



Tuberculosis-associated Immune Restoration Disease is associated with increased PPD-specific T-cell responses detected by a whole blood interferon-gamma release assay

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Objective and methods



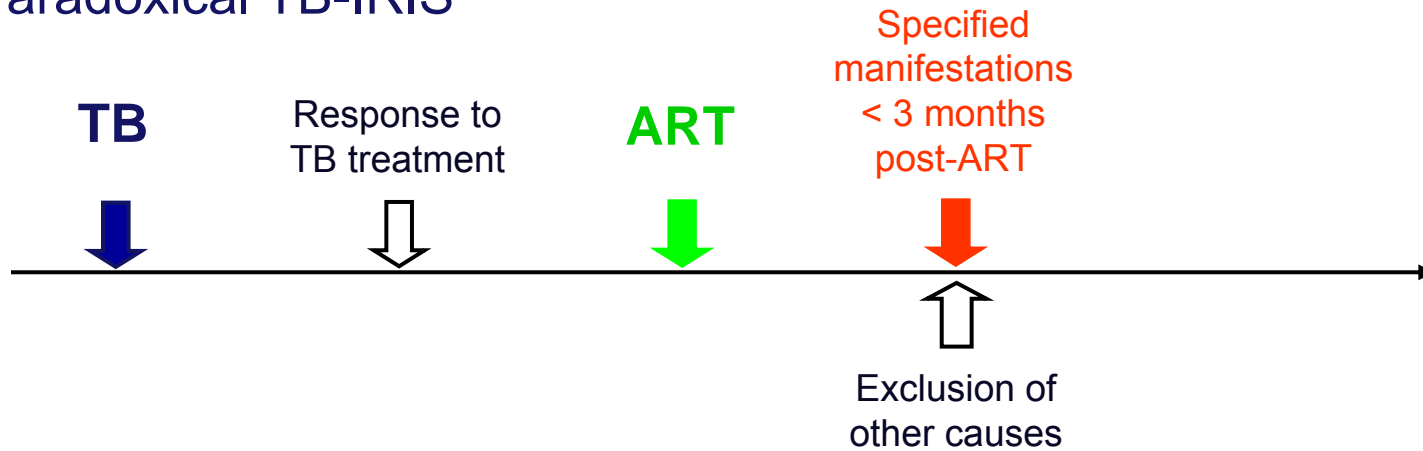
- To investigate immune reconstitution inflammatory syndrome (IRIS) in a setting with high incidence of tuberculosis
 - Incidence, characteristics and outcomes
 - Immunopathogenesis
 - Performance characteristics of simple tests
- Prospective single site cohort study at the NCHADS Social Health Clinic, an ambulatory clinic in Phnom Penh, Cambodia
- Anti-retroviral therapy naïve HIV positive adults followed for 24 weeks from time of ART initiation
- QuantiFERON-TB Gold In-Tube assays: RD1 antigens, PPD
- Skin tests: tuberculin, *M. avian* tuberculin, candida and trichophyton
- Analysis of all participants who had completed follow up by 31 December 2006

Methods

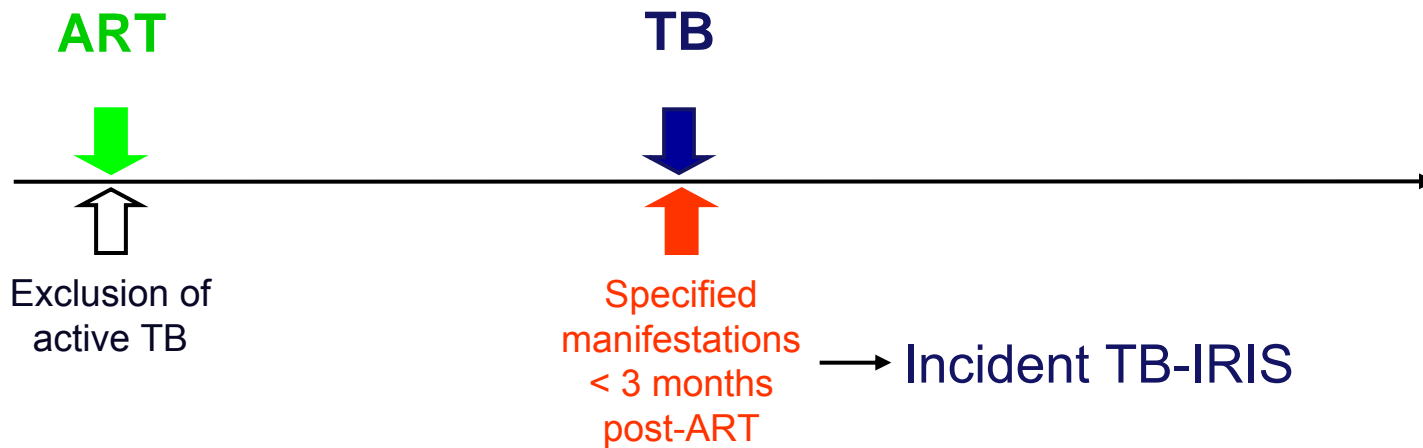


Case definitions

Paradoxical TB-IRIS



Incident TB on ART



Results



Characteristics of cohort pre-ART

Variable	Value	Number	Percent
Gender	Male	83	54
	Female	72	46
Age	Median (years)	33	
WHO stage	I/II	32	21
	III	88	57
	IV	35	23
CD4 count	Median (cells/mm ³)	61	
	0 – 49 (cells/mm ³)	68	44
	50 – 199 (cells/mm ³)	74	48
	≥ 200 (cells/mm ³)	13	8

