
T-cell IFN-gamma responses in patients treated for latent TB infection

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Background

- For LTBI therapy, the most widely used treatment is Isoniazid (INH) for 9 months; other regimens are available (e.g. 4 months of Rifampin)
 - A major problem with evaluating LTBI therapies is that there is no biomarker to assess efficacy of treatments; therefore researchers have to rely on clinical outcomes (i.e. development of active TB during follow-up)
 - One of the reasons why RCTs require long term follow-up of a large sample size (expensive - \$\$\$\$)
 - IGRAs are promising for diagnosing LTBI, but is there potential for IGRAs as a bio-marker of treatment success in LTBI?
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IGRA studies in persons treated for LTBI

Research

Open Access

Persistently elevated T cell interferon- γ responses after treatment for latent tuberculosis infection among health care workers in India: a preliminary report

Madhukar Pai^{*1,2,3}, Rajnish Joshi^{1,2}, Sandeep Dogra², Deepak K Mendiratta², Pratibha Narang², Keertan Dheda⁴ and Shriprakash Kalantri²

INH for 6 months in Indian HCWs did not lower IFN-g responses (Repeat exposures?)

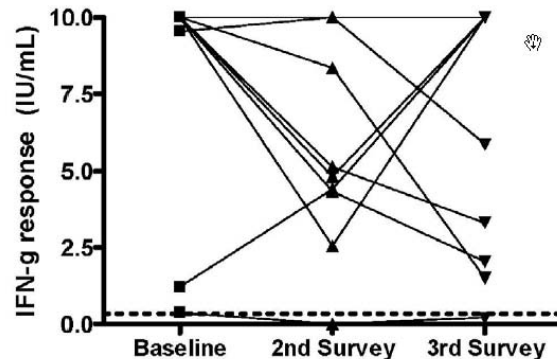


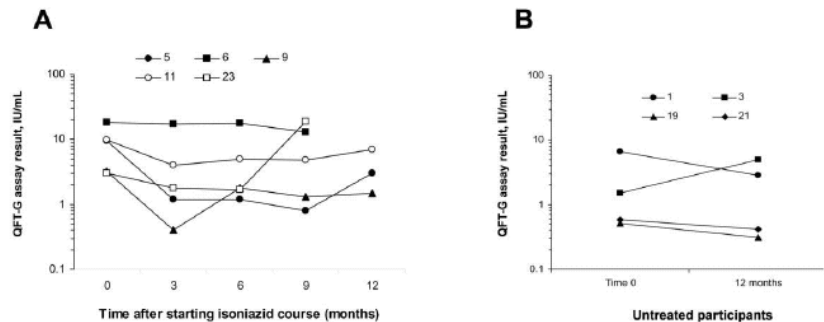
Figure 1 Pre-treatment and post-treatment interferon- γ responses in nursing students treated with isoniazid preventive therapy for 6 months (N = 10). Baseline interferon- γ (IFN- γ) levels were measured using the QuantiFERON-TB Gold In Tube assay at the time of latent tuberculosis infection diagnosis (January/February 2004). The second measurement was made in January 2005, 4 months after isoniazid (INH) preventive therapy completion. The third measurement was made in July 2005, 10 months after INH treatment completion. All subjects were positive by the QuantiFERON-TB Gold In Tube assay and tuberculin skin test at baseline. The QuantiFERON-TB Gold diagnostic cut-point of 0.35 IU/mL is shown as a horizontal dotted line. IFN- γ levels >10.0 IU/mL have been shown as 10 IU/mL

Evaluation of the Effect of Treatment of Latent Tuberculosis Infection on QuantiFERON-TB Gold Assay Results

Nira R. Pollock, MD, PhD; Suely S. Kashino, PhD; Danielle R. Napolitano, PhD; Alex Sloutsky, PhD; Swati Joshi, PhD; Jasmine Guillet, MPH; Michael Wong, MD; Edward Nardell, MD; Antonio Campos-Neto, MD, PhD

To evaluate the utility of the QuantiFERON-TB Gold assay for monitoring latent tuberculosis treatment efficacy, the assay was performed serially for healthcare workers receiving isoniazid therapy. After 9 months of isoniazid therapy, all of these healthcare workers remained QuantiFERON-TB Gold positive, and cellular proliferation assays revealed persistently strong purified protein derivative responses. These results do not support the use of the QuantiFERON-TB Gold assay to monitor therapy.

Infect Control Hosp Epidemiol 2009; 30:392-395



HCWs in the US remained QFT positive after 9 months of INH

TECHNICAL REPORT

Interferon- γ responses after isoniazid chemotherapy for latent tuberculosisKAZUE HIGUCHI,¹ NOBUYUKI HARADA¹ AND TORU MORI²¹Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, and ²Leprosy Research Center, National Institute of Infectious Diseases, Tokyo, Japan

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K Higuchi et al.

