Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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PREDNISONE FOR PREVENTION OF PARADOXICAL TUBERCULOSIS-ASSOCIATED IRIS

APPENDIX: PROTOCOL DEVIATIONS, ADDITIONAL RESULTS, AND SUPPLEMENTARY METHODS

Contents

Supplementary methods

Standard treatment of tuberculosis and HIV

Antiretroviral therapy (ART) and antituberculous treatment were provided for free according to the South African Department of Health guidelines [1, 2]. First line ART consisted of tenofovir (TDF) 300 mg daily, emtricitabine (FTC) 200 mg or lamivudine (3TC) 300 mg daily, and efavirenz (EFV) 600 mg daily. Antituberculous treatment consisted of weight-based daily doses of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) for 2 months, followed by INH and RIF for another 4 months. All participants were eligible for co-trimoxazole prophylaxis (960 mg daily) unless contra-indicated.

Cryptococcal antigen screening and pre-emptive treatment

All patients were screened for cryptococcal antigenaemia at the trial screening visit. This was performed using a lateral flow assay (Immy, Norman, Oklahoma, US) in a laboratory of the National Health Laboratory Services (NHLS). In those with a positive serum cryptococcal antigen (CrAg) test, a lumbar puncture was performed to exclude cryptococcal meningitis. Patients in whom cryptococcal meningitis was diagnosed before enrolment and randomization were excluded from the trial because of ineligibility to start ART within 30 days of starting TB treatment. Patients with a positive serum CrAg without meningitis were treated with fluconazole according to the national guidelines (800 mg daily for 2 weeks, followed by 400 mg daily for 8 weeks, then 200 mg as maintenance therapy) and were eligible to participate.

Reasons for stopping study medication

Study medication was stopped in both arms for any of the following reasons: new WHO stage 4 opportunistic condition, rifampin-resistant tuberculosis, requirement for prohibited concomitant medication, pregnancy, request by participant, clinical reasons believed to be life threatening by the study doctor, or interruption of ART or study medication for more than five days by participant's or clinician's decision.

TB-IRIS Adjudication Committee

During the trial, all participants who deteriorated clinically with any potential TB-IRIS symptom (even if mild) after starting antiretroviral therapy (ART) were considered as potentially having developed TB-IRIS and a 'Suspected TB-IRIS' case report form was completed by the study doctor.

A TB-IRIS Adjudication Committee reviewed all the 'Suspected TB-IRIS' case report forms and records of all the deaths that occurred in the first 12 weeks of the trial. The committee comprised of 3 investigators not active at the clinical site: Gary Maartens (a trial investigator), Lut Lynen (a trial investigator), and Tom Boyles (an expert clinical investigator independent of the trial). These members were blinded to treatment arm allocation of the cases they were reviewing; the committee met before database unblinding.

A two-day meeting involving all 3 members, the PI, and the study doctor, was held during which the members reviewed all the cases. The committee had (read only) access to the electronic database and were able to view all the clinical and laboratory data entered. They read each 'Suspected TB-IRIS' case report form that included a narrative summary of the case. All available chest X-rays were viewed on a screen. All discussion regarding adjudication occurred between the 3 committee members. The study doctor and PI were present to present the cases and provide more clinical detail when requested.

TB-IRIS was adjudicated using the International Network for the Study of HIV-associated IRIS (INSHI) paradoxical TB-IRIS case definition. Each committee member made an individual decision that was recorded. Each case was then discussed and a consensus decision was made. In the event that consensus could not be reached, it was intended that the committee members would vote, with a 2-1 vote being decisive. The decisions were entered onto a case report form and then the electronic database.
The committee reviewed 147 cases. There was a high level of agreement between the committee members. In only 5 cases was there not initial agreement of the individual decisions. Consensus was reached in discussion in these 5 cases without the need to vote. 95 cases were adjudicated to have developed paradoxical TB-IRIS fulfilling INSHI criteria.

References

1. The South African Antiretroviral Treatment Guidelines, Republic of South Africa, Department of Health, 2015.
2. National Tuberculosis Management Guidelines Republic of South Africa, Department of Health, 2014.

Table S1: Primary and secondary endpoints

Data shown are medians (interquartile range) or number (percentage). For contingency analyses, the Chi square test was used unless the expected cell frequency was < 6, when Fisher's exact tests was used. Wilcoxon rank-sum test was used to compare continuous variables.

More sustained TB-IRIS was defined as duration > 14 days and/or open-label corticosteroid treatment.

For duration of TB-IRIS and duration of corticosteroid treatment, we excluded two patients who died with ongoing TB-IRIS (and on corticosteroid treatment) and one patient who was lost to follow-up with ongoing TB-IRIS (and on corticosteroid treatment). Duration of corticosteroid treatment excludes interval days if more than one course was given.

Grade 1-4 adverse events were defined using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004). The total number of Grade 1, 2, 3 and 4 adverse events in the prednisone arm were 517, 167, 66 and 10; and 660, 218, 112 and 12 in the placebo arm respectively (Table S17).

Adverse Drug Reactions included those AEs attributed as possibly, probably or definitely related to study medication, but not open-label prednisone.

Endpoint	Prednisone arm	Placebo arm	Relative risk (95%CI)	p-value
Primary endpoint	**n=120**	**n=120**		
TB-IRIS fulfilling INSHI criteria	39 (32.5%)	56 (46.7%)	0.70 (0.51-0.96)	0.03
Secondary efficacy endpoints	**n=120**	**n=120**		
TB-IRIS fulfilling at least 1 major INSHI criterion	25 (20.8%)	44 (36.7%)	0.57 (0.37-0.87)	0.01
More sustained TB-IRIS	35 (29.2%)	50 (41.7%)	0.70 (0.49-0.99)	0.06
Duration of TB-IRIS (days)	49 (31-97)	35 (19-82)	-	0.19
Open-label corticosteroid treatment of TB-IRIS	16 (13.3%)	34 (28.3%)	0.47 (0.27-0.81)	0.007
Treatment duration in those treated with open-label corticosteroids (days)	46 (29-67)	38 (29-60)	-	0.83
Hospitalization for TB-IRIS	5 (4.2%)	9 (7.5%)	0.56 (0.19-1.61)	0.41
All cause-hospitalization	17 (14.2%)	27 (22.5%)	0.63 (0.36-1.09)	0.13
Neurological features of TB-IRIS	0 (0%)	0 (0%)	-	-
All-cause mortality	5 (4.2%)	4 (3.3%)	1.25 (0.34-4.54)	1.0
Mortality attributed to TB-IRIS	0 (0%)	1 (0.8%)	Not calculable	1.0

