Knowledge gaps in HIV-TBM

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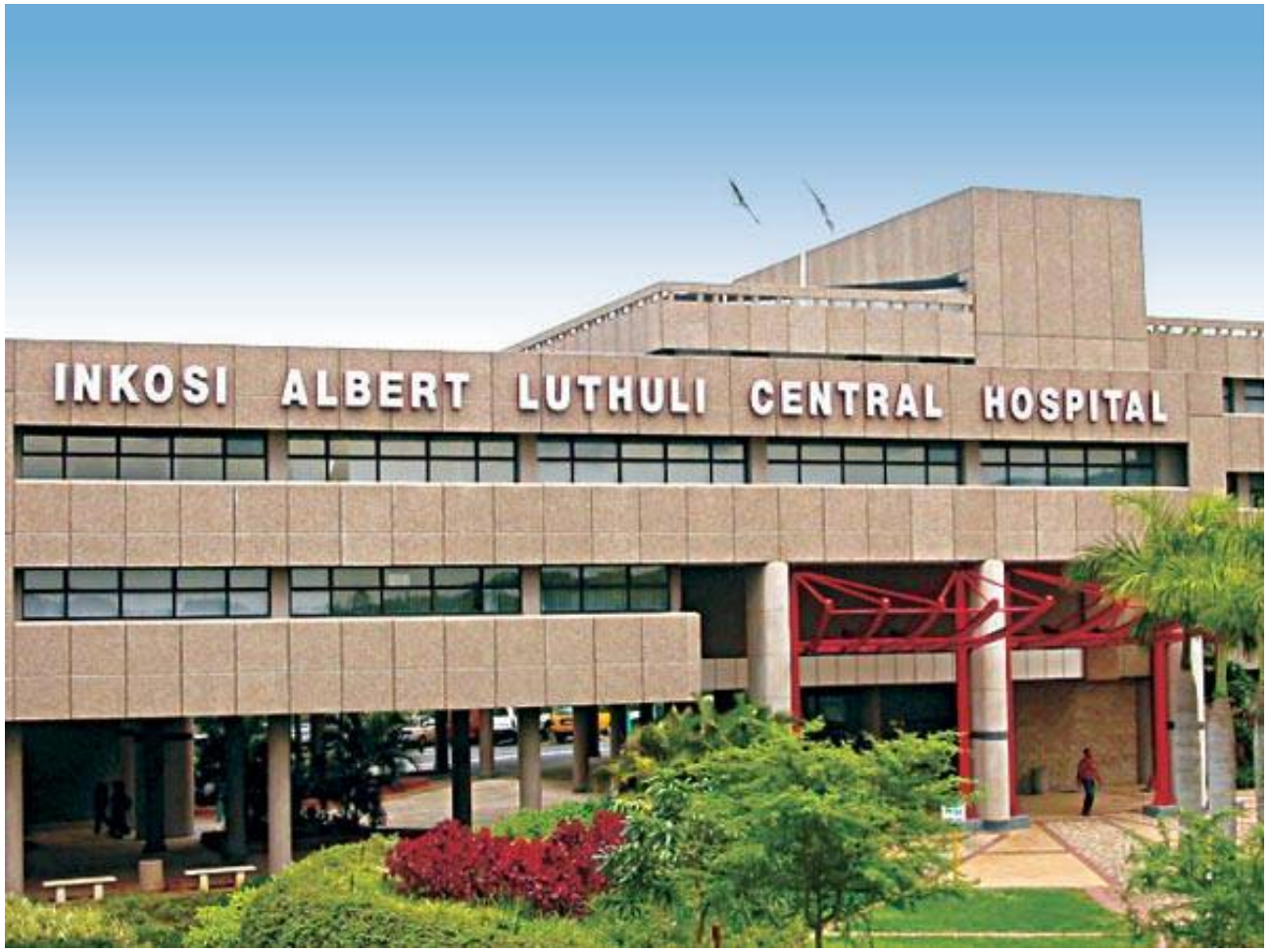
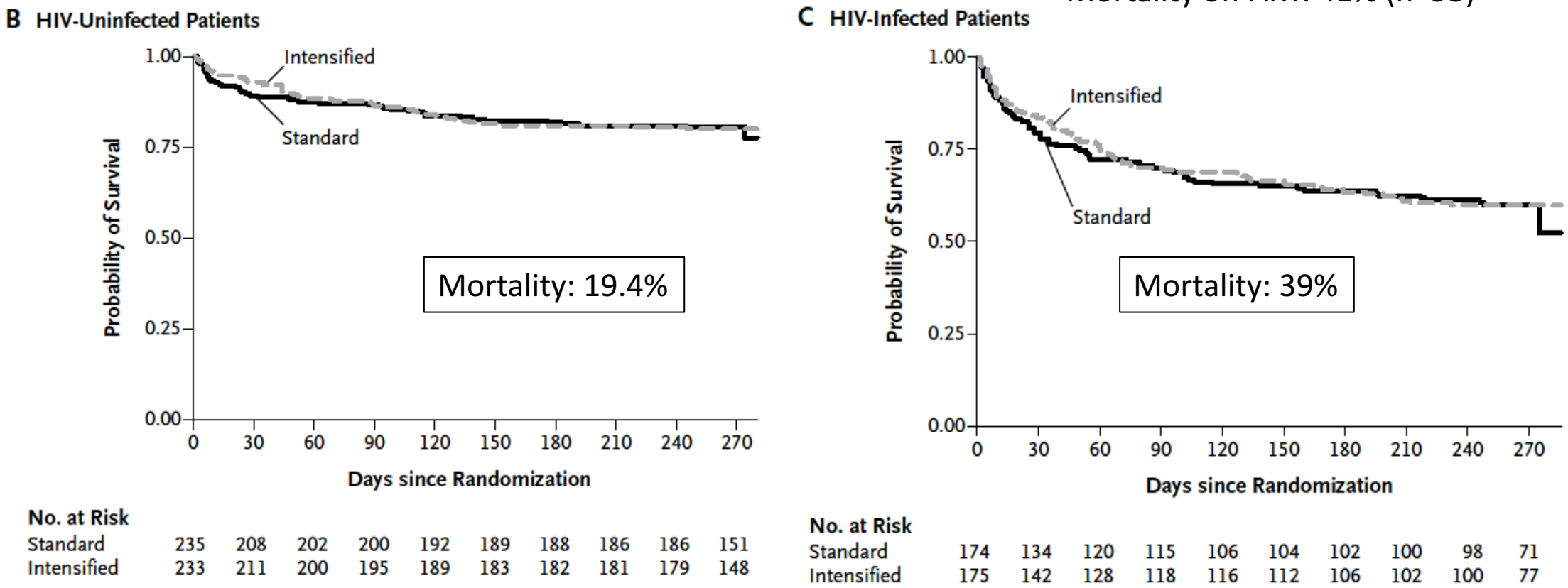


HIV = predictor of mortality in TBM: HR 2.53; 95% CI: 1.90-3.36

On ART at enrollment: 34%
Mortality on ART: 36% (n=43)
Mortality off ART: 41% (n=93)

p=0.42



Heemskerk D. NEJM 2016

Contributing factors to poor outcome

- Spinal complications/presentation

- Immune reconstitution inflammatory syndrome/paradoxical reaction
    - pathogenesis
    - prevention
    - management

- Hydrocephalus

Spinal involvement in HIV-associated neurological TB

- Anderson et al:

Clinical radiculomyelitis in 3% of 104 TBM patients (HIV-infected: n=1)

- Gupta et al:

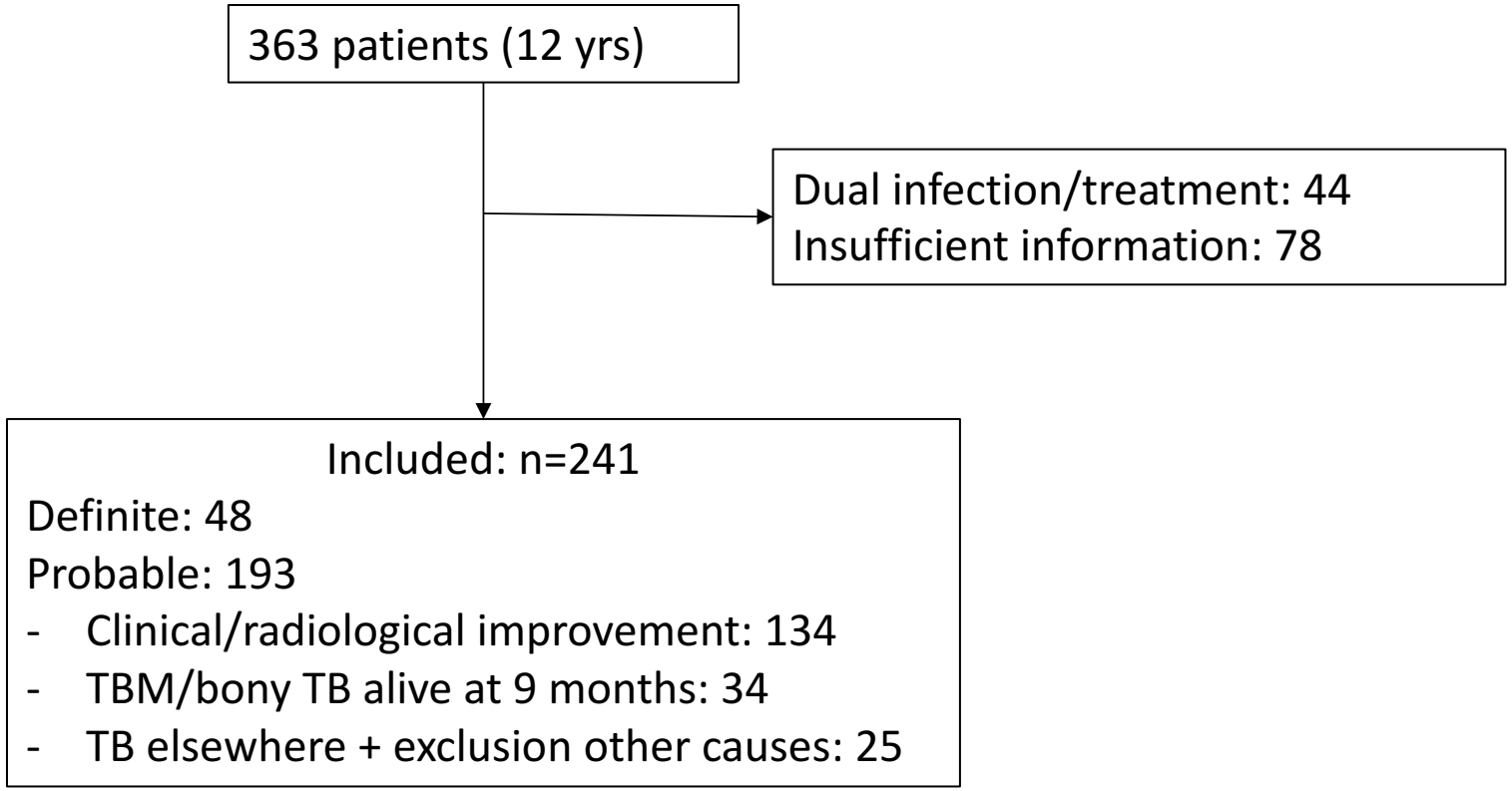
Clinical radiculomyelitis in 46% of 71 TBM patients (HIV-infected: n=2)

- Candy et al:

TBM in 16% of 55 HIV-infected patients with radiculomyelitis

Anderson NE. J Clin Neurosci 2010; Gupta R. Medicine (Baltimore) 2015, Candy S. Spine 2014

Retrospective review of spinal TB at IALCH



Marais S. Unpublished

Patient characteristics

Variable	Median/n	IQR/%
Age	32	(27-41)
Sex (female)	141	(59)
Duration of symptoms	31	(14-87)
Paraplegia	113	(47)
Unable to walk	**196**	**(81)**
Spine and brain involvement	162	(52)
HIV infected	**192**	**(83)**
- CD4 count cells/mm^3	169	(100-284)
- On ART	102	(53)
Spinal symptoms on TB treatment		
- HIV-uninfected	6	(16)
- HIV-infected	**65**	**(34)**

Outcome

Variable	Median/n	IQR/%
Duration of hospital stay (days)	10	(6-16)
In-hospital mortality	3	(0.01)
Follow-up at hospital	120	(50)
Duration of follow-up (months)	12	(3-25)
Followed-up for 9 months	71	(29)
Regained ability to walk	**48**	**(46)**

- HIV-ass spinal TB = significant burden on health services in high TB/HIV settings
- Often occurs after initial improvement on TB treatment for TB elsewhere
- Associated with significant morbidity and poor outcome

Paradoxical neurological TB-IRIS/paradoxical reactions

- **Paradoxical TB reactions more common in HIV:**
- All TB: aOR = 5.05; 95 % CI 1.28-19.85, p = 0.028
- TBM: HIV+ 11/44 (25%), HIV-: 2/97 (2%) p=0.01

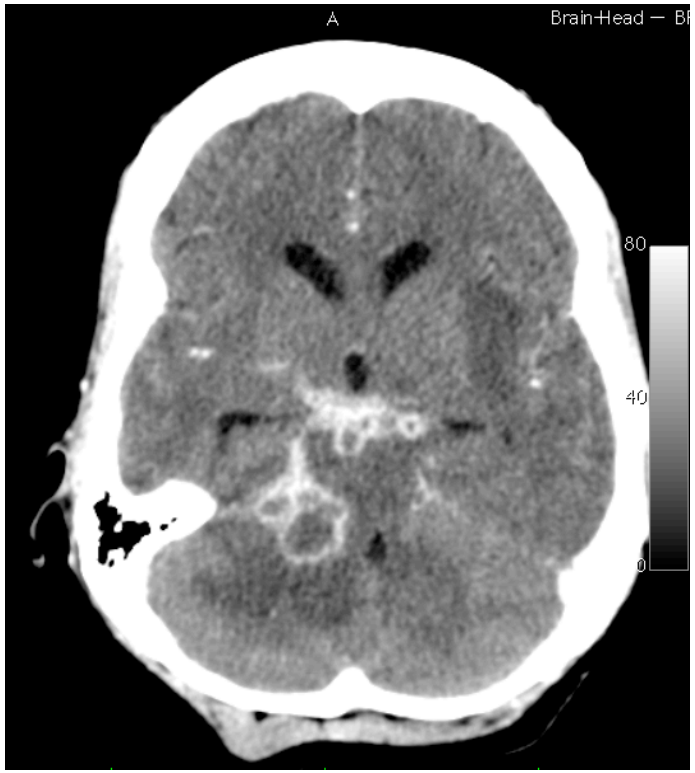
- **Paradoxical TB-IRIS common in high TB/HIV settings:**
- 12% (23/190) TB-IRIS patients
- 21% (16/75) of patients with CNS deterioration within 1 yr of starting ART
- 47% (16/34) of TBM patients who initiated ART 2 weeks after TB treatment

- Mortality is high: 13-30%

Brown CS. BMC Infect Dis; Singh AK. BMC Infect Dis 2016; Pepper DJ. Clin Infect Dis 2009; Asselman V. AIDS 2010; Marais S. Clin Infect Dis 2013