Results



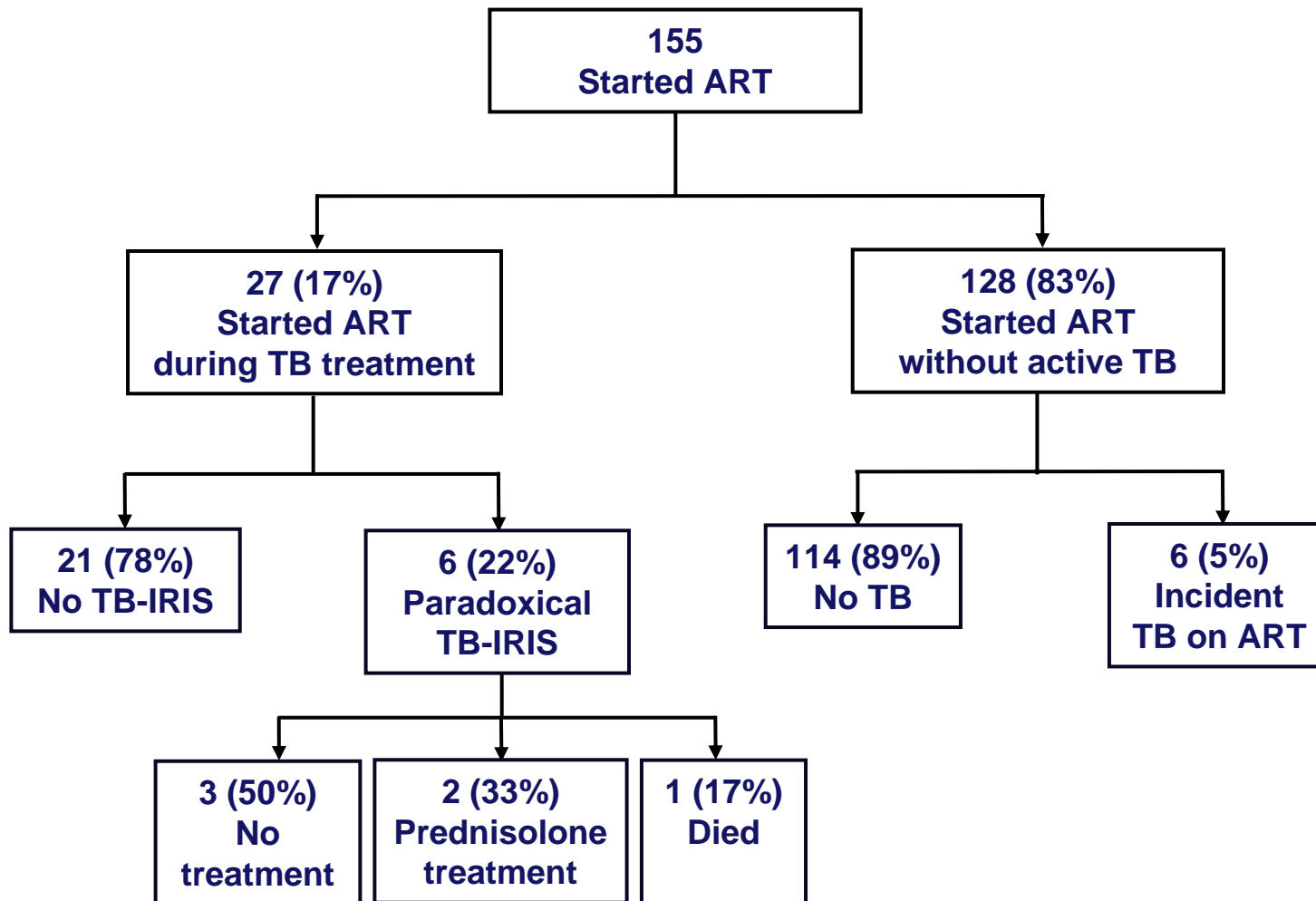
Tuberculosis

Variable	Value	Number	Percent
Timing	TB before ART	20	38
	ART start during TB	27	51
	TB start during ART	6	11
Site	Pulmonary smear positive	8	15
	smear negative	9	17
	smear unknown	10	19
	Extra-pulmonary	23	43
	PTB and EPTB	1	2
	Unknown	2	4
Treatment category	I	36	68
	II	8	15
	Unknown	9	17

Results



Tuberculosis associated IRIS



Results



Factors associated with paradoxical TB-IRIS

Variable	Total	IRIS (%)	Univariate		Multivariate		
			OR	P	AOR	95%CI	P
Gender							
Female	72	2 (2.7)					
Male	83	4 (4.8)	1.77	0.52	1.33	0.22 – 8.10	0.31
Age							
< 33 years	70	3 (4.3)					
≥ 33 years	85	3 (3.5)	0.82	0.81	1.11	0.20 – 6.18	0.90
WHO stage							
I/II/III	120	1 (0.8)					
IV	35	5 (14.3)	19.83	0.01	19.83	2.23 – 176.16	0.01
Baseline CD4 count							
≥ 50 cells/mm ³	87	2 (2.3)					
0 – 49 cells/mm ³	68	4 (5.9)	2.66	0.27	1.20	0.19 – 7.66	0.85
Time to ART start							
≥ 60 days	14	2 (14)					
< 60 days	13	4 (31)	2.67	0.31	1.83	0.23 – 14.45	0.57

Results



Factors associated with paradoxical TB-IRIS

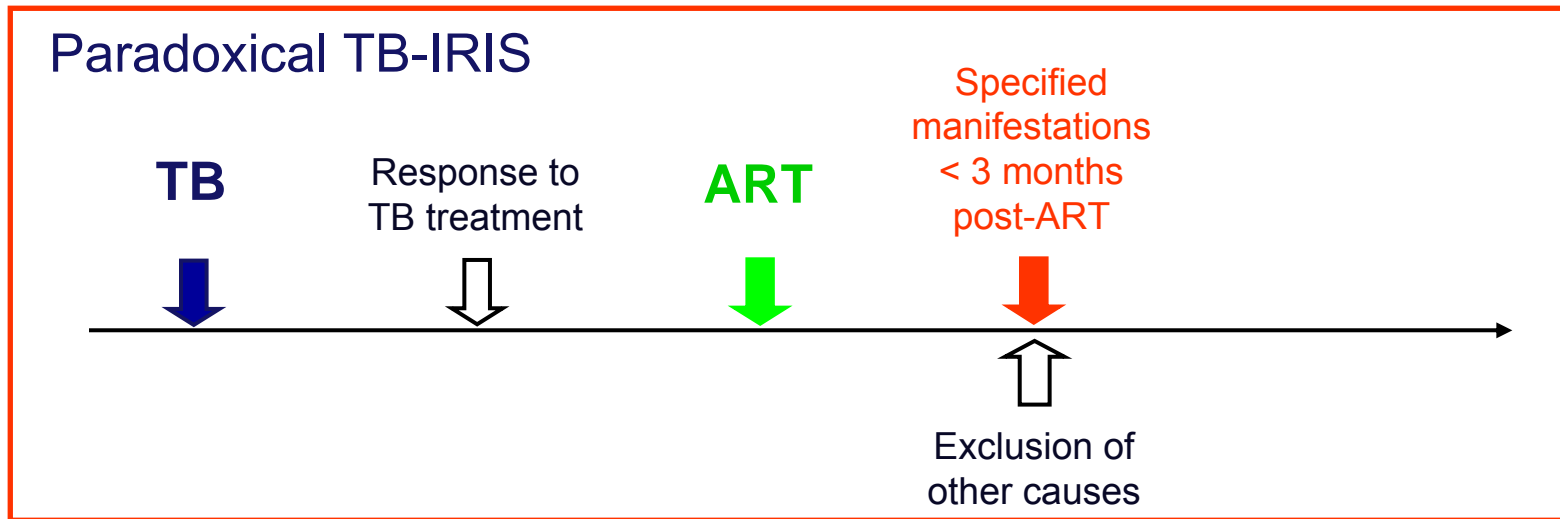
Participants starting ART during TB treatment

Variable	Total	IRIS (%)	Univariate	
			OR	P
Gender				
Male	21	4 (50)		
Female	6	2 (33)	0.47	0.46
Age				
≤ 33 years	12	3 (25)		
> 33 years	15	3 (20)	0.75	0.76
WHO stage				
III	10	1 (10)		
IV	17	5 (29)	3.75	0.26
Baseline CD4 count				
≥ 50 cells/mm ³	13	2 (15)		
0 – 49 cells/mm ³	14	4 (29)	2.20	0.42
Time to ART start				
≥ 60 days	14	2 (14)		
< 60 days	13	4 (31)	2.67	0.31

