Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS)

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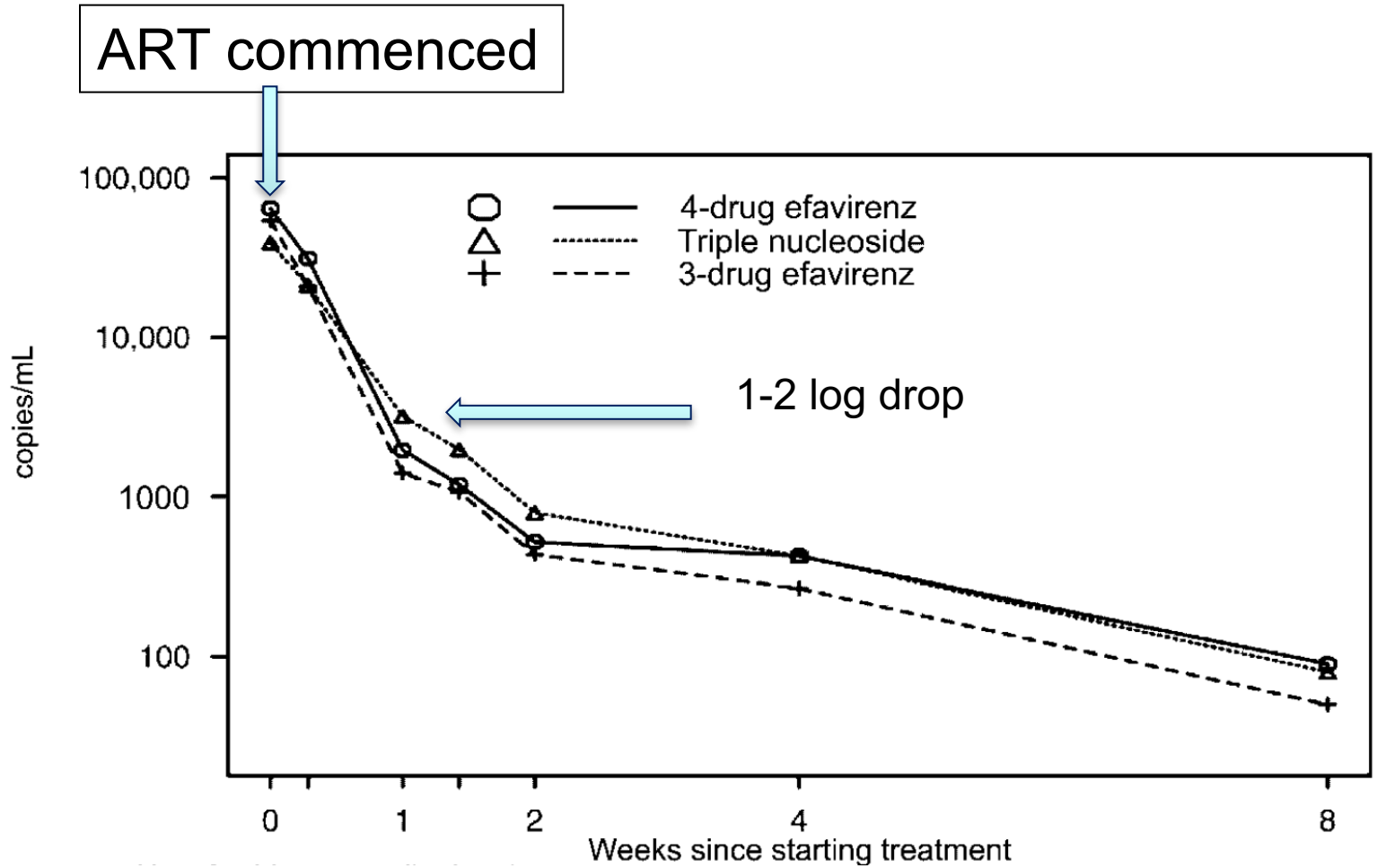
Overview

