Insights into the host response and the potential for HDT from studies of HIV-TB associated TBM-IRIS

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Tuberculosis Meningitis: Advancing Immunopathogenesis, Diagnosis, and Treatment
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NIAID, Rockville, MD

THE FRANCIS CRICK INSTITUTE

Imperial College London

wellcome centre infectious diseases research in africa

IDM INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

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TB in Khayelitsha, South Africa

- **Population: 391,749**
- **Antenatal HIV prevalence: ~ 30%**
- **TB incidence 917/100,000 (i.e. ~ 1 % per annum)**
- **~60% TB is HIV associated**
- **~ 4040 cases per year**
- **Vastly expanded antiretroviral access and coverage**

Data courtesy of Judy Caldwell, Provincial government

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MEDECINS SANS FRONTIERES
SOUTH AFRICA

The medical consequences of large scale antiretroviral roll out

1. **Access, and adherence, to care**
2. **Drug interactions**
3. **Shared side effects**
4. **Antiretroviral and antibiotic resistance**
5. **Immune reconstitution inflammatory syndrome**
6. **Metabolic effects of antiretrovirals**
7. **Interaction with non-communicable disease**

Asselman V, *et al.* AIDS (2010) **24**:2871.
Meintjes G, *et al.* Am J Respir Crit Care Med (2012) **186**:369
Marais S, *et al.* Lancet Infect Dis (2010) **10**: 803
Meintjes G, *et al.* Clin Infect Dis (2009) **48**:667
Meintjes G, *et al.* AIDS (2010) **24**:2381
Pepper DJ, *et al.* PLoS ONE (2011) **6**:e19484.
Wilkinson KA, *et al.* Am J Respir Crit Care Med (2009) **180**:674
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Marais, S., *et al.* (2013) Clin Infect Dis **56**:450-460

Secondary care

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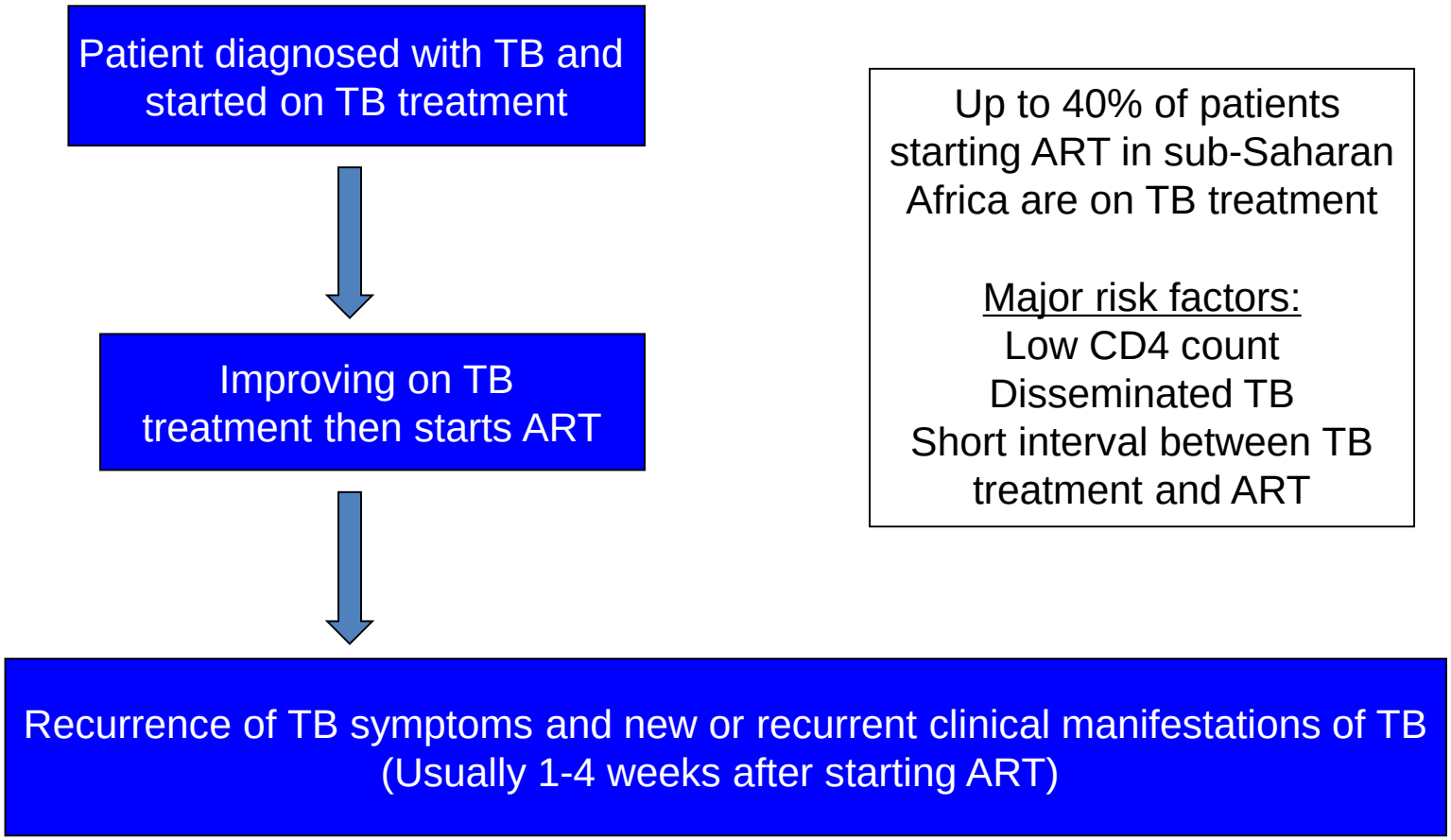
Paradoxical TB-IRIS

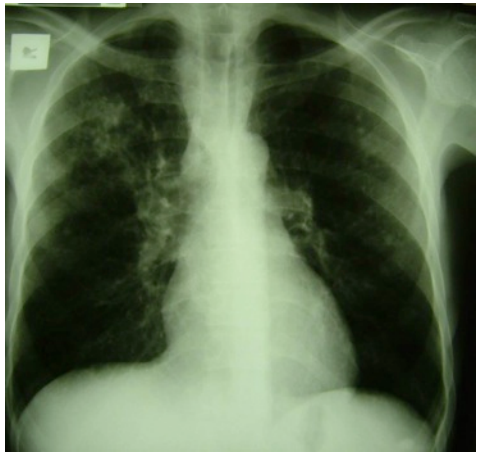


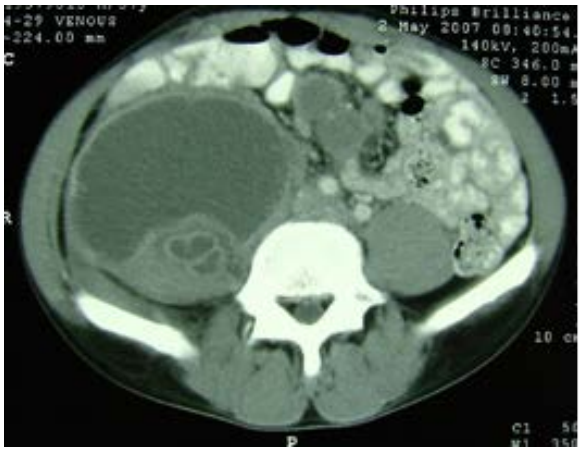
Up to 40% of patients starting ART in sub-Saharan Africa are on TB treatment

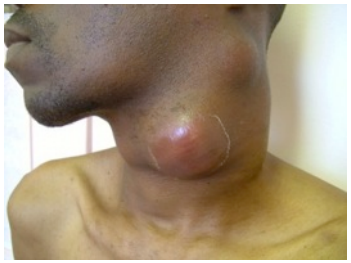
Major risk factors:
Low CD4 count
Disseminated TB
Short interval between TB treatment and ART

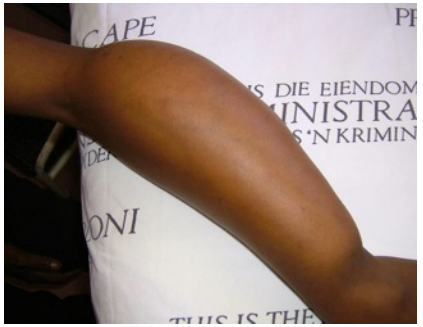
Meintjes GA, *et al.* Lancet Infect Dis (2008) **8**:516