34 patients completed 6 months INH, post treatment 25% were negative and others showed a statistically significant decline, 18 months post treatment no additional decline was seen

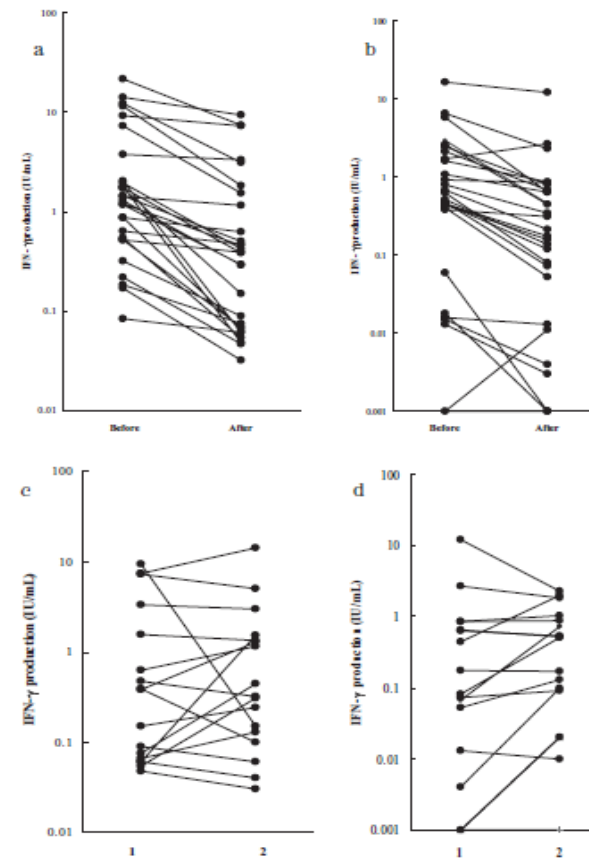
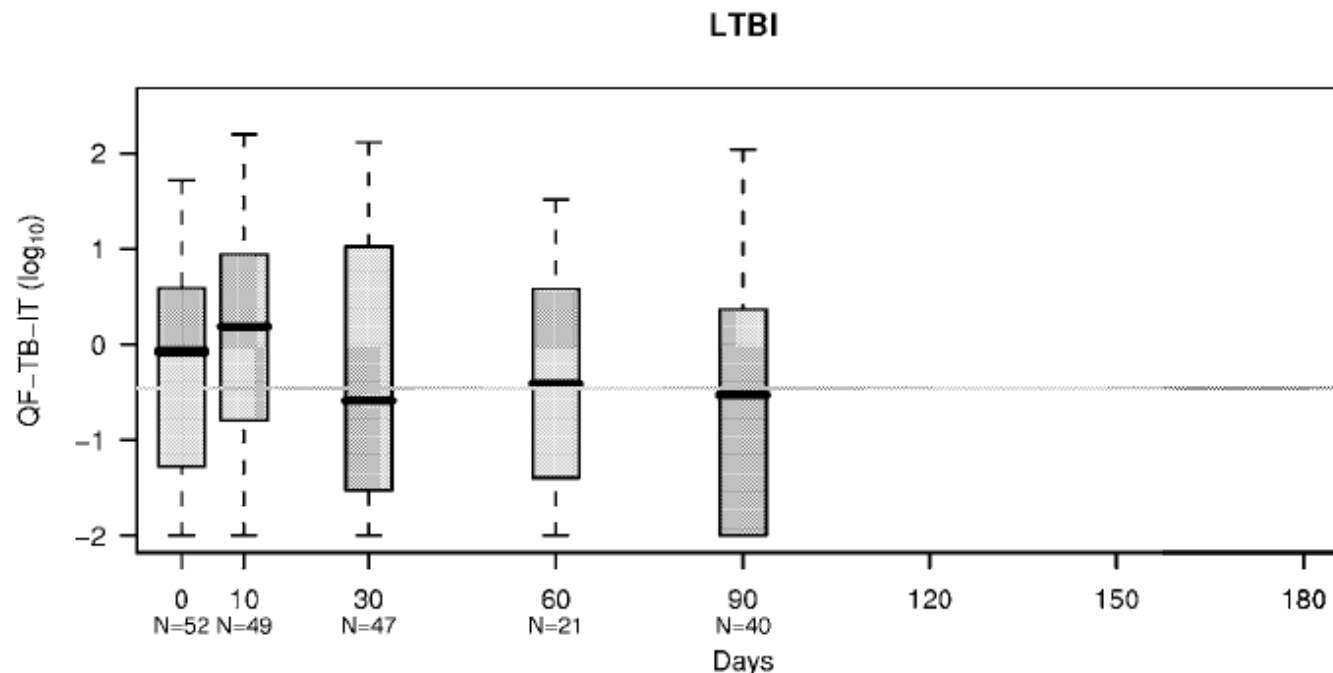


Figure 1 Interferon (IFN)- γ responses before and after chemotherapy. IFN- γ levels measured before and immediately after chemotherapy by Quantiferon-TB Gold (QFT-G) for early secretory antigenic target (ESAT)-6 (a) and culture filtrate protein (CFP)-10 (b) are plotted for each individual. IFN- γ levels measured immediately after chemotherapy (data point 1) and 18 months after chemotherapy (data point 2) by QFT-G for ESAT-6 (c) and CFP-10 (d) are plotted for each individual.