Composite endpoint of death, hospitalization and hepatotoxicity	22 (18.3%)	32 (26.7%)	0.69 (0.43-1.11)	0.16
Interruption of ART and/or TB treatment due to AE	10 (8.3%)	19 (15.8%)	0.53 (0.26-1.08)	0.11
Interruption of ART and/or TB treatment due to DILI or rash	6 (5.0%)	8 (6.7%)	0.75 (0.27-2.10)	0.78
Secondary safety endpoints	**n=119**	**n=119**		
Severe infections (AIDS-defining or invasive bacterial)	11 (9.2%)	18 (15.1%)	0.61 (0.30-1.24)	0.23
Grade 1 clinical AE 4	111 (93.3%)	114 (95.8%)	0.97 (0.92-1.04)	0.57
Grade 2 clinical AE 4	74 (62.2%)	84 (70.6%)	0.88 (0.73-1.06)	0.22
Grade 3 clinical AE 4	33 (27.7%)	53 (44.5%)	0.62 (0.44-0.89)	0.01
Grade 4 clinical AE 4	8 (6.7%)	10 (8.4%)	0.80 (0.33-1.96)	0.81
Serious AE	24 (20.2%)	30 (25.2%)	0.80 (0.50-1.28)	0.44
Adverse drug reactions	Definite: 0 Probable: 1 Possible: 21 Total: 22	Definite: 0 Probable: 2 Possible: 19 Total: 21	1.05 (0.61-1.80)	1.00
Week 12 CD4 count (cells/µl) (n=212)	164 (97-226)	150 (100-226)	-	0.73
Week 12 HIV RNA drop < 2 log10 (n=210)	6/105 (5.7%)	9/105 (8.6%)	0.67 (0.25-1.81)	0.59

Table S2: Major protocol deviations

16 major protocol deviations occurred: 7 in the prednisone arm and 9 in the placebo arm.

No.	Treatment Arm	Details
1	Prednisone	Participant included in study even though CD4 count < 100 had been performed greater than 3 months prior to screening date, and the inclusion criterion states that it should be within 3 months.
2	Placebo	Participant included even though he had taken 31 days of TB treatment at week 0. A participant should have <30 days of TB treatment prior to enrolment and randomization.
3	Placebo	Participant received ibuprofen from the clinic pharmacist even though the study doctor prescribed tramadol. This medication is prohibited while the participant is receiving study medication.
4	Placebo	Participant had 30 doses of TB treatment when randomised and not less than 30 as stated in the protocol
5	Placebo	Study team found out after participant completed week 12 visit that participant was not ART naïve at time of enrolment
6	Prednisone	Participant took single dose of AZT 8 days before randomization and was thus not ART naïve at time of enrolment on the trial
7	Placebo	Participant received 9 doses of ibuprofen during the time participant was on study medication. This was dispensed without knowledge of the study team. Ibuprofen was prohibited while receiving study medication.
8	Prednisone	Participant continued to take 8 tablets of study medication into the third week of treatment and forgot to decrease this dose to 4 as instructed.
9	Prednisone	Participant continued to take 8 tablets of study medication into the third week of treatment and forgot to decrease this dose to 4 as instructed.
10	Placebo	Participant continued to take 8 tablets of study medication into the third week of treatment and forgot to decrease this dose to 4 as instructed.
11	Prednisone	Participant had 30 days TB treatment at week 0.
12	Placebo	Participant denied prior ART at screening visit. Information was obtained after randomization which proved that he had taken ART in the past. This was an exclusion criterion.
13	Prednisone	Participant discovered to be ART experienced after randomization. This was an exclusion criterion.
14	Prednisone	Began ART on day 33 of TB treatment. Participants were required to start ART within 30 days of starting TB treatment.
15	Placebo	The members of the study team had been under the impression that the participant has been adherent to all medication including ART and study medication. However, she later admitted that she took only TB treatment

		and disposed of all other treatment due to underlying depression. This came to light when she became ill again with TB and was again questioned with respect to adherence.
16	Placebo	During hospital admission (for a deep vein thrombosis) study medication was incorrectly replaced with prednisone 40mg daily by the attending (non-study) physician for 5 days. There was no clinical indication to switch to open-label prednisone. This was a misunderstanding of the trial.

Table S3: Deaths occurring within 12 weeks

9 participants died during the initially planned 12 weeks of follow-up in the trial: 5 in the prednisone arm and 4 in the placebo arm.

No.	Treatment arm	Days from Week 0 to death	Cause of death	TB-IRIS committee decision (meet INSHI criteria)	Death attributable to TB-IRIS (committee view)
1	Prednisone	69	Unknown: acute deterioration after hospital discharge	No	No
2	Placebo	18	Unknown: acute deterioration in hospital (sepsis or pulmonary embolus suspected)	No	No
3	Placebo	21	*Clostridium difficile* infection complicated by enterococcal sepsis	No	No
4	Prednisone	40	XDR-TB	No	No
5	Prednisone	29	Enteric infection and sepsis	No	No
6	Placebo	29	Pericardial tamponade	Yes	Probable
7	Placebo	56	Pneumonia	No	No
8	Prednisone	14	Unknown: sudden death at home	No	No
9	Prednisone	21	Neurological cause: no other details available	No	No

Table S4: Deaths after 12 weeks and within one year

9 deaths occurred between week 12 and 1 year: 3 in the prednisone arm and 6 in the placebo arm. Ascertainment of vital status was achieved for 239 participants at 1 year (see Table S11).

No.	Treatment arm	Days from Week 0 to death	Cause of death	TB-IRIS committee decision (meet INSHI criteria)	Death attributable to TB-IRIS (committee view)
1	Placebo	173	Interpersonal violence	Yes	No
2	Prednisone	170	Autoimmune hemolytic anemia	Not reviewed	No
3	Placebo	138	Unknown: Died on arrival at hospital	Yes	No
4	Placebo	151	Pneumonia, defaulted ART, extensive leukoencephalopathy	Not reviewed	No
5	Placebo	122	Pneumocystis pneumonia, defaulted ART	Not reviewed	No
6	Prednisone	245	Prolonged abdominal TB-IRIS with protein losing enteropathy; terminal event likely sepsis	Yes	Probable
7	Placebo	264	Final cause unknown. Severe lumbosacral radiculopathy with bedsores and deep vein thrombosis	Not reviewed	No
8	Prednisone	162	Multiple ring enhancing lesions on CT head (likely IRIS tuberculomas) after 5 months on TB treatment	No (There was no deterioration compatible with TB-IRIS within first 3 months of ART)	Probable
9	Placebo	171	Unknown	Yes	No

Table S5: Serious Adverse Events

111 serious adverse events were recorded during 12 weeks follow-up. In the prednisone arm 24 participants experienced 55 serious adverse events; and in the placebo arm 30 participants experienced 56 serious adverse events.

