



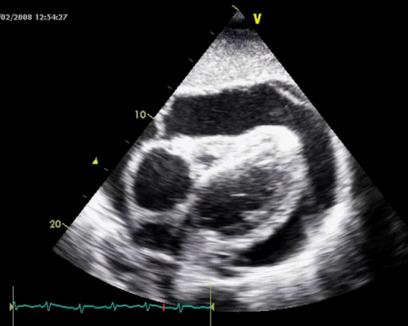
The management of TB pericarditis. Lessons from the **IMPI** project

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2





Acknowledgement and Thanks!

- All the many patients who consented to participate
- Eastern Cape investigators and collaborators

- Funders
 - MRC
 - CIHR
 - Cadilla

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2001



Thabo Mbeki is President

Nkosi Johnson house hold name

Marike de Klerk is murdered in
CT

Gordon Igesund & SANTOS win
PSL

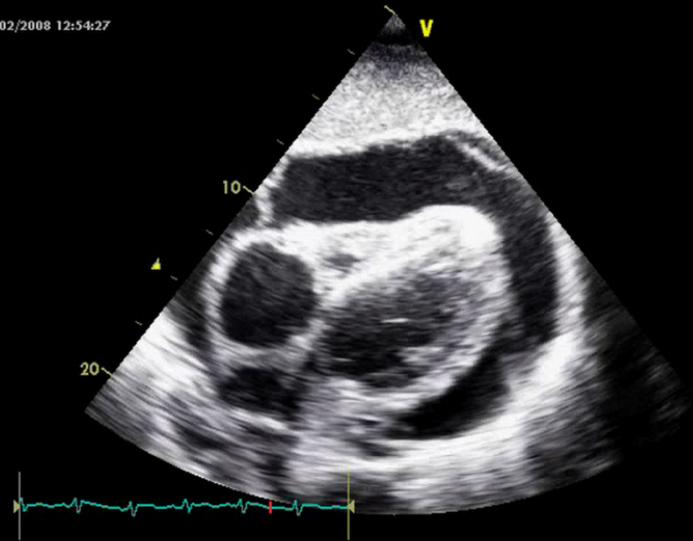
Springboks bottom of Tri
Nations

Approach to TB pericarditis-2001

32 year old woman

- HIV infected CD4 198
- DOE and JVP peripheral edema
- Constitutional illness
- large pericardial effusion with shaggy pericardial border

05/02/2008 12:54:27
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- ✓ Empiric dx of TB pericarditis
- ✓ 6 months anti-TB therapy
- ✓ Bactrim prophylaxis
- ?? Corticosteroids
- ?? Tx pericardiocentesis
- ?? ART

TB pericarditis-HIV uninfected

HIV Uninfected

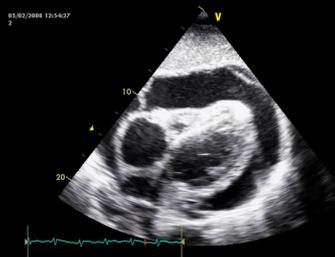
- Paucibacillary condition
- Spread via lymph nodes
- Viable antigens presented by CD4 cells trigger inflammation, granuloma formation, cytolysis and a fibrinous exudate rich with profibrotic cytokines

HIV Uninfected

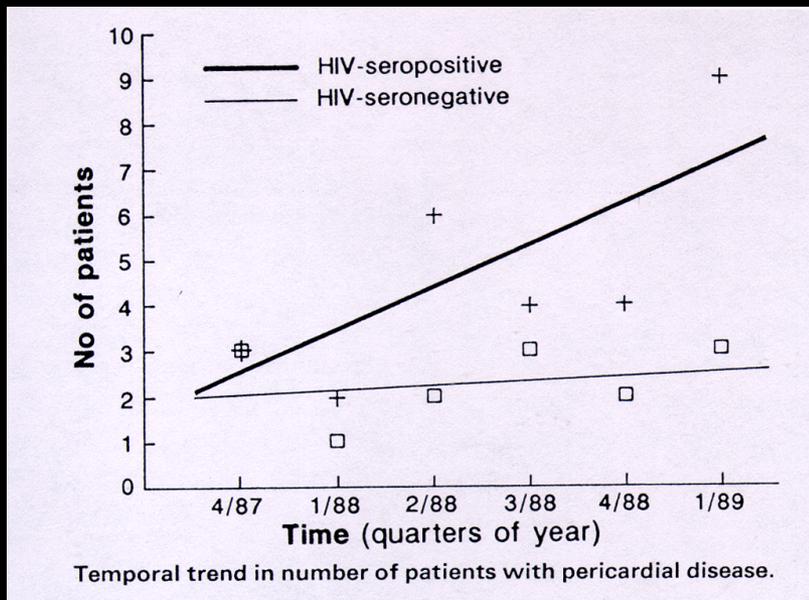
- Mortality **8-15%**
- Constrictive Pericarditis **25%**
- **Consensus on** Corticosteroid use growing



Impact of HIV on TB pericarditis?



