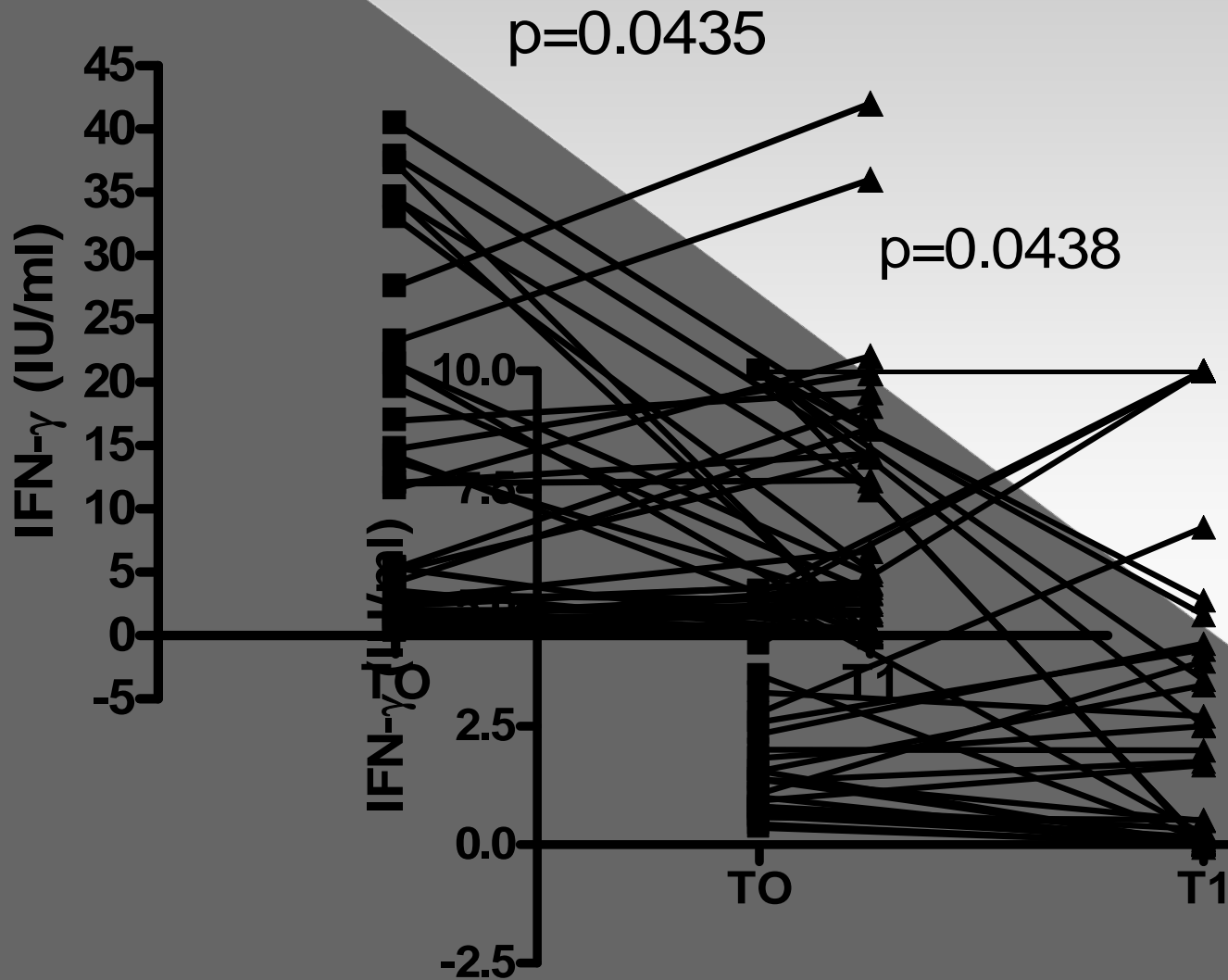
QFT	Criteria	Number at baseline	n (%)	95% CI
Conversions T0 IFN- γ < 0.35 IU/ml, T1 IFN- γ \geq 0.35 IU/ml		33	6 (18)	7-35
Negative-to-negative T0 IFN- γ < 0.35 IU/ml, T1 IFN- γ < 0.35 IU/ml		33	27 (82)	65-93
Reversions T0 IFN- γ \geq 0.35 IU/ml, T1 IFN- γ < 0.35 IU/ml		46	17 (37)	23-52
Positive-to-positive T0 IFN- γ \geq 0.35 IU/ml, T1 IFN- γ \geq 0.35 IU/ml		46	29 (63)	48-77