No.	Treatment arm	Details	ACTG Grade	Reason Classified as SAE	Relation to study medication	Outcome
1[a]	Placebo	Vomiting	2	Hospitalization	Not related	Resolved
2	Placebo	Acute renal failure	3	Intervention required	Not related	Resolved
3	Placebo	CSF culture Cryptococcus positive	4	Intervention required	Not related	Resolved
4[a]	Placebo	Possible sepsis	3	Hospitalization	Not related	Resolved
5[b]	Prednisone	Abdominal pain	3	Hospitalization	Not related	Resolved
6[b]	Prednisone	*Salmonella non-typhi* bacteraemia and peritonitis	4	Hospitalization	Not related	Resolved
7	Prednisone	Vomiting and abdominal pain	2	Hospitalization	Not related	Resolved
8	Prednisone	Raised creatinine	3	Required change in medication	Not related	Resolved
9	Prednisone	Exacerbation of chronic obstructive airways disease with dyspnea	3	Hospitalization	Not related	Resolved
10	Prednisone	Exacerbation of chronic obstructive airways disease with dyspnea	3	Hospitalization	Not related	Resolved
11	Placebo	Corneal ulcer	2	Intervention required	Not related	Resolved
12	Prednisone	Raised creatinine	4	Hospitalization	Not related	Resolved

13	Placebo	Neutropenia	4	Intervention required	Not related	Resolved
14	Placebo	Lower respiratory tract infection	3	Hospitalization	Not related	Resolved
15	Placebo	Dysphagia	3	Hospitalization	Not related	Resolved
16[c]	Prednisone	Vomiting	3	Hospitalization	Not related	Resolved
17[c]	Prednisone	Shortness of breath	2	Hospitalization	Not related	Resolved
18[c]	Prednisone	Generalized weakness	3	Hospitalization	Not related	Resolved
19	Prednisone	Deep Vein Thrombosis	3	Hospitalization	Not related	Ongoing at Wk 12
20[d]	Placebo	Raised ALT	2	Hospitalization	Not related	Resolved
21[d]	Placebo	Raised bilirubin	3	Hospitalization	Not related	Resolved
22	Placebo	Deep Vein Thrombosis	3	Hospitalization	Not related	Resolved
23	Prednisone	Deep Vein Thrombosis	3	Hospitalization	Not related	Ongoing at Wk 12
24	Placebo	Hyperkalemia	3	Intervention required	Not related	Resolved
25	Placebo	High creatinine	3	Hospitalization	Not related	Resolved
26	Placebo	Anemia	4	Intervention required	Not related	Resolved
27	Prednisone	Parasuicide	3	Hospitalization	Not related	Ongoing at Wk 12
28[e]	Prednisone	Headache	3	Hospitalization	Not related	Resolved
29[e]	Prednisone	Cryptococcal meningitis	4	Hospitalization	Not related	Resolved
30[f]	Prednisone	Nausea	3	Hospitalization	Not related	Ongoing at Wk 12
31[f]	Prednisone	Vomiting	3	Hospitalization	Not related	Ongoing at Wk 12
32	Placebo	Shortness of breath	3	Intervention required	Not related	Resolved
33[g]	Placebo	Abdominal cramps	3	Hospitalization	Not related	Ongoing at Wk 12
34[g]	Placebo	Pneumonia	3	Hospitalization	Not related	Ongoing at Wk 12

35	Placebo	Anemia	4	Intervention required	Not related	Ongoing at Wk 12
36	Placebo	Sepsis	5	Death	Not related	N/A
37	Placebo	Diarrhoea	3	Hospitalization	Not related	Ongoing at Wk 12
38	Placebo	Advanced HIV	5	Death	Not related	N/A
39	Prednisone	Nausea and vomiting	2	Hospitalization	Not related	Resolved
40	Prednisone	Weakness	3	Hospitalization	Not related	Ongoing at Wk 12
41	Prednisone	Deep Vein Thrombosis	3	Hospitalization	Not related	Ongoing at Wk 12
42	Prednisone	Possible sepsis/high white blood cell count	3	Intervention required	Not related	Resolved
43	Prednisone	Possible sepsis	3	Hospitalization	Not related	Ongoing at Wk 12
44	Prednisone	Advanced HIV	5	Death	Not related	N/A
45	Placebo	Lumbar pain and pain in left flank	3	Hospitalization	Not related	Resolved
46	Placebo	Anemia	4	Intervention required	Not related	Resolved
47	Placebo	Possible sepsis	3	Hospitalization	Not related	Resolved
48	Placebo	Deep Vein Thrombosis	3	Hospitalization	Not related	Ongoing at Wk 12
49	Placebo	Deep Vein Thrombosis	3	Hospitalization	Not related	Ongoing at Wk 12
50	Placebo	Maculopapular rash	3	Intervention required	Not related	Resolved
51	Prednisone	Headache	3	Hospitalization	Not related	Resolved
52	Prednisone	Arthritis knees and ankles	3	Intervention required	Not related	Resolved
53[h]	Prednisone	Abdominal pain	3	Hospitalization	Not related	Resolved
54	Prednisone	Anemia	3	Intervention required	Not related	Resolved

55	Prednisone	Anemia	3	Intervention required	Not related	Resolved
56[h]	Prednisone	Weakness	4	Hospitalization	Not related	Resolved
57	Prednisone	Weakness	4	Hospitalization	Not related	Ongoing at Wk 12
58	Prednisone	Renal dysfunction	3	Intervention required	Not related	Unknown
59	Prednisone	XDR-TB	5	Death	Not related	N/A
60	Prednisone	Possible sepsis	3	Intervention required	Not related	Unknown
61	Placebo	Acute renal failure	4	Hospitalization	Not related	Resolved
62	Placebo	Low potassium	4	Intervention required	Not related	Resolved
63	Placebo	Low calcium	4	Intervention required	Not related	Resolved
64	Placebo	Cryptococcal meningitis	2	Intervention required	Not related	Resolved
65	Placebo	Diarrhoea	3	Hospitalization	Not related	Resolved
66	Prednisone	Deep Vein Thrombosis	3	Hospitalization	Not related	Resolved
67	Prednisone	Epigastric pain	3	Hospitalization	Not related	Resolved
68	Placebo	Hypotension	3	Hospitalization	Not related	Resolved
69	Placebo	Deep vein thrombosis	3	Hospitalization	Not related	Resolved
70[i]	Prednisone	Vomiting	3	Hospitalization	Not related	Resolved
71[i]	Prednisone	Diarrhoea	3	Hospitalization	Not related	Resolved
72	Prednisone	Possible sepsis	5	Death	Not related	N/A
73	Prednisone	Possible undiagnosed intestinal pathology	5	Death	Not related	N/A
74	Prednisone	Vomiting	3	Hospitalization	Not related	Ongoing at Wk12
75	Placebo	Weakness	4	Hospitalization	Not related	Resolved
76	Prednisone	Vomiting	2	Hospitalization	Not related	Resolved