Pericardial disease and HIV in 1 hospital, Dar es Salaam, Tanzania



- Growing number of publications from **E.Africa**
- Incidence of TB pericarditis rising, driven by HIV
- Autopsy data from patients who die with advanced HIV reveal pericardial TB is frequent (**15-30%**)



Unanswered questions in 2001



1. How does HIV influence the **clinical characteristics and presentation and natural history** of pericardial TB?
2. Does HIV alter the **immune response** within the pericardium of patients with TB pericarditis
3. How does HIV alter the **diagnostic considerations** of TB in patients with suspected pericarditis
4. Is 6 months TB treatment long enough for TB pericarditis in pts with HIV?
5. What is the role of **adjunctive steroids**?

What is the role of **adjunctive steroids** in patients with and without HIV

1. *Systematic review of the evidence from the literature*
2. *Conducted a Pan African survey across hospitals and clinicians about their current practice*

Q J Med 2003; **96**:593–599
doi:10.1093/qjmed/hcg100

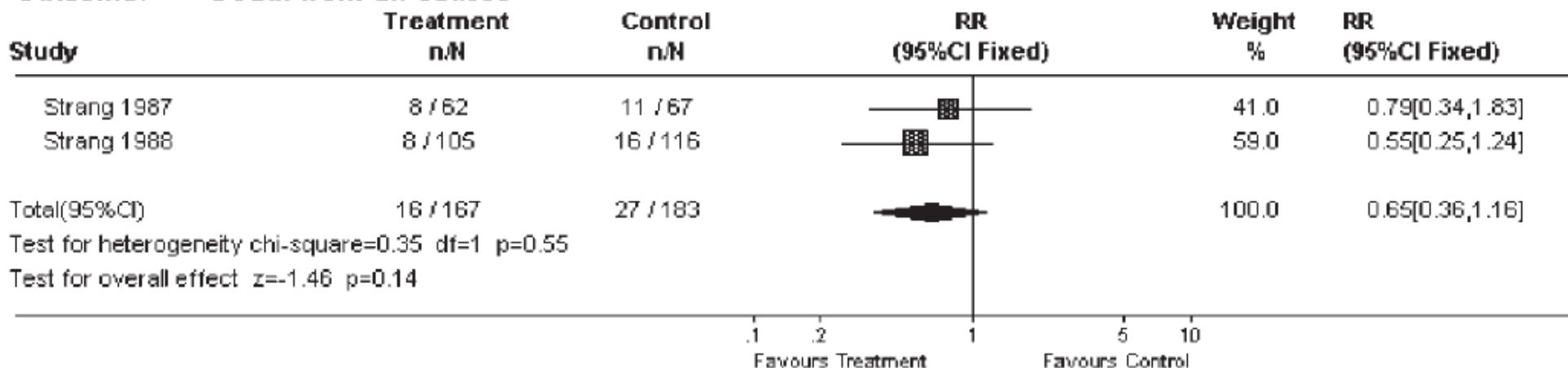
Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven

M. NTSEKHE¹, C. WIYSONGE², J.A. VOLMINK³, P.J. COMMERFORD¹ and
B.M. MAYOSI¹

From the ¹Cardiac Clinic, Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa, ²Ministry of Public Health, BP 25125 Messa, Yaoundé, Cameroon, and ³School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