Temporal Dynamics of Interferon Gamma Responses in Children Evaluated for Tuberculosis

Jean-Louis Herrmann^{1*}, Marie Belloy², Raphael Porcher³, Nancy Simonney¹, Rola Aboutaam⁴, Muriel Lebourgeois⁴, Joel Gaudelus⁵, Laure De LosAngeles⁶, Katarina Chadelat⁷, Pierre Scheinmann⁴, Nicole Beydon⁶, Brigitte Fauroux⁷, Martine Bingen², Mustapha Terki², Dominique Barraud², Philippe Cruaud⁵, Catherine Offredo³, Agnes Ferroni³, Patrick Berche³, Didier Moissenet⁶, Hoang Vuthien⁶, Catherine Doit⁷, Edouard Bingen⁷, Philippe Henri Lagrange^{1*}



Children diagnosed with LTBI received chemoprophylaxis for a period of 3 months (Isoniazid+Rifampicin) and were followed up at day 0 (day of inclusion), 10, 30, 60 and 90 (end of treatment). QF-TB-IT values were significantly lower at day 90 as compared to day 0

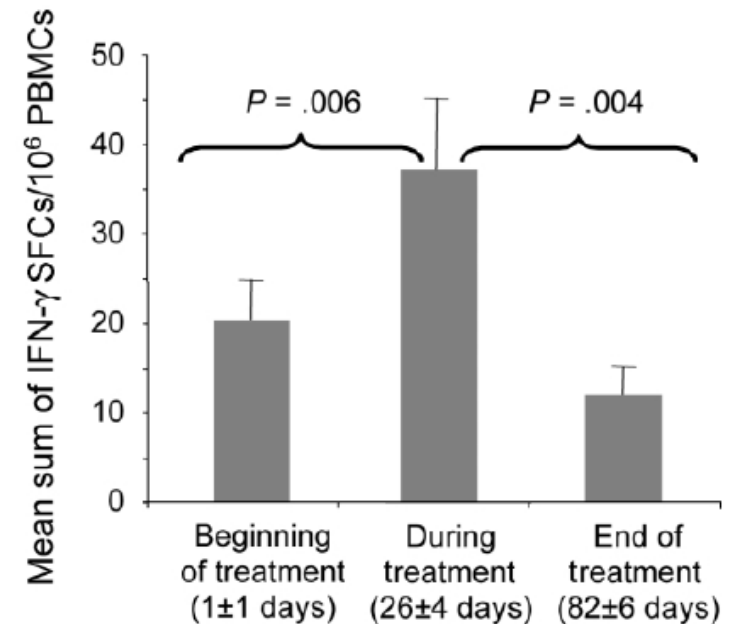
Effect of Treatment of Latent Tuberculosis Infection on the T Cell Response to *Mycobacterium tuberculosis* Antigens

Katalin A. Wilkinson,^{1,4} Onn M. Kon,² Sandra M. Newton,¹ Graeme Meintjes,^{1,4} Robert N. Davidson,³ Geoffrey Pasvol,^{1,3} and Robert J. Wilkinson^{1,3,4}

¹Wellcome Trust Center for Research in Clinical Tropical Medicine, Division of Medicine, Imperial College London, Wright Fleming Institute, and ²Chest and Allergy Clinic, St. Mary's Hospital, London, and ³Tuberculosis Clinic, Department of Infection and Tropical Medicine, Northwick Park Hospital, Harrow, United Kingdom; ⁴Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Most cases of latent tuberculosis infection (LTBI) do not cause symptoms during the lifetime of the infected person. Longitudinal analysis of the immune response of healthy *Mycobacterium tuberculosis*-infected people might, therefore, give insight into the basis of protective immunity. In a longitudinal study, we documented the effect that treatment had on the T cell response to *M. tuberculosis* antigens in 33 healthy people with LTBI. Preventive treatment of LTBI resulted in a 1.8-fold average increase in the numbers of interferon (IFN)- γ -producing T cells within 26 ± 4 days ($P = .006$), followed by a decrease by the end of the treatment period (82 ± 6 days; $P = .004$). There was no significant overall change in the T cell response to any antigen in a control group ($n = 8$) of patients who elected radiological follow-up. Using live *M. tuberculosis* strain H37Rv as a stimulant in an enzyme-linked immunospot assay in sensitized individuals, we showed that isoniazid, but not rifampin, led to an increase in the number of IFN- γ -producing cells. These results suggest that the integrity of the bacterial cell wall is important for *M. tuberculosis* in avoiding immune recognition by T cells and favor a dynamic model of LTBI.