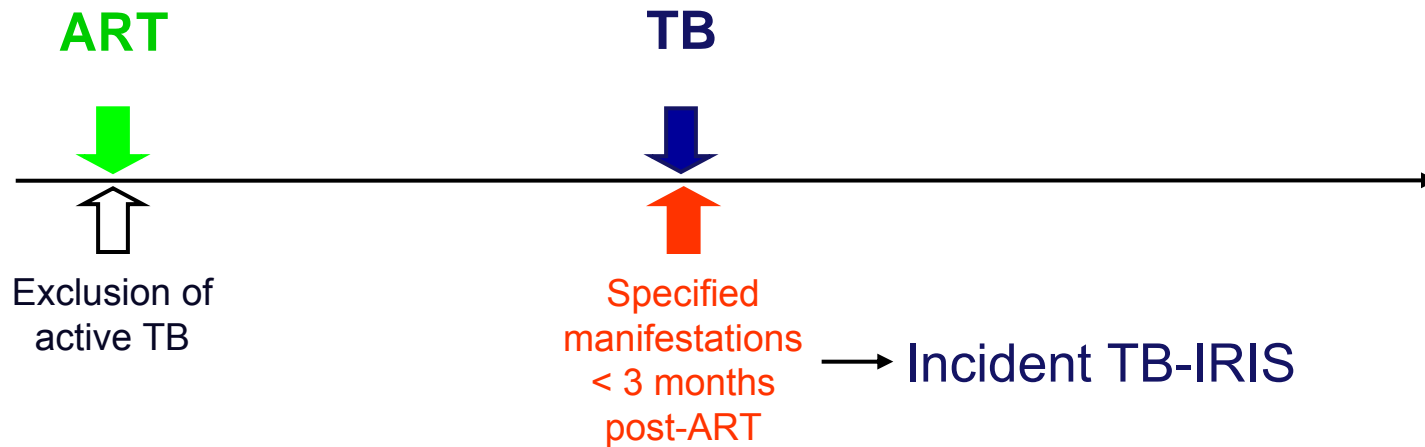
Methods



Case definitions



Incident TB on ART

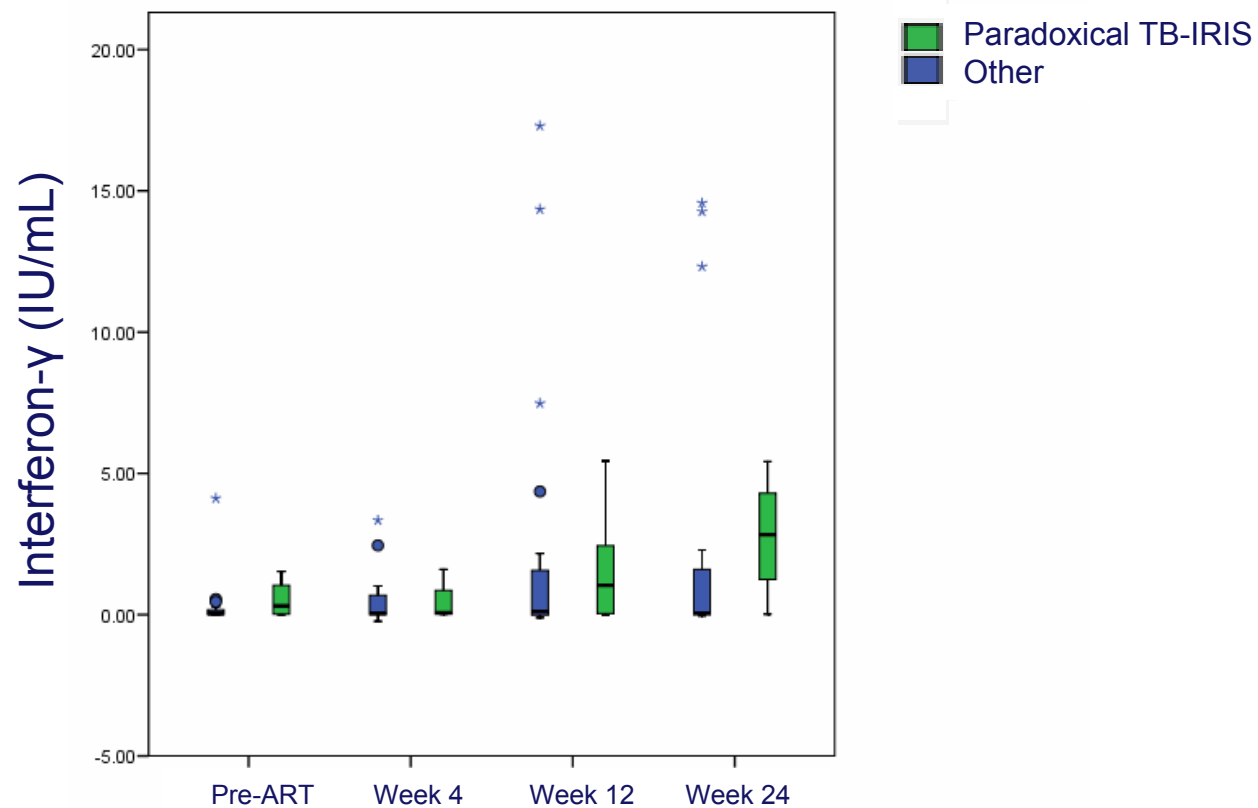


Results



QuantiferON-TB Gold In-tube assay: RD1 antigens

Participants starting ART during TB treatment

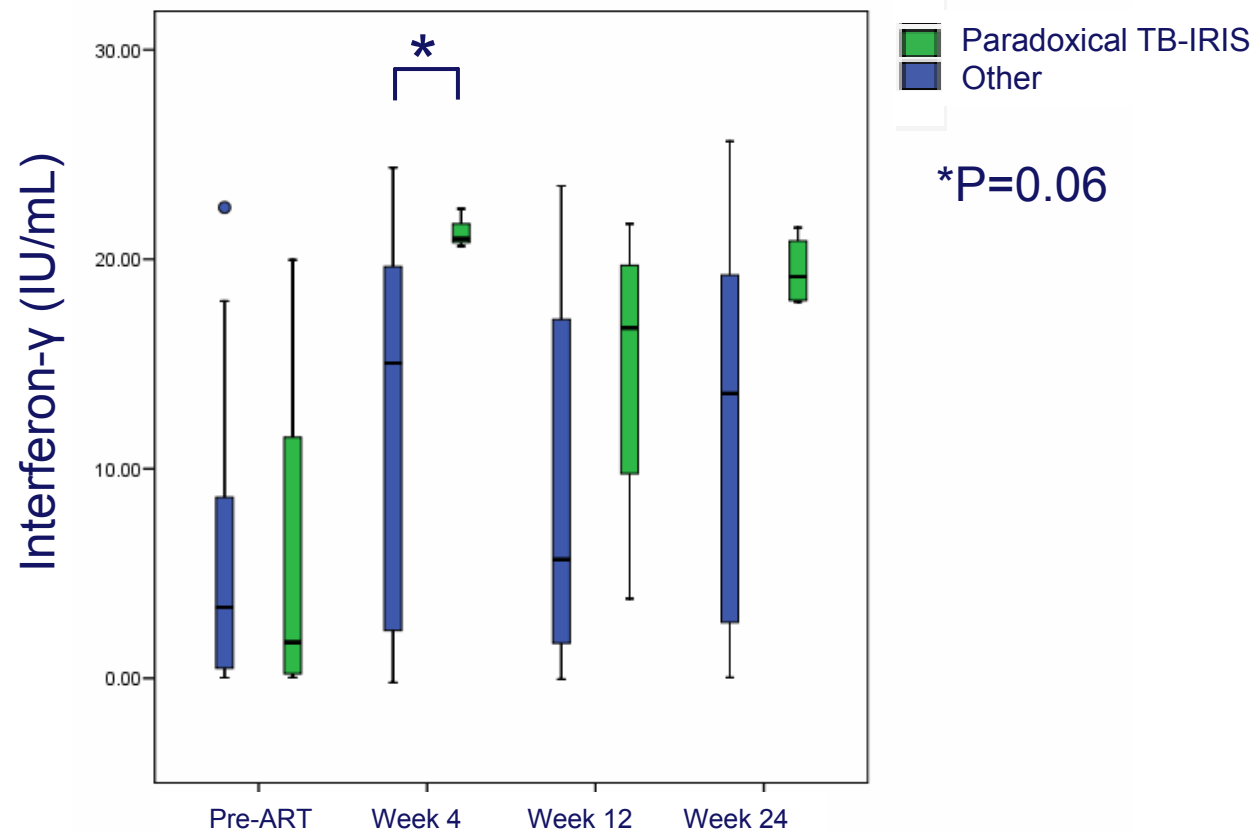


Results



QuantiFERON-TB Gold In-tube assay: PPD

Participants starting ART during TB treatment

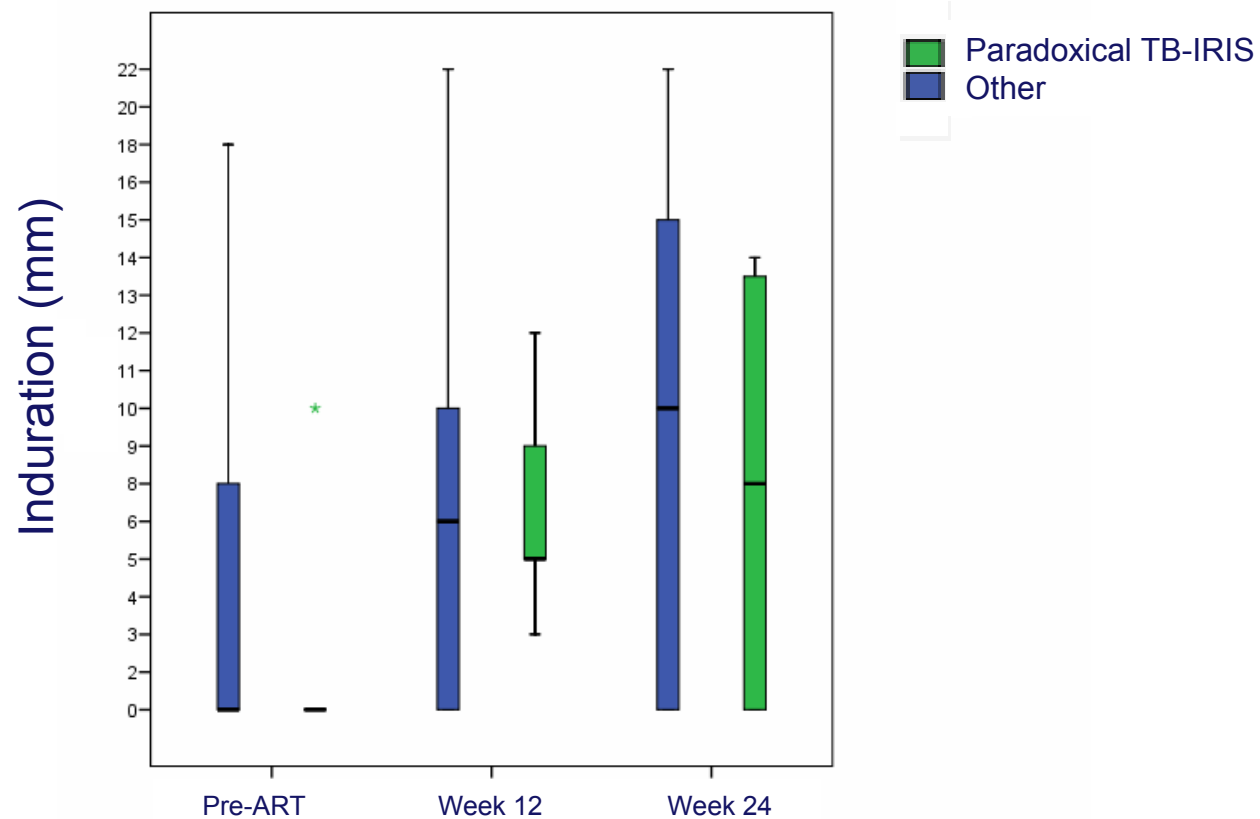


Results



Skin tests: tuberculin

Participants starting ART during TB treatment

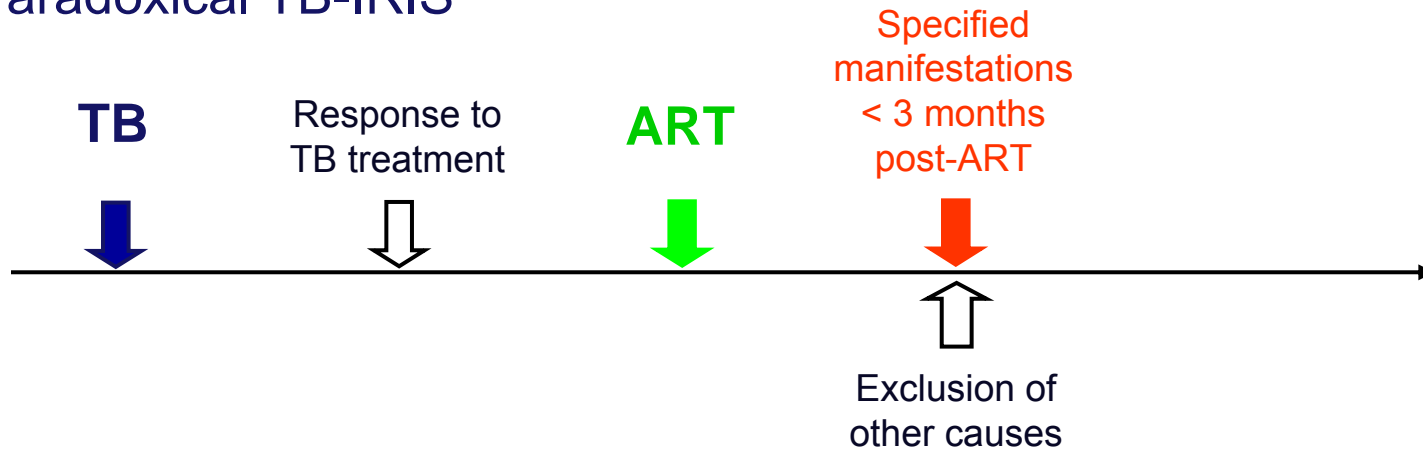


Methods

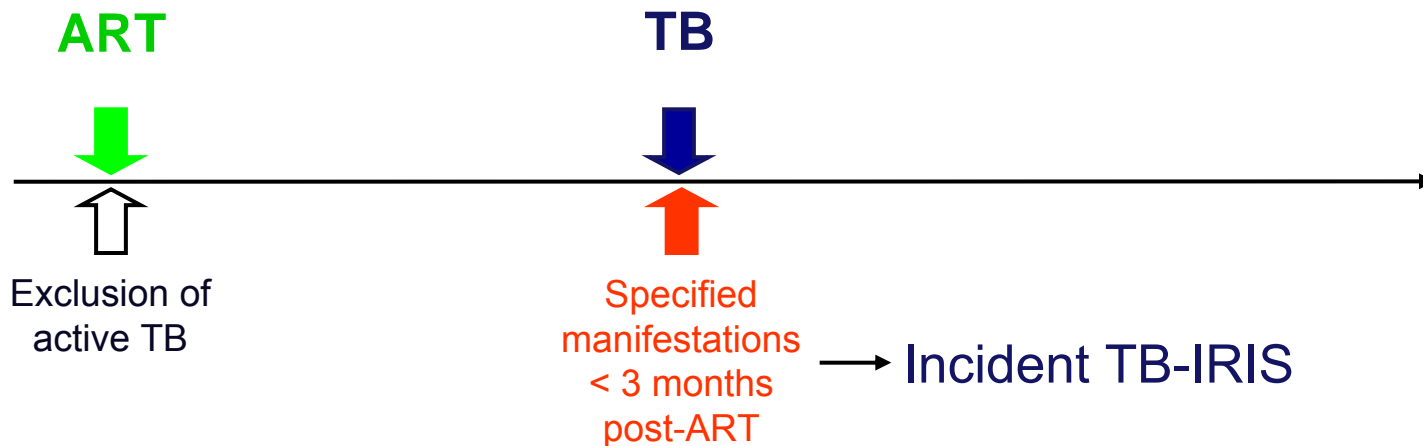


Case definitions

Paradoxical TB-IRIS