77	Prednisone	Pneumothorax	3	Hospitalization	Not related	Resolved
78	Prednisone	Pneumothorax	3	Hospitalization	Not related	Resolved
79	Placebo	Leg weakness	3	Hospitalization	Not related	Ongoing at W12
80	Placebo	Vomiting	3	Hospitalization	Not related	Resolved
81	Placebo	Pericardial effusion	5	Death	Not related	N/A
82	Prednisone	*Salmonella non-typhi* sepsis	3	Hospitalization	Not related	Resolved
83	Prednisone	Deep vein thrombosis	3	Hospitalization	Not related	Ongoing at Wk12
84	Placebo	Renal failure	4	Hospitalization	Not related	Resolved
85	Prednisone	Raised creatinine	3	Intervention required	Not related	Resolved
86	Prednisone	Deep vein thrombosis	3	Hospitalization	Not related	Resolved
87	Prednisone	Abnormal renal function	4	Intervention required	Not related	Ongoing at Wk12
88	Placebo	Abdominal cramps	2	Intervention required	Not related	Resolved
89	Placebo	Clostridium difficile diarrhea	2	Intervention required	Not related	Resolved
90	Placebo	High creatinine	3	Intervention required	Not related	Resolved
91	Placebo	Episode of confusion	3	Hospitalization	Unlikely related	Resolved
92[k]	Prednisone	Unknown cause	5	Death	Not related	NA
93[j]	Placebo	Weakness	3	Hospitalization	Not related	Ongoing at Wk12
94[j]	Placebo	Pneumosepsis	3	Hospitalization	Not related	Ongoing at Wk12
95	Placebo	Hypoglycemia	5	Death	Not related	NA
96	Placebo	Anemia	4	Hospitalization	Not related	Resolved
97	Prednisone	Weakness	4	Hospitalization	Not related	Ongoing at Wk12
98	Prednisone	Undiagnosed neurological problem	5	Death	Not related	Ongoing at Wk12

99	Prednisone	Anemia	4	Hospitalization	Not related	Ongoing at Wk12
100	Prednisone	Generalized rash	2	Intervention required	Not related	Resolved
101	Prednisone	High ALT/DILI	3	Intervention required	Not related	Resolved
102	Placebo	Diarrhoea	3	Hospitalization	Not related	Resolved
103	Placebo	Clostridium difficile in stool	3	Intervention required	Not related	Resolved
104	Placebo	High creatinine	1	Hospitalization	Not related	Resolved
105	Placebo	Deep vein thrombosis	3	Hospitalization	Not related	Ongoing at w12
106	Placebo	Hemoptisis	2	Hospitalization	Not related	Resolved
107	Placebo	Renal failure	3	Intervention required	Not related	Ongoing at w12
108	Placebo	Anemia	4	Intervention required	Not related	Resolved
109	Prednisone	High creatinine	4	Hospitalization	Not related	Ongoing
110	Placebo	High creatinine	3	Hospitalization	Not related	Resolved
111	Placebo	Community acquired pneumonia	3	Hospitalization	Not related	Resolved

[a-j] Indicate one hospital admission for more than one SAE

[k] This participant did not start study medication or ART and was thus not included in all-patients-treated analysis

Table S6: Adverse Drug Reactions related to study medication

Adverse Drug Reactions included those AEs attributed as possibly, probably or definitely related to study medication, but not open-label prednisone. 45 probably or possibly-related ADRs were reported in 43 participants. No definitely-related ADRs were reported. In the prednisone arm 1 participant had a probably and 21 possibly-related ADRs; and in the placebo arm 2 participants had probably and 19 possibly-related ADRs. None of the 45 ADRs were categorized as serious adverse events.

No.	Treatment Arm	Days from Week 0	Description of Adverse Drug Reaction to Study Medication	Relationship to study Medication
1	Placebo	3	Hypomania	Probably related
2	Placebo	14	Hypertension	Possibly related
3	Placebo	10	Epigastric pain	Possibly related
4	Prednisone	14	Hypertension	Possibly related
5	Placebo	8	Hypomania	Probably related
6	Placebo	7	Hypertension	Possibly related
7	Prednisone	7	Hypertension	Possibly related
8	Placebo	28	Hypertension	Possibly related
9[a]	Prednisone	4	Epigastric pain	Possibly related
10[a]	Prednisone	4	Heartburn	Possibly related
11	Placebo	7	Hypertension	Possibly related
12	Placebo	7	Hypertension	Possibly related
13	Prednisone	8	Epigastric pain	Possibly related
14	Prednisone	17	Epigastric pain	Probably related
15	Prednisone	8	Hypertension	Possibly related
16	Placebo	14	Hypertension	Possibly related
17	Prednisone	7	Hypertension	Possibly related
18	Placebo	0	Insomnia	Possibly related
19	Prednisone	14	Hypertension	Possibly related
20	Prednisone	8	Hypertension	Possibly related
21	Placebo	12	Hypertension	Possibly related
22	Prednisone	5	Hypertension	Possibly related

23	Placebo	10	Epigastric pain	Possibly related
24	Prednisone	6	Hypertension	Possibly related
25	Prednisone	9	Epigastric pain	Possibly related
26	Prednisone	13	Epigastric pain	Possibly related
27[b]	Placebo	25	Increased thirst and increased urine production in known diabetic with normal glucose	Possibly related
28[b]	Placebo	56	Increased urine production	Possibly related
29	Placebo	12	Hypertension	Possibly related
30	Placebo	14	Hypertension	Possibly related
31	Prednisone	14	Hypertension	Possibly related
32	Prednisone	5	Epigastric pain	Possibly related
33	Placebo	7	Hypertension	Possibly related
34	Prednisone	22	Hypertension	Possibly related
35	Placebo	7	Intermittent vomiting	Possibly related
36	Placebo	26	Hypertension	Possibly related
37	Prednisone	7	Mild diastolic hypertension	Possibly related
38	Prednisone	6	Hypertension	Possibly related
39	Prednisone	25	Hypertension	Possibly related
40	Placebo	7	Hypertension	Possibly related
41	Placebo	5	Epigastric pain	Possibly related
42	Prednisone	27	High random glucose	Possibly related
43	Prednisone	14	Hypertension	Possibly related
44	Prednisone	12	Hypertension	Possibly related
45	Placebo	7	Hypertension	Possibly related

[a,b] Indicates two ADRs in one participant

Table S7: Severe infections (defined as new AIDS-defining and invasive bacterial infections)
There were 33 severe infections in 29 participants (11/119 in prednisone arm (9.2%) vs 18/119 in placebo arm (15.1%), p=0.23). In terms of a possible relationship between open-label corticosteroids and severe infections, only 3 of the 33 severe infections were diagnosed after participants were prescribed open-label corticosteroids.