Wilkinson et al. JID 2006



Among 33 healthy subjects being treated for LTBI, an initial increase in IFN-gamma was observed followed by a subsequent decrease at the end of treatment. Also found differential effects of INH and RIF.

In summary

- Available studies are a mixed bag
 - There is no consistent pattern on kinetics of T-cell IFN-g responses in persons treated for LTBI
 - Regression to the mean is not well accounted
 - No data on whether INH vs RIF will have a differential effect on T-cell responses
 - No long-term data on correlation between biomarkers such as IFN-g and clinical outcomes
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Objective

- * To make use of a completed Phase II RCT and evaluate the QuantiFERON TB Gold In-Tube (QFT-GIT) responses in patients treated for LTBI and to explore potential associations between QFT-GIT positivity and:
 - * type of treatment (4 mo RIF v. 9 mo of INH)
 - * treatment completion
 - * patient demographics

Adverse Events with 4 Months of Rifampin Therapy or 9 Months of Isoniazid Therapy for Latent Tuberculosis Infection

A Randomized Trial

Dick Menzies, MD, MSc; Richard Long, MD; Anete Trajman, MD, PhD; Marie-Josée Dion, MSc; Jae Yang, MD; Hamdan Al Jahdali, MD; Ziad Memish, MD; Kamran Khan, MD, MPH; Michael Gardam, MD; Vernon Hoepfner, MD; Andrea Benedetti, PhD; and Kevin Schwartzman, MD, MPH

Background: Treatment of latent tuberculosis infection with isoniazid for 9 months is complicated by poor patient adherence and the need for close follow-up of side effects, especially hepatotoxicity. Shorter and safer regimens are needed.

Objective: To compare the frequency of adverse events and treatment completion in 2 treatment regimens for latent tuberculosis infection.

Design: Multicenter, randomized, open-label trial.

Setting: Tuberculosis clinics located in university hospitals in Canada, Brazil, and Saudi Arabia.

Patients: 847 patients without a contraindication for rifampin and requiring treatment for latent tuberculosis infection.

Intervention: Four months of daily rifampin therapy or 9 months of daily isoniazid therapy.

Measurements: Grade 3 to 4 drug-related adverse events resulting in drug discontinuation (primary outcome), and on-time treatment completion, grade 1 to 2 drug-related adverse events, and changes in liver enzymes and hematologic variables (secondary outcomes).

Results: Seventeen of 422 participants who started isoniazid therapy developed grade 3 to 4 adverse events compared with 7 of

418 who started rifampin therapy (risk difference [rifampin minus isoniazid], -2.3% [95% CI, -5% to -0.1%]; $P = 0.040$). Grade 3 or 4 hepatitis occurred in 16 of 422 isoniazid recipients compared with 3 of 418 rifampin recipients (risk difference, -3.1% [CI, -5% to -1%]; $P = 0.003$). Grade 1 or 2 adverse events attributed to study drugs occurred with similar frequency. Asymptomatic reduction in platelet and leukocyte counts were more frequent in rifampin recipients. More patients completed rifampin treatment (78%) than isoniazid treatment (60%) (difference, 18% [CI, 12% to 24%]; $P < 0.001$).

Limitation: The study did not measure efficacy, and the open-label design may increase the chance of bias in ascertainment of adverse events.

Conclusion: Treatment of latent tuberculosis with 4 months of rifampin leads to fewer serious adverse events and better adherence than 9 months of isoniazid. These findings justify a large-scale trial to compare the efficacy of rifampin with that of isoniazid.

Ann Intern Med. 2008;149:689-697.

For author affiliations, see end of text.

ClinicalTrials.gov registration number: NCT00170209.

www.annals.org

Phase II RCT Completed

- ❑ Mix of low, moderate and high risk categories
 - ❑ Two treatments of varying duration [RIF vs INH]
 - ❑ Varying levels of treatment completion
 - ❑ Varying time periods since completion of preventive therapy
 - ❑ Unlikely to have been re-exposed to TB
 - ❑ Already under regular follow-up
 - ❑ We used this opportunity to evaluate antigen-specific T-cell responses among persons treated for LTBI
-

INH v RIF:

Mechanism of Action

Isoniazid is bactericidal to rapidly-dividing mycobacteria but is bacteriostatic if the mycobacterium is slow-growing.

- Works to inhibit the synthesis of mycolic acid required for the mycobacterial cell wall.

Rifampin may be bacteriostatic or bactericidal, depending on the concentration of the drug and the relative susceptibility of the organism. Rifampin is most effective when cell division is occurring.