Incident TB on ART

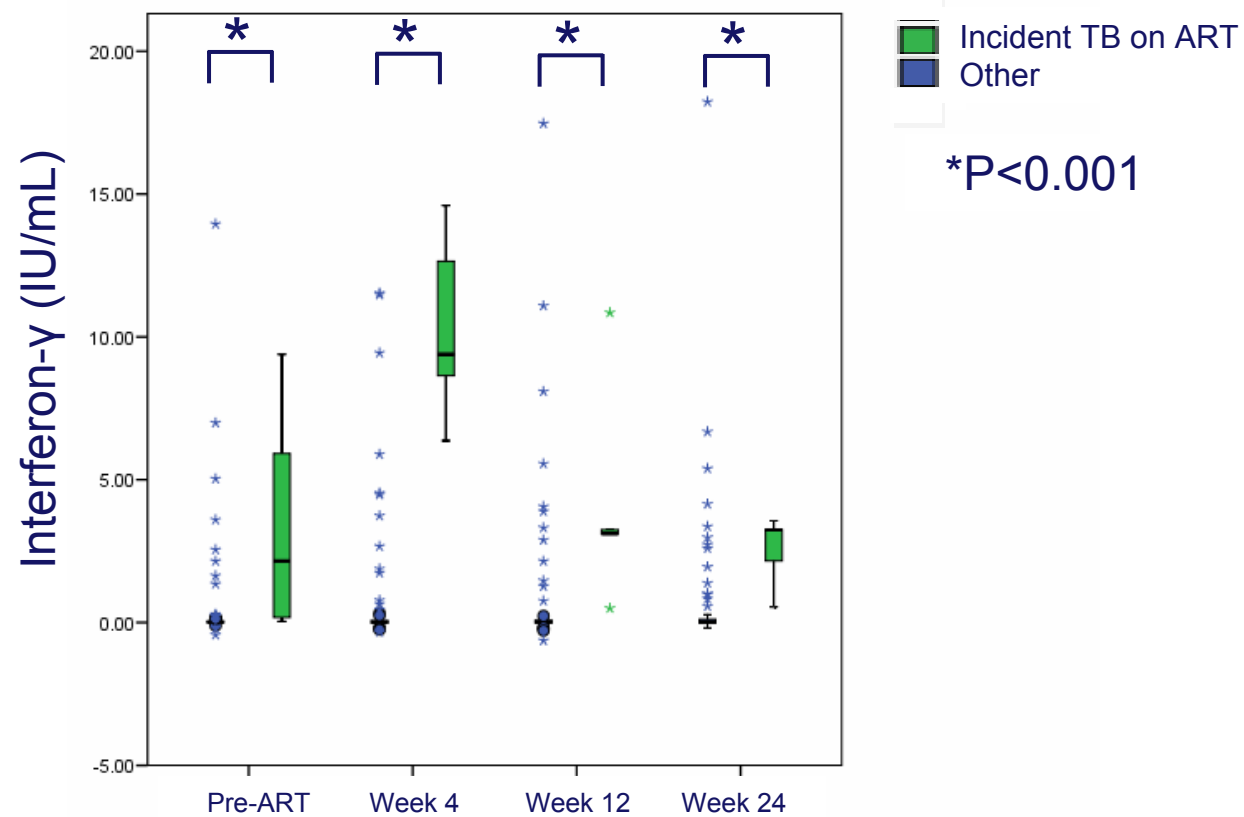


Results



QuantiferON-TB Gold In-tube assay: RD1 antigens

No TB treatment at time of ART initiation

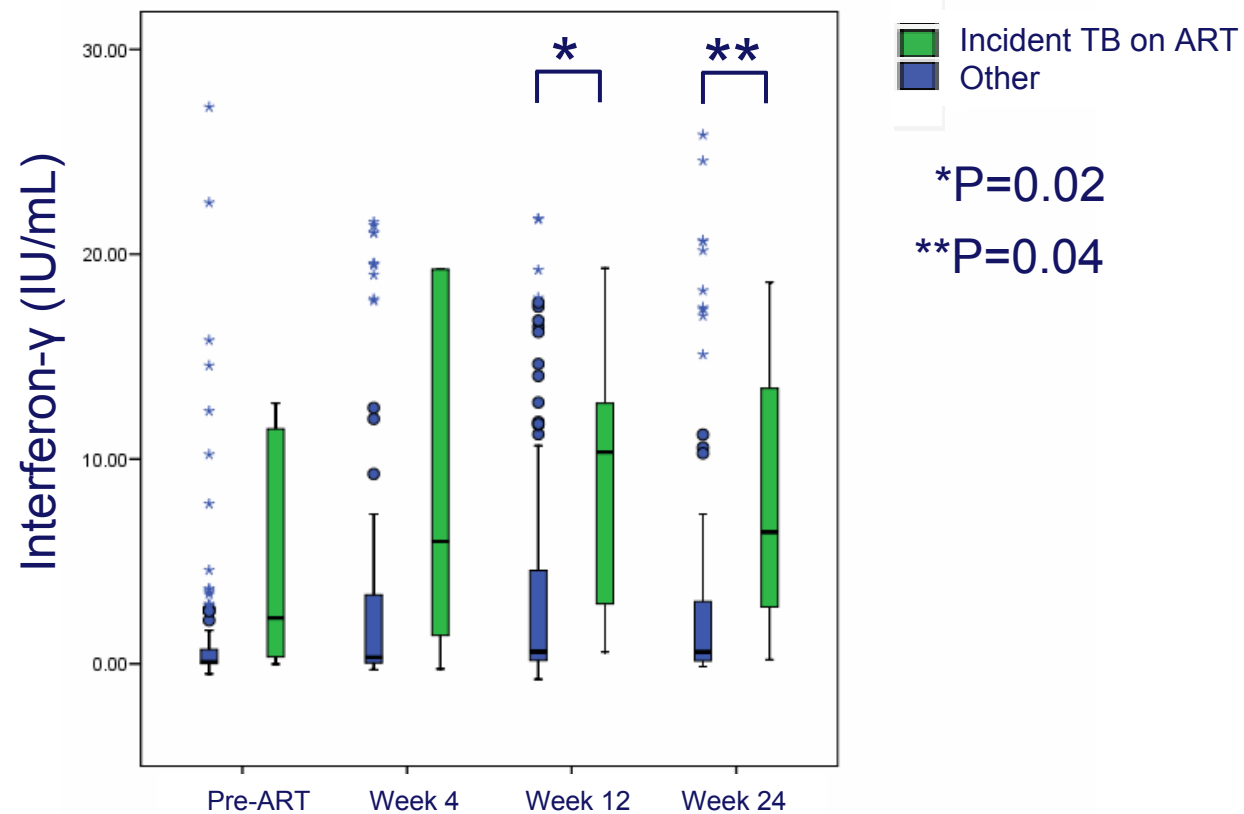


Results



QuantiFERON-TB Gold In-tube assay: PPD

No TB treatment at time of ART initiation

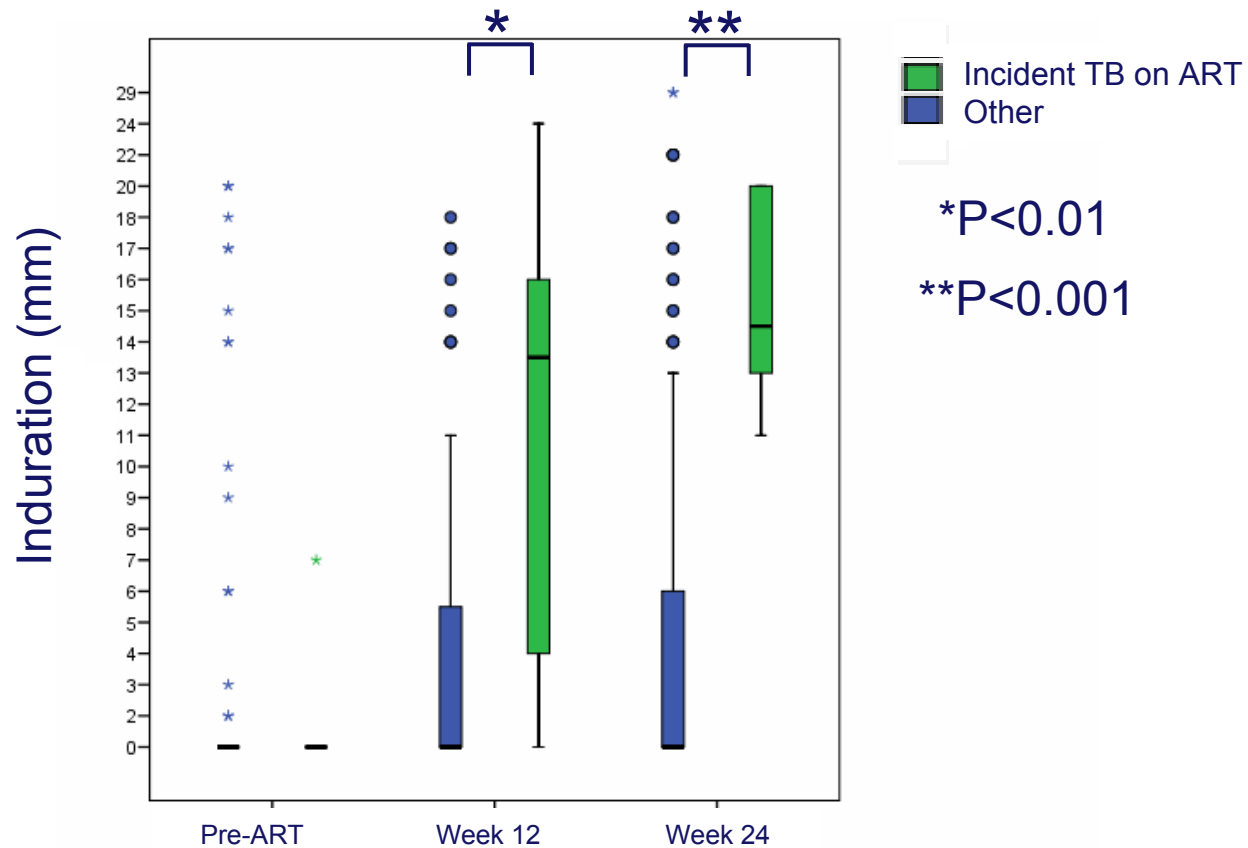


Results



Skin tests: tuberculin

No TB treatment at time of ART initiation



Conclusions



- Incidence of paradoxical TB-IRIS of 22% in the first 6 months of ART when treatment was initiated during TB treatment with trends towards associations with WHO Stage 4 disease, low baseline CD4 count and earlier initiation of ART.