No.	Treatment Arm	Infection	Days from week 0 to onset of infection	Open-label corticosteroids for TB-IRIS or for other indication	Days from initiation of open-label corticosteroid to onset of infection [e]
1	Placebo	Bacterial pneumonia	7		
2	Prednisone	Bacterial pneumonia	18		
3	Placebo	Bacterial pneumonia	27		
4	Prednisone	Bacterial pneumonia	11	Prednisone for TB-IRIS	2
5[a]	Placebo	Bacterial pneumonia	41		
6[b]	Placebo	Bacterial pneumonia	16		
7	Placebo	Bacterial pneumonia	15		
8[c]	Placebo	*C. difficile*	12	Hydrocortisone for sepsis	-9
9	Placebo	*C. difficile*	51		
10[b]	Placebo	*C. difficile*	7		
11	Prednisone	Cryptococcal meningitis	76		
12	Placebo	Cryptococcal meningitis	53		
13	Placebo	Cryptococcal meningitis (asymptomatic)	67	Prednisone for TB-IRIS	25
14	Prednisone	Dysentry	2		
15	Placebo	Dysentry	7		
16	Placebo	Oesophageal candidiasis	6		
17	Placebo	Oesophageal candidiasis	52		
18	Prednisone	Oesophageal candidiasis	20		
19	Prednisone	Oesophageal candidiasis	4		
20[d]	Prednisone	Oesophageal candidiasis	8		
21	Placebo	Oesophageal candidiasis	5	Prednisone for TB-IRIS	-15
22	Placebo	Oesophageal candidiasis	4		

23	Placebo	Oesophageal candidiasis	42	Prednisone for TB-IRIS	22
24	Prednisone	Oesophageal candidiasis	11		
25	Placebo	Oesophageal candidiasis	13	Prednisone for TB-IRIS	-1
26[a]	Placebo	Pyelonephritis	60		
27[c]	Placebo	Sepsis	21	Hydrocortisone for sepsis	0
28	Placebo	Sepsis	7	Prednisone for TB-IRIS	-27
29	Prednisone	Sepsis	30		
30[d]	Prednisone	Sepsis	29		
31	Placebo	Sepsis	50	Prednisone for Pneumocystis pneumonia	-3
32	Prednisone	Sepsis, *Salmonella non-typhi*	13	Prednisone for TB-IRIS	-138
33	Prednisone	Sepsis, *Salmonella non-typhi*	30	Dexamethasone for anesthesia	-7

[a-d] Indicates more than one infection occurring in same participant

[e] If value negative, onset of severe infection was before start of open-label corticosteroids

Table S8: All infections

192 infections of any severity were diagnosed in 118 participants: in 58 participants in prednisone arm and 60 in placebo arm.

Infection	**Prednisone arm**	**Placebo arm**
Axillary abscess	1 (0.8%)	0 (0%)
Bacterial pneumonia	2 (1.7%)	5 (4.2%)
Clostridium difficile	0 (0%)	3 (2.5%)
Dystentry	1 (0.8%)	1 (0.8%)
Urinary tract infection	1 (0.8%)	4 (3.4%)
Sepsis	4 (3.4%)	3 (2.5%)
Cryptococcal meningitis	1 (0.8%)	2 (1.7%)
Oesophageal candidiasis	4 (3.4%)	6 (5.0%)
Oral candidiasis	22 (18.5%)	19 (16.0%)
Vaginal candidiasis	3 (2.5%)	3 (2.5%)
Tinea	7 (5.9%)	8 (6.7%)
Amoebic liver abscess	1 (0.8%)	0 (0%)
Helminth infection	1 (0.8%)	0 (0%)
Nematode infection	1 (0.8%)	0 (0%)
Scabies	0 (0%)	3 (2.5%)
Exacerbation chronic obstructive airway disease	2 (1.7%)	0 (0%)
Bronchitis	0 (0%)	1 (0.8%)
Upper respiratory tract infection	11 (9.2%)	10 (8.4%)
Lower respiratory tract infection	2 (1.7%)	1 (0.8%)
Otitis media	0 (0%)	2 (1.7%)
H. simplex, corneal	0 (0%)	1 (0.8%)
H. simplex, genital	13 (10.9%)	7 (5.9%)
H. simplex, labial	11 (9.2%)	8 (6.7%)
H. zoster	4 (3.4%)	2 (1.7%)
Molluscum contagiosum	1 (0.8%)	0 (0%)
Genital warts	2 (1,7%)	0 (0%)

IRIS folliculitis	1 (0.8%)	0 (0%)
Conjunctivitis	3 (2.5%)	2 (1.7%)
Eye Inflammation	0 (0%)	1 (0.8%)
Uveitis	0 (0%)	1 (0.8%)
Total	**99**	**93**
Total number of participants with 1 or more infections	**58 (48.7%)**	**60 (50.4%)**

Table S9: INSHI criteria met for the diagnosis of TB-IRIS by study arm

For each of the 95 participants with TB-IRIS, the adjudication committee came to a consensus decision on the presence or absence of each of the major and minor criteria of the International Network for the Study of HIV-associated IRIS (INSHI) case definition for TB-IRIS[1]. The second major criterion could only be assessed for those participants for whom a chest radiograph was performed at the time of TB-IRIS occurrence.

INSHI criterion	Prednisone arm (n = 39)	Placebo arm(n = 56)
Major 1: new or enlarging lymph nodes	10 (26%)	23 (41%)
Major 2: new or worsening radiological features	15 (42%)[a]	26 (48%)[a]
Major 3: new or worsening CNS tuberculosis	0 (0%)	0 (0%)
Major 4: new or worsening serositis	2 (5%)	2 (4%)
Minor 1: new or worsening constitutional symptoms	39 (100%)	47 (84%)
Minor 2: new or worsening respiratory symptoms	30 (77%)	37 (66%)
Minor 3: new or worsening abdominal pain accompanied by peritonitis, hepato- or splenomegaly or abdominal adenopathy	5 (13%)	11 (20%)

[a] 36 of 39 participants in the prednisone arm and 54 of 56 participants in the placebo arm had a chest radiograph performed at the time of TB-IRIS

Reference:

1. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516-23.

Table S10: Open-label corticosteroids prescribed to treat paradoxical TB-IRIS

Open-label corticosteroids were prescribed by the study doctor to treat TB-IRIS fulfilling INSHI criteria in 50 participants: 34 in the placebo arm and 16 in the prednisone arm. In these 50 participants the median duration from start of ART to open-label corticosteroids was 14 days (IQR 12-26.5) and the median duration of treatment with open-label corticosteroids was 39 days (IQR 29-62.3). There were another 4 participants in whom open-label corticosteroids were prescribed to treat TB-IRIS, but on review by the TB-IRIS adjudication committee the decision was that they did not fulfil INSHI criteria for the diagnosis of paradoxical TB-IRIS.

No.	Decision regarding TB-IRIS by review committee	Treatment arm	Duration of open-label corticosteroids (days)[a]	Days from start of ART to start of open-label corticosteroids	Days from TB-IRIS symptom onset to start of open-label corticosteroids
1	INSHI paradoxical TB IRIS	Placebo	56	42	39
2	INSHI paradoxical TB IRIS	Prednisone	27	14	8
3	INSHI paradoxical TB IRIS	Placebo	29	22	4
4	INSHI paradoxical TB IRIS	Placebo	74	13	6
5	INSHI paradoxical TB IRIS	Prednisone	51	12	11
6	INSHI paradoxical TB IRIS	Placebo	36	12	7
7	INSHI paradoxical TB IRIS	Placebo	165	7	4
8	INSHI paradoxical TB IRIS	Placebo	62	7	6
9	INSHI paradoxical TB IRIS	Placebo	29	34	29
10	INSHI paradoxical TB IRIS	Prednisone	140	13	3
11	INSHI paradoxical TB IRIS	Placebo	28	34	3
12	INSHI paradoxical TB IRIS	Placebo	29	26	15
13	INSHI paradoxical TB IRIS	Placebo	102	11	3
14	INSHI paradoxical TB IRIS	Placebo	29	19	2
15	INSHI paradoxical TB IRIS	Placebo	49	7	4
16	INSHI paradoxical TB IRIS	Placebo	29	12	11
17	INSHI paradoxical TB IRIS	Prednisone	28	31	17
18	INSHI paradoxical TB IRIS	Prednisone	29	33	28
19	INSHI paradoxical TB IRIS	Prednisone	63	12	11
20	INSHI paradoxical TB IRIS	Placebo	35	11	8