1. Clinical features
2. Diagnosis
3. Treatment
4. Prevention: PredART trial

HIV viral load response to ART



Kuritzkes, JID 2007

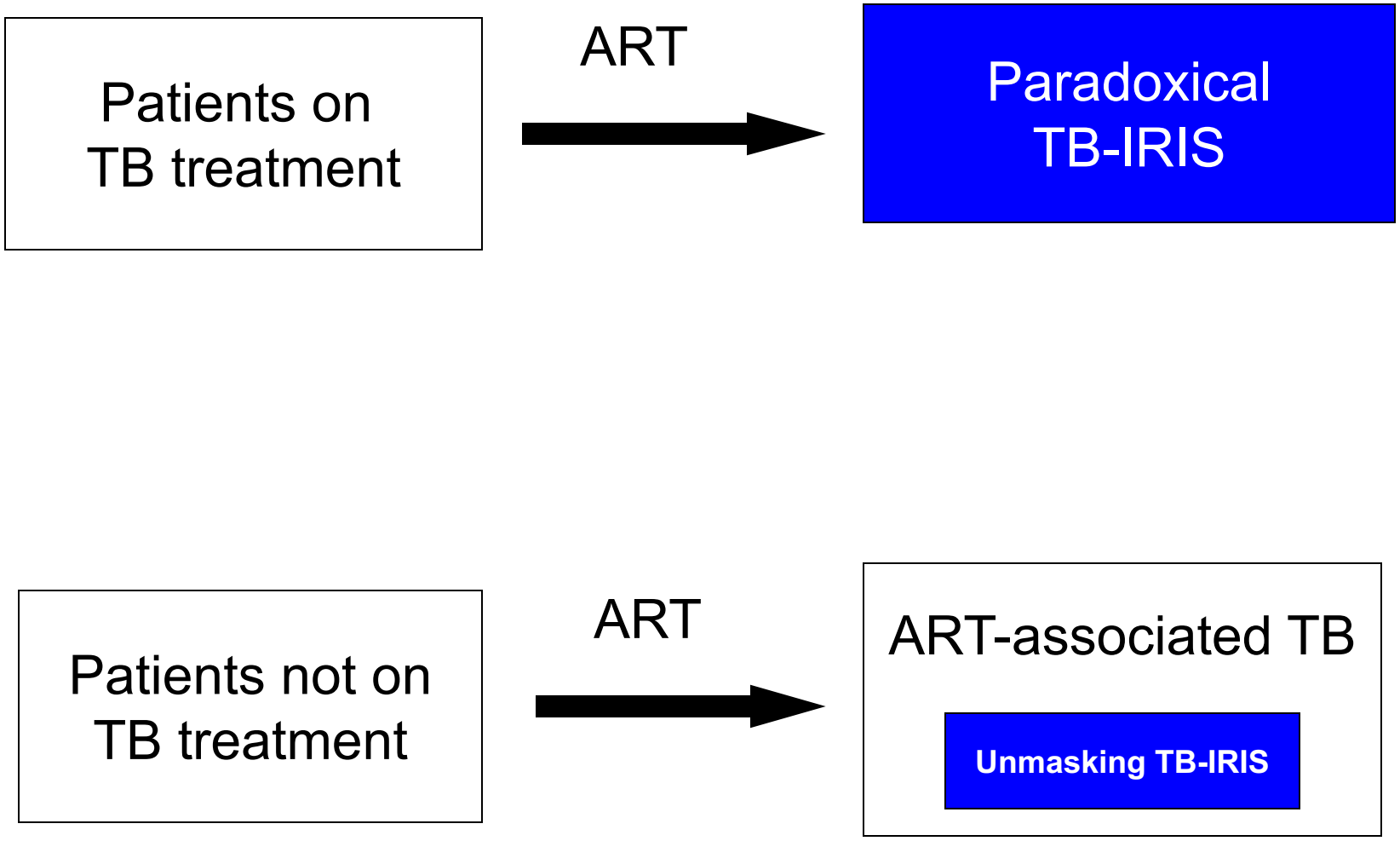
Suppression of HIV replication on ART

Early reversal of immune suppression

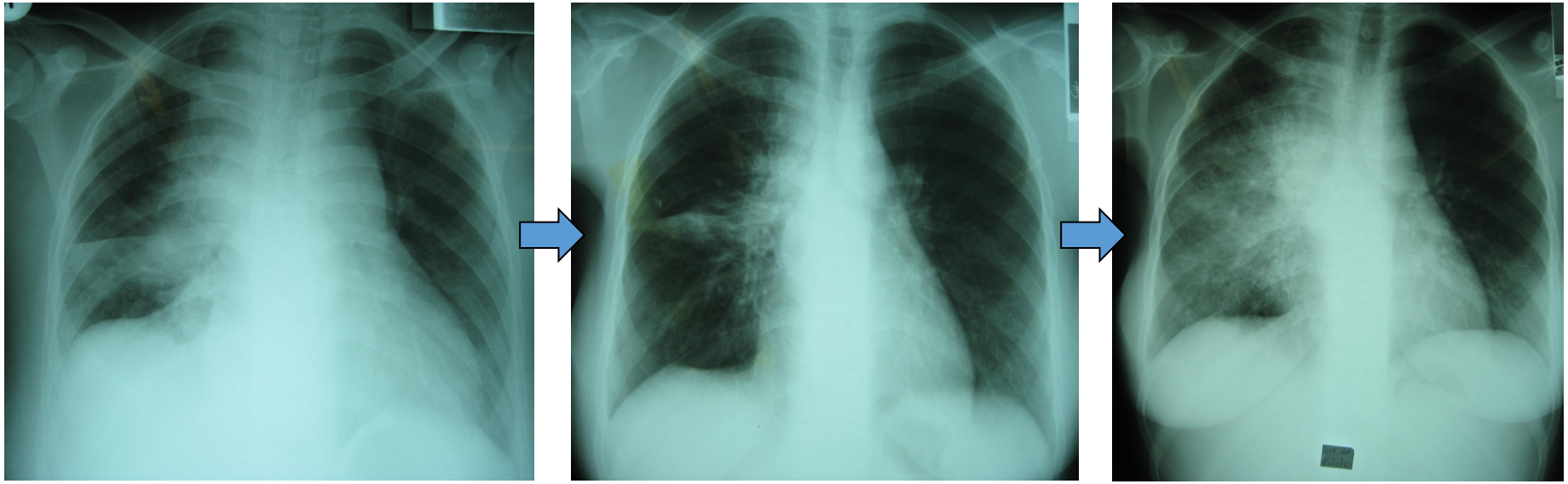
Inflammatory reactions

Targeted at MTB antigens 

IRIS = Immune reconstitution inflammatory syndrome


Patients on
TB treatment
ART
Paradoxical
TB-IRIS
Patients not on
TB treatment
ART
ART-associated TB
Unmasking TB-IRIS