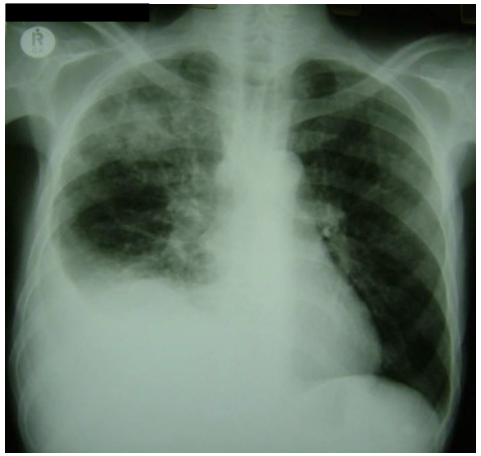
Paradoxical TB-IRIS is clinically highly heterogenous

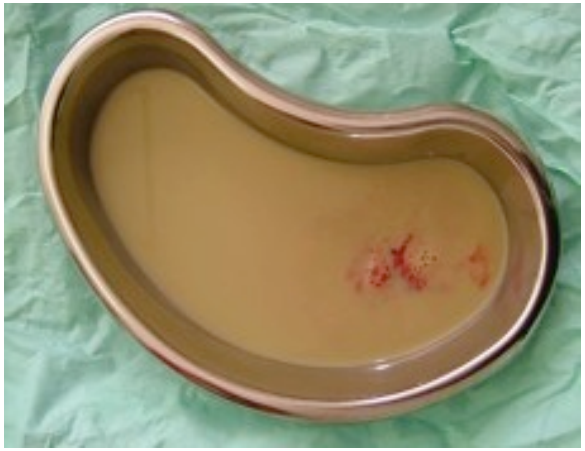


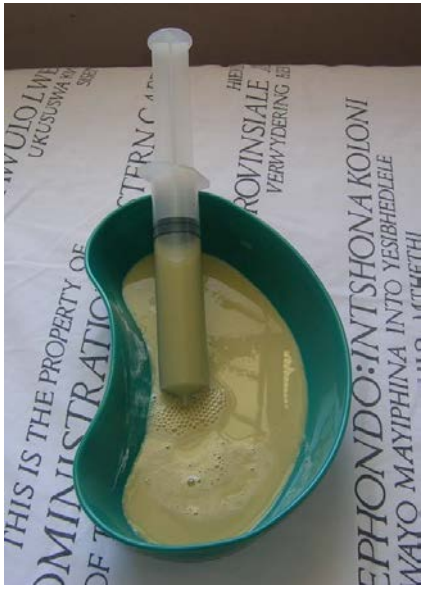






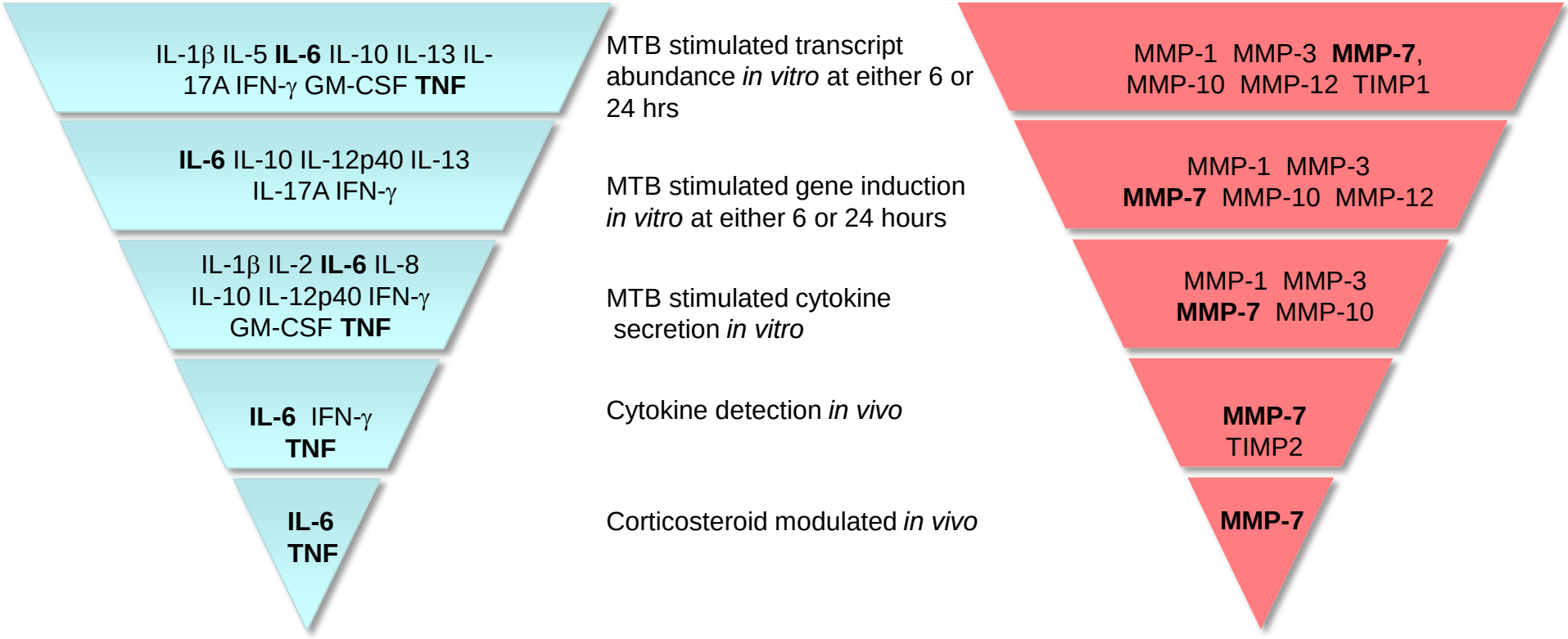






Meintjes G *et al*. Lancet Infect Dis (2008) **8**:516
Maartens G, Wilkinson RJ Lancet (2007) **370**:2030
Meintjes, G *et al.* Clin Infect Dis (2009) **48:**667
Meintjes, G *et al.* AIDS (2010) **24**:2381-2390

Multiply elevated cytokines, a distinct pattern of matrix metalloproteinase, and innate immune activation characterizes TB-IRIS



Andrade B, *et al.* PLOS Pathog (2014) **10**:e1004433
Tadokera R, *et al*. Eur Respir J. (2011) **37**:1248
Tadokera R, *et al*. J Infect Dis (2013) **207**:1148
Tadokera R, *et al.* Eur J Immunol (2014) **44**:127-36
Meintjes G, *et al.* Am J Respir Crit Care Med (2012) **186**:369
Meintjes G, *et al*. Am J Respir Crit Care Med (2008) **178**:1083
Marais S, *et al.* Clin Infect Dis (2014) **59**:1638-47
Walker N, *et al.* J Immunol (2015)

Transcriptomic profiling in human tuberculosis

Active tuberculosis has a transcriptomic signature dominated by a neutrophil-driven type 1 and type 2 interferon-inducible gene profile[1]

The transcriptomic signature relates to disease extent and resolves during successful treatment[1,2]

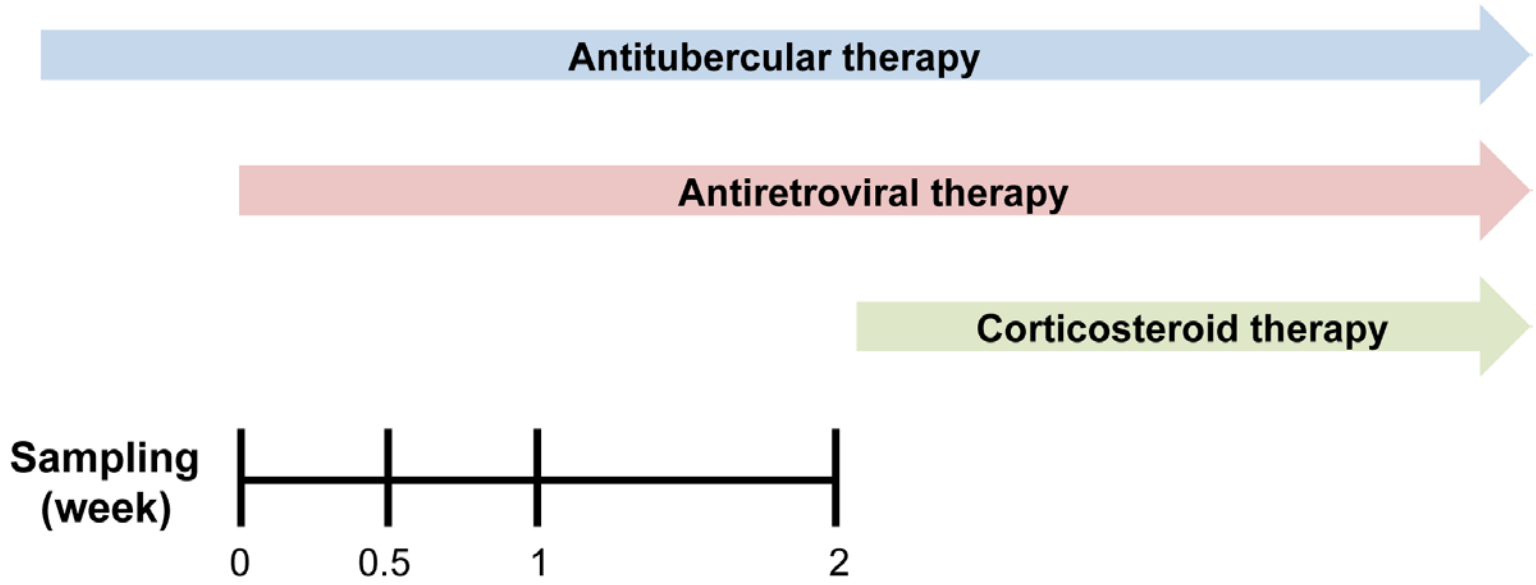
The differentiation of active from latent tuberculosis and other conditions may be aided by transcriptomic profiling[3,4]