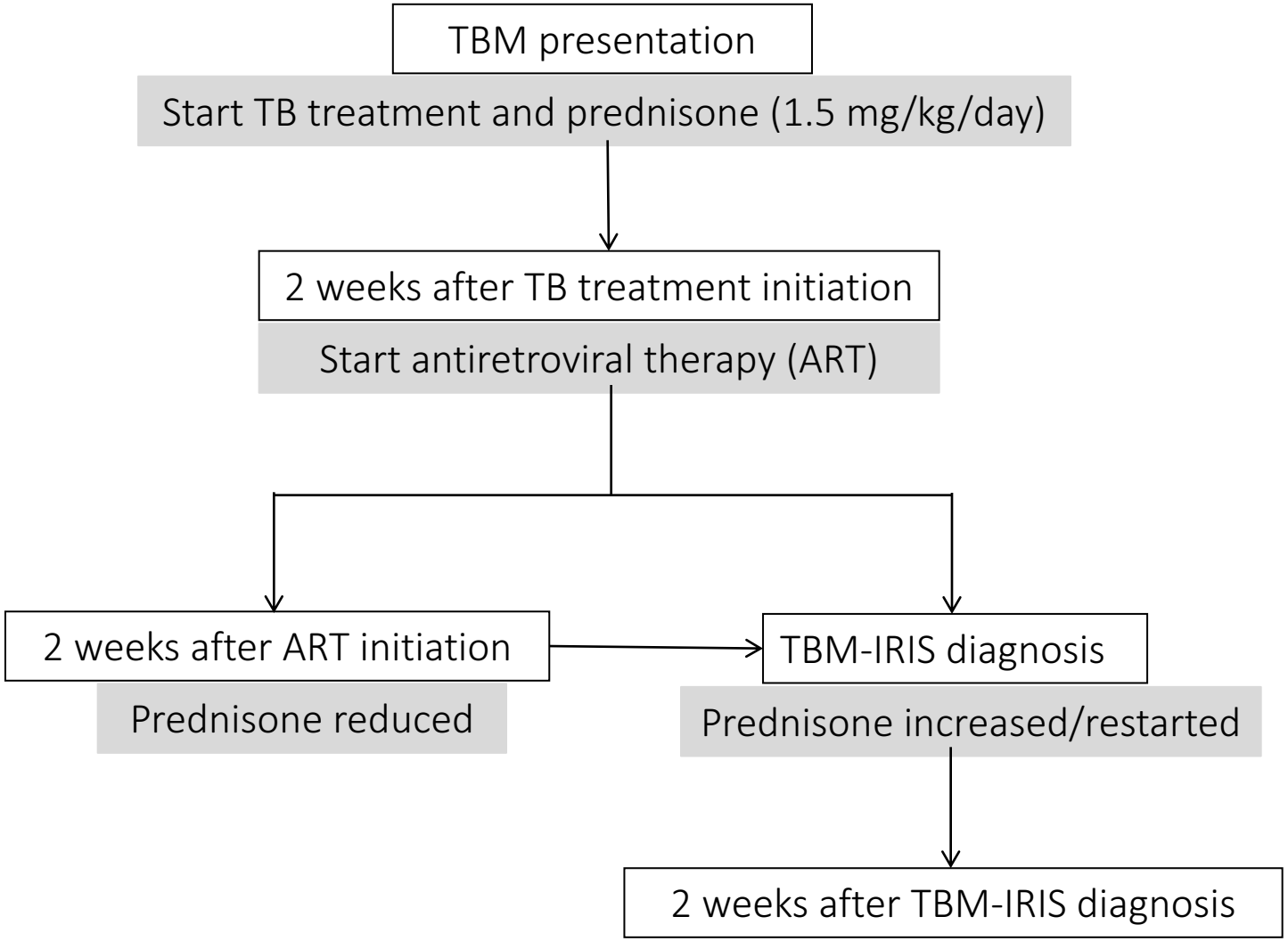
Radiological features of neurologic TB-IRIS

Meningitis and/or tuberculoma



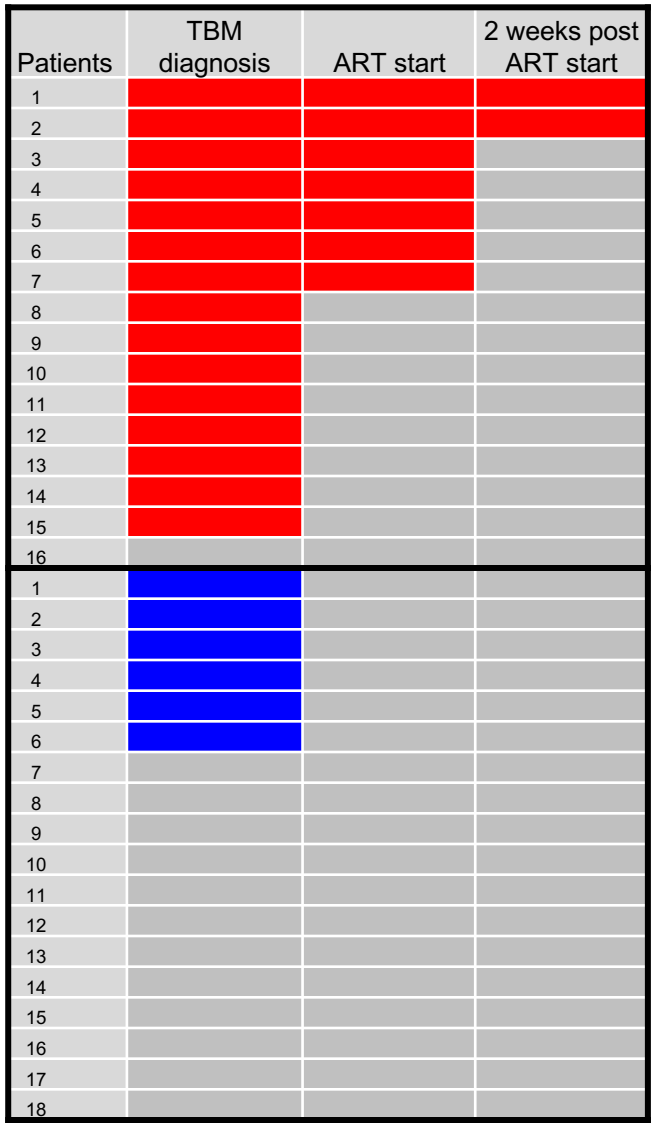
Focal pachymeningitis

Lumbar puncture and phlebotomy performed



Marais S. Clin Infect Dis 2013

CSF *M.tuberculosis* culture positivity



IRIS 15/16
16 days
(IQR 15-20)

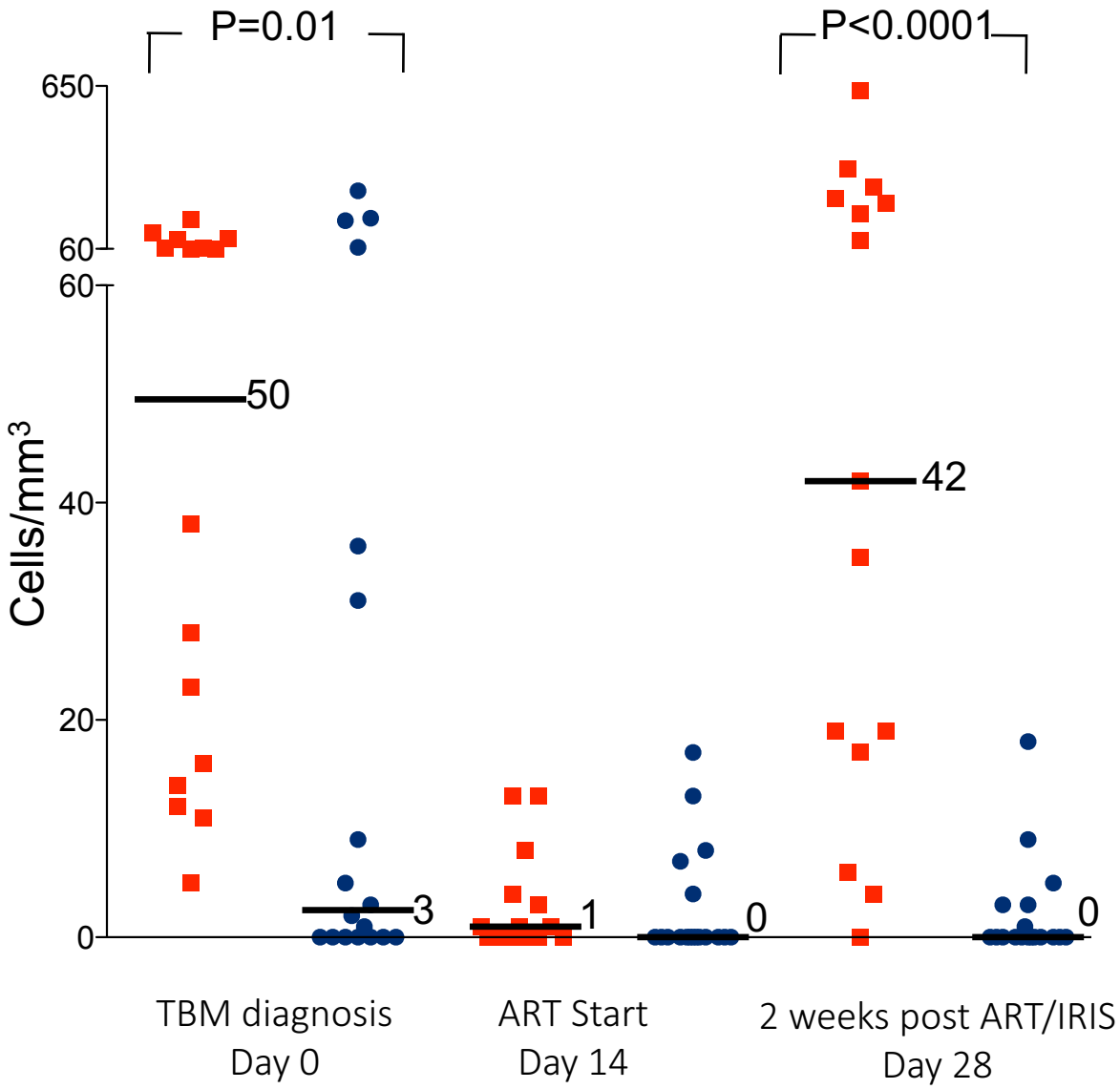
Non IRIS 6/18
(range 4-32 days)