Pulmonary TB-IRIS

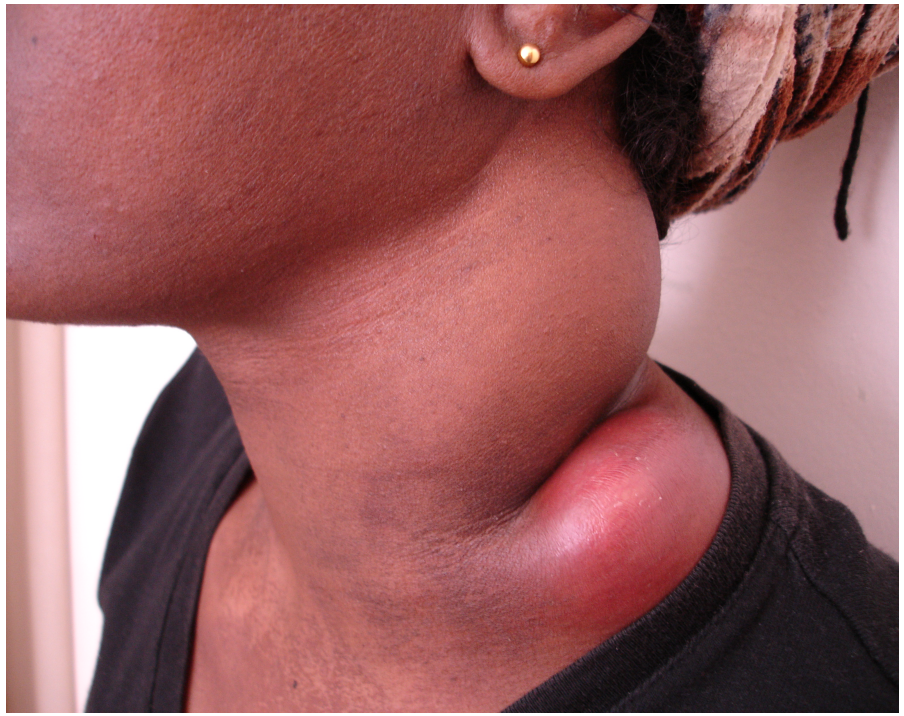


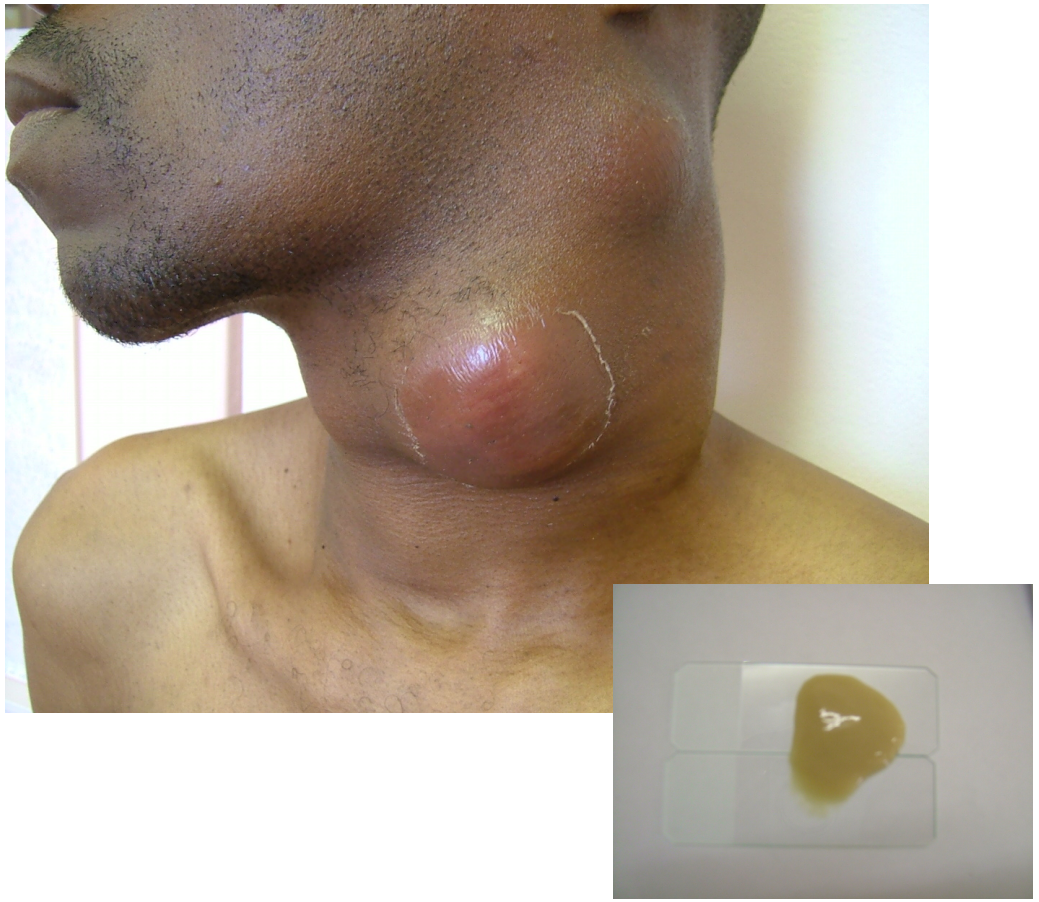
TB diagnosis

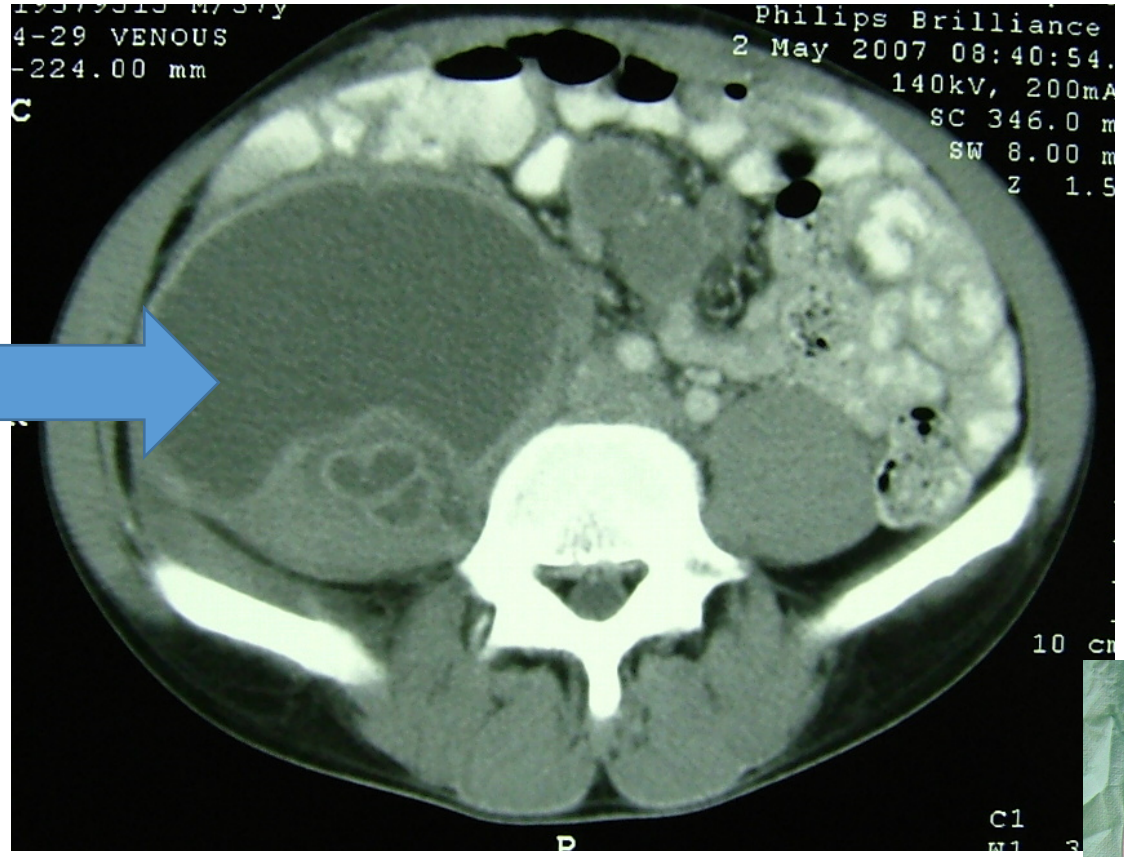
Improvement on
TB treatment

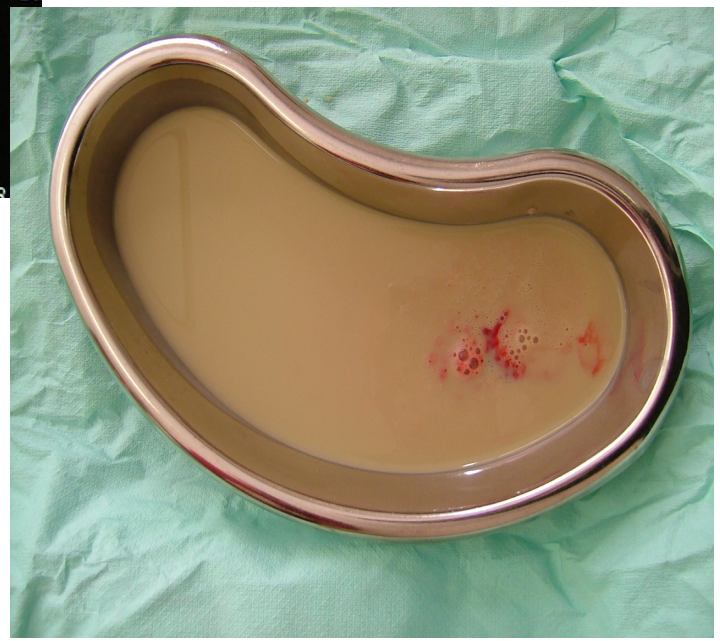
Deterioration
with TB-IRIS

TB-IRIS lymphadenitis



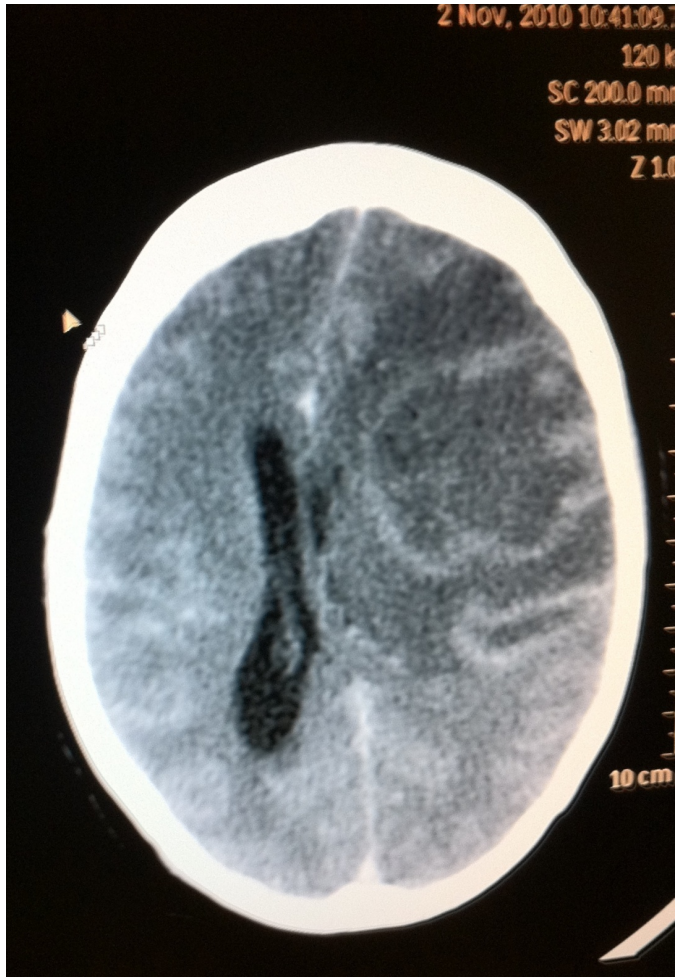






Psoas abscess

Central nervous system involvement



Constitutional features are common

Fever Temp > 37.7	**34%**
Tachycardia Pulse rate > 120	**69%**
Night sweats On questioning	**61%**
Weight loss > 2.5% in 2 weeks or > 5% in 4 weeks	**52%**

Frequency of TB-IRIS symptoms among 95 TB-IRIS cases in PredART trial

Paradoxical TB-IRIS: Key features

- Recurrent, new or worsening inflammatory features of TB occurring during early ART
- Onset typically in the first 4 weeks of ART
- Meta-analysis of cohort studies
  - Incidence 18% among HIV-TB patients initiating ART
  - Hospitalisation in 25%
  - TB-IRIS attributable mortality in 2%
  - Major risk factors include low CD4 count and early ART

Namale Future Microbiol 2015;10:1077

Diagnosis

- No confirmatory diagnostic test

- Typical clinical course
  - Improvement on TB treatment
  - Deterioration in first 4 weeks of ART
  - Symptoms and inflammatory features of TB

- Exclude drug-resistant TB and other causes for deterioration

RESEARCH ARTICLE Open Access

Prolonged tuberculosis-associated immune reconstitution inflammatory syndrome: characteristics and risk factors

Tasnim M. Bana[1], Maia Lesosky[1], Dominique J. Pepper[2], Helen van der Plas[3], Charlotte Schutz[1,4], Rene Goliath[4], Chelsea Morroni[5], Marc Mendelson[3], Gary Maartens[6], Robert J. Wilkinson[8,4,7,3] and Graeme Meintjes[3,4,8*]

- Median duration of symptoms = 71 days (IQR 41 –113)
- Duration > 90 days in 40%
- Duration > 1 year in 3%
  - 426, 462, 519, 746, 824 and 1362 days