The diagnosis of tuberculosis in children may be aided by transcriptomic profiling[5]

Differentially abundant transcripts in TB-IRIS are associated with innate signalling pathways[6]

1. Berry MP *et al.* Nature (2010) **466**: 973-977
2. Bloom, CI*, et al.* PLOS One (2012) **7**:e46191
3. Bloom, CI *et al.* PLOS One (2013) **8**: e70630
4. Kaforou M *et al.* PLOS Med (2013) **10**: e1001538
5. Anderson TB *et al.* N Engl J Med (2014) **370**: 1712-23
6. Lai RP, Meintjes G *et al.* Nature Commun (2015) **6**: 8451

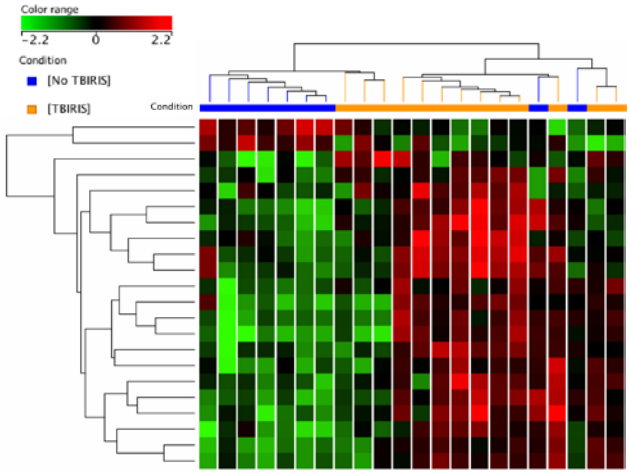
Sample schedule



Meintjes G *et al.*(2012) Am J Respir Crit Care Med **186**:369-377

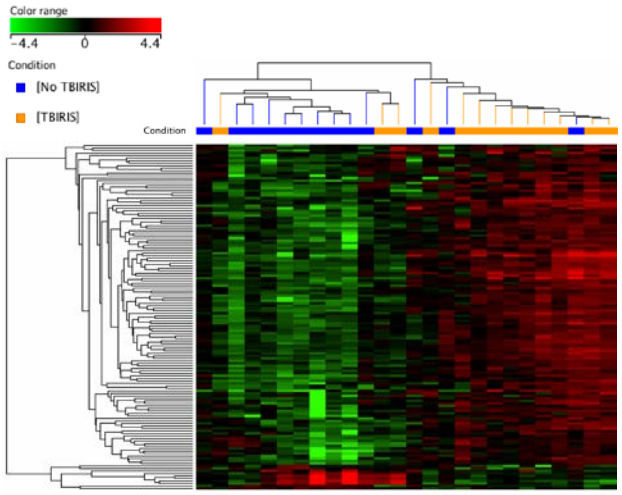
Differentially abundant transcripts in TB-IRIS are associated with innate signaling pathways

Week 0.5



Top 5 Canonical Pathways	*p*-value
Role of JAK family kinases in IL-6-type cytokine signaling	1.14E-06
Acute phase response signaling	9.96E-06
Role of macrophages, fibroblasts & endothelial cells in Rheumatoid Arthritis	8.23E-05
Role of JAK2 in hormone-like cytokine signaling	3.33E-04
Role of JAK1 & JAK3 in cytokine signaling	1.17E-03

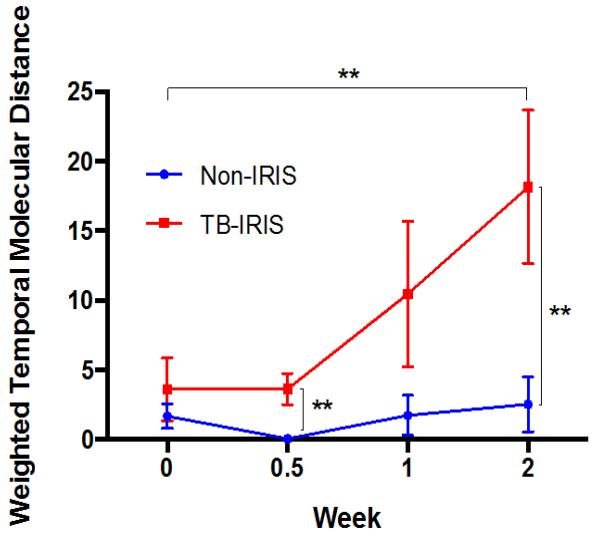
Week 2



Top 5 Canonical Pathways	*p*-value
Toll-like-receptor signaling	1.29E-06
TREM1 signaling	2.55E-05
Role of pattern recognition receptors in recognition of bacteria & viruses	2.62E-04
Role of macrophages, fibroblasts & endothelial cells in Rheumatoid Arthritis	4.43E-04
Production of nitric oxide & reactive oxygen species in macrophages	8.99E-04