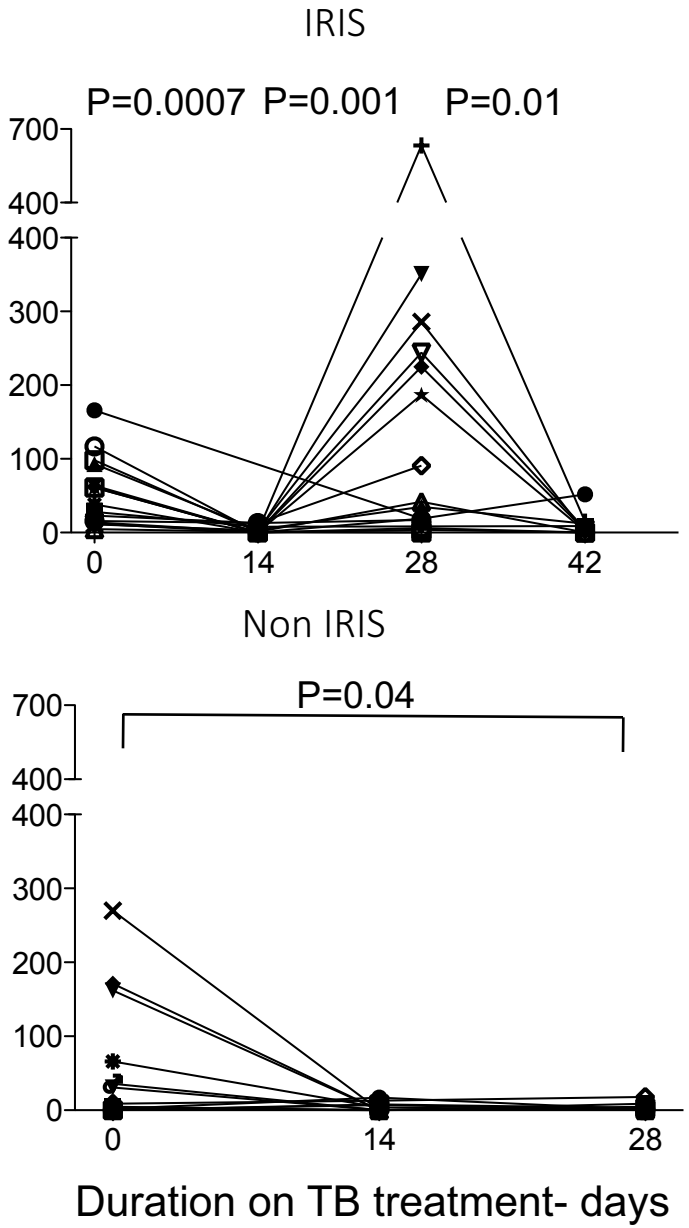
Relative risk of IRIS if culture positive= 9.3, 95% CI 1.4-62.2
P=0.004