BMC Infectious Diseases (2016) 16:518

Two trials of prednisone

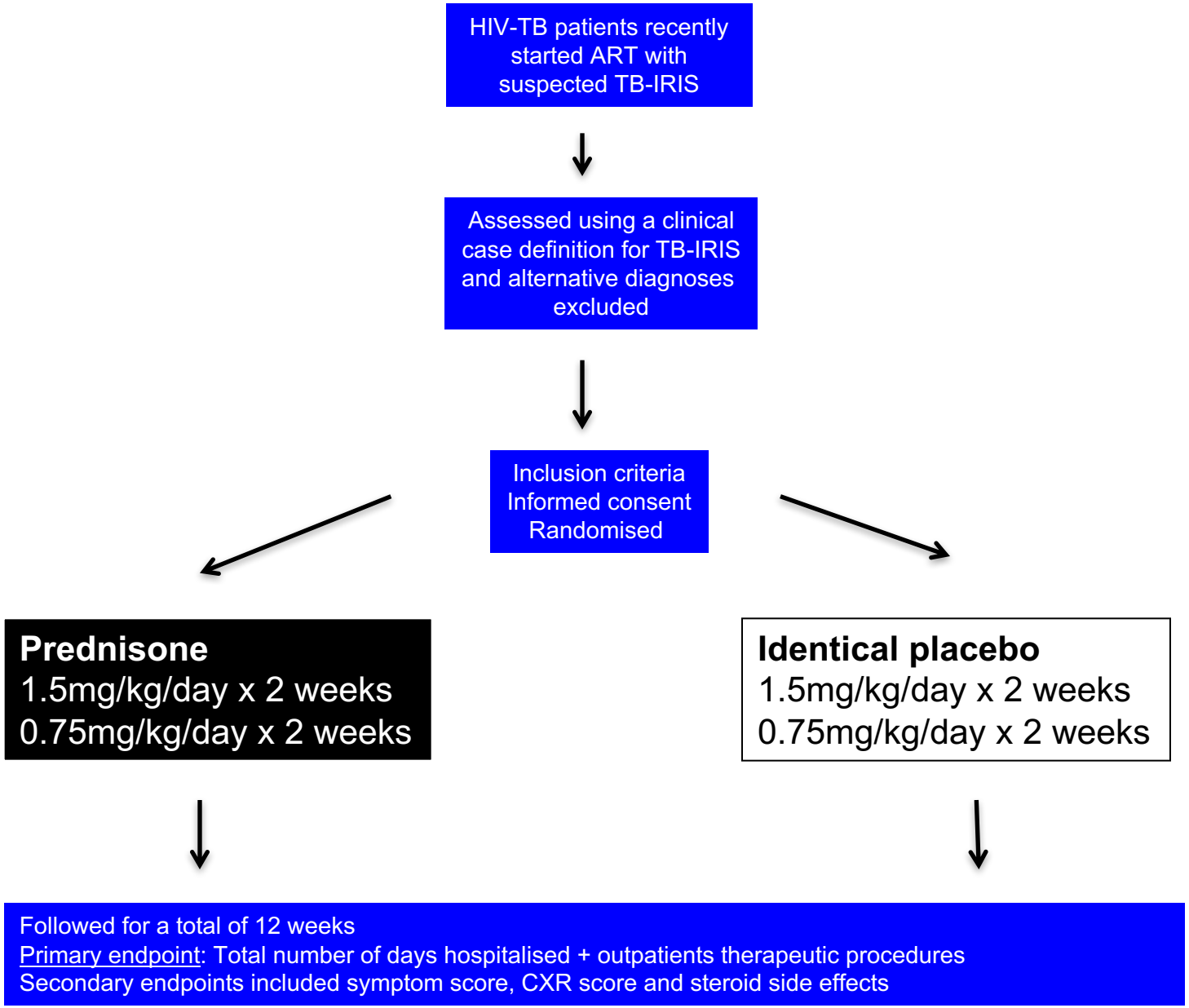
- Treatment trial
  - 2005-2008
- Prevention trial
  - 2013-2016

Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome

Graeme Meintjes[a,b,c], Robert J. Wilkinson[a,b,c,d,e], Chelsea Morroni[a,f], Dominique J. Pepper[a,b,c], Kevin Rebe[b,c], Molebogeng X. Rangaka[a], Tolu Oni[a,d] and Gary Maartens[a,g]

- Rationale for steroid trial
  - Anecdotal reports of symptomatic response
  - Potential risks in patients with advanced HIV
- 110 participants (55 each arm)
- Life-threatening TB-IRIS was an exclusion
- Open-label prednisone at physician discretion if clinical deterioration/relapse

Meintjes et al, AIDS 2010;24:2381


HIV-TB patients recently started ART with suspected TB-IRIS
Assessed using a clinical case definition for TB-IRIS and alternative diagnoses excluded
Inclusion criteria
Informed consent
Randomised
Prednisone
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks
Identical placebo
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks
Followed for a total of 12 weeks
Primary endpoint: Total number of days hospitalised + outpatients therapeutic procedures
Secondary endpoints included symptom score, CXR score and steroid side effects

RCT of prednisone for paradoxical TB-IRIS treatment

	Placebo n = 55	Prednisone n = 55	p-value
Total days hospitalized	463	282	-
Total number outpatient procedures	28	24	-
Cumulative primary endpoint (median, IQR)	**3 (0-9)**	**0 (0-3)**	**0.04**
Death on study	2 (4%)	3 (5%)	0.65
New WHO stage 4 conditions or invasive bacterial infections	4 (7%)	2 (4%)	0.40

Meintjes, AIDS 2010;24:2381

RANDOMIZED CONTROLLED TRIAL OF PREDNISONE FOR PREVENTION OF PARADOXICAL TB-IRIS

PredART
Investigating TB-IRIS Prevention

Graeme Meintjes, Cari Stek, Liz Blumenthal, Friedrich Thienemann, Charlotte Schutz, Jozefien Buyze, Gary Maartens, Robert J. Wilkinson, Lut Lynen
on behalf of the *PredART* trial team

wellcome centre infectious diseases research in africa

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Imperial College London

INSTITUTE OF TROPICAL MEDICINE ANTWERP

Presented at CROI 2017
Abstract 81LB

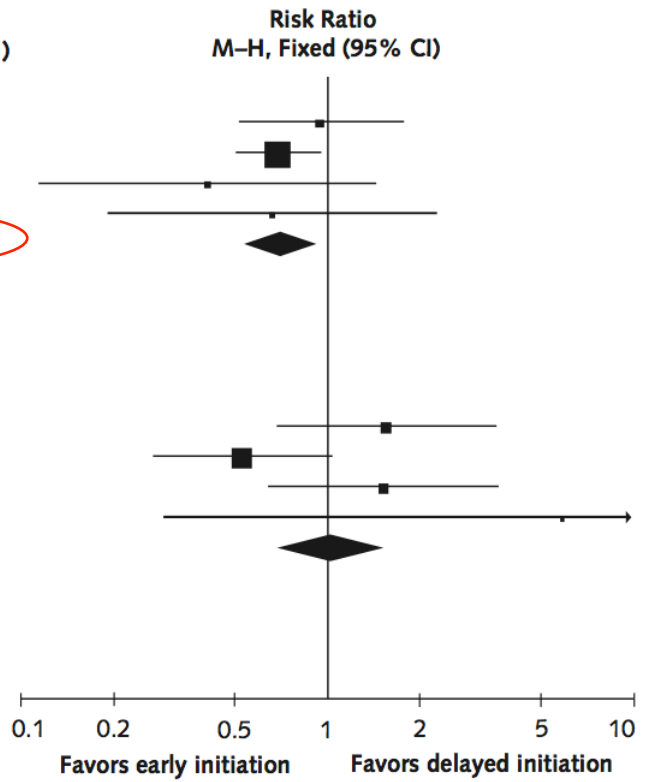
Rationale for PredART trial

- Patients with low CD4 count
  - Are at higher risk for paradoxical TB-IRIS when start ART while on TB treatment
  - ART initiation around 2 weeks on TB treatment reduces mortality
  - But increases TB-IRIS incidence by > 2- fold
  - No evidence-based intervention to prevent TB-IRIS in this situation exists

Early ART reduces mortality by 29% (if CD4<50)

Figure 4. All-cause mortality comparing early versus delayed initiation of ART, stratified by baseline CD4⁺ T-cell counts.