Lai RP, Meintjes G *et al.* Nature Commun (2015) **6**: 8451

Tracking the transcriptomic dysregulation that leads to TB-IRIS

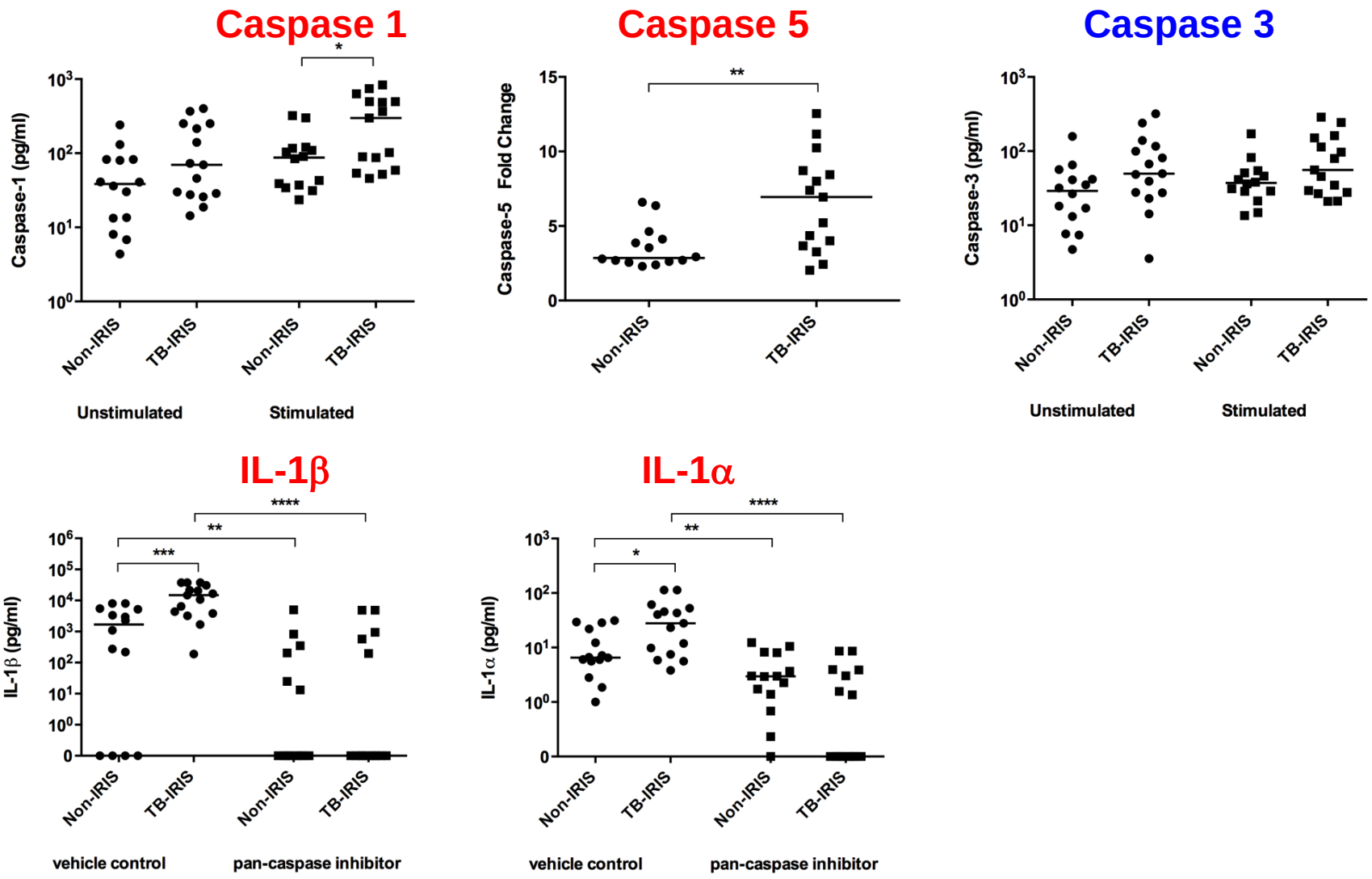


Top 5 Canonical Pathways (43 genes)	*p*-value
TREM1 signaling	2.01E-04
Toll-like receptor signaling	2.01E-04
Endothelin-1 signaling	3.84E-04
Role of pattern recognition receptors in recognition of bacteria & viruses	8.83E-04
IL-1 signaling	8.83E-04

Week 2 (43 consistently overabundant transcripts)			
ACSL1	C19orf35	HECW2	RHOBTB1
ADCY3	CARD17	IFIT3	SERPING1
AGPAT9	CASP5	IFITM3	SIGLEC9
AIG1	CDK5RAP2	KCNJ15	SIPA1L2
ANXA3	DHRS13	KLHL2	SMARCD3
APOB48R	DKFZp761E198	LOC100128460	TLR2
ASPRV1	DOK3	MANSC1	TLR5
B3GNT8	ECE1	MAPK14	TPST1
BAMBI	GNB4	OAS1	TRIB1
BASP1	GPR160	PFKFB3	TUFT1
BCL2A1	GPR97	PSG9	

Lai RP, Meintjes G *et al.* Nature Commun (2015) **6**: 8451

Both canonical and non-canonical inflammasomes are activated in TB-IRIS



Lai RP, Meintjes G *et al.* Nature Commun (2015) **6**: 8451

The worst form of TB-IRIS is neurological IRIS

TBM was diagnosed in 120/211 patients (57%) with meningitis

Retrospective study

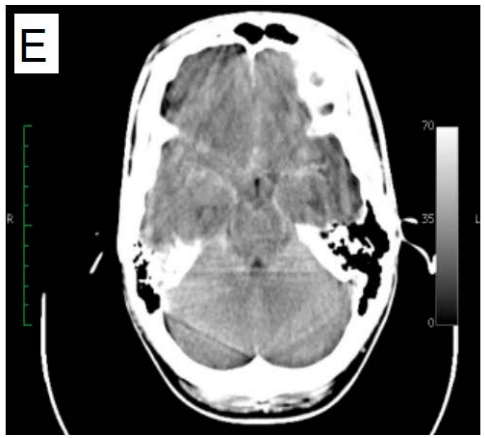
- 23 (12%) of 190 TB-IRIS patients had neurologic TB-IRIS
  8 meningitis, 7 tuberculoma, 5 both, 3 radiculomyelopathy
- 87% required hospital admission (median 12 days)
- 91% received corticosteroids (median 58 days)
- 6 month outcome: 70% alive, 13% dead, 17% LTFU

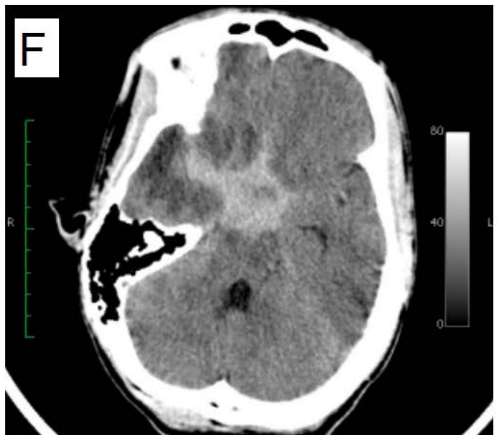
Prospective study

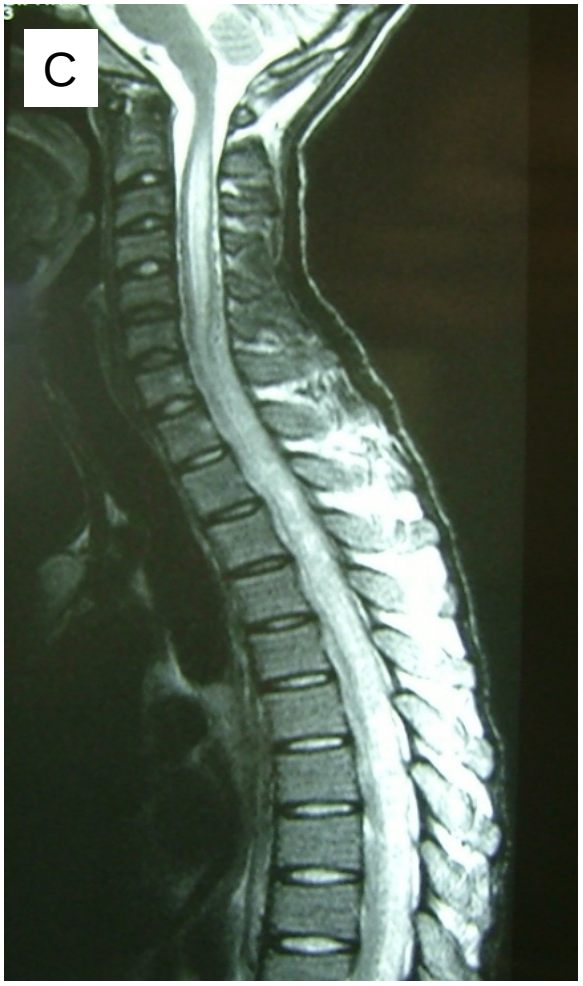
- 16/34 (47%) TBM patients developed TBM-IRIS despite steroids in 13/16
- Death occurred in 4 (25%) TBM-IRIS patients
- TBM-IRIS patients had higher CSF neutrophil counts
- *Mycobacterium tuberculosis* culture +ve CSF in 94% TBM-IRIS compared with 33% non-IRIS

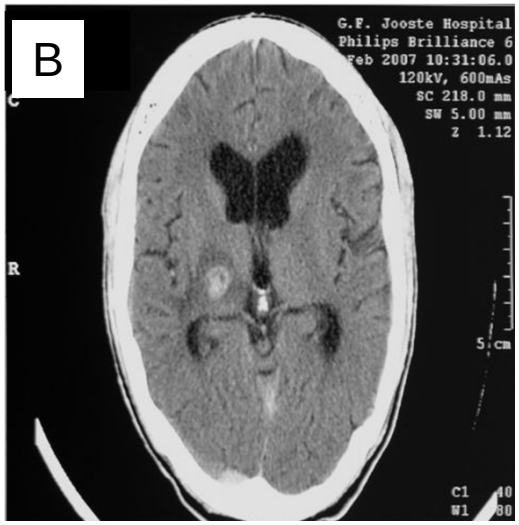
Pepper DJ, et al. Clin Infect Dis (2009) **48**:e96
Marais S, *et al.* PLoS ONE (2011) **5**: e20077
Marais S, *et al.* Clin Infect Dis (2013) **56**: 450

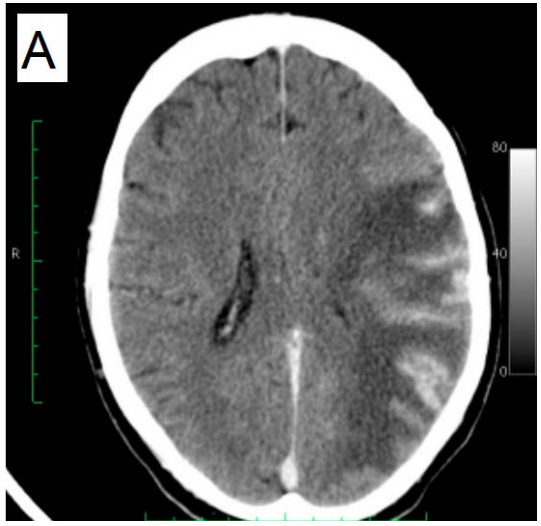
Radiographic examples of neurological TB-IRIS