QFT results pre- and post-LTBI therapy

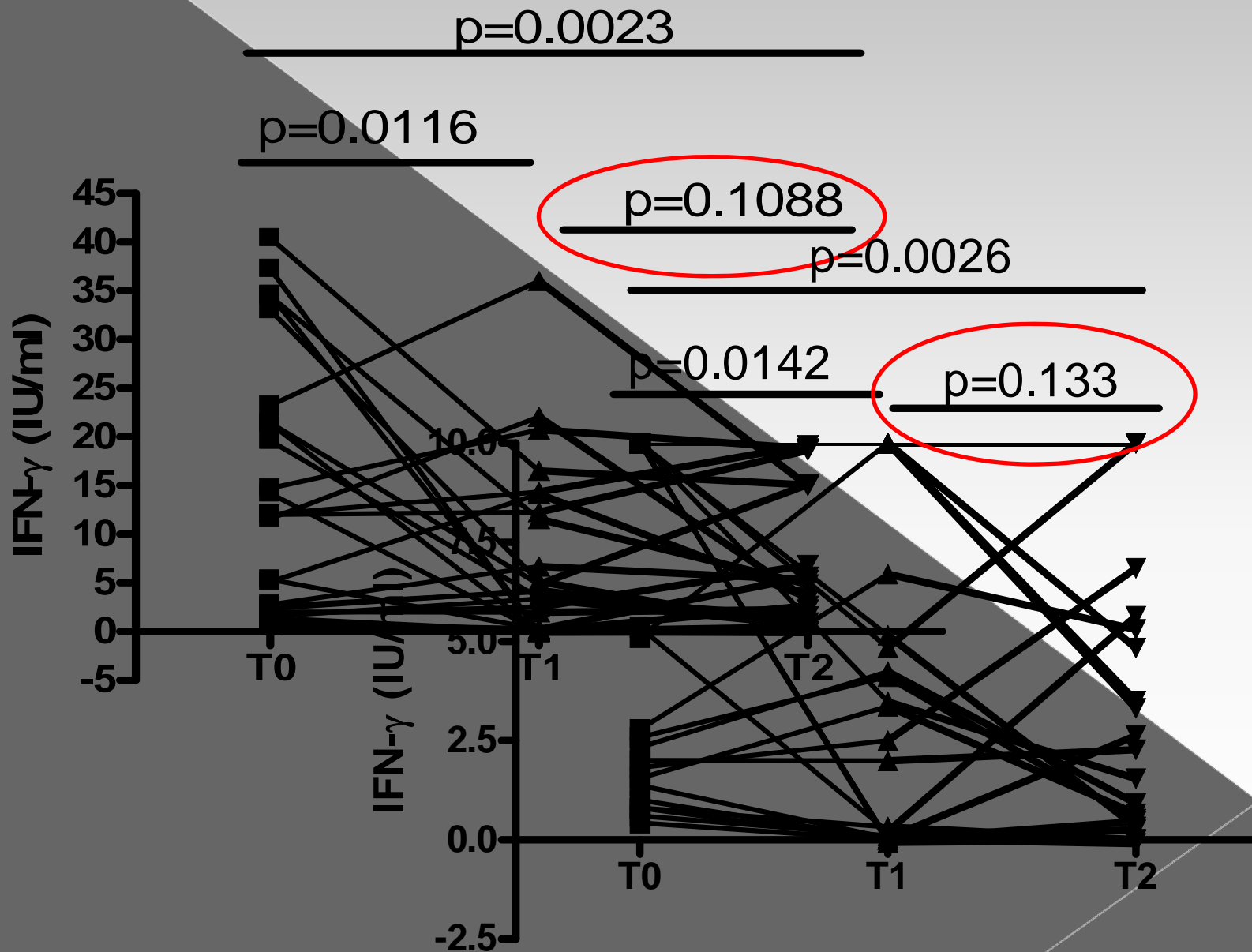
using two different cut-off criteria for QFT result interpretation