Study, Year (Reference)	Events/Total, *n/N* Early ART	Events/Total, *n/N* Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
CD4⁺ T-cell counts <0.050 × 10⁹ cells/L				
Amogne et al, 2015 (27)	27/111	10/39	15.2	0.95 (0.51–1.78)
Blanc et al, 2011 (25 [CAMELIA])	48/237	70/238	71.8	0.69 (0.50–0.95)
Abdool Karim et al, 2011 (24 [SAPiT])	3/37	7/35	7.4	0.41 (0.11–1.45)
Manosuthi et al, 2012 (28 [TIME])	4/46	5/38	5.6	0.66 (0.19–2.29)
Subtotal	431	350	100.0	0.71 (0.54–0.93)
Total events	82	92		
Heterogeneity: $X^2 = 1.62$ ($P = 0.66$); $I^2 = 0\%$				
Test for overall effect: $Z = 2.52$ ($P = 0.01$)				
CD4⁺ T-cell counts >0.050 × 10⁹ cells/L				
Amogne et al, 2015 (27)	20/212	7/116	23.9	1.56 (0.68–3.59)
Blanc et al, 2011 (25 [CAMELIA])	11/95	20/91	53.9	0.53 (0.27–1.04)
Abdool Karim et al, 2011 (24 [SAPiT])	12/177	8/180	20.9	1.53 (0.64–3.64)
Manosuthi et al, 2012 (28 [TIME])	2/33	0/39	1.2	5.88 (0.29–118.36)
Subtotal	517	426	100.0	1.05 (0.68–1.61)
Total events	45	35		
Heterogeneity: $X^2 = 6.84$ ($P = 0.08$); $I^2 = 56\%$				
Test for overall effect: $Z = 0.22$ ($P = 0.83$)				
Test for subgroup differences: $X^2 = 2.36$ ($P = 0.12$); $I^2 = 57.7\%$				



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel-Haenszel; SAPiT = Starting ART at Three Points in TB; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

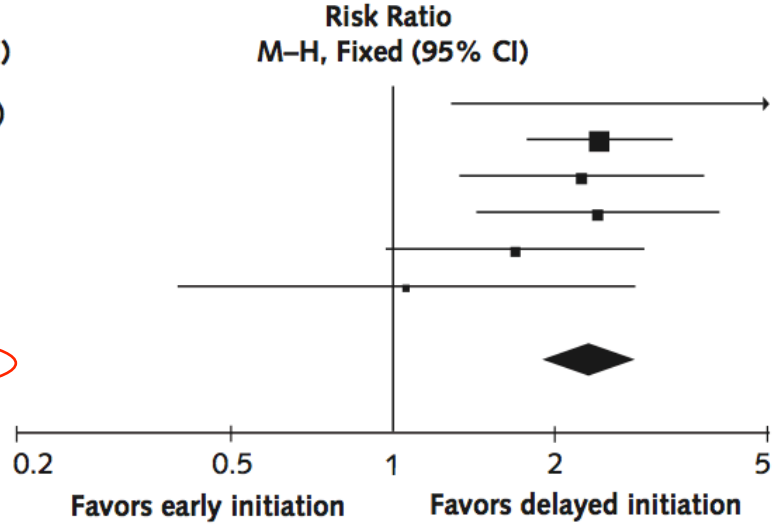
Early ART increases TB-IRIS risk 2.3-fold

Figure 5. TB-IRIS comparing early versus delayed initiation of ART.

Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
Amogne et al, 2015 (27)	22/332	0/155	0.6	21.08 (1.29–345.28)
Blanc et al, 2011 (25 [CAMELIA])	110/332	45/329	43.0	2.42 (1.77–3.31)
Havlir et al, 2011 (26 [STRIDE])	43/405	19/401	18.2	2.24 (1.33–3.78)
Abdool Karim et al, 2011 (24 [SAPiT])	43/214	18/215	17.1	2.40 (1.43–4.02)
Manosuthi et al, 2012 (28 [TIME])	26/79	15/77	14.4	1.69 (0.97–2.94)
Sinha et al, 2012 (29)	9/88	6/62	6.7	1.06 (0.40–2.82)
Total	1450	1239	100.0	2.31 (1.87–2.86)
Total events	253	103		

Heterogeneity: $X^2 = 6.20$ ($P = 0.29$); $I^2 = 19\%$

Test for overall effect: $Z = 7.71$ ($P < 0.001$)



ART = antiretroviral therapy; CAMELIA = Cambodian Early Versus Late Introduction of Antiretrovirals; M-H = Mantel–Haenszel; SAPiT = Starting ART at Three Points in TB; STRIDE = Immediate Versus Deferred Start of Anti-HIV Therapy in HIV-Infected Adults Being Treated for Tuberculosis; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; TIME = Appropriate Timing of HAART in Co-infected HIV/TB Patients.

Background: Corticosteroids

- Prednisone treatment of TB-IRIS reduces duration of symptoms and hospitalisation [1]
- Steroids have been associated with increased risk of infections and Kaposi's sarcoma in HIV-infected patients [2-4]
  - Mainly in patients not on ART
- Rifampicin increases clearance of prednisone by 45% [5]
- Hypothesis: Prednisone safely prevents TB-IRIS

1. Meintjes AIDS 2010;24:2381
2. Elliott QJM 1992;85:855
3. Elliott JID 2004;190:869
4. Mayosi NEJM 2014;371:1121
5. McAllister BMJ 1983;286:923

PredART trial design

- 1:1 randomized, double-blind, placebo-controlled trial
- Prednisone or identical placebo
  - **40 mg/day for 2 weeks then 20 mg/day for 2 weeks (total 4 weeks)**
  - Started with ART in patients at high risk of TB-IRIS
- Block randomisation (blocks of 8)
  - Medication packaged according to sequence by independent pharmacist off-site and participants given next available medication package
- Two interim reviews by DSMB

ClinicalTrials.gov NCT01924286
Stek JIMR Research Protocols 2016;5:e173

Trial setting: Khayelitsha, Cape Town

Population ~ 500,000

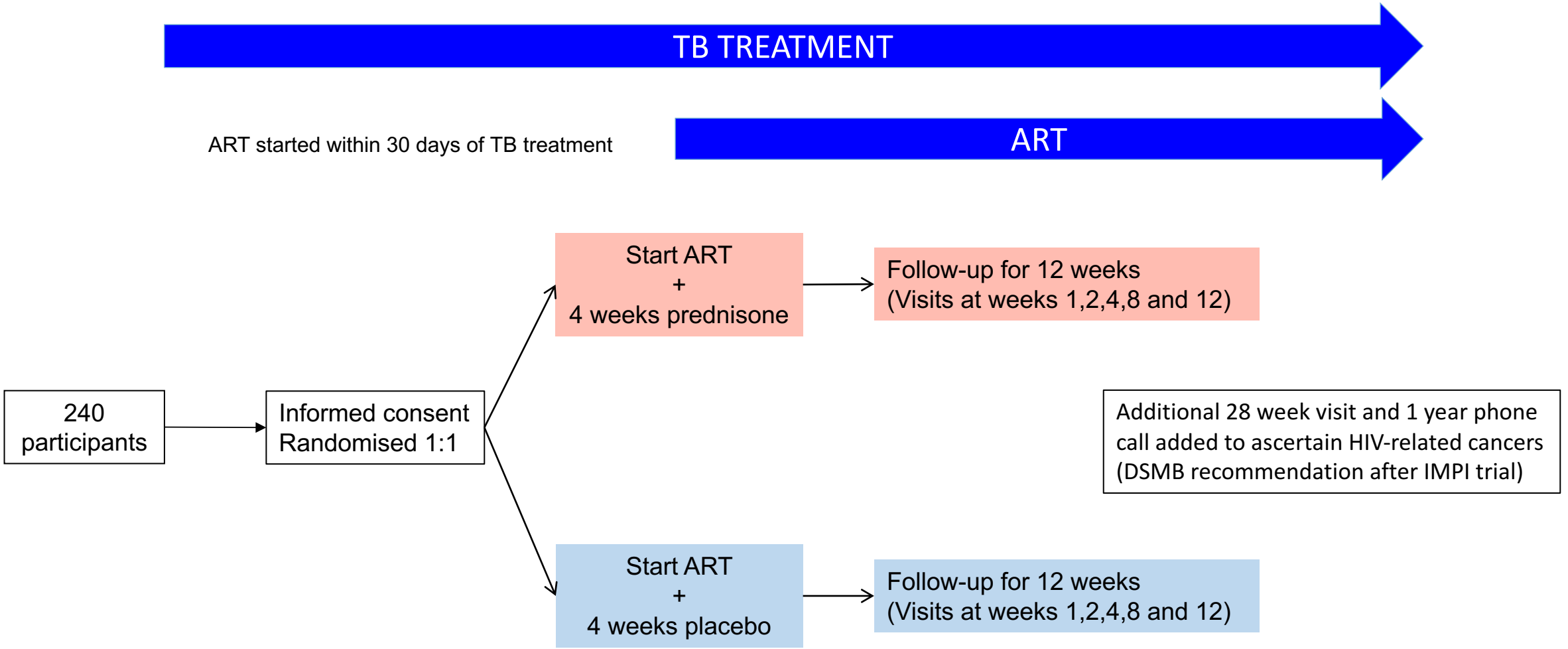
TB incidence 917/100,000 (60% HIV co-infected)