IRIS

Non IRIS

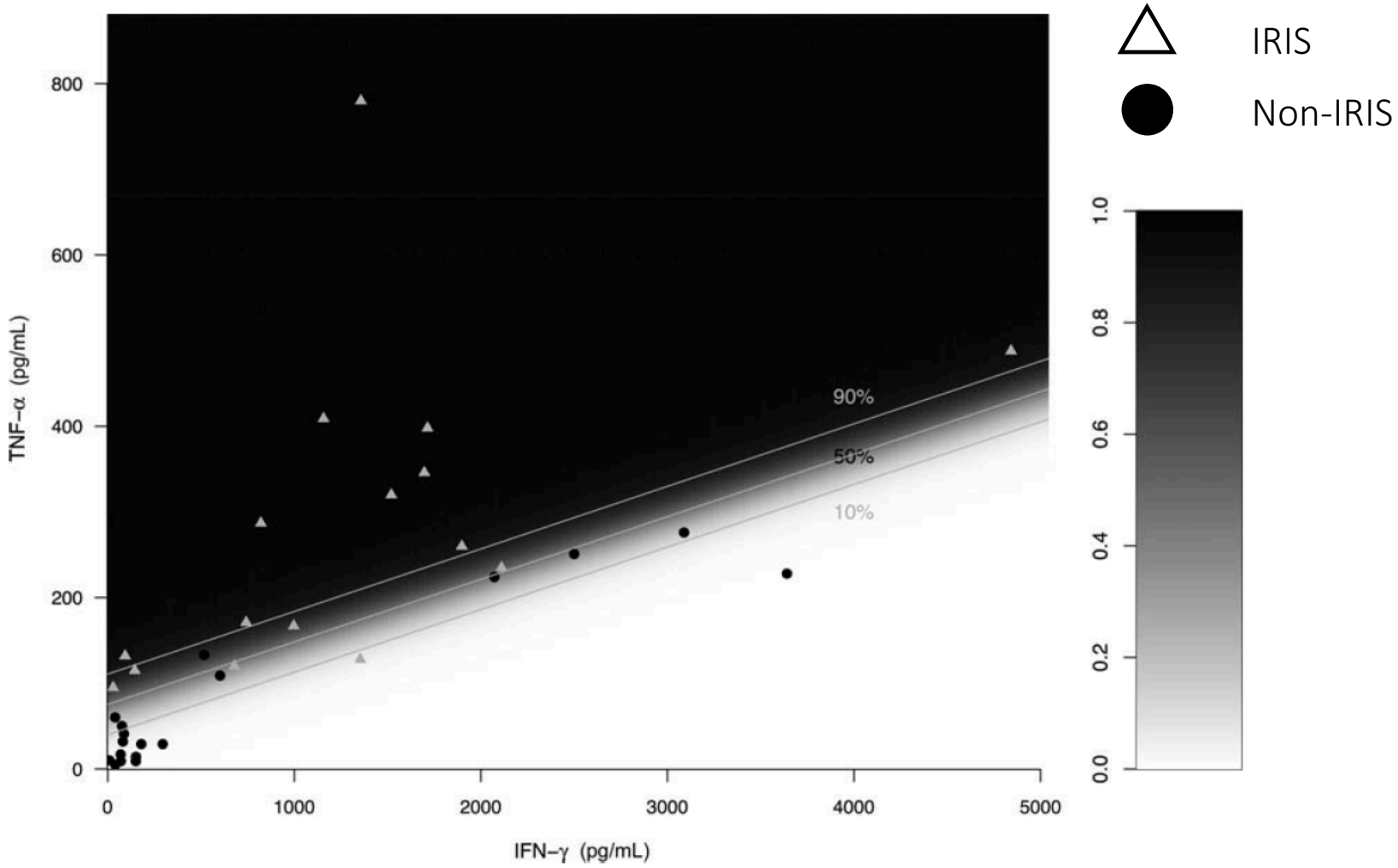
CSF Neutrophil count

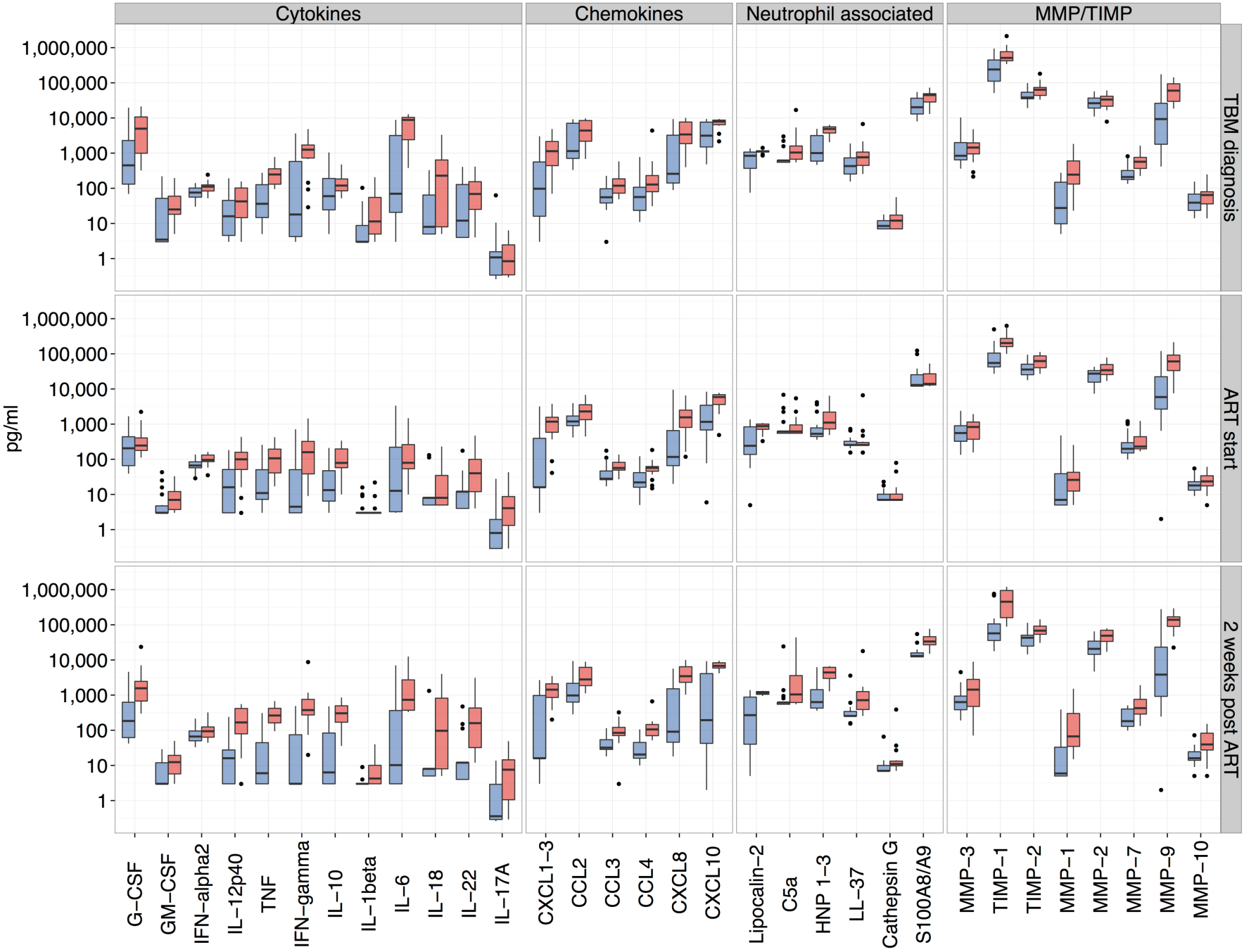




CSF IFN-γ and TNF-α

AUC 0.91 (95% CI 0.53-0.99) p=0.02



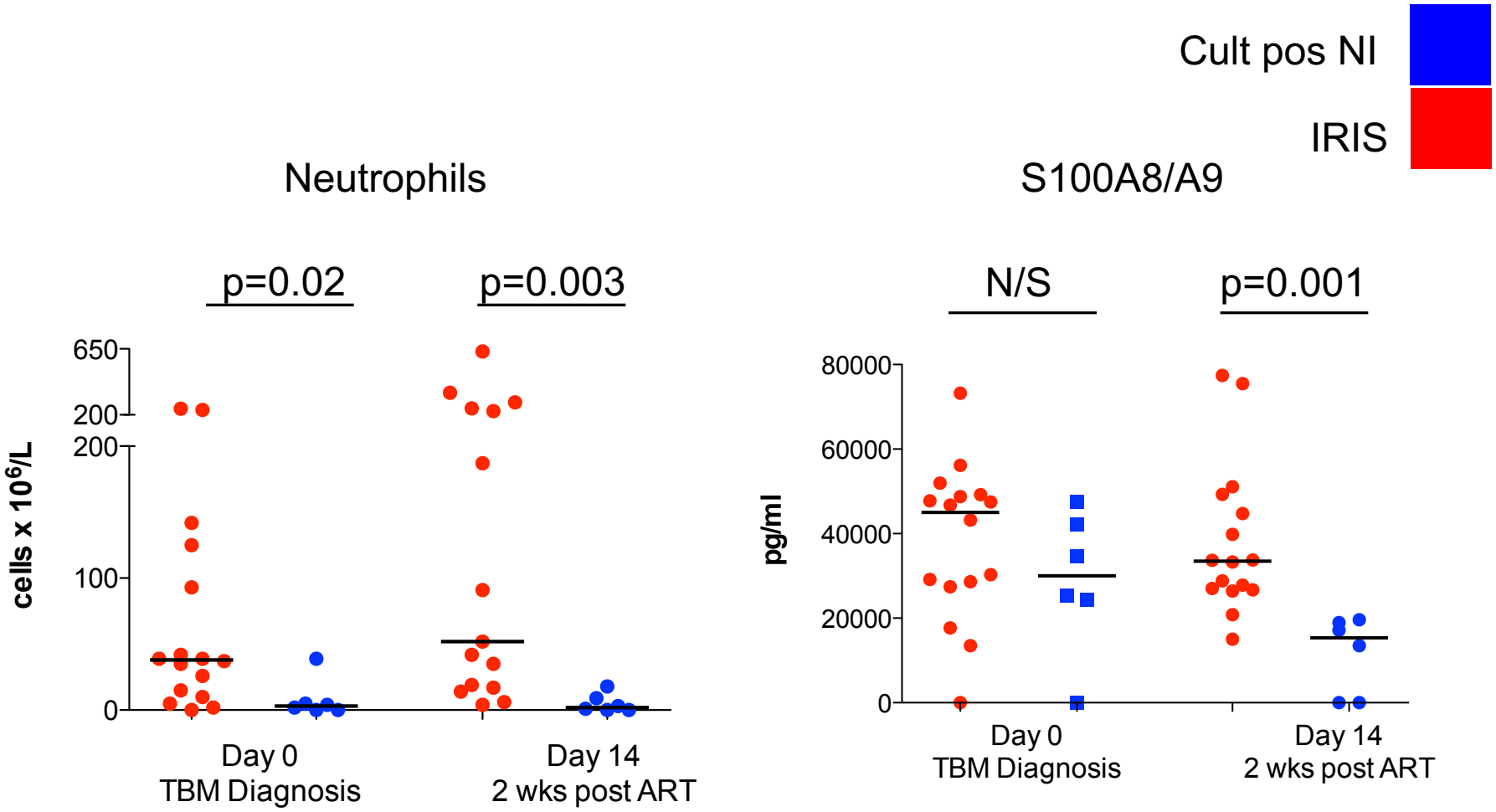


IRIS (n=16)