Comparison: Tuberculous pericarditis: steroids vs. placebo

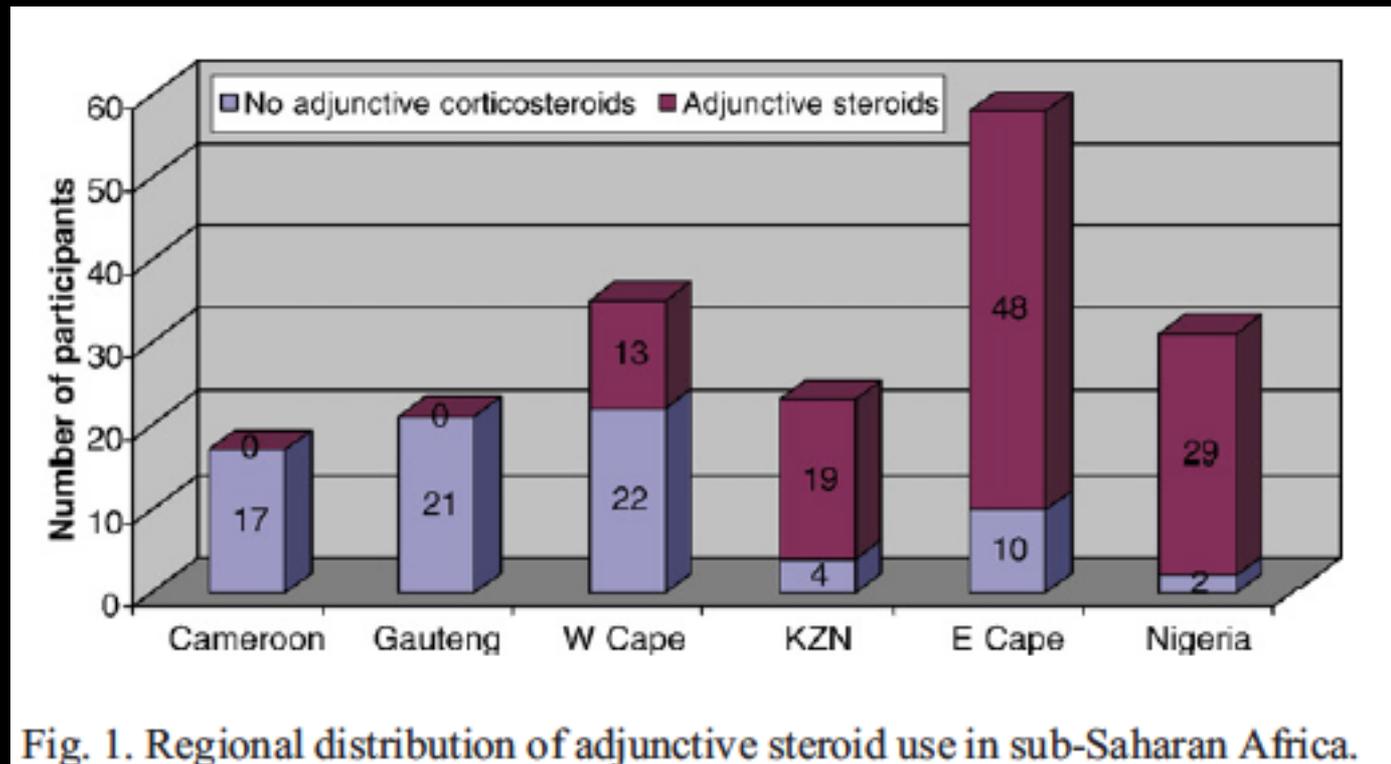
Outcome: Death from all causes



Contemporary use of adjunctive corticosteroids in tuberculous pericarditis[☆]

Charles S. Wiysonge^a, Mpiko Ntsekhe^a, Freedom Gumedze^b,
Karen Sliwa^c, Kathleen Ngu Blackett^d, Patrick J. Commerford^a,
Jimmy A. Volmink^{e,1}, Bongani M. Mayosi^{a,*}

International Journal of Cardiology 124 (2008) 388–390



1)-CLINICAL EQUIPOISE and 2)-Inconclusive evidence from small studies

Need Large Simple Randomized Control Trial

1)-Clinical equipoise 2)-Inconclusive evidence from small studies 3] Potential for important benefits

Discussion: Steroids could have large beneficial effects on mortality and morbidity in tuberculous pericarditis, but published trials are too small to be conclusive. Large placebo-controlled trials are required, and should include sufficient numbers of HIV-positive and HIV-negative participants, and an adequate adjuvant steroid dose.



2004



Initiative for the **I**nvestigation and **M**anagement of **P**ericarditis **I**n Africa