Participants referred from 4 TB clinics

Eligibility criteria

- Inclusion criteria
  - Age 18 or older
  - ART-naïve
  - Within 30 days of TB treatment initiation
  - CD4 count ≤100 cells/µl

- Exclusion criteria
  - Rifampicin resistance
  - Neurological TB
  - Kaposi’s sarcoma
  - Hepatitis BsAg+
  - Not on standard first line TB treatment
  - Poor clinical response to TB treatment



Recruitment at 4 public sector HIV-TB clinics in Khayelitsha, Cape Town, South Africa
August 2013 – February 2016

Endpoints

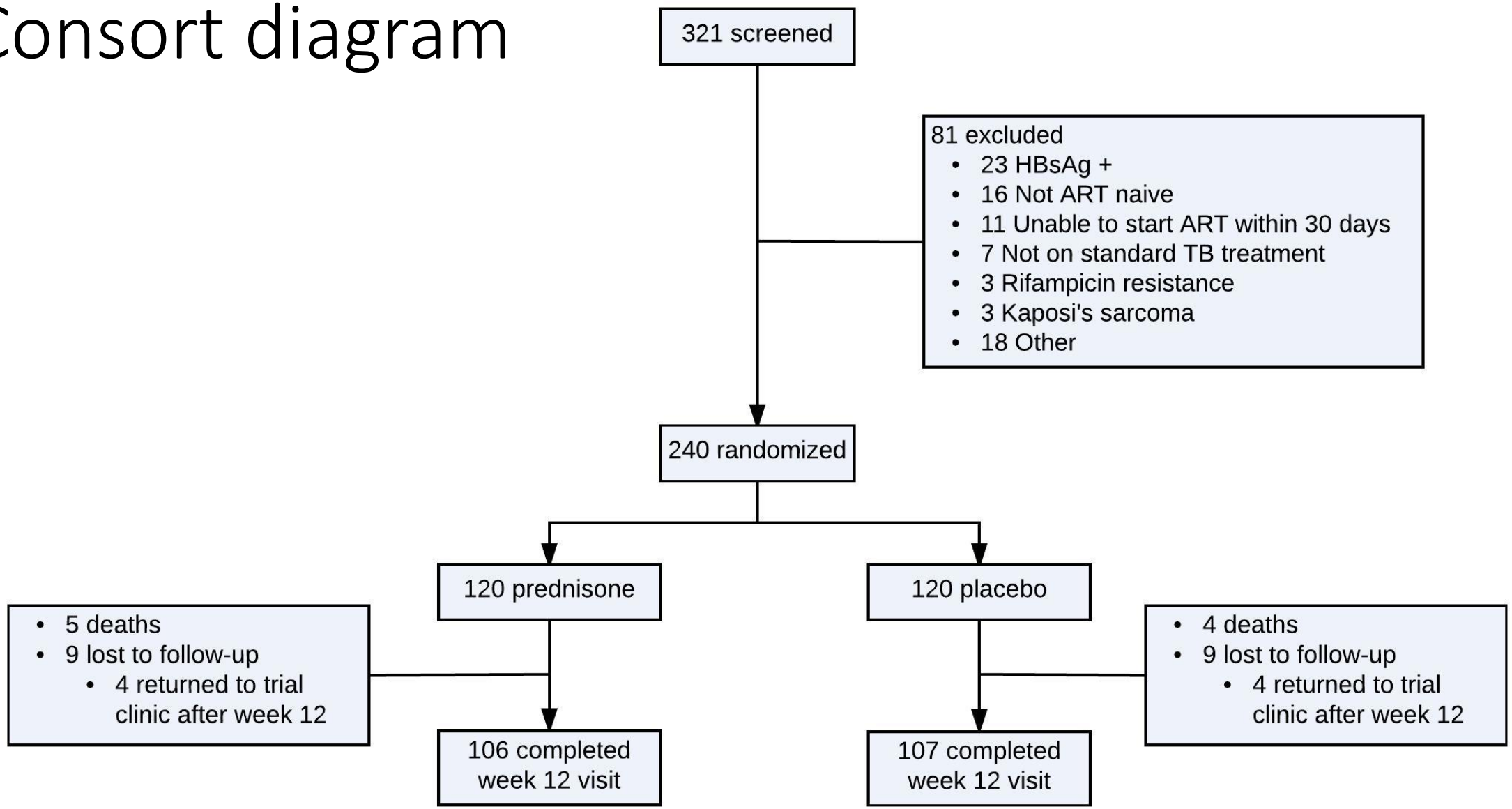
- **Primary endpoint = Paradoxical TB-IRIS**
  - International Network for the Study of HIV-associated IRIS (INSHI) case definition*
  - Adjudicated by an independent expert committee
  - By intention to treat

- **Secondary endpoints included**
  - Time to TB-IRIS
  - Mortality
  - Hospitalisation
  - Interruption of ART or TB treatment for adverse events

- **Safety endpoints included**
  - Severe infections and malignancies
  - ACTG graded adverse events
  - CD4 count & HIV viral load at week 12

* Meintjes, Lancet Infect Dis 2008;8:516

Consort diagram



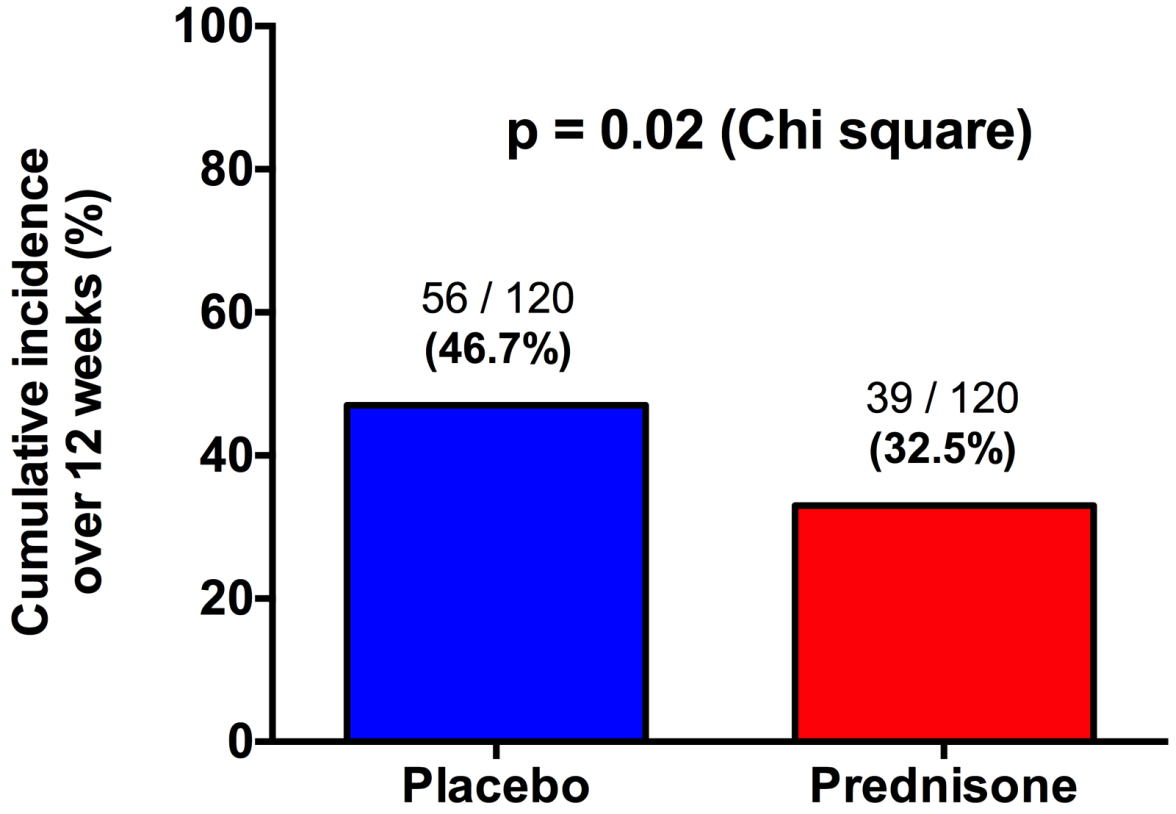
Baseline characteristics

	Placebo arm (n = 120)	Prednisone arm (n= 120)
Age	36 (29 – 43)	37 (31 – 43)
Men	73 (61%)	71 (59%)
CD4 count (cells/µl)	49 (23 – 88)	51 (26 – 84)
HIV viral load (log_{10} copies/ml)	5.6 (5.2 – 5.9)	5.5 (5.2 – 5.9)
TB microbiologically confirmed	89 (74%)	86 (72%)
Haemoglobin (g/dl)	9.8 (8.5– 10.9)	9.7 (8.8 – 11.1)
Duration from TB treatment to ART (days)	17 (15– 21)	16 (15 – 22)
Karnofsky Performance Score	90 (80 - 90)	80 (80 – 90)