Non-IRIS (n=18)

Marais S. Clin Infect Dis 2014

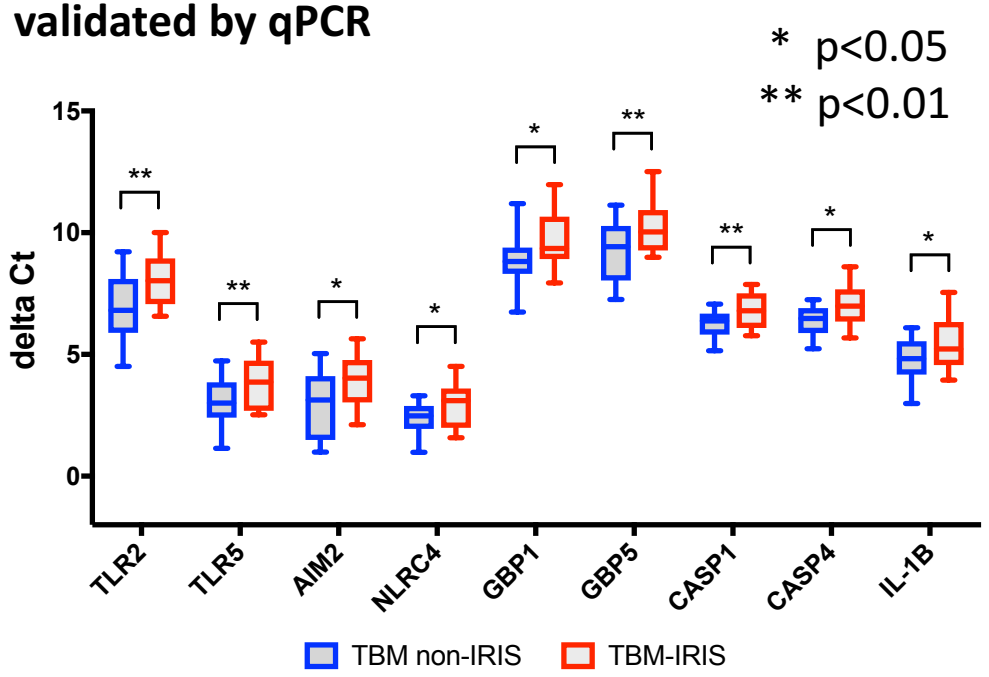
IRIS vs Culture positive Non-IRIS



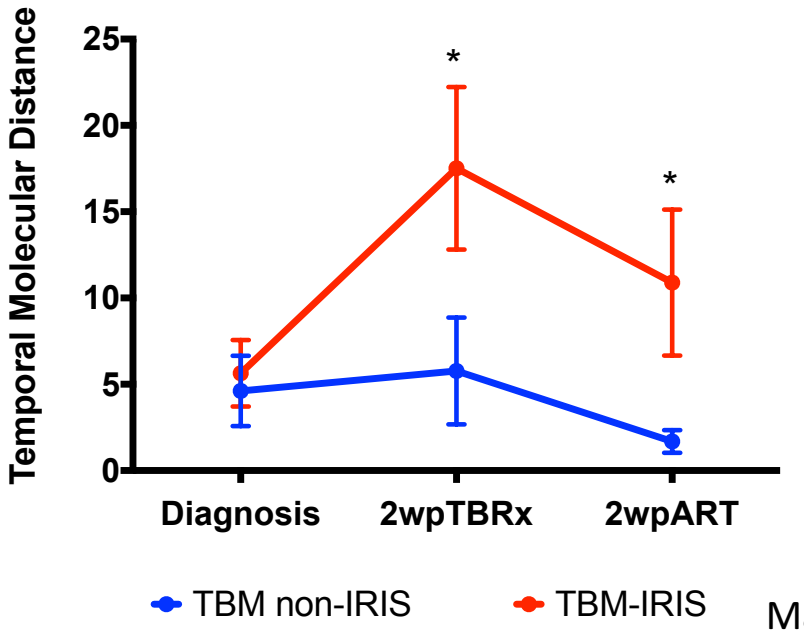
Blood transcriptomic profile in TBM-IRIS

Transcripts upregulated in TBM-IRIS	TBM diagnosis	ART initiation (2 wks after TBM diagnosis)	IRIS presentation (4 wks after TBM diagnosis)
Neutrophil-mediated immune responses			
Inflammasome activation			

mRNA abundance of inflammasome-related genes validated by qPCR



21 Transcripts associated with inflammasome



Marais S & Lai R. J Infect Dis 2017

Conclusion

- High baseline bacillary load
- Corticosteroids was insufficient to prevent production of inflammatory mediators
- Neutrophil-dependent inflammatory responses present prior to TB treatment therapy- ? genetic predisposition (LTA4H, IL-18, TNF-α)
- Inflammasome activation during prior to ART and at time of IRIS

Narendran G. PLoS ONE 2016; Affandi JS. Dis Markers 2013

Reducing bacillary load faster with more effective regimen

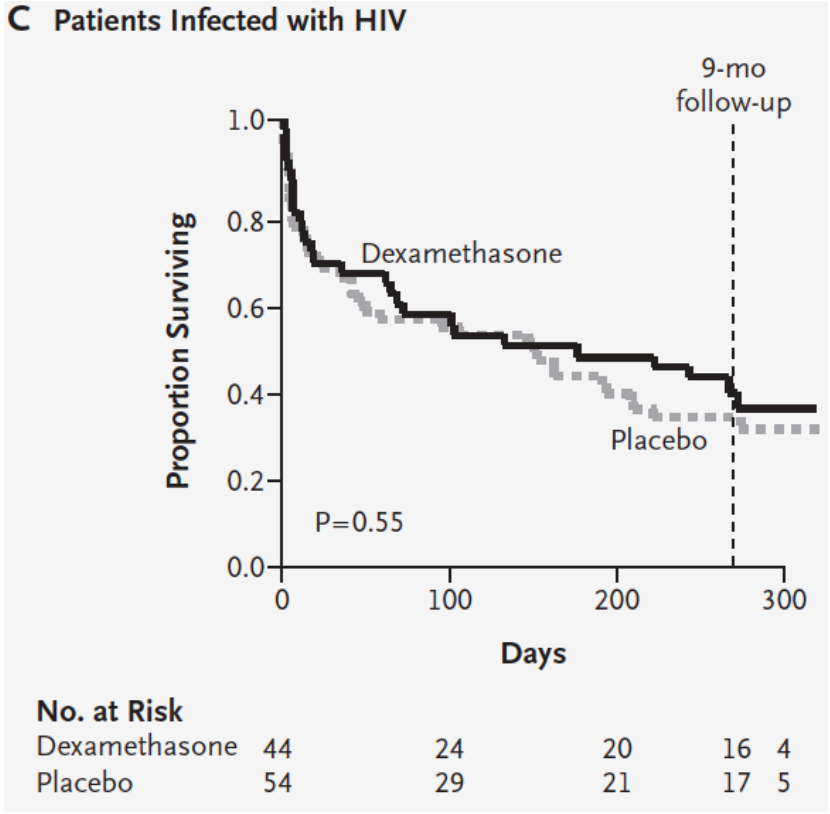
- HIV patients often have malabsorption
- Low rifampicin exposure common in HIV
- Increased oral rifampicin (15 vs 10 mg/kg/day)= no survival benefit
- ? Much higher rifampicin doses ? Intravenously
- Derive and test novel combination antibiotic regimes bespoke for TBM and which can be combined with ART