I nvestigation of the M anagement of P ericarditis I n Africa

Phase 1

Set up research network to conduct a large simple RCT

2004



2009

Prospective Registries
Collect data to allow the appropriate design of RCT

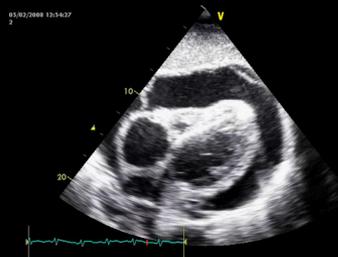
Phase 2

2009



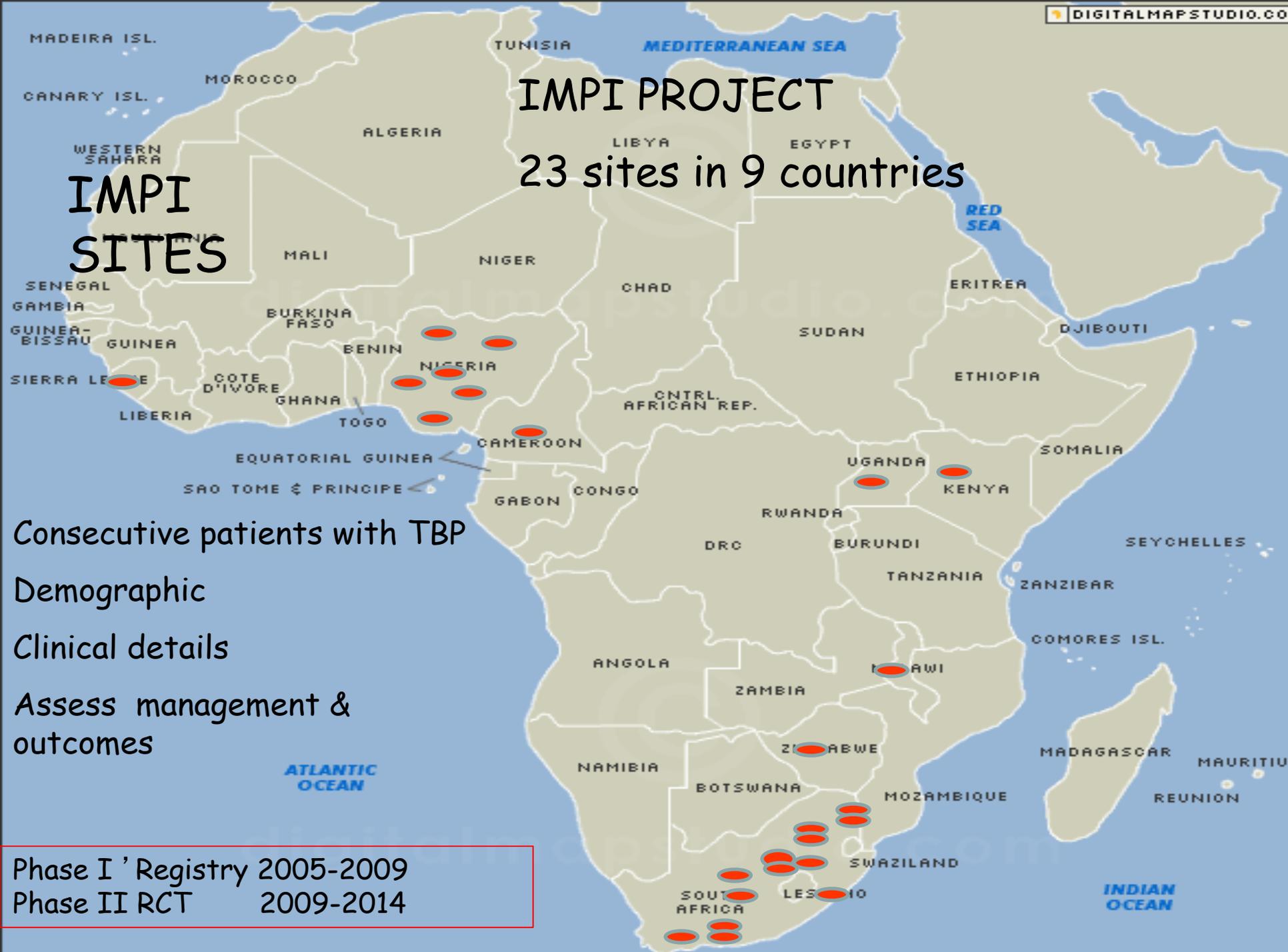
2014

Large Simple multi center Pan Africa Randomized Control Trial



IMPI SITES

IMPI PROJECT 23 sites in 9 countries



Consecutive patients with TBP

Demographic

Clinical details

Assess management & outcomes

Phase I ' Registry 2005-2009
Phase II RCT 2009-2014

Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: the *Investigation of the Management of Pericarditis in Africa* (IMPI Africa) registry

Bongani M Mayosi^{1*}, Charles Shey Wiysonge¹, Mpiko Ntsekhe¹, Jimmy A Volmink², Freedom Gumedze³, Gary Maartens⁴, Akinyemi Aje⁵, Baby M Thomas⁶, Kandathil M Thomas⁶, Abolade A Awotedu⁶, Bongani Thembela⁷, Phindile Mntla⁸, Frans Maritz [Late]⁹, Kathleen Ngu Blackett¹⁰, Duquesne C Nkouonlack¹⁰, Vanessa C Burch¹¹, Kevin Rebe¹¹, Andy Parish¹², Karen Sliwa¹³, Brian Z Vezi¹⁴, Nowshad Alam¹⁵, Basil G Brown¹⁶, Trevor Gould¹⁷, Tim Visser¹⁸, Muki S Shey¹⁹, Nombulelo P Magula²⁰, Patrick J Commerford¹

200 pts

- 64% of patients treated empirically
- 21% of those with centesis had an alternative non-TB diagnosis (bacteria, TB plus bacteria, other)
- 40% advanced HIV
- 60% treated with corticosteroids
- Those with HIV less likely to receive steroids, or pericardiocentesis



ORIGINAL ARTICLES

Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa

Bongani M Mayosi, Charles Shey Wiysonge, Mpiko Ntsekhe, Freedom Gumedze, Jimmy A Volmink, Gary Maartens, Akinyemi Aje, Baby M Thomas, Kandathil M Thomas, Abolade A Awotedu, Bongani Thembela, Phindile Mntla, Frans Maritz, Kathleen Ngu Blackett, Duquesne C Nkouonlack, Vanessa C Burch, Kevin Rebe, Andy Parrish, Karen Sliwa, Brian Z Vezi, Nowshad Alam, Basil G Brown, Trevor Gould, Tim Visser, Nombulelo P Magula, Patrick J Commerford

S Afr Med J 2008; 98: 36-40.