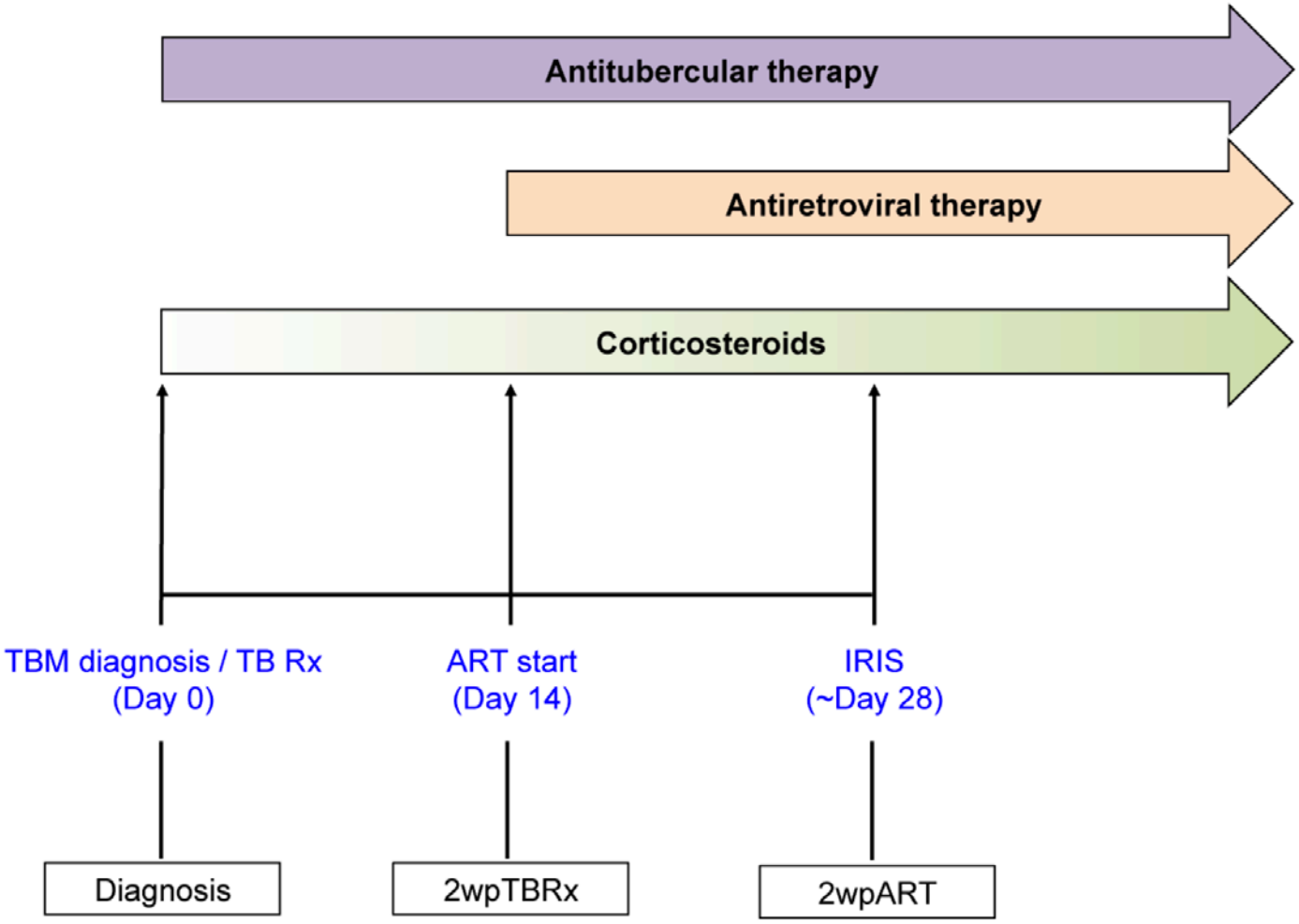




Marais S, *et al.* Clin Infect Dis (2013) **56**: 450
Marais S, *et al.* Lancet Infect Dis (2010) **11**:803

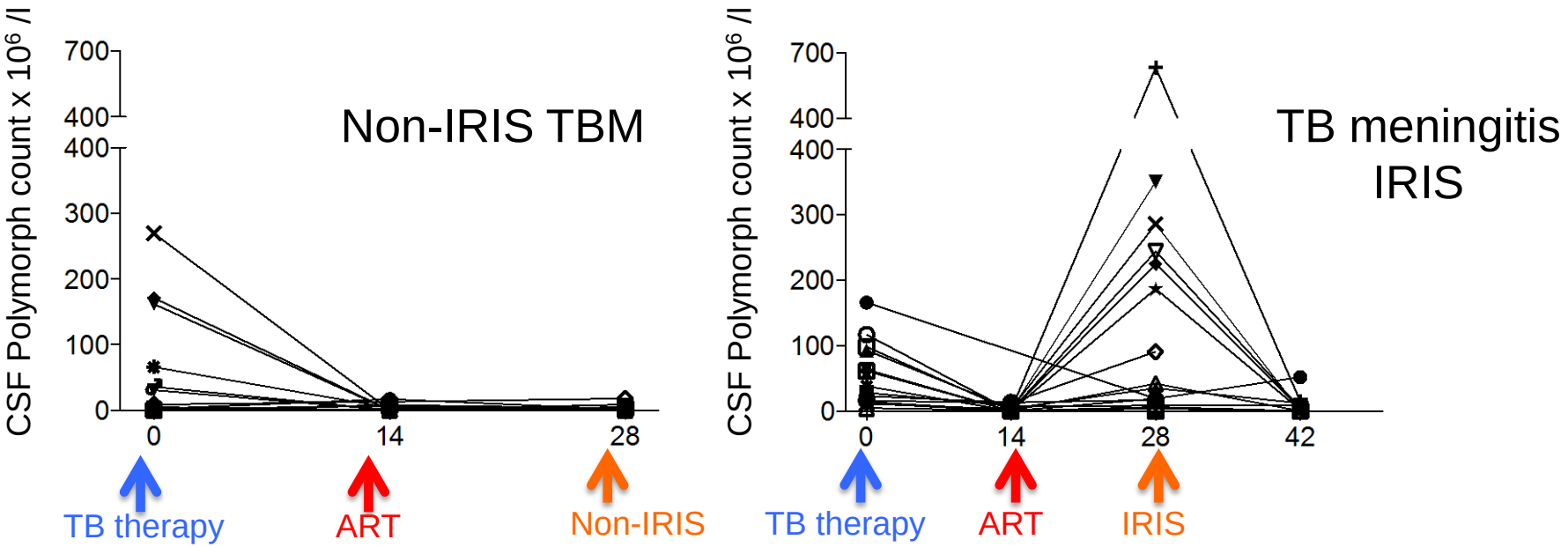
Marais S, *et al.* Int J Tuber Lung Dis (2010) **14**:188
Pepper DJ, et al. Clin Infect Dis (2009) **48**:e96

Study schema



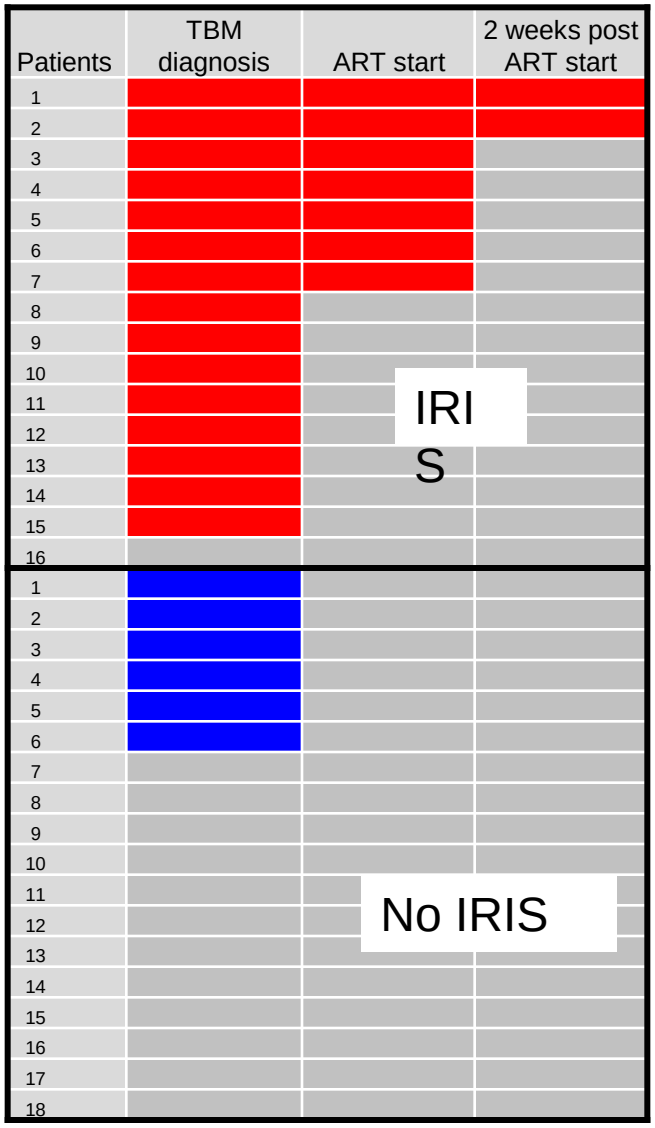
Marais S *et al.* (2013) Clin Infect Dis **56**: 450