Gurumurthy P. Clin Infect Dis 2004; McIlleron H. Antimicrob Agents Chemother 2006; Vinnard C. J Antimicrob Chemother 2017; Antwi S. Antimicrob Agents Chemother 2017; Heemskert D. NEJM 2016, Ruslami R. Lancet Infect Dis. 2013

Corticosteroids: ?Benefit ?Harm

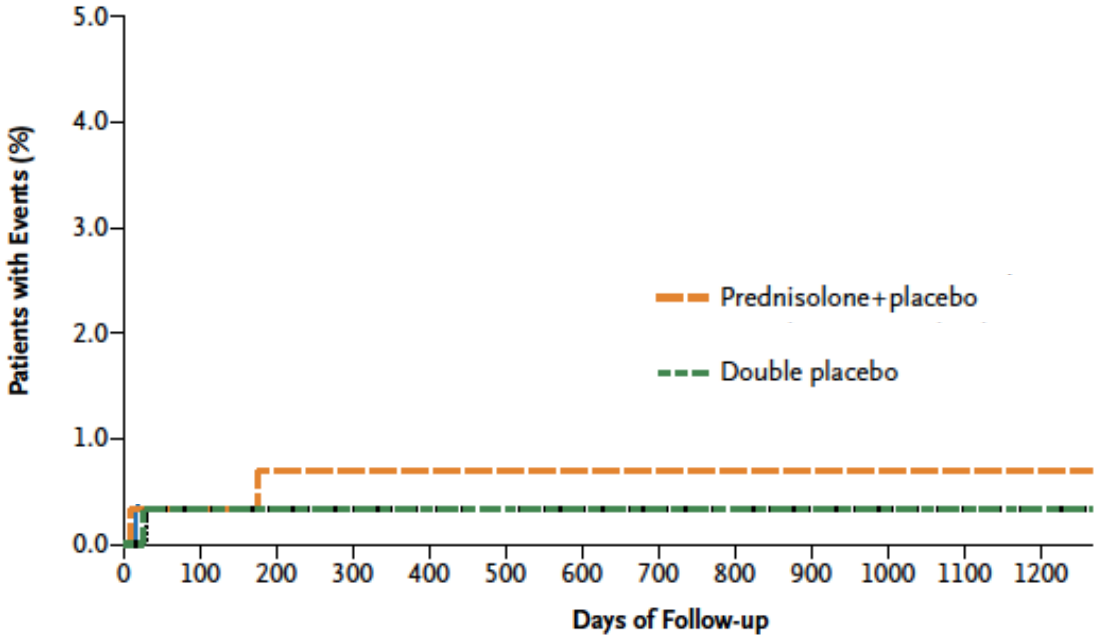
Thwaites et al.

Less severe A/E's



Mayosi et al.

Increased incidence of HIV-related cancers: 0.73 vs. 0.08 p 100 py



Thwaites G. N Engl J Med. 2004, Mayosi BM. N Engl J Med. 2014

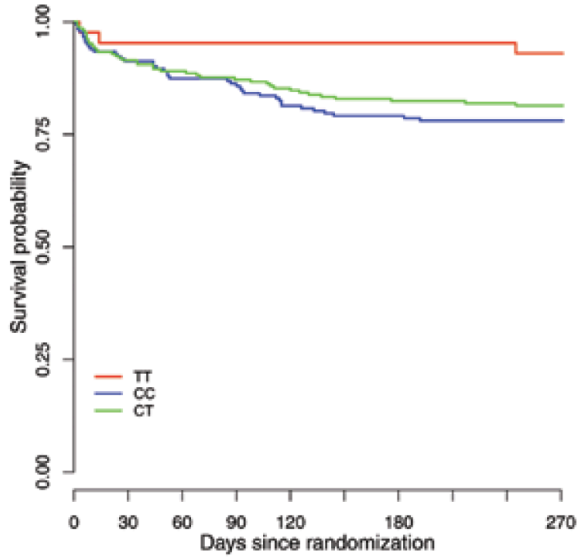
? Benefit of corticosteroids dependent on degree of immunosuppression

- Association of LTA4H genotype and outcome in HIV-uninfected TBM patients in Vietnam, but not Indonesia