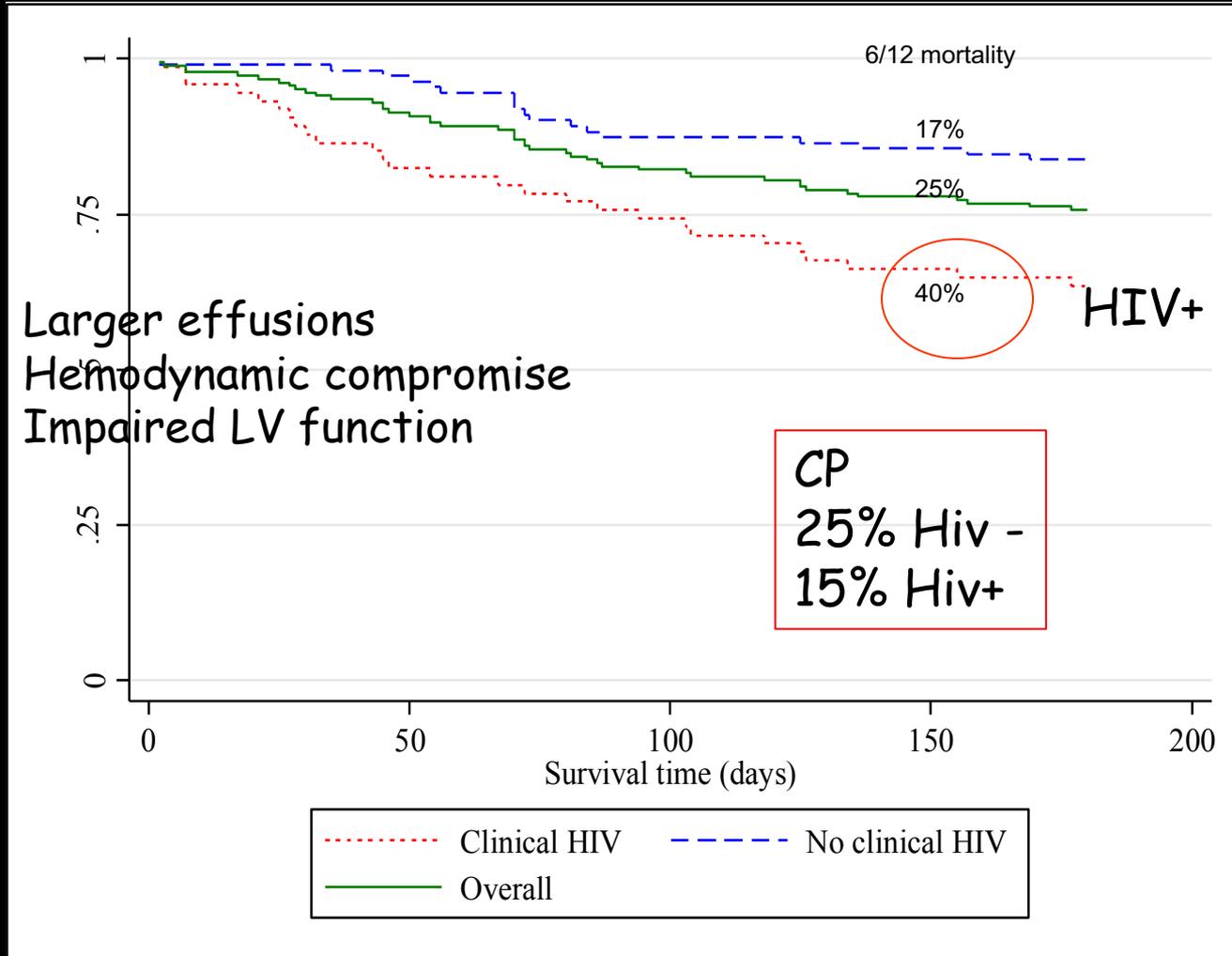


Figure 1: Survival during follow-up in the whole study population and by clinical HIV status (P = 0.001 for the difference in survival experiences between groups defined by clinical HIV)



2009



- Network of research sites
- Research infrastructure and capacity
- Feasibility assessment complete
- Shoe string budget raised
- Ready to conduct RCT



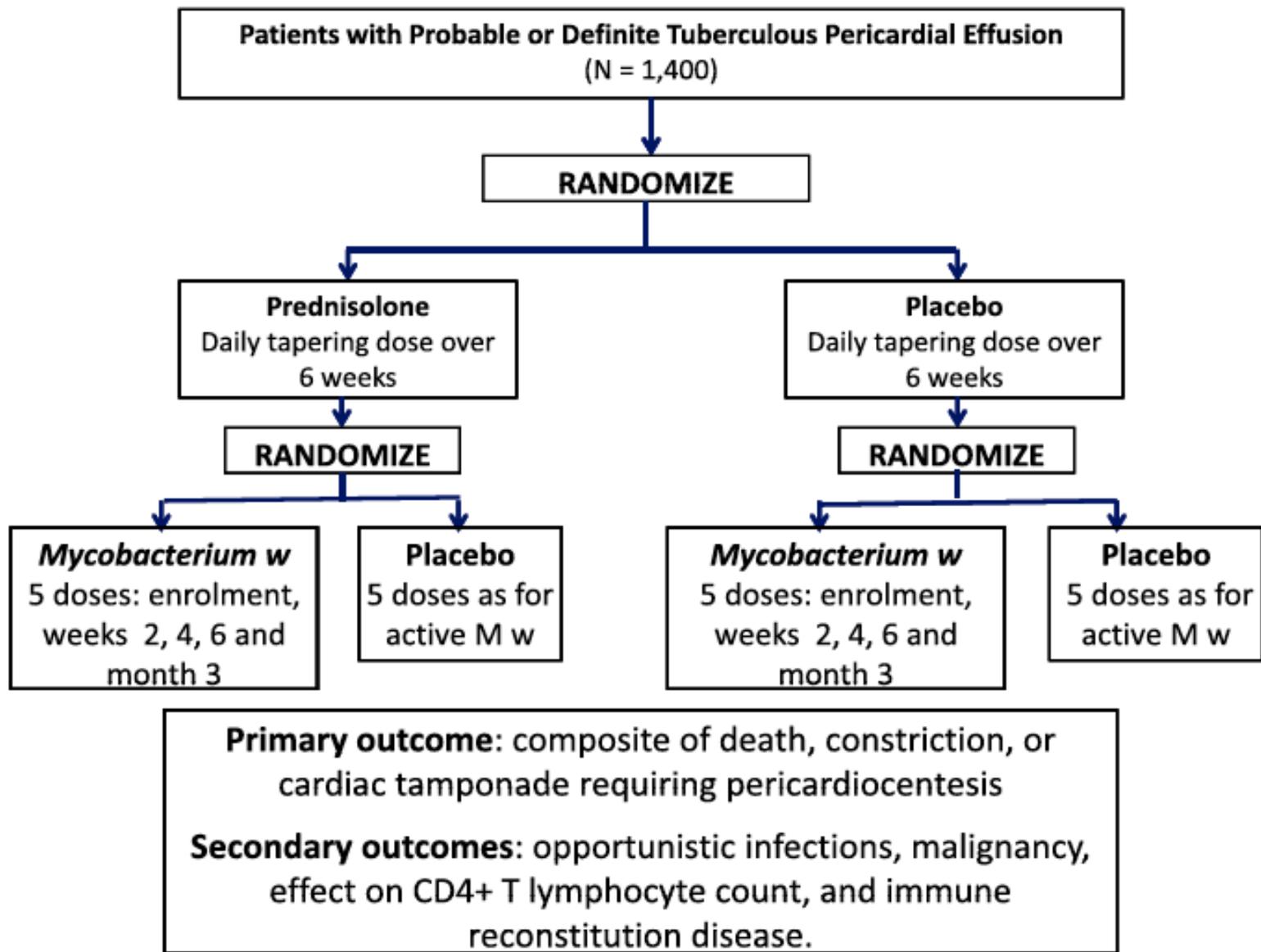
Rationale and design of the Investigation of the Management of Pericarditis (IMPI) trial: A 2 × 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and *Mycobacterium w* immunotherapy in tuberculous pericarditis