- Rifampin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing transcription to RNA and subsequent translation to proteins.
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Methods: A pilot project

- * Approached patients from one site (Montreal Chest Institute) participating in the RCT assessing safety of 4RIF versus 9INH for LTBI
- * Patients were recruited between Dec 2008-Dec 2009 (n=50)
- * All patients had completed or stopped treatment at least two years prior to be contacted
- * Invited to return to complete a new informed consent and blood draw
- * QuantiFERON-TB Gold In-Tube, cut point IFN-g \geq .35 IU/ml
- * Values over 10 IU/ml cannot be precisely measured and have been truncated at 10

Results: Demo- graphics

Characteristic	N=50 (%)
Age (Median, IQR)	28.7 yrs (21.4 -37.6 yrs)
Female	25 (50%)
INH	28/50 (56%)
Compliant with treatment	24/28 (86%)
Noncompliant	1/28 (4%)
Drop Out	1/28 (4%)
Serious Adverse Events	2/28 (7%)
RIF	22/50 (44%)
Compliant with treatment	21/22 (95%)
Noncompliant	0
Drop Out	1/22 (5%)
Serious Adverse Events	0
Started Treatment (Range)	December 2004 - January 2007

Results

QFT-G-IT Result	Total n=50	Compliant n=41	INH (compliant) n=24	RIF (compliant) n=21	Noncompliant n=1	Drop Out n=2	Serious Adverse Events n=2
Positive	18 (36%)	17 (38%)	11 (46%)	6 (29%)	1 (100%)	-	-
Negative	31 (62%)	27 (60%)	13 (54%)	14 (67%)	-	2 (100%)	2 (100%)
Indeterminate	1 (2%)	1 (2%)	-	1 (5%)	-	-	-
Mean absolute IFN-g: IU/mL (Range)	2.1 (0-9.96)	2.1 (0.9.96)	2.7 (0-9.96)	1.4 (0-9,92)	9.35	0.09 (0-.18)	0.1 (0-.2)