QFT	Criteria	Number at baseline	n (%)	95% CI
Conversions				
	T0 IFN- γ < 0.35 IU/ml, T1 IFN- γ \geq 0.35 IU/ml	33	6 (18)	7-35
	T0 IFN-γ < 0.20 IU/ml, T1 IFN-γ > 0.50 IU/ml	27	3 (11)	2-29
Negative-to-negative				
	T0 IFN- γ < 0.35 IU/ml, T1 IFN- γ < 0.35 IU/ml	33	27 (82)	65-93
	T0 IFN-γ < 0.20 IU/ml, T1 IFN-γ < 0.20 IU/ml	27	24 (89)	71-98
Reversions				
	T0 IFN- γ \geq 0.35 IU/ml, T1 IFN- γ < 0.35 IU/ml	46	17 (37)	23-52
	T0 IFN-γ > 0.50 IU/ml, T1 IFN-γ < 0.20 IU/ml	44	13 (30)	17-45
Positive-to-positive				
	T0 IFN- γ \geq 0.35 IU/ml, T1 IFN- γ \geq 0.35 IU/ml	46	29 (63)	48-77
	T0 IFN-γ > 0.50 IU/ml, T1 IFN-γ > 0.50 IU/ml	44	28 (64)	48-78
Doubtful				
	T0 e/o T1 IFN- γ 0.20-0.50 IU/ml	79	11 (14)	7-24

**QUANTITATIVE TREND T0-T1
(46 QFT POSITIVE AT T0)**



QUANTITATIVE TREND T0-T1-T2 (28 QFT POSITIVE AT T0)



Rate of reversion at T1 (EOT) by baseline IFN- γ value among 46 subjects with QFT-positive result at T0

T0 IFN- γ response IU/ml	Retested n	TST + at T0 n(%)	QFT reversions n (%)
0.35-0.69	4	3 (75)	3(75)
0.70-1.0	7	6 (86)	6(86)
1.01-3.0	11	8 (73)	2(18)
3.01-6.0	6	5 (83)	2(33)
6.01-10.0	18	13 (72)	4(22)
Total	46	35 (76)	17(37)

Baseline IFN- γ response, IU/ml	Retested n	TST-positive at baseline n (%)	Frequency of QFT reversions	Annual incidence of QFT reversions %	P value for trend in QFT reversion rates*
0.35-0.69	10	5 (50)	2	20.0	0.001
0.70-1.0	5	2 (40)	1	20.0	
1.01-3.0	23	15 (65)	4	17.4	
3.01-6.0	17	14 (82)	0	0	
6.01-10.0	54	49 (91)	0	0	
Total	109	85 (78)	7	6.4	

Pai et al.

Published articles on IGRA trend in LTBI treated subjects

First author	Country	IGRA	Studied population	Number of subjects	LTBI therapy	Trends of IGRA
Pai, 2006	India	QFT-GIT	Health care workers	10 cases	INH, 6 months	No change
Chee, 2006	Singapore	T-SPOT.TB	Close contacts	226 cases	INH, 6 months	Decrease
Ewer, 2006	UK	ELISpot	Contacts	38 cases 25 controls	RIF+INH, 3 months	Decrease
Wilkinson, 2006	UK	Elispot	Recent immigrants to the UK	16 cases 8 controls	RIF+INH, 3 months	No change
Goletti, 2006	Italy	RD1 proteins RD1 select.pept QFT-G	Contacts	35 cases 11 controls	INH, 6 months	Decrease
Higuchi, 2008	Japan	QFT-G	Contacts	28 cases 5 controls	INH, 6 months	Decrease
Pollock, 2009	Israel	QFT-G	Health care workers	5 cases 4 controls	INH, 9 months	No change

CONCLUSIONS

- ▶ First results on the effect of LTBI treatment on QFT response in subjects with rheumatic diseases
- ▶ Relevant rate of reversion (30-37%, depending of reversion criteria)
- ▶ Significant decreasing trend of QFT response, also in 25% of subjects with elevated (>3 IU/ml) IFN- γ response at baseline
- ▶ No significant changes in the response in the follow-up period after the end of treatment

Measuring T-cell responses to M. tuberculosis-specific antigens may reflect the effect of LTBI treatment on reduction of antigen load