Number (%) or median (IQR) shown

233/240 (97%) initiated on tenofovir + FTC or 3TC + efavirenz as initial ART regimen

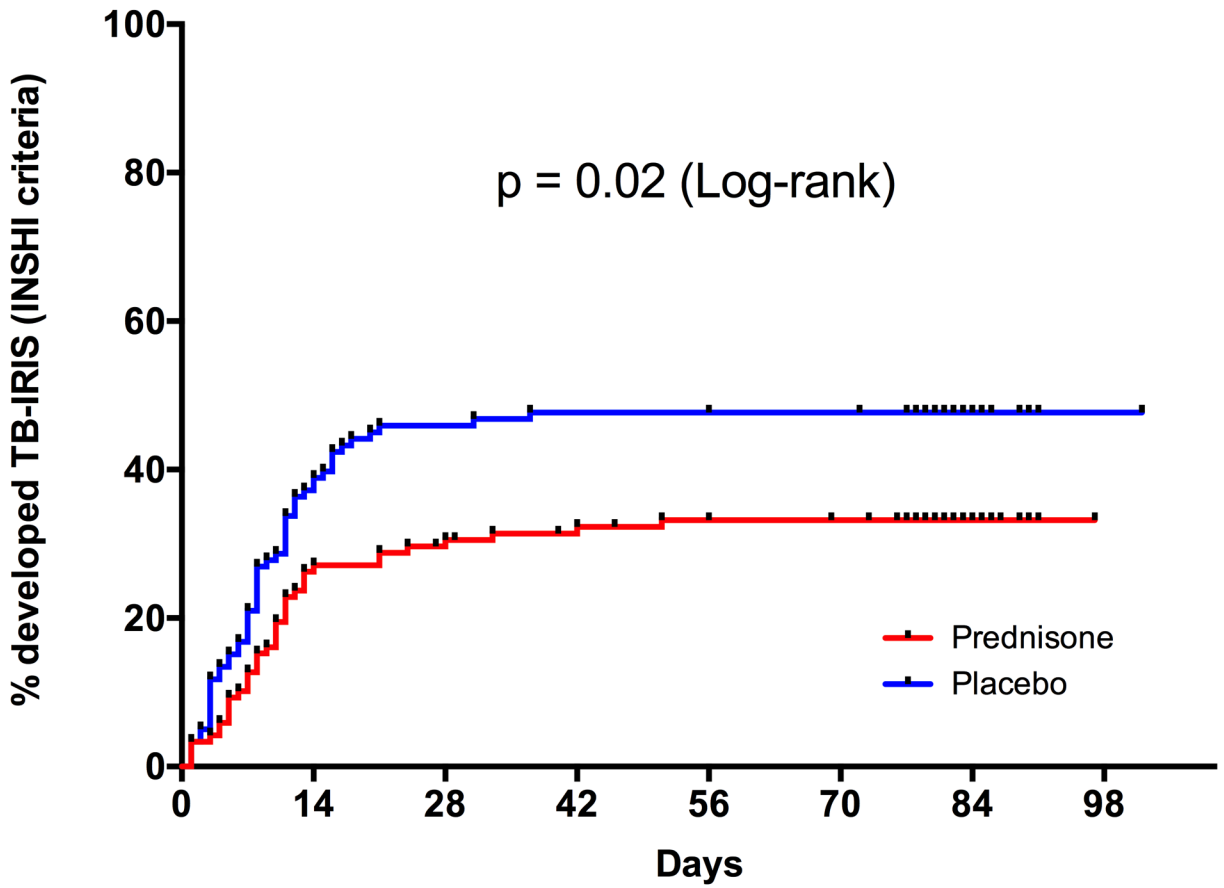
Primary endpoint: Paradoxical TB-IRIS



Number needed to treat
to prevent one case = 7.0

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

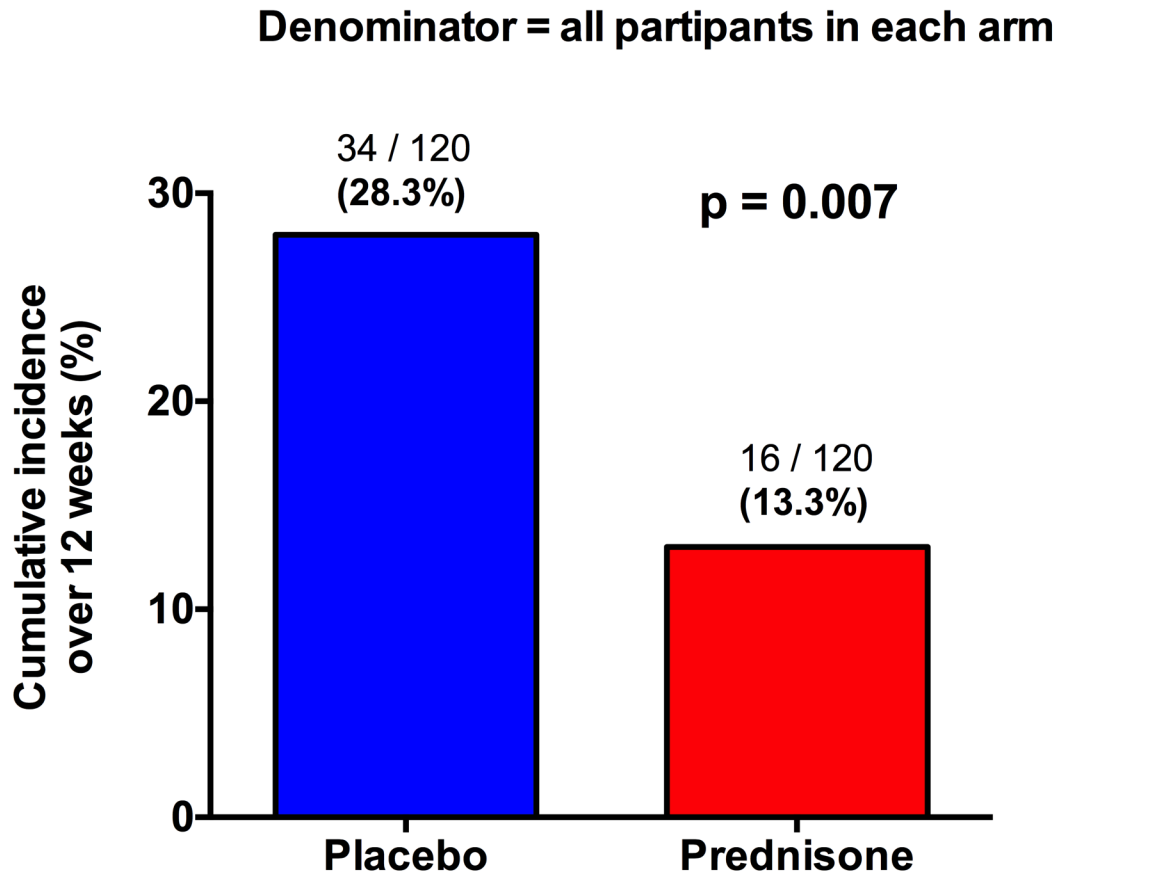
Time to TB-IRIS event



Median time to TB-IRIS restricted to those who developed TB-IRIS:
Placebo arm = 8 days (IQR 3-12)
Prednisone arm = 10 days (IQR 5-13)

Hazard ratio = 0.61 (95%CI = 0.41 - 0.92) (Mantel-Haenszel)