*p value comparing INH compliers with RIF compliers = 0.24

Figure 1. Absolute Interferon gamma responses by varying levels of compliance

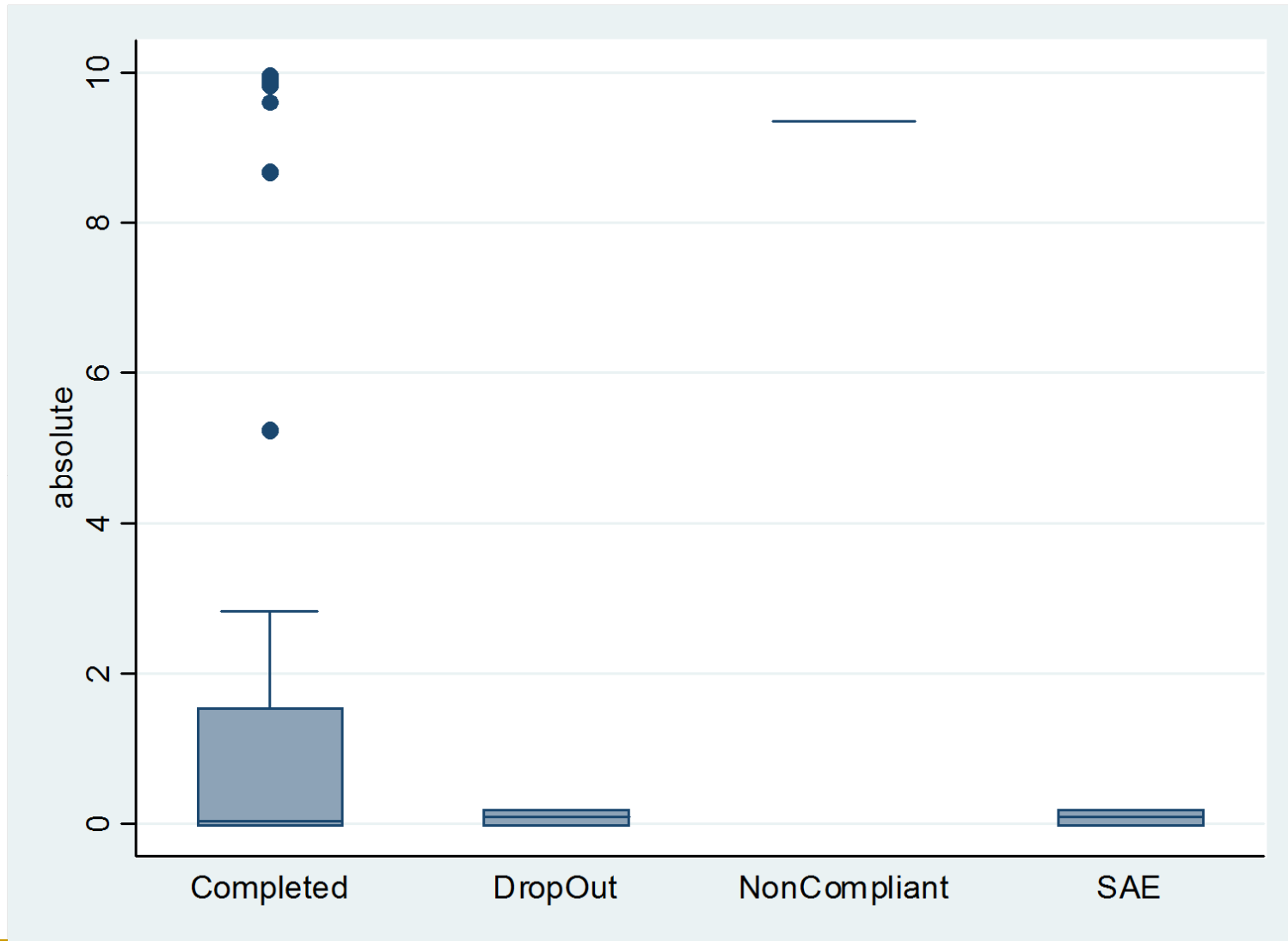


Figure 2. Absolute Interferon gamma responses among compliers on 4RIF and 9INH

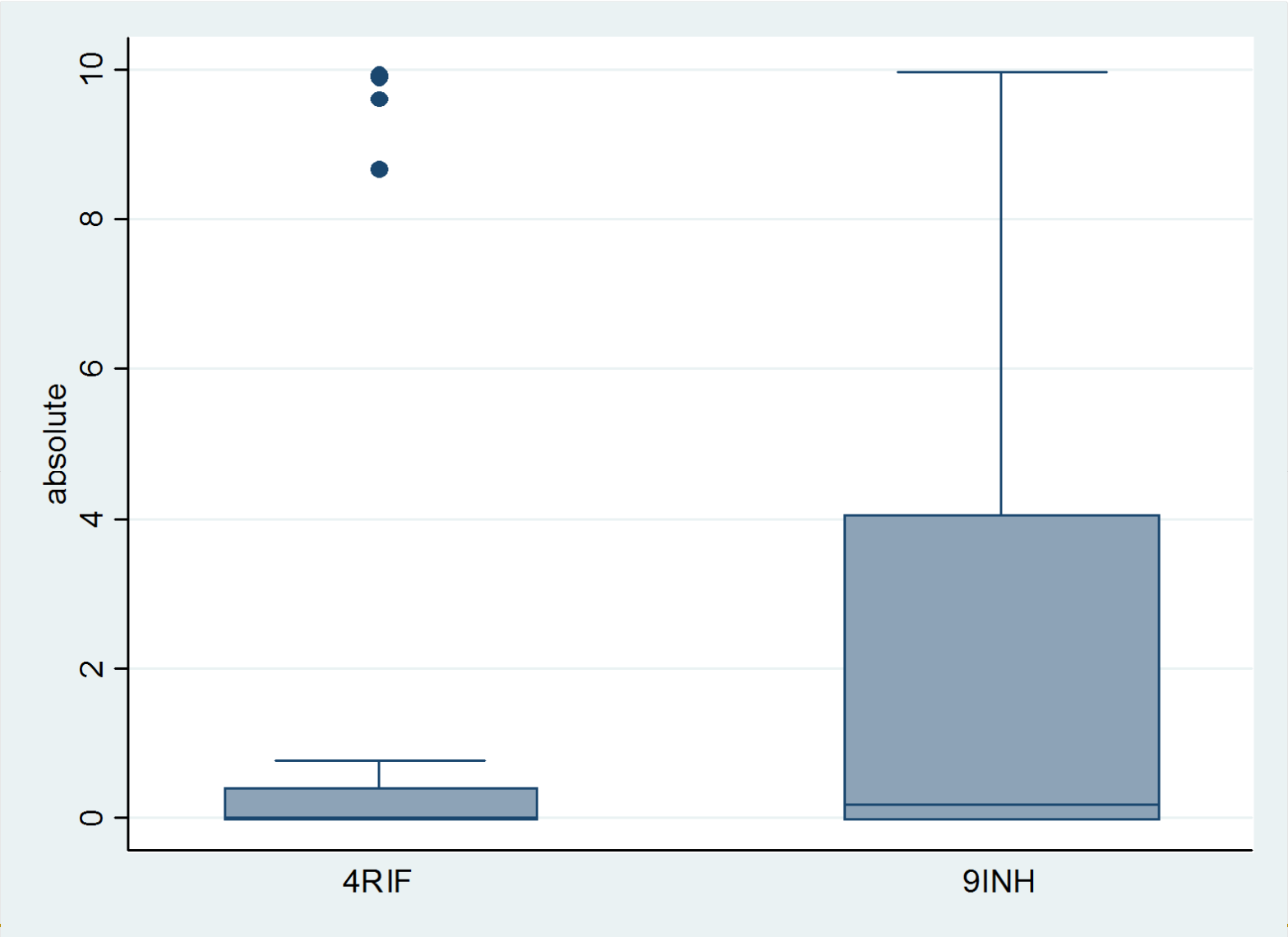


Figure 3. Absolute Interferon-gamma at different points post treatment initiation