21	INSHI paradoxical TB IRIS	Placebo	34	9	3
22	INSHI paradoxical TB IRIS	Prednisone	21[b]	224	191
23	INSHI paradoxical TB IRIS	Placebo	216	20	6
24	INSHI paradoxical TB IRIS	Prednisone	27	9	2
25	INSHI paradoxical TB IRIS	Placebo	10[b]	20	13
26	INSHI paradoxical TB IRIS	Prednisone	41	14	5
27	INSHI paradoxical TB IRIS	Placebo	27	12	4
28	INSHI paradoxical TB IRIS	Prednisone	29	24	17
29	INSHI paradoxical TB IRIS	Placebo	41	20	6
30	INSHI paradoxical TB IRIS	Placebo	64	20	4
31	INSHI paradoxical TB IRIS	Prednisone	98	146	136
32	INSHI paradoxical TB IRIS	Placebo	30	31	20
33	INSHI paradoxical TB IRIS	Placebo	57	8	6
34	INSHI paradoxical TB IRIS	Prednisone	46	21	8
35	INSHI paradoxical TB IRIS	Prednisone	56	70	19
36	INSHI paradoxical TB IRIS	Placebo	30	41	34
37	INSHI paradoxical TB IRIS	Placebo	27	14	2
38	INSHI paradoxical TB IRIS	Placebo	40	12	9
39	INSHI paradoxical TB IRIS	Prednisone	67	14	6
40	INSHI paradoxical TB IRIS	Prednisone	85	20	15
41	INSHI paradoxical TB IRIS	Placebo	93	7	3
42	INSHI paradoxical TB IRIS	Placebo	14[b]	14	3
43	INSHI paradoxical TB IRIS	Placebo	36	14	3
44	INSHI paradoxical TB IRIS	Placebo	31	9	8
45	INSHI paradoxical TB IRIS	Placebo	44	28	20
46	INSHI paradoxical TB IRIS	Placebo	53	12	4
47	INSHI paradoxical TB IRIS	Prednisone	39	15	4
48	INSHI paradoxical TB IRIS	Placebo	29	28	20
49	INSHI paradoxical TB IRIS	Placebo	39	13	2
50	INSHI paradoxical TB IRIS	Placebo	147	10	3
Median (IQR)			40 (29-63)	14 (12-26)	6 (4-15)

In four participants, who later did not meet the INSHI criteria for TB-IRIS or in whom another diagnosis was considered more likely, open-label corticosteroids were prescribed for the indication TB-IRIS.					
1	Committee considered this participant had paradoxical TB-IRIS but did not fulfil INSHI criteria	Prednisone	48	35	32
2	This participant was thought to have TB-IRIS by study medical officer, but committee decided that the diagnosis was not TB-IRIS	Prednisone	11	151	143
3	This participant was thought to have TB-IRIS by study medical officer, but committee decided that the diagnosis was not TB-IRIS	Placebo	42	24	3
4	This participant was thought to have TB-IRIS by study medical officer, but committee decided that the diagnosis was not TB-IRIS	Placebo	28	72	71

[a] If participant received two or more courses of open-label corticosteroids, the days between courses are excluded from calculation of duration.
[b] In these 3 participants, TB-IRIS and open label corticosteroid treatment was ongoing at the time of death or loss to follow-up and they are excluded from calculation of median duration.

Table S11: Open-label corticosteroids prescribed for other indication (other than paradoxical TB-IRIS)
Open-label corticosteroids were prescribed for reasons other than TB-IRIS during 12 weeks follow-up in 8 participants: 4 in the prednisone arm and 4 in the placebo arm.

No.	Treatment arm	Drug name	Indication	Duration (days)	Days between start of ART and start of open-label corticosteroids
1	Prednisone	Dexamethasone	Anesthesia	1	37
2	Prednisone	Prednisone	COPD	7	24
3	Prednisone	Prednisone	COPD	9	75
4	Placebo	Hydrocortisone	Sepsis	1	21
5	Placebo	Prednisone	Pneumocystis pneumonia	3	53
6	Placebo	Prednisone	Auto-immune haemolytic anemia	1	48
7	Prednisone	Dexamethasone	Seizures	10	11
8	Placebo	Prednisone	Medication error in hospital (Major protocol deviation 16)	5	17

Table S12: Adherence to study medication

A pill count of study medication was performed at week 1, 2 and 4, provided participants returned their medication container as requested. At week 1, 2, and 4 participants were also asked how many doses of study medication they had missed since the previous scheduled study visit. The study doctor used both these parameters to make an assessment of adherence to study medication. These assessments at week 1, 2 and 4 were aggregated over 28 days.

The proportion of doses of prescribed study medication taken is shown in the table below. For participants in whom study medication was stopped early by the study doctor (eg. switched to open-label corticosteroids to treat TB-IRIS) or who terminated study participation early (eg. due to death), study medication adherence was calculated until the day of stopping medication or terminating, respectively. Participants with any missing information are not included in this analysis (ie. excluded from the denominator).

	Prednisone arm	**Placebo arm**	**p-value**
100% of prescribed doses of study medication taken, n (%)	89/115 (77%)	95/116 (82%)	0.40
>90% of prescribed doses of study medication taken, n (%)	106/115 (92%)	107/116 (92%)	1.0

Table S13: Reason for stopping study medication early

66 participants (22 in the prednisone arm and 44 in the placebo arm) stopped study medication early, most commonly for prescription of open-label corticosteroids to treat TB-IRIS (n=36), diagnosis of severe infection leading clinician to stop study medication (n=8), admission to hospital while study medication was at home or stopped in hospital due to misunderstanding (n=7), and poor adherence to study medication (n=5).