Open-label corticosteroids for TB-IRIS treatment

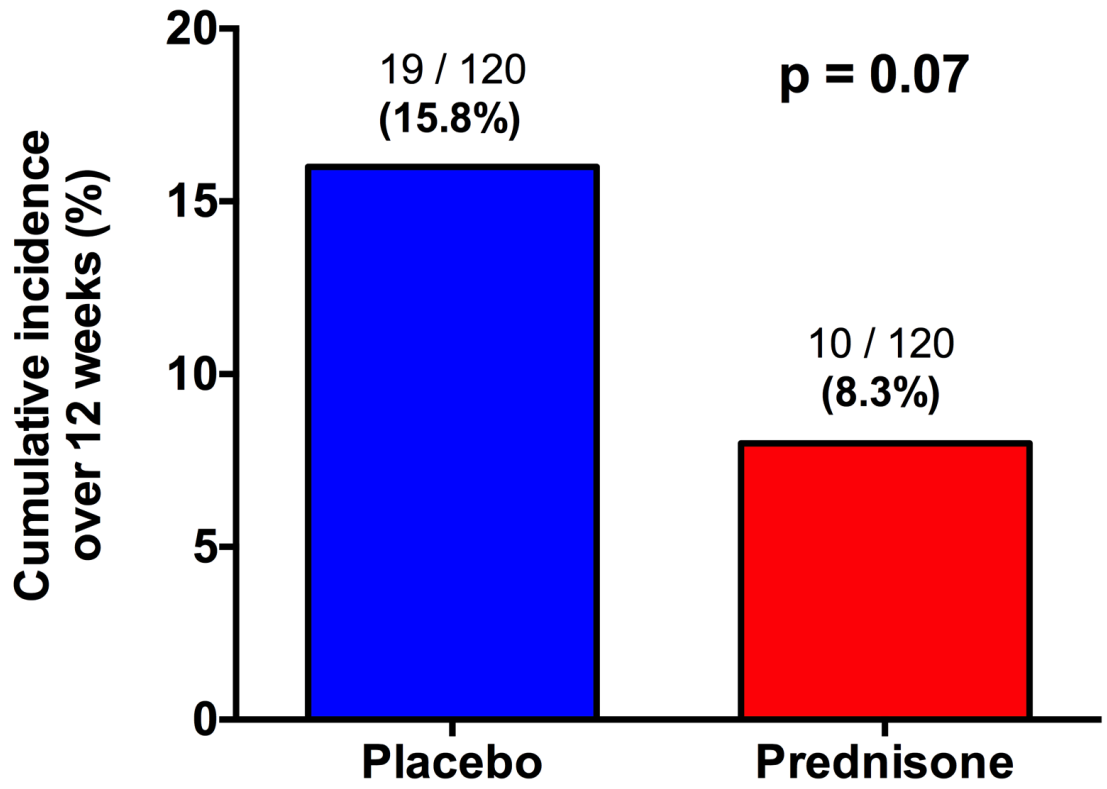


Relative risk = 0.47 (95%CI = 0.27 – 0.83)

Deaths and hospitalisation within 12 weeks

		Placebo (n=120)	Prednisone (n=120)	P-value
DEATH	**All-cause**	**4 (3.3%)**	**5 (4.2%)**	**1.0**
	TB-IRIS related	1 (0.8%)	0 (0%)	1.0
HOSPITALISATION	**All-cause**	**27 (22.5%)**	**17 (14.2%)**	**0.10**
	TB-IRIS related	9 (7.5%)	5 (4.2%)	0.41

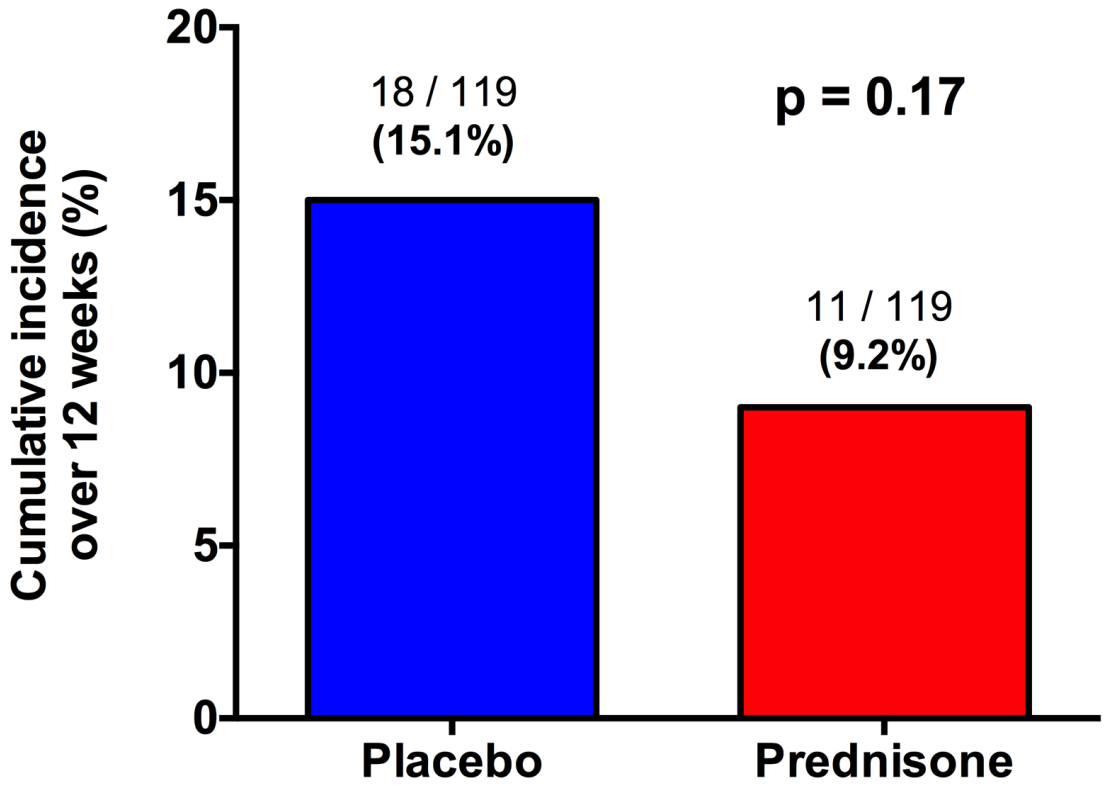
ART or TB drug switch or interruption



37 episodes of drug switches or interruptions due to adverse event in 29 participants

Relative risk = 0.53 (95%CI = 0.26 - 1.08)

New AIDS-defining & invasive bacterial infections



Relative risk = 0.61 (95%CI = 0.30 – 1.24)

33 events in 29 patients:
Cryptococcal meningitis (n=3)
Oesophageal candida (n=10)
Sepsis (n=7)
Pneumonia (n=7)
Pyelonephritis (n=1)
Clostridium difficile (n=3)
Dysentry (n=2)

1 Kaposi's sarcoma case at week 28 in a participant in placebo arm who discontinued ART at week 20

Which patients do PredART findings apply to?

- ART-naïve and starting ART within 4 weeks of TB treatment
- Low CD4 count
- Outpatient setting
- Improving on TB treatment
- Exclusion of conditions that may be worsened by corticosteroids
  - Kaposi’s sarcoma
  - Chronic hepatitis B
  - Rifampicin resistant TB

Conclusions

- TB-IRIS occurs in 47% with TB and CD4<100 starting ART early after TB treatment
- Before diagnosing TB-IRIS ensure other causes for deterioration are excluded
- Prednisone reduced TB-IRIS incidence by 30% in high risk patients in the PredART trial and was not associated with excess risk of infection or malignancy
- Prednisone is also effective for treatment of TB-IRIS and results in more rapid symptom improvement

PredART: Acknowledgements

Investigators: Cari Stek, Liz Blumenthal, Friedrich Thienemann, Charlotte Schutz, Jozefien Buyze, Gary Maartens, Robert J. Wilkinson, Lut Lynen, Bob Colebunders, Joris Menten, Raffaella Ravinetto, Harry van Loen, Amy Nair, Alison Swartz, Amanda Jackson, Edwin Wouters, Christiana Noestlinger

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Independent member of endpoints committee: Tom Boyles
DSMB: Gavin Churchyard, Julian Elliott, Guy Thwaites, Maia Lesosky

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