Bongani M. Mayosi, DPhil,^a Mpiko Ntsekhe, PhD,^a Jackie Bosch, Msc,^b Janice Pogue, PhD,^b Freedom Gumedze, PhD,^c Motasim Badri, PhD,^{a,v} Hyejung Jung, Msc,^b Shaheen Pandie, FCP(SA),^a Marek Smieja, PhD,^b Lehana Thabane, PhD,^b Veronica Francis, RN,^a Kandithal M. Thomas, MBBS,^d Baby Thomas, MBBS,^d Abolade A. Awotedu, MBBS, FWACP,^d Nombulelo P. Magula, FCP(SA),^c Datshana P. Naidoo, MD,^c Albertino Damasceno, PhD,^f Alfred Chitsa Banda, MBChB,^g Arthur Mutyaba, MBChB,^h Basil Brown, FCP(SA),^h Patrick Ntuli, FCP(SA),ⁱ Phindile Mntla, FCP(SA),ⁱ Lucas Ntyintyane, PhD,^j Rohan Ramjee, FCP(SA),^j Pravin Manga, FCP(SA),^j Bruce Kirenga, MBChB,^k Charles Mondo, PhD,^k James B. W. Russell, MBChB,^l Jacob M. Tsitsi, FCP(SA),^m Ferande Peters, FCP(SA),^m Mohammed R. Essop, FCP(SA),^m Ayub Felix Barasa, MBChB,ⁿ Muhammad S. Mijinyawa, MBChB,^o Mahmoud U. Sani, MBChB,^o Taiwo Olunuga, MBChB,^p Okechukwu Ogah, MBChB,^p Adewole Adebisi, FWACP,^q Akinyemi Aje, FMCP,^q Victor Ansa, MBBS, FWACP,^r Dike Ojji, MBChB,^s Solomon Danbauchi, MBChB,^t James Hakim, FRCP,^u Jonathan Matenga, FRCP,^u and Salim Yusuf, DPhil^b *Cape Town, Mthatha, Durban, Port Elizabeth, Pretoria, Gauteng, and Soweto, South Africa; Ontario, Canada; Maputo, Mozambique; Lilongwe, Malawi; Kampala, Uganda; Freetown, Sierra Leone; Eldoret, Kenya; Kano, Ogun State, Oyo State, Calabar, Abuja, and Kaduna State, Nigeria; and Harare, Zimbabwe*



Research Question?

- In a **population of 1400** patients with and without HIV
 - Will a tapering dose of adjuvant **Prednisolone 120mg** added to TB Rx and ART (as per local guidelines)
 - Compared to TB Rx alone plus ART
- Improve the composite of death, cardiac tamponade and constrictive pericarditis over 2 years
 - Each component of the composite
 - OIs, Malignancy, IRIS, CD4 counts
 - Over 24 months



IMPI Trial study design.