Implication of neutrophils in TBM-IRIS



Marais S, *et al.* Clin Infect Dis (2013) **56**: 450
Marais S, *et al.* Clin Infect Dis (2014) **59**:1638

CSF *M. tuberculosis* culture positivity strongly associates with TBM-IRIS



IRIS 15/16
16 (15-20 days)

No IRIS 6/18
(14-32 days)

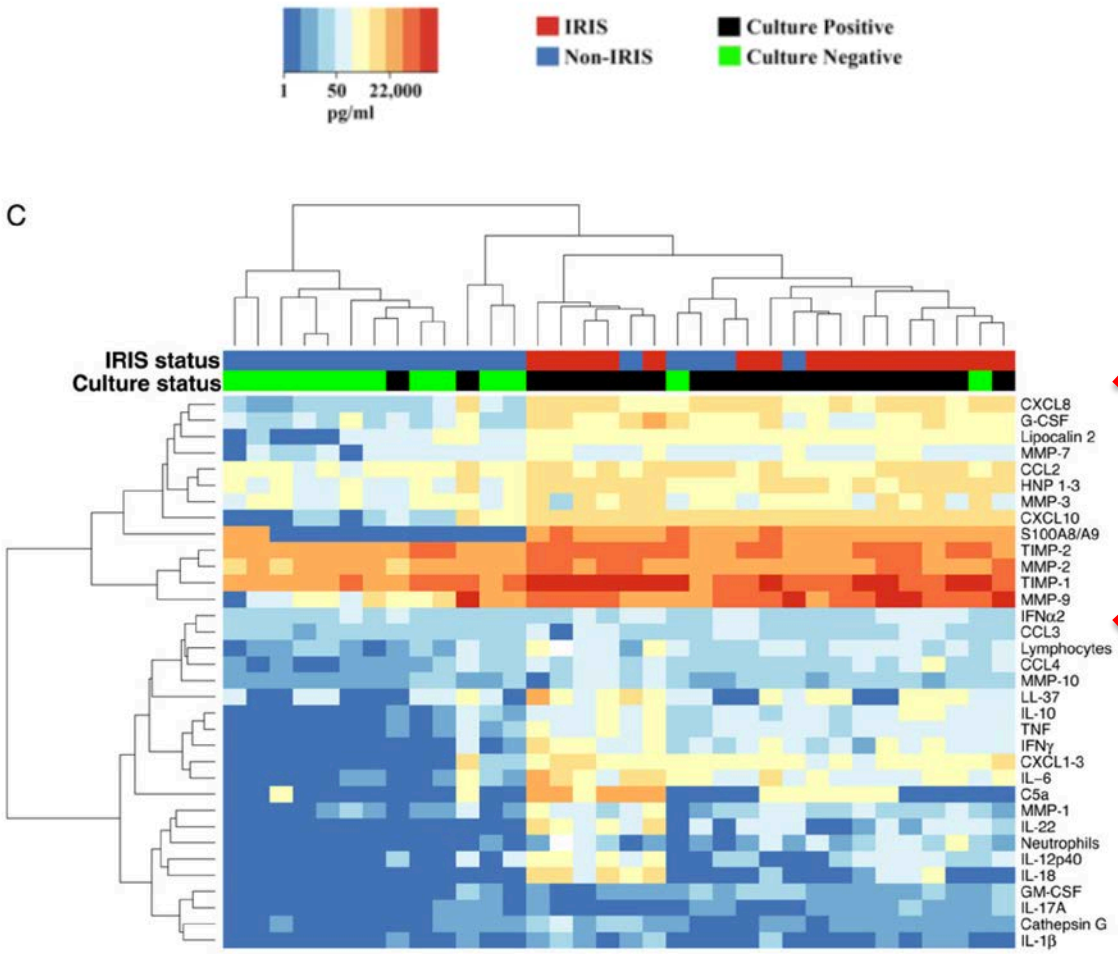
Relative risk of IRIS if culture positive= 9.3 95% CI 1.4-62.2 P=0.0004

Risk of death from TBM-IRIS ~ 25%

Marais S, *et al.* Clin Infect Dis (2013) **56**: 450-460

CSF mediators 2 weeks after starting ART

(typical time of TBM-IRIS)

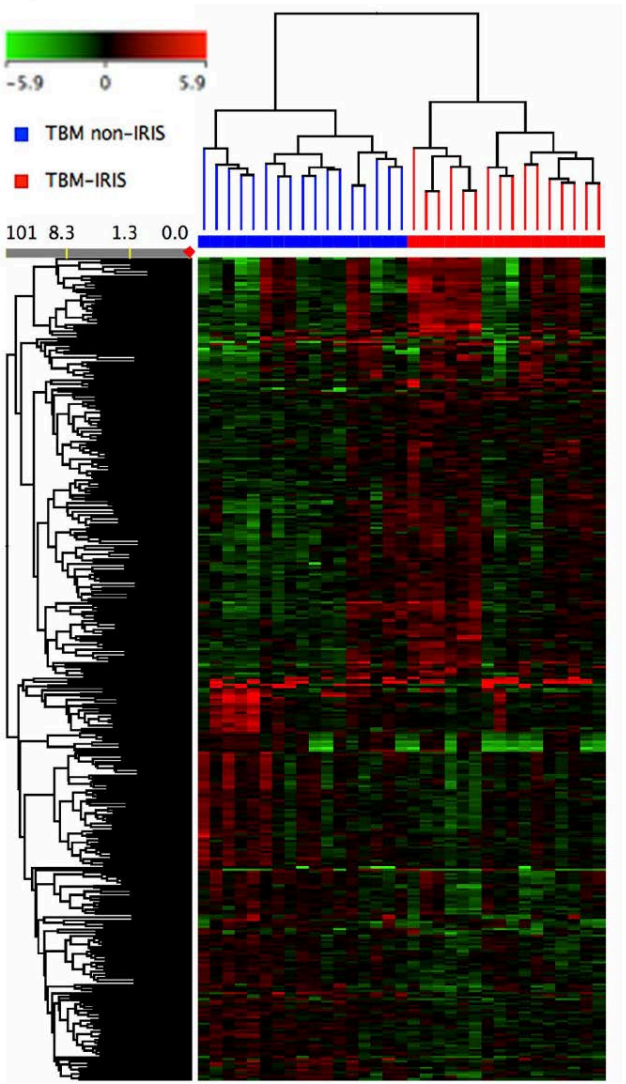


CXCL8
G-CSF
Lipocalin 2
MMP-7
CCL2
HNP 1-3
MMP-3
CXCL10
S100A8/A9
TIMP2
MMP2
TIMP1
MMP9

Marais S, *et al.* Clin Infect Dis (2014) **59**:1638

Blood transcriptomic signature at time of TBM diagnosis

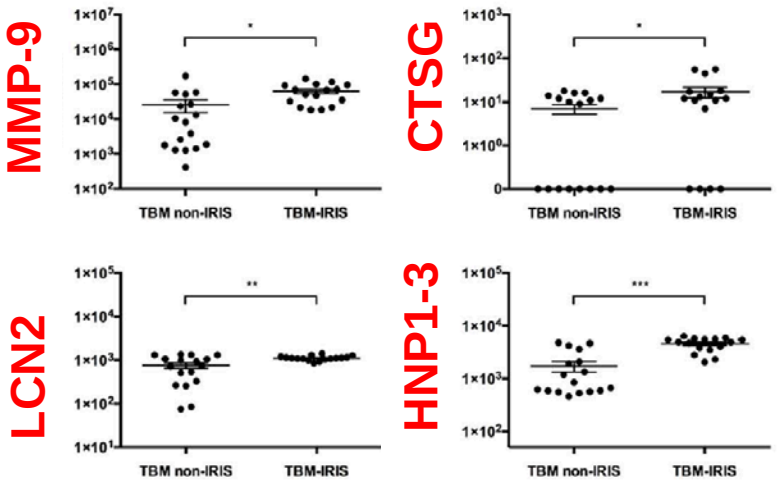
a)



b)