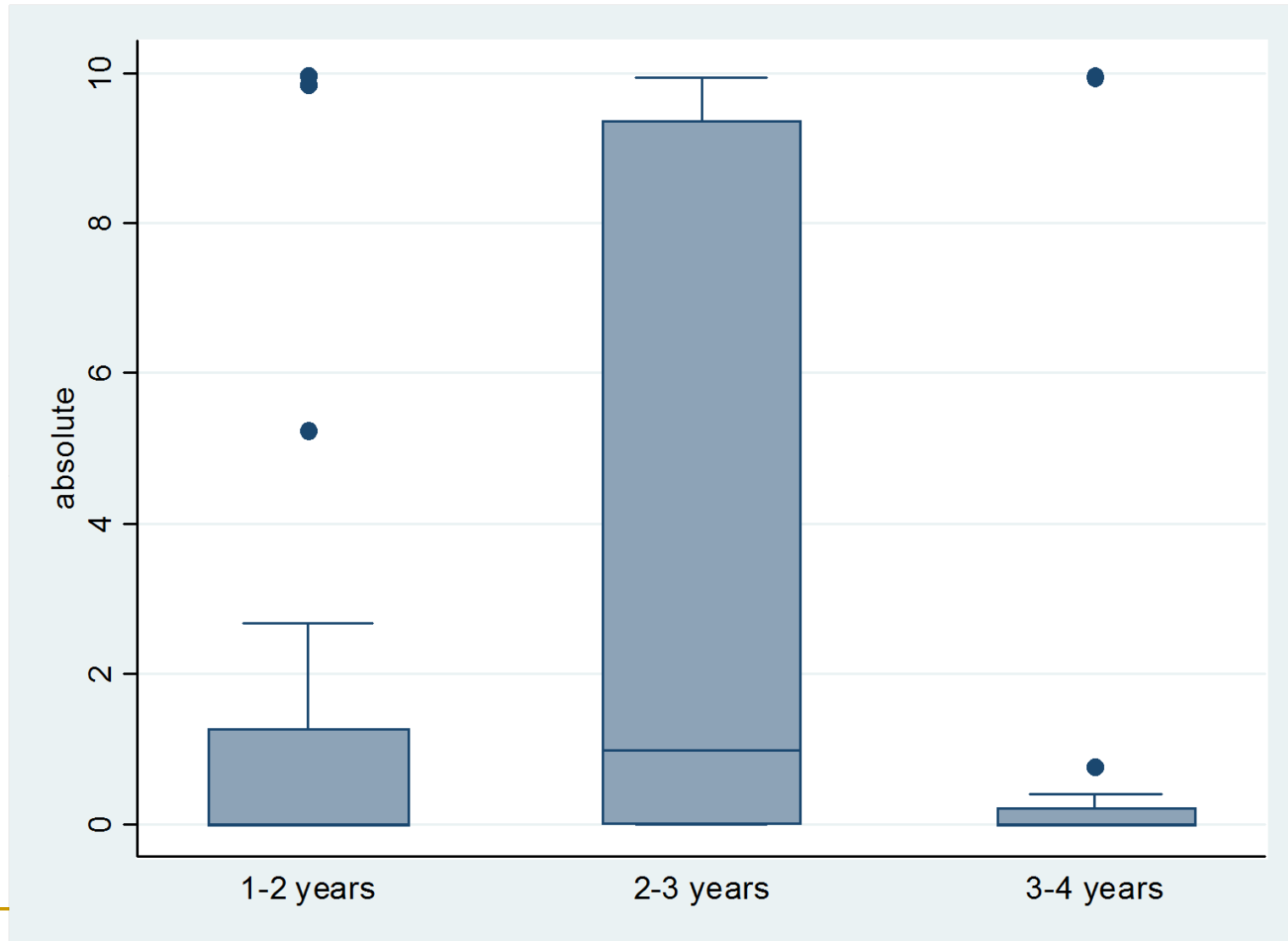
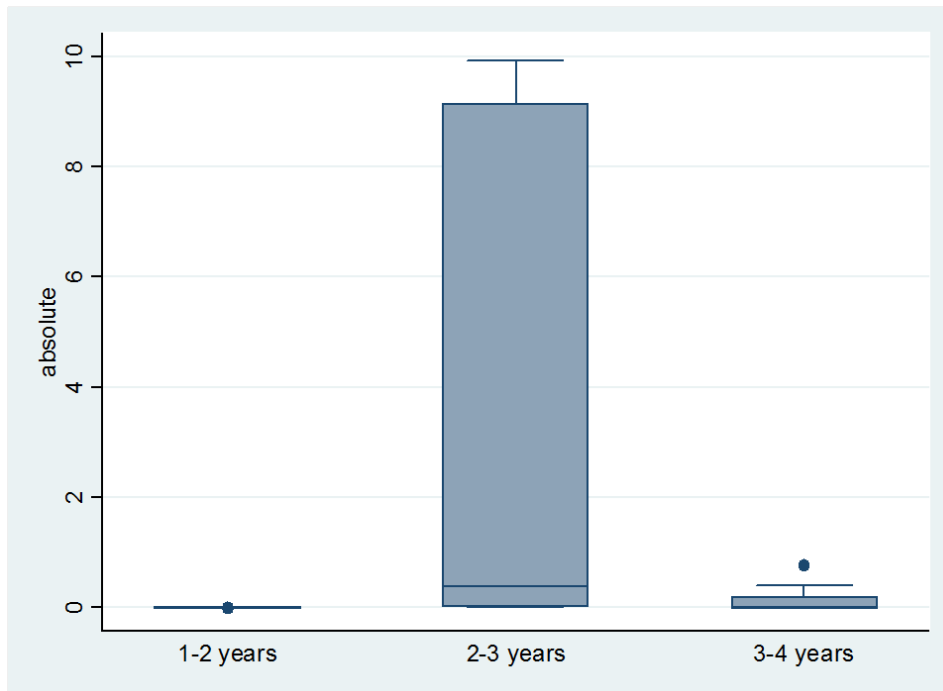
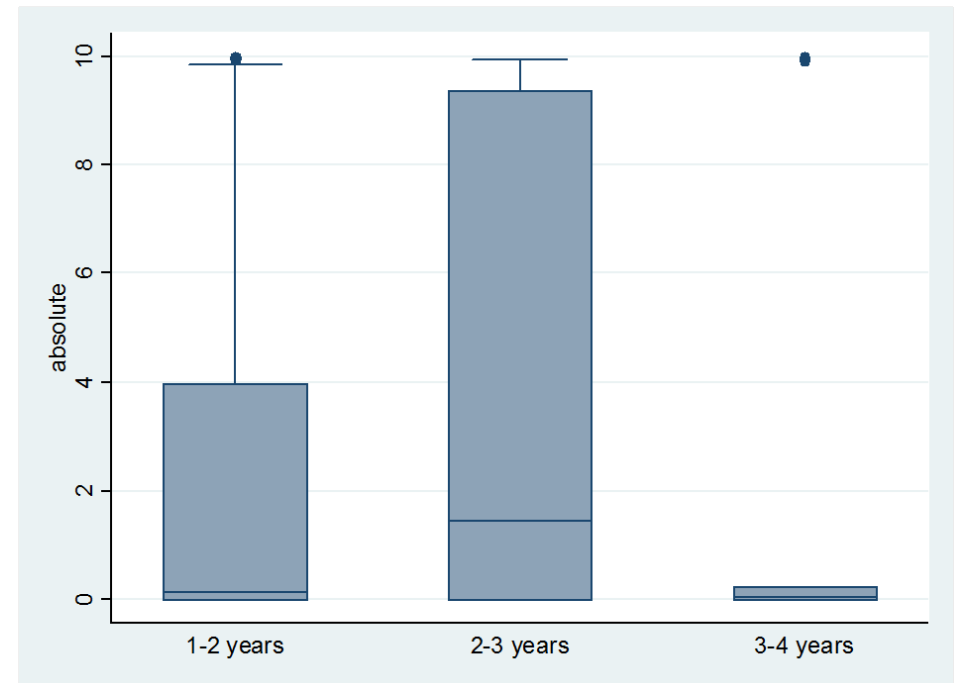


Figure 4. Absolute Interferon-gamma among those taking 9 months INH and 4 months RIF post treatment initiation

4 MONTHS RIF



9 MONTHS INH



Conclusions

- * QFT results are often positive even years after LTBI treatment completion
 - * However, tendency towards lower IFN-gamma responses in individuals treated with RIF compared with INH, particularly in those 1-2 years post treatment completion
 - * But numbers are small, and will need confirmation in larger trials with baseline QFT data
 - * If RIF proves to be more effective at killing latent bacteria, this may lead to a reduced IFN-gamma response, will need a larger trial to investigate.
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Limitations

- * Pilot study - small numbers
 - * No baseline data or longitudinal data QFT results
 - * No control group of untreated patients
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Next steps...

- New multi-national RCT investigating efficacy of 4RIF v 9INH just funded by the Canadian Institutes of Health Research
 - (PI: Dr Dick Menzies, Montreal Chest Institute, \$5 million CDN over 7 years, funding from the CIHR)
- Opportunity to collect *baseline* and longitudinal IGRA data and other biomarkers
- Opportunity to examine potential differences between treatment regimens, and time-points post treatment in a randomized setting

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