- An early, rapid increase in IFN- γ production measured by QuantiFERON-TB Gold In-tube assay in participants with paradoxical TB-IRIS in response to PPD but not RD1 antigens.
- An association between the development of incident TB on ART and increased IFN- γ production measured by QuantiFERON-TB Gold In-tube assay in response to RD1 antigens pre-ART and in response to both RD1 antigens and PPD during early ART. Similar responses were seen with PPD skin testing.
- Whole blood IFN- γ release assays may have a role in the differentiation of paradoxical TB-IRIS from other causes of clinical deterioration during early ART and in the prediction and diagnosis of early incident TB on ART.

Acknowledgements



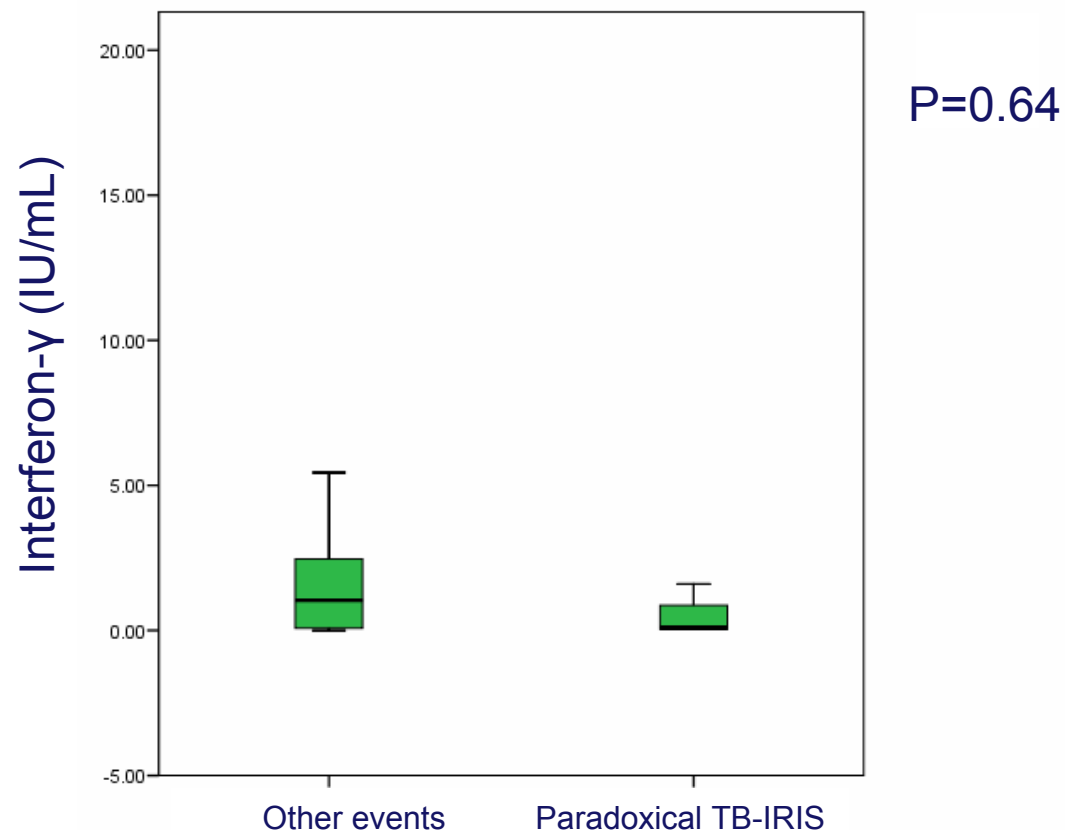
- Study participants
- AusAID
- National Center for HIV/AIDS, Dermatology and STDs
 - Mean Chhi Vun
 - Saphonn Vonthanak
 - Sarun Saramony
 - SHC Clinical staff
 - Chel Sarim
 - Teng Huort
 - Teng Kim Hong
 - Pouv Sophea
 - Khol Vohith
- National Institute of Public Health
 - Ung Sam An
 - Chan Dara
 - Robert Oelrichs
 - Chin Savuth
- University of Western Australia
 - Martyn French
 - Patricia Price
- National Centre in HIV Epidemiology and Clinical Research
 - David Cooper
 - John Kaldor
 - Sarah Huffam