Thuong NTT. J Infect Dis 2017; van Laarhoven A. J Infect Dis 2017

Survival in TBM stratified according to LTA4H genotype

B

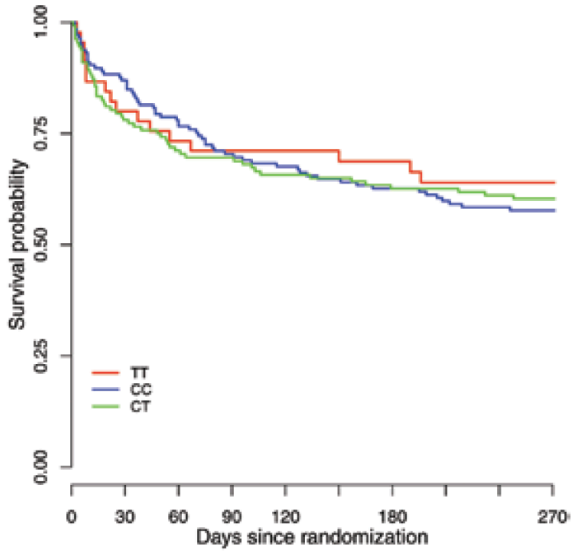


No. at risk

TT	43	41	41	41	41	41	36
CC	184	167	160	157	147	143	110
CT	212	193	186	182	178	172	141

HIV-uninfected

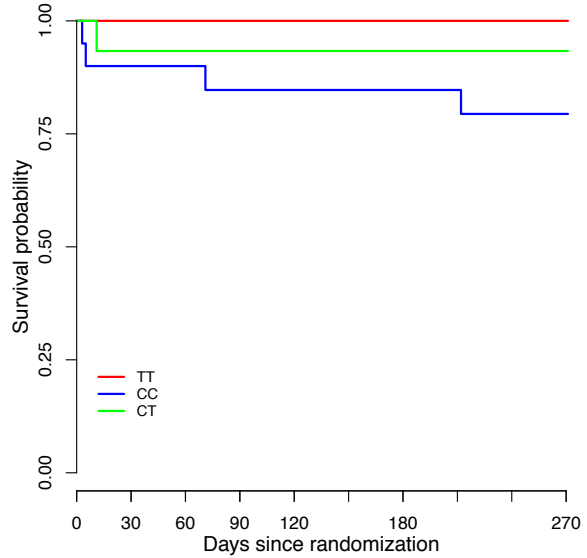
C



No. at risk

TT	46	36	33	32	31	29	18
CC	146	126	113	101	96	89	60
CT	133	103	92	90	85	80	62

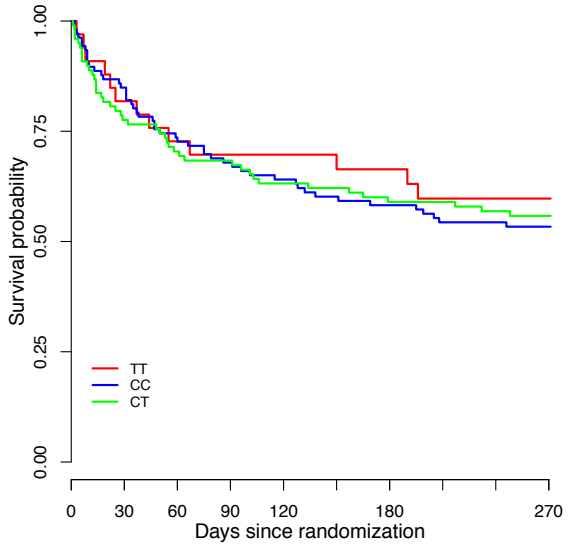
All HIV-infected



No. at risk

TT	4	4	4	4	4	4	2
CC	20	17	17	16	16	16	11
CT	15	14	14	14	14	14	9

HIV-infected
CD4 ≥ 150



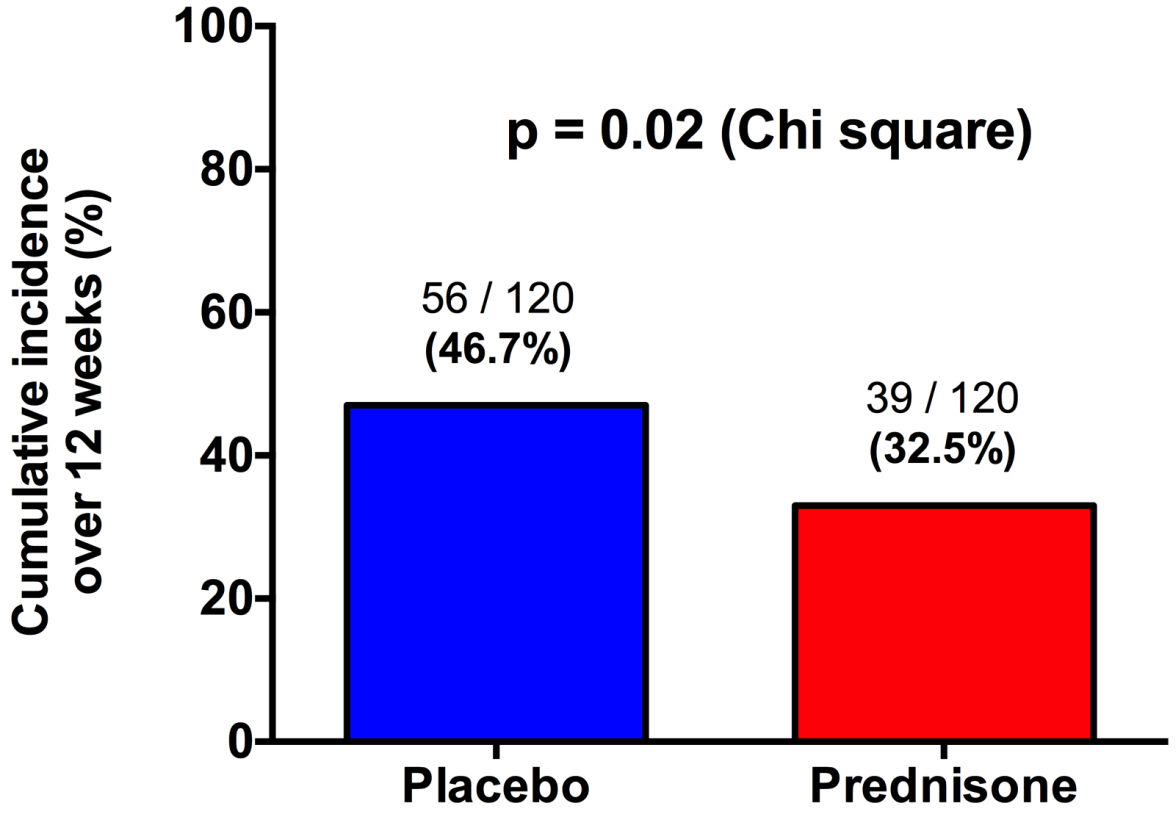
No. at risk

TT	33	27	24	23	22	20	13
CC	106	90	78	71	66	60	40
CT	99	76	68	66	61	56	43

HIV-infected
CD4 < 150

Thuong NTT. J Infect Dis 2017

Prednisone effective for prevention of TB-IRIS in mild/moderate TB



Prednisone 40 mg/day for 2 weeks
then 20 mg/day for 2 weeks
or placebo

Relative risk = 0.70 (95%CI = 0.51 - 0.96)

Meintjes G. CROI 2017 Abstract 81LB, ClinicalTrials.gov NCT01924286, Stek JIMR Research Protocols 2016;5:e173 (*Slide courtesy of G Meintjes)*

Management of neurological TB-IRIS

- ? Higher doses corticosteroids
- ? Alternative agents case reports of benefit in TB-IRIS
  - Thalidomide (Anti-TNF)
  - Montelukast (Leucotriene receptor antagonist)
- ? Alternative agents approved for other indications
  - Tasquinimod (S100A9 inhibitors)

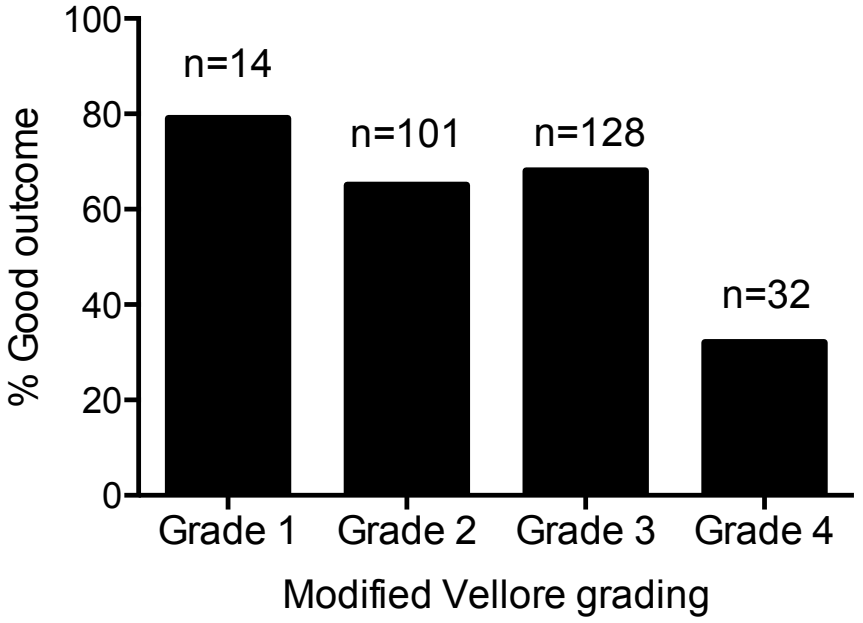
? Investigation of experimental agents

- MCC950 (inhibits NLRP3 inflammasome activation)

Fourcade C. AIDS Patient Care and STDs 2014; van Toorn, R. Eur J Paediatr Neurol 2012; Hardwick C. Sex Transm Infect 2006; Maiga MC. Antimicrob Agents Chemother 2015; Coll RC. Nature Med 2015.

Ventriculo-peritoneal shunting for hydrocephalus in TBM

"Good outcome" (GOS 4-5)
GOS 4: Moderate disability
GOS 5: Good recovery



Modified Vellore grading

1: GCS 15 - deficit
2: GCS 15 + deficit
3: GCS 9-14 ± deficit
4: GCS 3-8 ± deficit

Rizvi I. J Neurol Sci 2017

Ventriculo-peritoneal shunting for hydrocephalus in TBM according to HIV status

	Nadvi (South Africa)	Sharma (India)
Patients/group (n)	15	30
Age HIV+/HIV- (years, mean±SD)	26 ±16 /10±9	31±7/31±9
CD4: HIV (cells/mm^3)	183 ±161 (mean ± SD)	143 (26-445) (median, range)
ART prescription	No	??
Mortality HIV+/HIV- (%)	67/27 (p<0.067) 1 month	67/31 Follow-up (p=0.03)
Good outcome (GOS 4 or 5) HIV+/HIV- (%)	27/60	24/65

Nadvi SS. Neurosurgery 2000; Sharma RM. J Neurosurgery 2015

Research priorities in HIV-associated TBM

- Spinal complications of TB
- Pathogenesis of neurological TB-IRIS/paradoxical reactions

- genetics
- neutrophils
- Inflammasome

- Prevention/management neurological TB-IRIS/paradoxical reactions
- Management of hydrocephalus

Acknowledgements

UCT

Robert J Wilkinson
Graeme Meintjes
Katalin Wilkinson
Rachel Lai
Monica Magwayi
Dominique J Pepper
Zahiera Ismail
Charlotte Schutz
Ronnett Seldon
Nzwaki Bangani
Armin Deffur
Kathy Wood
Rene Goliath
Anna Coussens
Maia Lesosky

IALCH/UKZN

Ahmed I Bhigjee
Vinod Patel
Izanne Roos

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