No.	Treatment arm	Days study medication taken	Reason for stopping study medication
1	Prednisone	9	Paradoxical TB IRIS requiring steroid treatment
2	Placebo	22	Paradoxical TB IRIS requiring steroid treatment
3	Placebo	12	Paradoxical TB IRIS requiring steroid treatment
4	Placebo	12	Paradoxical TB IRIS requiring steroid treatment
5	Placebo	7	Paradoxical TB IRIS requiring steroid treatment
6	Placebo	7	Paradoxical TB IRIS requiring steroid treatment
7	Prednisone	13	Paradoxical TB IRIS requiring steroid treatment
8	Placebo	23	Paradoxical TB IRIS requiring steroid treatment
9	Placebo	11	Paradoxical TB IRIS requiring steroid treatment
10	Placebo	18	Paradoxical TB IRIS requiring steroid treatment
11	Placebo	7	Paradoxical TB IRIS requiring steroid treatment
12	Placebo	12	Paradoxical TB IRIS requiring steroid treatment
13	Prednisone	12	Paradoxical TB IRIS requiring steroid treatment
14	Placebo	11	Paradoxical TB IRIS requiring steroid treatment
15	Placebo	9	Paradoxical TB IRIS requiring steroid treatment
16	Placebo	20	Paradoxical TB IRIS requiring steroid treatment
17	Prednisone	9	Paradoxical TB IRIS requiring steroid treatment
18	Prednisone	14	Paradoxical TB IRIS requiring steroid treatment
19	Placebo	11	Paradoxical TB IRIS requiring steroid treatment
20	Prednisone	24	Paradoxical TB IRIS requiring steroid treatment
21	Placebo	20	Paradoxical TB IRIS requiring steroid treatment
22	Placebo	20	Paradoxical TB IRIS requiring steroid treatment

23	Placebo	8	Paradoxical TB IRIS requiring steroid treatment
24	Prednisone	20	Paradoxical TB IRIS requiring steroid treatment
25	Placebo	14	Paradoxical TB IRIS requiring steroid treatment
26	Placebo	24	Paradoxical TB IRIS requiring steroid treatment
27	Placebo	12	Paradoxical TB IRIS requiring steroid treatment
28	Prednisone	14	Paradoxical TB IRIS requiring steroid treatment
29	Prednisone	20	Paradoxical TB IRIS requiring steroid treatment
30	Placebo	7	Paradoxical TB IRIS requiring steroid treatment
31	Placebo	14	Paradoxical TB IRIS requiring steroid treatment
32	Placebo	9	Paradoxical TB IRIS requiring steroid treatment
33	Placebo	12	Paradoxical TB IRIS requiring steroid treatment
34	Placebo	28	Paradoxical TB IRIS requiring steroid treatment
35	Placebo	13	Paradoxical TB IRIS requiring steroid treatment
36	Placebo	10	Paradoxical TB IRIS requiring steroid treatment
37	Prednisone	24	Prednisone for COPD exacerbation
38	Placebo	7	Sepsis
39	Prednisone	15	*Salmonella non-typhi* bacteraemia
40	Placebo	18	Pneumonia
41	Prednisone	1	Cryptococcal meningitis
42	Placebo	9	Ileitis and colitis (unknown aetiology)
43	Placebo	11	Cryptosporidiosis
44	Prednisone	17	Herpes zoster opthalmicus
45	Placebo	14	*Clostridium difficile*
46	Placebo	13	Admitted with jaundice
47	Placebo	18	TB treatment stopped due to DILI
48	Prednisone	16	Rifampin-resistant TB diagnosed
49	Placebo	11	Admitted to hospital; study medication at home
50	Prednisone	23	Admitted to hospital; study medication not continued

51	Placebo	14	Admitted to hospital; no study medication
52	Placebo	7	Admitted to hospital; study medication not continued
53	Prednisone	7	Admitted to hospital; study medication not continued
54	Placebo	16	Admitted to hospital; study medication not continued
55	Placebo	12	Admitted to hospital; study medication not continued
56	Prednisone	0	Non-adherence
57	Prednisone	3	Non-adherence
58	Placebo	6	Non-adherence
59	Placebo	0	Non-adherence
60	Prednisone	0	Non-adherence
61	Prednisone	20	Dosing error; study medication finished 7 days early
62	Prednisone	25	Dosing error; study medication finished 3 days early
63	Placebo	25	Dosing error; study medication finished 3 days early
64	Placebo	16	ART interrupted for toxicity
65	Prednisone	0	Participant was diagnosed with drug-induced liver injury due to TB medication and never started ART or study medication
66	Placebo	11	Participant confused, concern this was prednisone side effect
Median (IQR)		12 (9-18)	

Table S14: Follow-up at week 28 and one year to ascertain vital status and malignancy status

During the course of the study results of a trial of prednisolone in tuberculous pericarditis became available, showing an increased incidence of cancer in HIV-infected participants in the prednisolone arm. Our data and safety monitoring board (DSMB) advised additional follow-up to one year to ascertain HIV-related cancers. Vital status was ascertained in 239 participants and malignancy status in 220 participants at one year.

	Prednisone arm (n=119) [a]	**Placebo arm (n=120)**
Week 28		
Vital status known	119 (100%)	120 (100%)
Alive	112 (98%)	111 (93%)
Malignancy status known	119 (100%) (85 visits, 10 phone calls, 19 clinic notes, 5 died on the trial without malignancy)	112 (93%) (87 visits, 6 phone calls, 15 clinic notes, 4 died on the trial without malignancy)
Malignancy	0	1 case of Kaposi's sarcoma [b]
One year		
Vital status known	119 (100%)	120 (100%)
Alive	111 (93%)	110 (92%)
Malignancy status known	113 (95%) (22 visits, 79 phone calls, 7 clinic notes, 5 died on the trial without malignancy)	107 (89%) (24 visits, 71 phone calls, 8 clinic notes, 4 died on the trial without malignancy)
Malignancy	0	1 case of Kaposi's sarcoma [b]

[a] No data available for the one participant that stopped participation in the study.

[b] Refers to same case of Kaposi's sarcoma diagnosed at week 28 visit

Table S15a: C-reactive protein at week 0, 2, 4 and 12 visits

	Prednisone arm	Placebo arm	p-value
Week 0 (n=235)	10.9 (4.0-30.1)	10.7 (4.6-29.9)	0.83
Week 2 (n=224)	45.0 (8.3-75.8)	63.0 (26.1-110.0)	0.001
Week 4 (n=222)	28.7 (10.0-59.7)	33.4 (11.7-74.2)	0.38
Week 12 (n=211)	11.7 (5.6-28.8)	13.1 (6.1-32.7)	0.76