Results



QuantiferON-TB Gold In-tube assay: RD1 antigens

Participants starting ART during TB treatment: clinical events

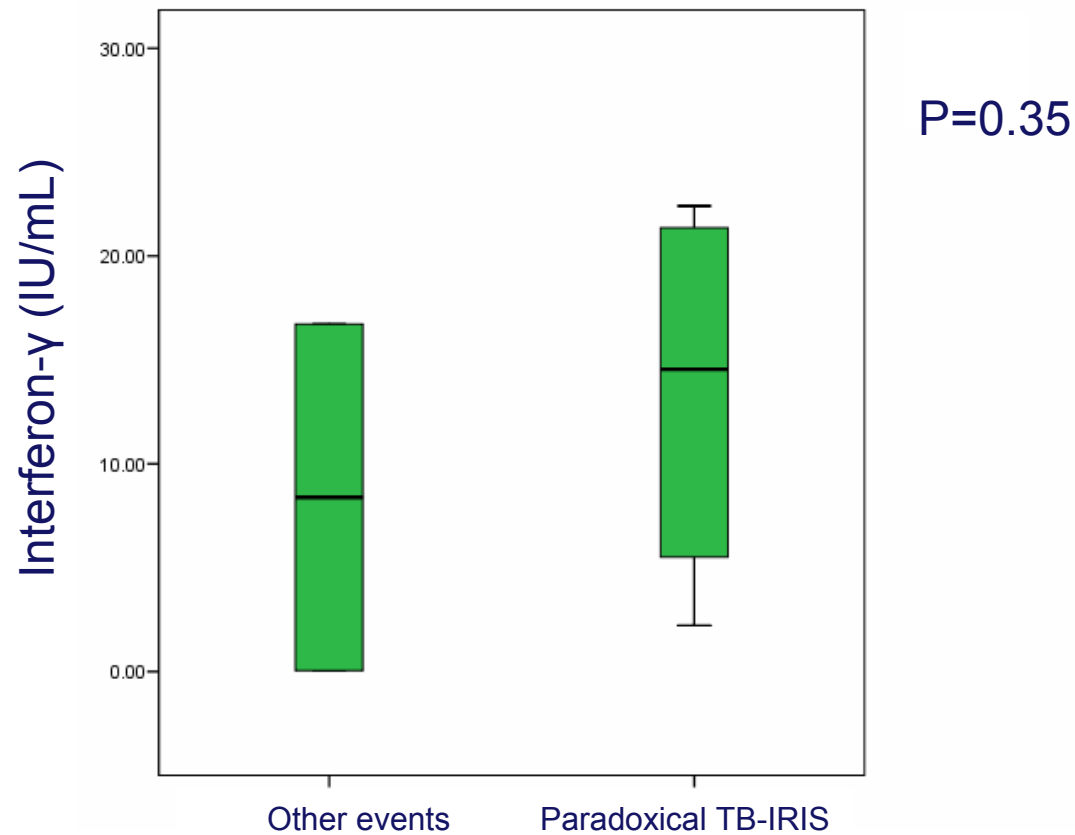


Results



QuantIFERON-TB Gold In-tube assay: PPD

Participants starting ART during TB treatment: clinical events

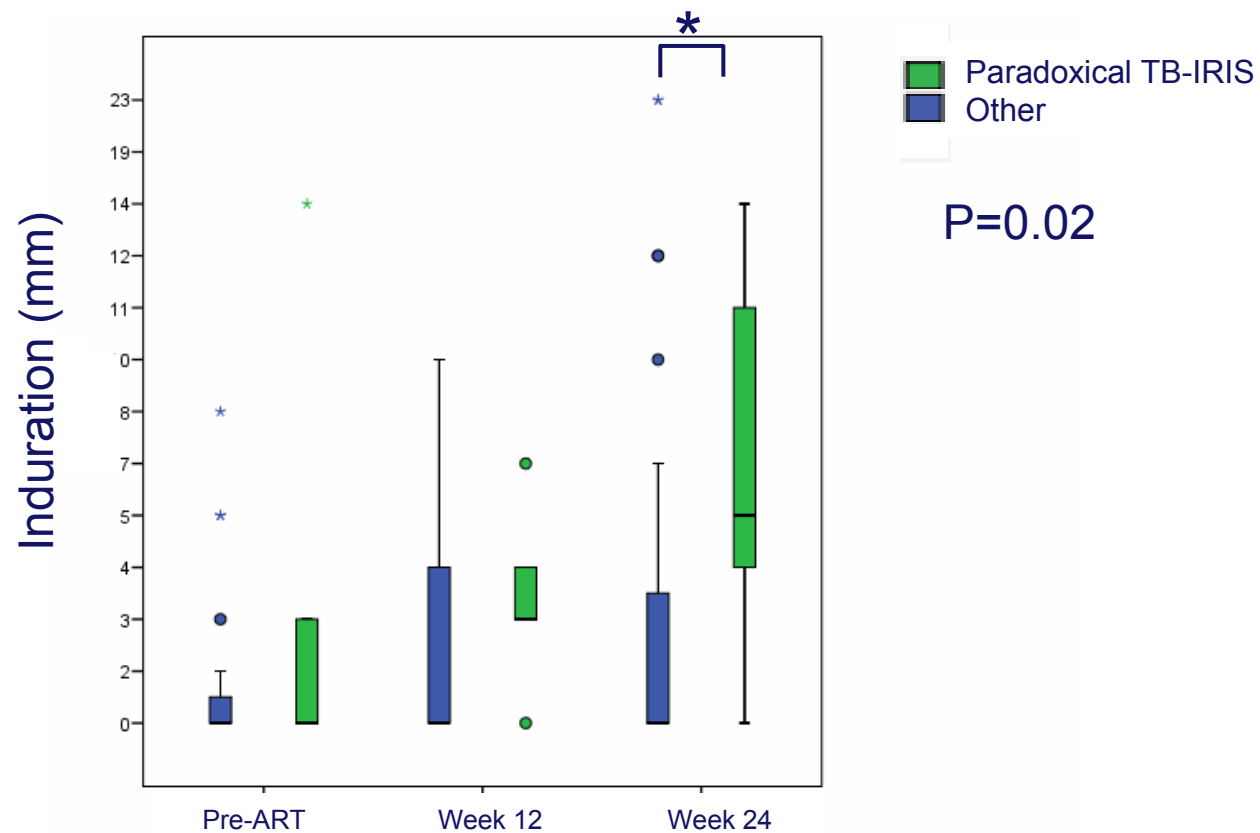


Results



Skin tests: *M. avian* tuberculin

Participants starting ART during TB treatment

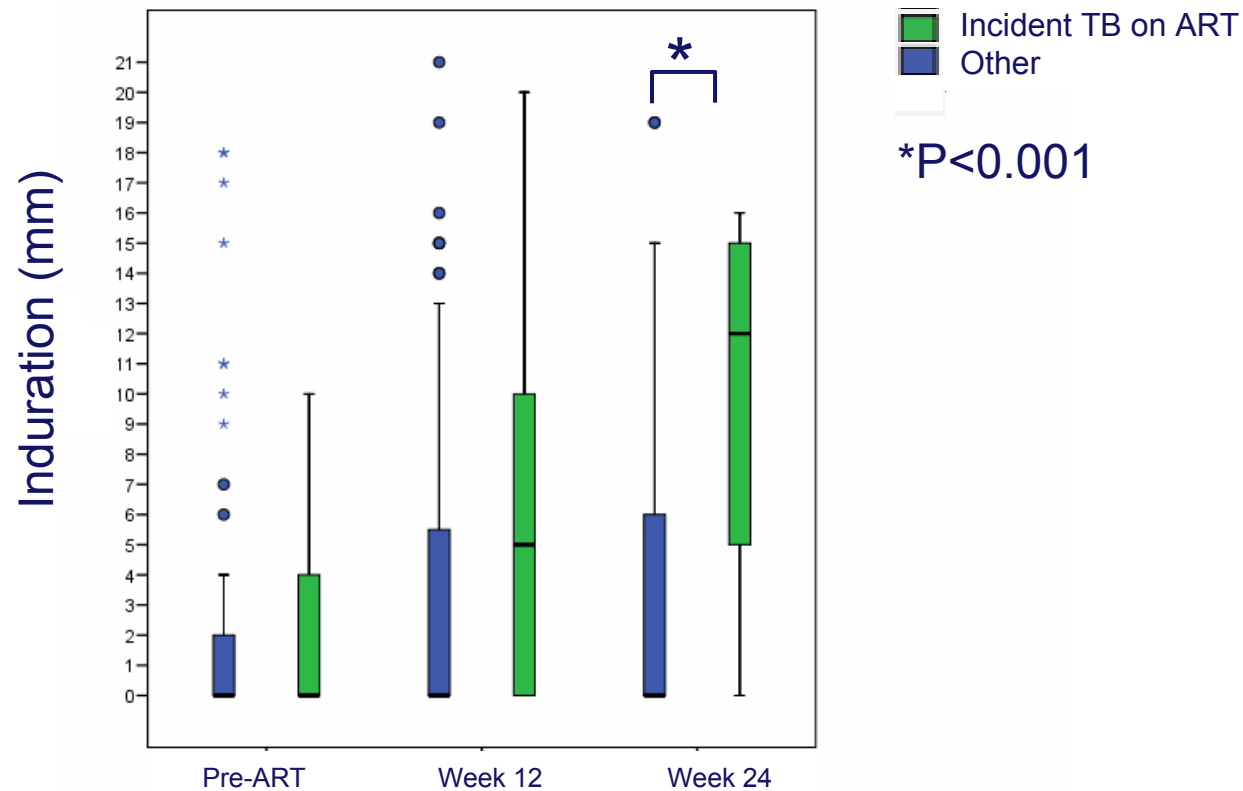


Results