Gene Ontology Term	*P*-value
Immune response	0.00E+00
Defense response to bacterium	0.00E+00
MHC class II protein complex	4.00E-03
Antigen processing & presentation	3.70E-02
Regulation of leukocyte activation	4.80E-02

c) **CSF mediators pg/ml**



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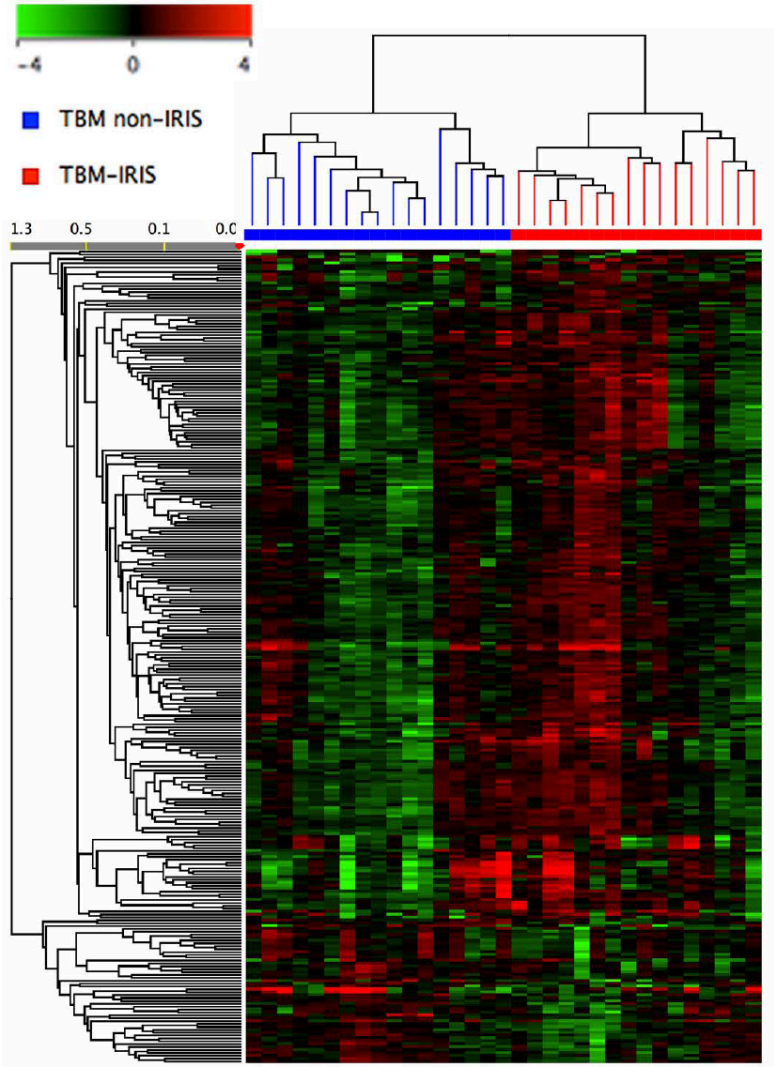
Transcriptional signature at onset of ART

a)

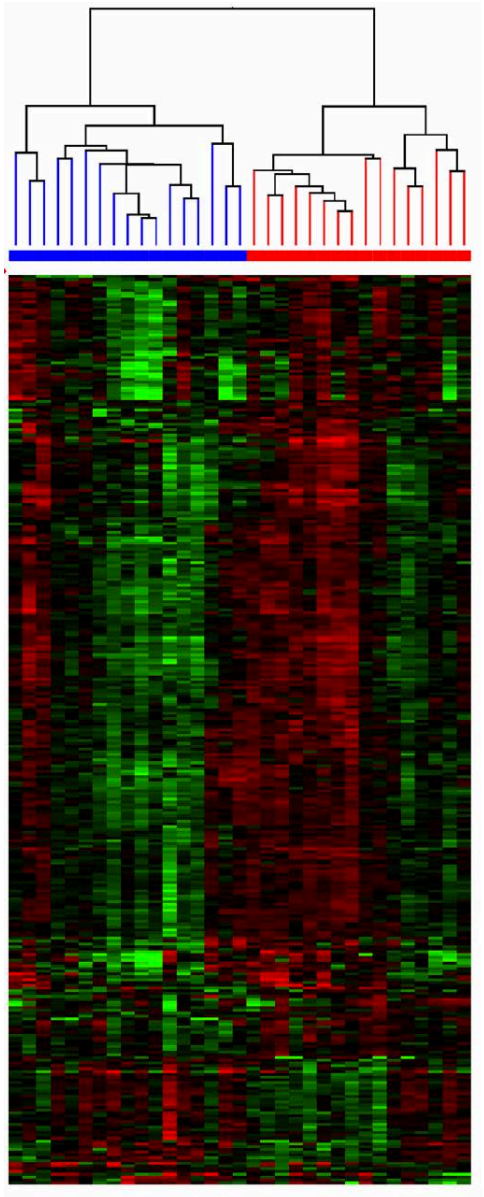


b)

Top 5 canonical pathways	*P*-value
Inflammasome activation	7.29E-03
IL-8 signaling	1.56E-02
HIF1α signaling	2.43E-02
Phagosome formation	2.58E-02
Role of JAK family kinases in IL-6-type cytokine signaling	3.03E-02

Marais, S., Lai, R.P-J. *et al.* J Infect Dis (2017) 215:677-686

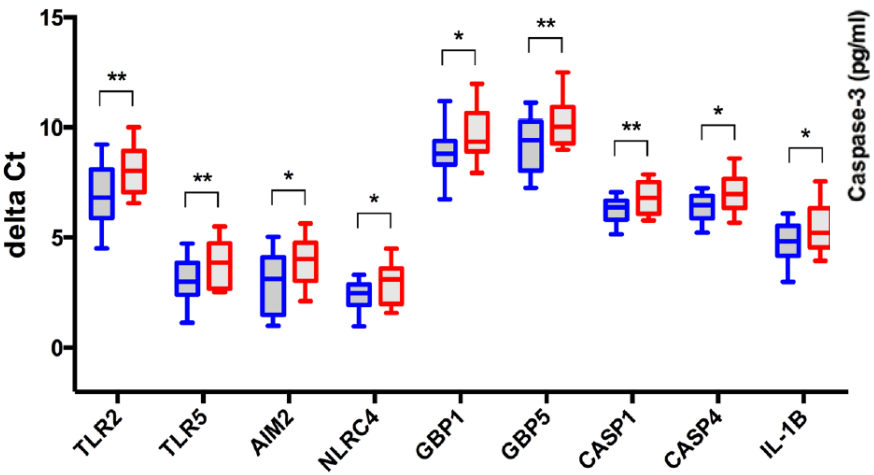
Transcriptional signature at time of TBM-IRIS onset



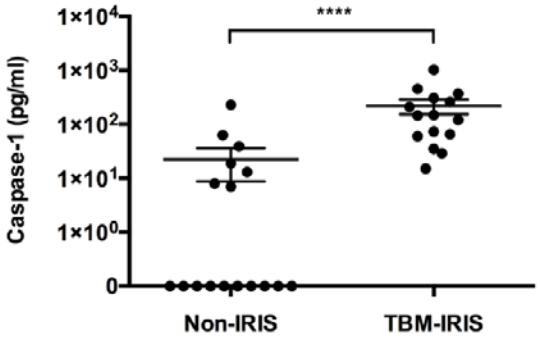
b)

Top 5 canonical pathways	*P*-value
Inflammasome activation	3.72E-05
Phagosome formation	6.08E-05
Role of PRR in recognition of bacteria & viruses	1.80E-04
Role of JAK family kinases in IL-6-type cytokine signaling	2.98E-04
Tol-like receptor signaling	3.99E-04

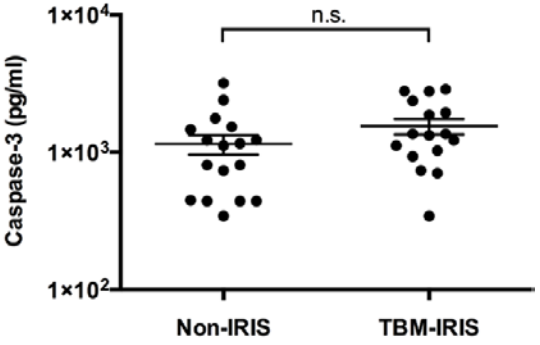
c)



d)