I nvestigation of the M anagement of P ericarditis I n Africa

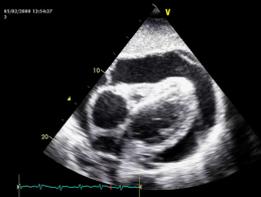
IMPI RCT

2009



2014

- 1400 patients over 41/2 years
- Interesting obstacles.....
Kenya 2013, Maputo 2012, Sierra Leone Ebola 2013, Nigeria (regulatory hurdles)
- 98% follow up for all enrolled pts
- >85% adherence to study drugs

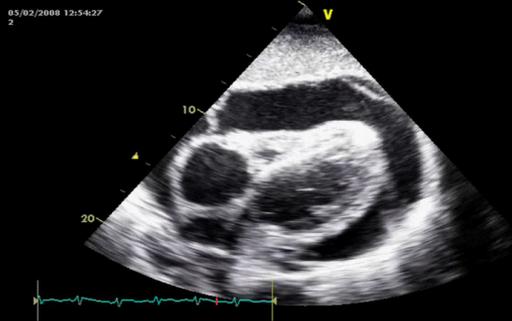


ORIGINAL ARTICLE

Prednisolone and *Mycobacterium indicus pranii* in Tuberculous Pericarditis

B.M. Mayosi, M. Ntsekhe, J. Bosch, S. Pandie, H. Jung, F. Gumedze, J. Pogue, L. Thabane, M. Smieja, V. Francis, L. Joldersma, K.M. Thomas, B. Thomas, A.A. Awotedu, N.P. Magula, D.P. Naidoo, A. Damasceno, A.C. Banda, B. Brown, P. Manga, B. Kirenga, C. Mondo, P. Mntla, J.M. Tsitsi, F. Peters, M.R. Essop, J.B.W. Russell, J. Hakim, J. Matenga, A.F. Barasa, M.U. Sani, T. Olunuga, O. Ogah, V. Ansa, A. Aje, S. Danbauchi, D. Ojji, and S. Yusuf, for the IMPI Trial Investigators*

N Engl J Med 2014;371:1121-30.

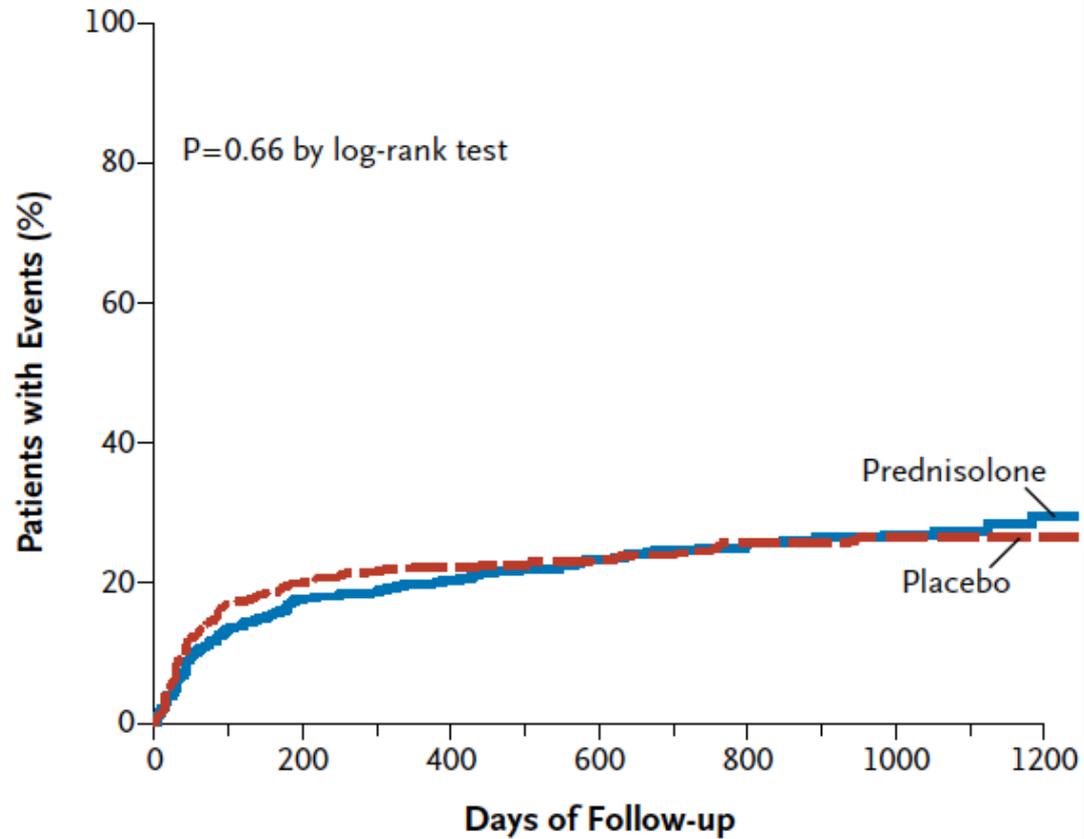


- <38.3 yrs
- >66% HIV infected
- <21% on ART at enrolment
- 74% at 6 months
- CD4 count **150** [71-283]

- >60% pericardiocentesis
- 16% had definitive microbiological diagnosis
- 73% biochem or TB elsewhere