Skin tests: *M. avian* tuberculin

No TB treatment at time of ART initiation

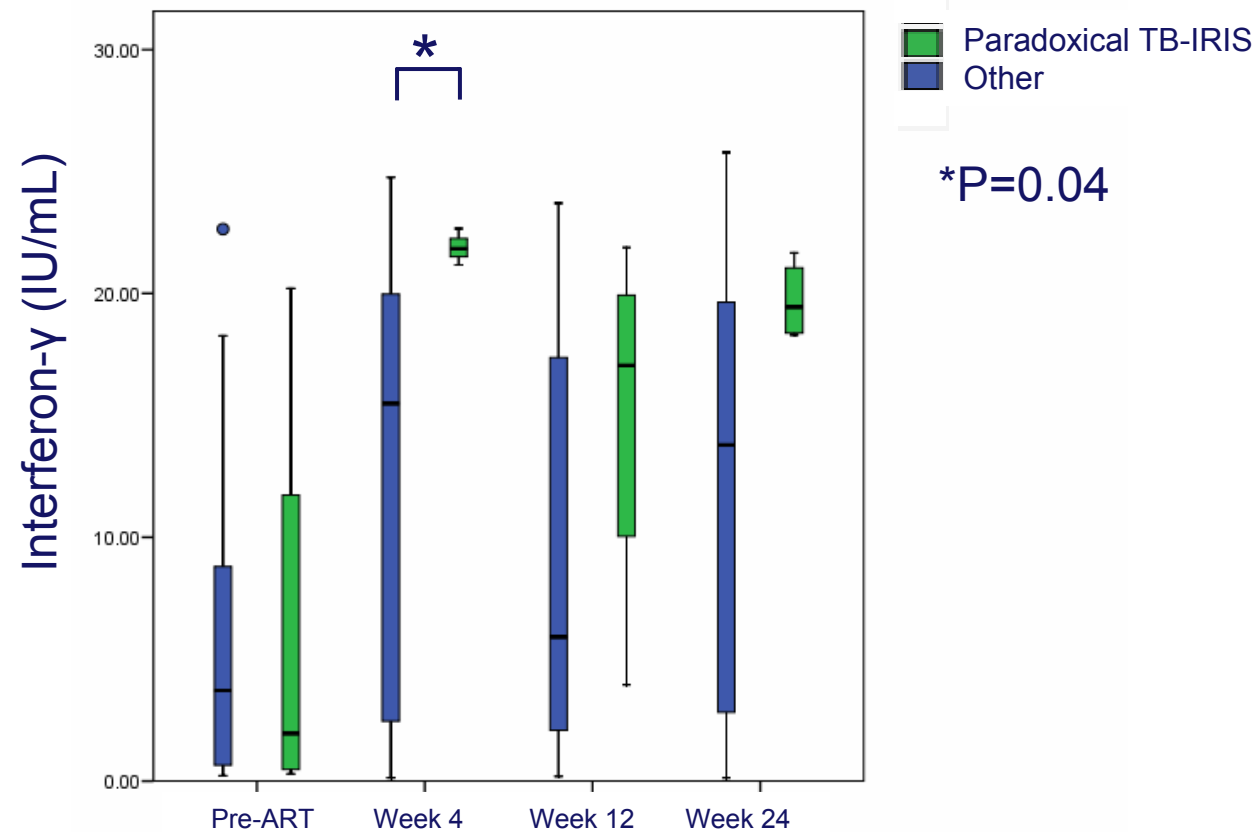


Results



QuantIFERON-TB Gold In-tube assay: PPD (raw)

Participants starting ART during TB treatment

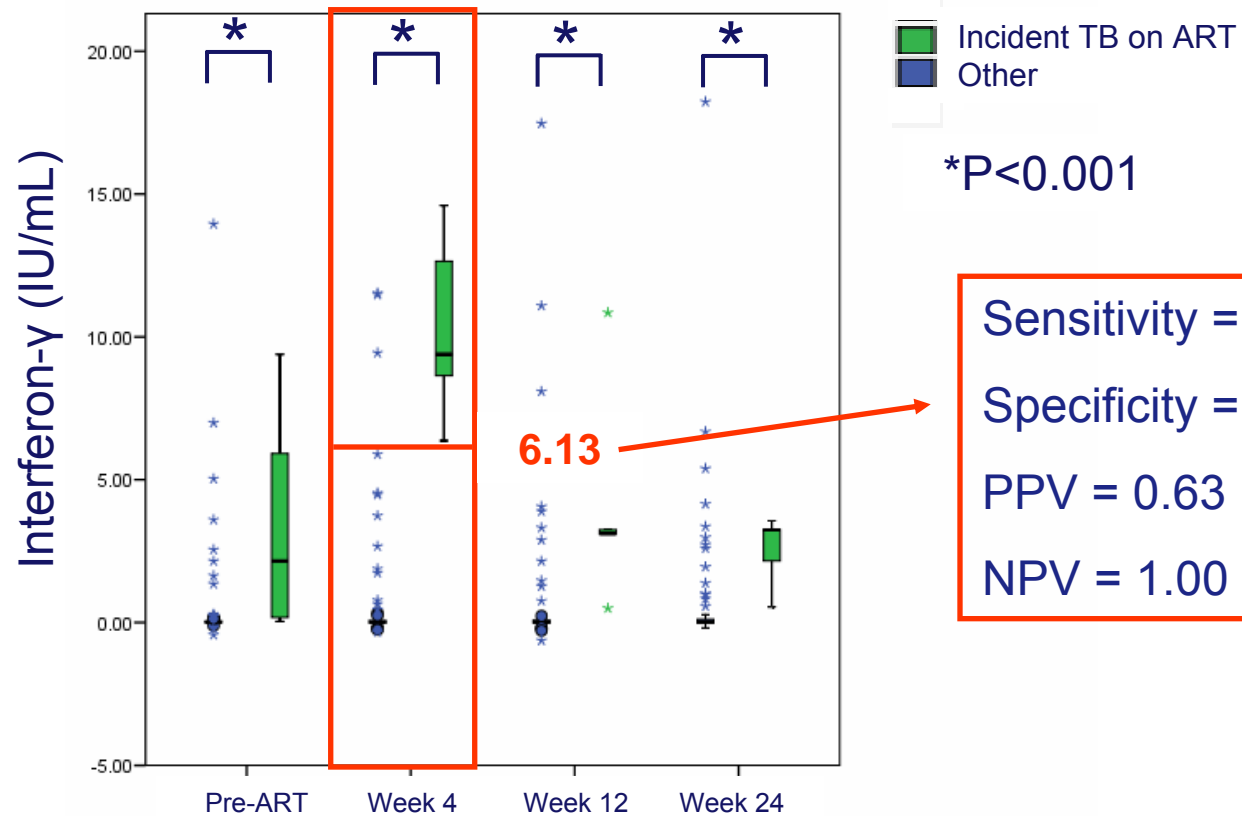


Results



QuantiferON-TB Gold In-tube assay: RD1 antigens

No TB treatment at time of ART initiation



Sensitivity = 1.00
Specificity = 0.97
PPV = 0.63
NPV = 1.00

Results



Participant disposition