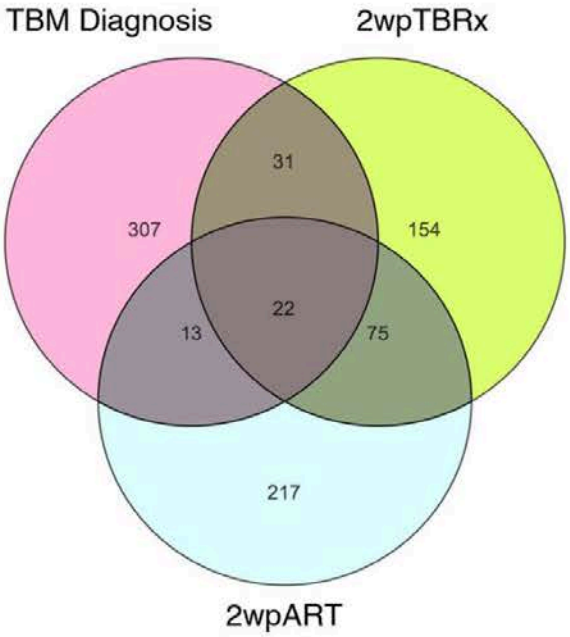


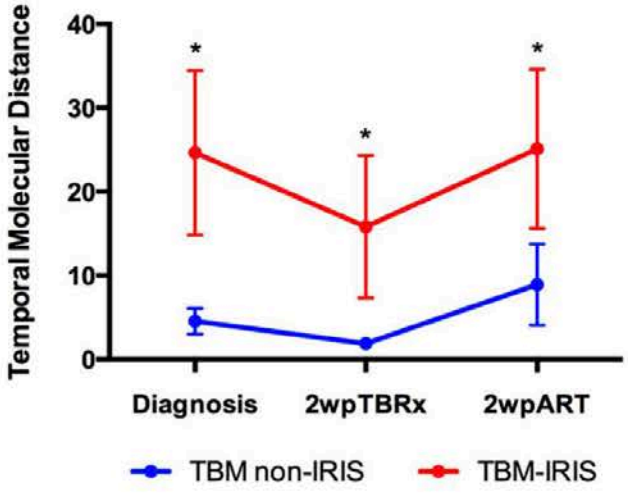
e)



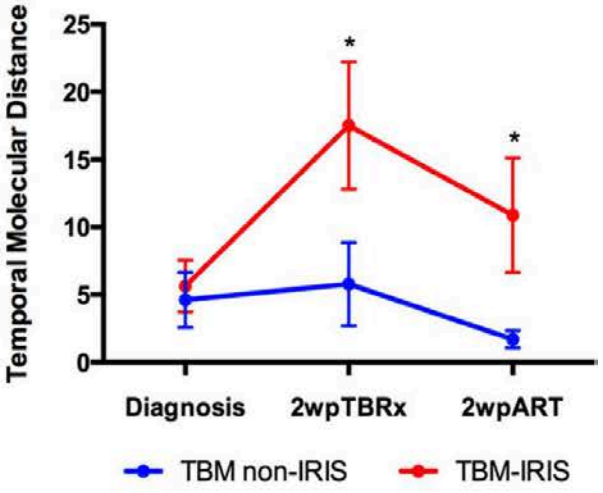
Marais, S., Lai, R.P-J. *et al.* J Infect Dis (2017) 215:677-686

Tracking the transcriptomic perturbation associated with TBM-IRIS





22 common transcripts



21 Inflammasome transcripts

Marais, S., Lai, R.P-J. *et al.* J Infect Dis (2017) 215:677-686

Conclusions

• Combined life-saving therapy for HIV-TB is frequently complicated by iatrogenic worsened immunopathology that can be fatal: TB-IRIS

• The cause of TB-IRIS appears to be a change in innate recognition of a pre-existing pathogen load with downstream inflammatory consequences

• The intense inflammation of TBM-IRIS is antigen load driven associated with inflammasome activation, neutrophil peptides, and elevation of MMP-9

Translational consequences

• Optimize antimicrobial penetration into CSF

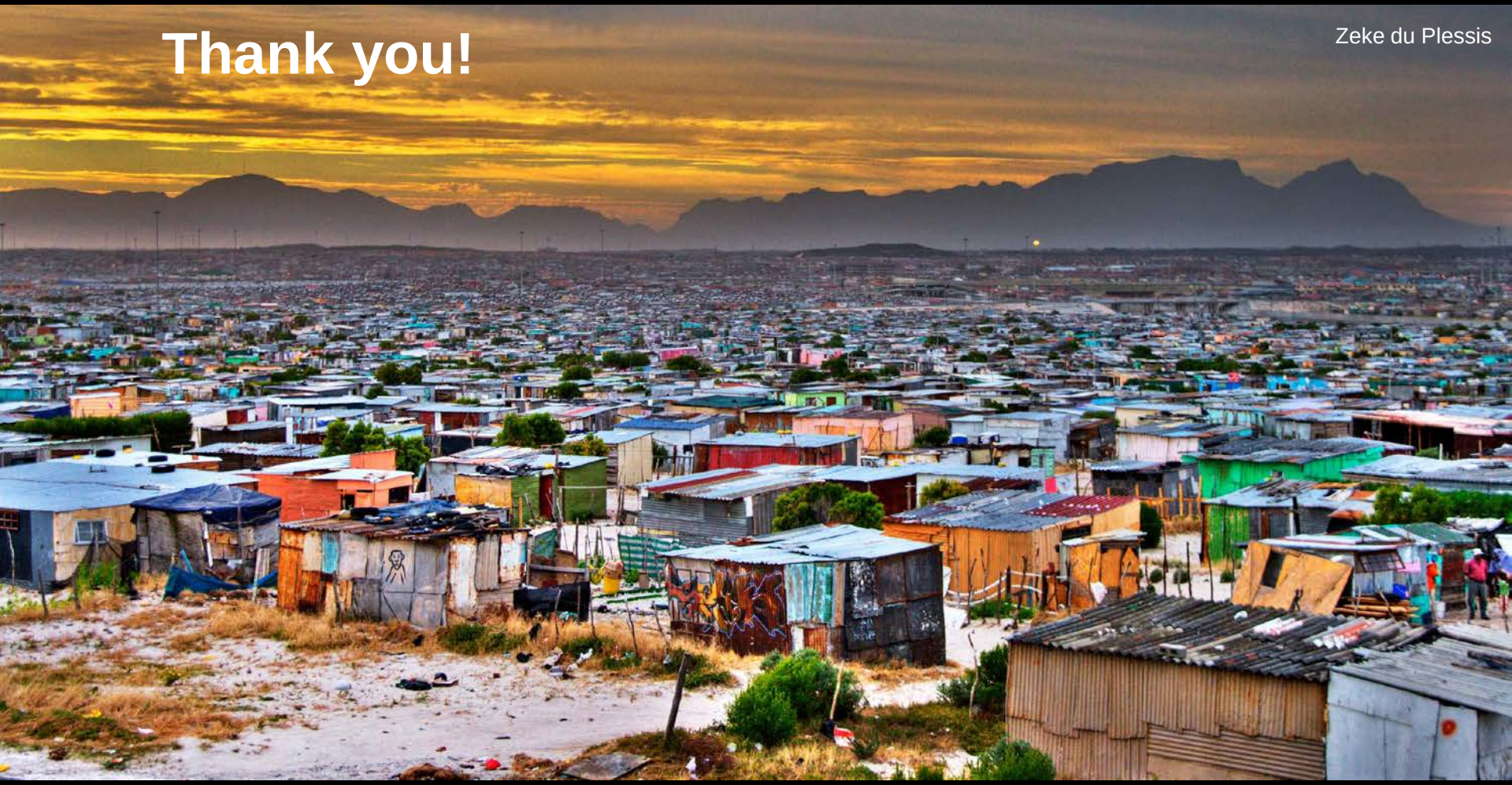
• More rational, effective and safe host-directed therapies of inflammation in tuberculosis should be feasible including both biologics and small molecules

- doxycycline
- anti-TNF
- anti-IL-6
- PDE4 inhibition
- CCR5 antagonism
- inflammasome or IL-1 blockade

Reflections on the road map toward improving HDT

- Insufficient knowledge of pathogenesis
- No *in vitro* or *ex vivo* assays of efficacy to rank and prioritise candidates
- Do preclinical models adequately reflect complexity esp. of HIV-TBM?
- *de novo* approaches would appear less feasible than repurposing
- Drug interactions with rifamycins and ART liable to be significant
- Significant heterogeneity: therapy may ideally be ‘personalised’
- Piggyback approaches in PTB but avoid assumption that ‘one size fits all’

Thank you!



Zeke du Plessis