A Prednisolone Comparison

Death, tamponade, constriction



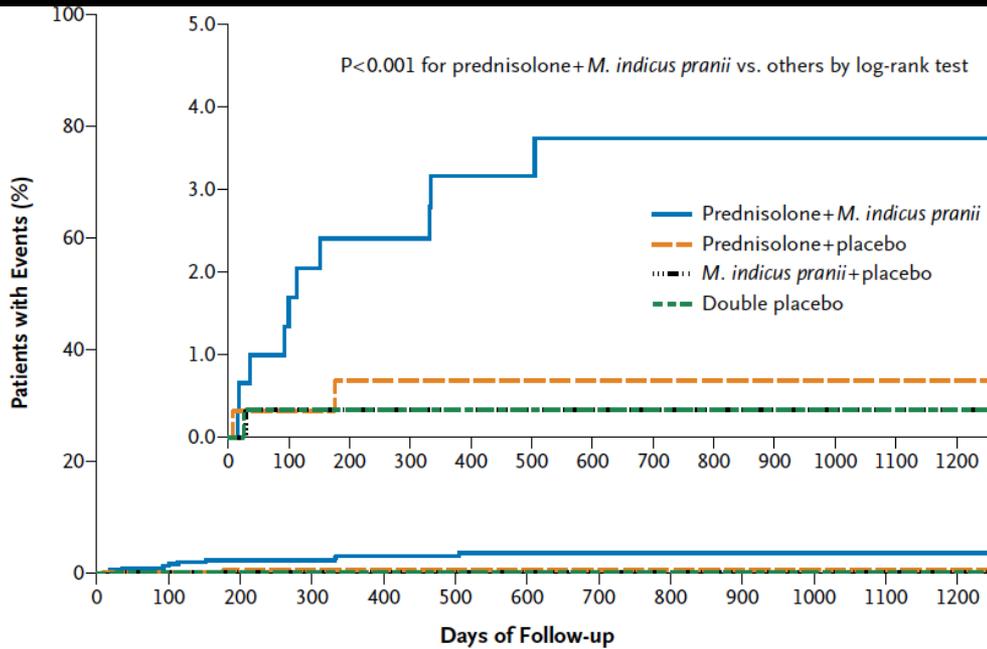
No. at Risk

Prednisolone	706	600	511	502	426	418	335	306	186	182	106	65	60
Placebo	694	572	487	473	404	395	316	289	185	181	111	84	73

Table 2. Effects of Prednisolone and *Mycobacterium indicus pranii* Immunotherapy on Efficacy Outcomes.*

Outcome	Prednisolone (N=706)		Placebo (N=694)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of events/100 person-yr	no. of patients (%)	no. of events/100 person-yr		
Primary composite outcome: death, cardiac tamponade, or constrictive pericarditis	168 (23.8)	14.3	170 (24.5)	14.8	0.95 (0.77–1.18)	0.66
Secondary outcomes						
Death from any cause	133 (18.8)	10.6	115 (16.6)	9.1	1.15 (0.90–1.48)	0.26
Cardiac tamponade	22 (3.1)	1.8	28 (4.0)	2.3	0.77 (0.44–1.35)	0.37
Constrictive pericarditis	31 (4.4)	2.58	54 (7.8)	4.56	0.56 (0.36–0.87)	0.009
Hospitalization	146 (20.7)	13.27	175 (25.2)	16.7	0.79 (0.63–0.99)	0.04

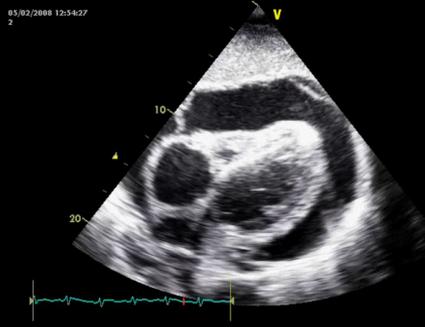
Figure 2. Time to Cancer Occurrence.



Prednisolone
 3=fold increase
 Kaposi Sarcoma
 V. Low incidence (.7/100)
 CD4 <50

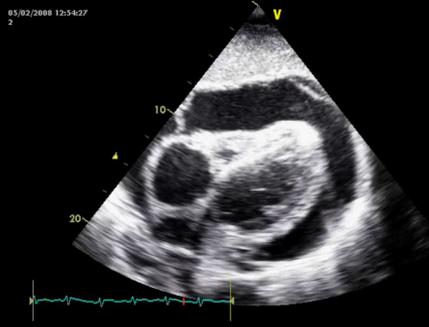
No. at Risk

Prednisolone+ <i>M. indicus prunii</i>	316	280	260	259	219	215	173	152	96	93	55	34	31
Prednisolone+placebo	315	284	266	262	227	222	181	171	104	103	62	37	35
<i>M. indicus prunii</i> +placebo	309	284	268	258	218	214	171	156	103	100	66	48	39
Double placebo	310	277	263	259	225	220	179	163	101	100	62	49	46



Conclusions?

- Despite the promise of earlier studies corticosteroids do not reduce overall mortality
- Corticosteroids reduce the incidence of by 50% Constrictive Pericarditis keep patients out of hospital
- In pts with advanced HIV with no access to ART steroids may increase opportunistic malignancies



Outstanding questions?

- Is 6 months therapy adequate?
- Should pericardiocentesis be routine or only performed in those with tamponade

ENKOSI! Kea Leboha! Baie Dankie!