Median (IQR) shown

Figure S1: C-reactive protein at week 0, 2, 4 and 12 visits

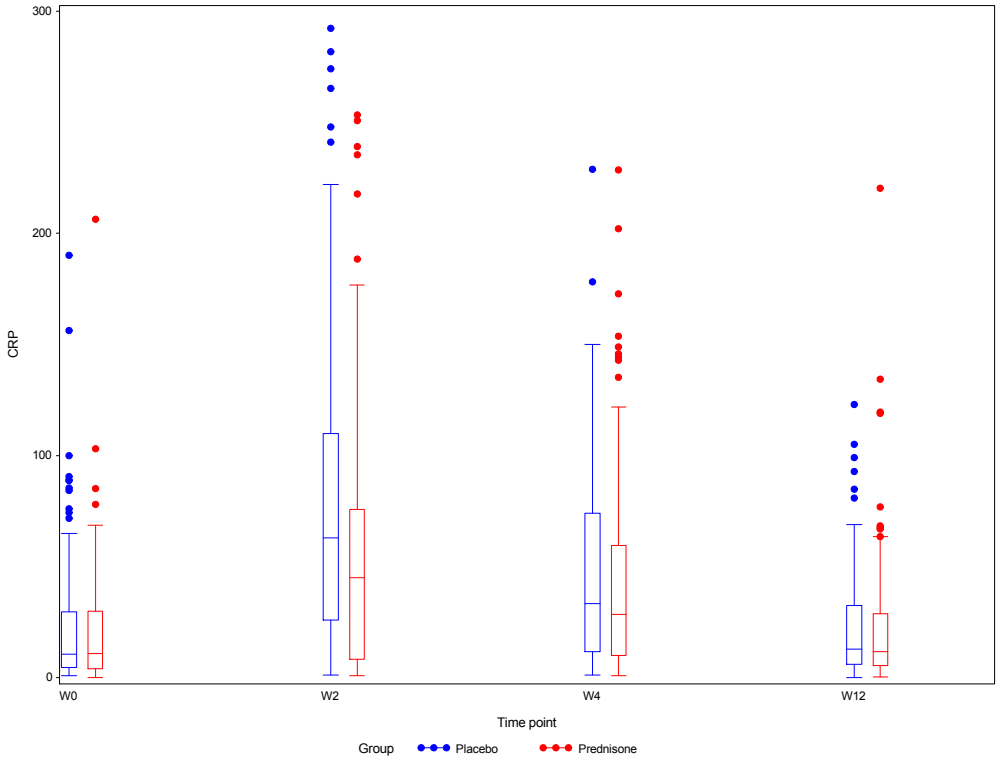

Table S15b: Mixed effects linear regression model of evolution of log(CRP) over time

A mixed effects linear regression model was fitted with log(CRP) as dependent variable and visit and the interaction between visit and treatment group as independent variables and a random intercept. The evolution over time is statistically significant different between the treatment arms (p=0.002).

Effect	**Estimate**	**95%CI**	**p-value**
Average at Week 0 in Placebo arm	2.36	2.20; 2.52	
Change from Week 0 in Placebo arm			<0.001
Week 2	1.49	1.26; 1.71	
Week 4	1.00	0.78; 1.23	
Week 12	0.19	-0.04; 0.42	
Difference in change from Week 0 between Prednisone and Placebo			0.002
Week2	-0.52	-0.81; -0.23	
Week4	-0.10	-0.39; 0.19	
Week12	0.04	-0.26; 0.34	

Variance of random intercept = 0.76
Residual variance = 0.82

Table S16: Safety blood tests at week 2, 4 and 12 visits

	Prednisone arm (median (IQR); n)	**Placebo arm** (median (IQR); n)	**p-value**
Sodium (mmol/L)			
Week 2	136 (133-139); 114	133 (130-136); 110	<0.001
Week 4	136 (134-138); 112	135 (133-137); 109	0.16
Week 12	137 (136-140); 106	137 (136-139); 105	0.92
Potassium (mmol/L)			
Week 2	4.2 (3.9-4.6); 111	4,5 (4,1-4,9); 106	0.001
Week 4	4.3 (3.9-4.7); 111	4.5 (4.0-4.8); 109	0.12
Week 12	4.5 (4.2-4.9); 106	4.4 (4.1-4.8); 104	0.06
Creatinine (umol/L)			
Week 2	62.5 (52.0-70.0); 114	64,5 (54.0-78.0); 110	0.08
Week 4	58 (51.0-69.0); 113	60.0 (53.0-72.0); 109	0.56
Week 12	66.0 (53.0-77.0); 106	63.0 (56.0-74.0); 105	1.0
Glucose (mmol/L)			
Week 2	5.2 (4.4-6.1); 114	5.4 (4.8-6.7); 109	0.07
Week 4	5.3 (4.4-6.0); 112	5.2 (4.5-5.9); 109	0.72
Week 12	4.9 (4.4-5.5); 106	4.7 (4.3-5.2); 105	0.10
Alanine transferase (U/L)			
Week 2	29.5 (22.0-43.0); 114	31.0 (23.0-42.0); 109	0.80
Week 4	31.5 (21.5-48.0); 112	28.5 (22.0-45.0); 110	0.59
Week 12	29.0 (20.0-40.0);105	27.0 (20.0-38.0); 105	0.63
Alkaline Phosphatase (U/L)			
Week 2	101 (84-129); 114	119 (90-161); 109	0.007
Week 4	115 (91-159); 111	130 (97-209); 110	0.09
Week 12	136 (95-212); 105	128 (100-186); 105	0.53
Bilirubin (umol/L)			
Week 2	5.0 (4.0-7.0); 113	6.0 (4.0-9.0); 110	0.11
Week 4	5.0 (4.0-6.0); 110	5.0 (4.0-7.0); 110	0.03
Week 12	4.0 (3.0-6.0); 105	4.0 (3.0-5.0); 105	0.52

Haemoglobin (g/dL)			
Week 2	10.7 (9.6-12.0); 114	10.2 (9.1-11.4); 110	0.017
Week 4	11.3 (9.8-12.3); 113	10.1 (8.9-11.3); 109	<0.001
Week 12	12.2 (10.9-13.1);105	11.7 (10.2-13.6); 106	0.32
White cell count ($x10^9$/L)			
Week 2	5.6 (4.5-8.2); 114	6.4 (4.7-8.7); 110	0.19
Week 4	5.0 (4.0-6.4); 113	5.6 (4.3-7.3);109	0.05
Week 12	4.6 (3.5-6.1); 105	4.7 (3.7-6.1); 106	0.94
Neutrophil count ($x10^9$/L)			
Week 2	3.9 (3.0-6.1); 113	4.4 (3.1-7.0); 109	0.33
Week 4	3.0 (2.3-4.7); 113	3.5 (2.6-5.3); 109	0.10
Week 12	2.5 (1.8-3.9); 105	2.6 (1.8-3.6); 105	0.80
Lymphocyte count ($x10^9$/L)			
Week 2	0.8 (0.6-1.1); 113	0.8 (0.6-1.0); 109	0.60
Week 4	1.0 (0.6-1.3); 113	0.9 (0.7-1.4); 109	0.98
Week 12	1.2 (0/9-1.6); 105	1.1 (0.9-1.5); 105	0.36
Platelet count ($x10^9$/L)			
Week 2	358 (287-461); 113	364 (268-466); 109	0.84
Week 4	363 (299-447); 112	378 (305, 474); 109	0.30
Week 12	352 (279-446); 105	338 (293-414); 105	0.49

Table S17: ACTG Grade 3 and 4 laboratory adverse events

Grade 3 and 4 laboratory adverse events combined:

	Prednisone arm	**Placebo arm**	**p-value**
Number of Grade 3 lab AEs	19	35	-
Number of Grade 4 lab AEs	8	6	-
Participants with Grade 3 lab AE	16 (13.4%)	21 (17.6%)	0.47
Participants with Grade 4 lab AE	8 (6.7%)	6 (5.0%)	0.78

Disaggregated by specific laboratory adverse events:

	Prednisone arm (n/N)	**Placebo arm** (n/N)	**p-value**
Sodium low (grade 3)	2/119	8/119	0.11
Sodium low (grade 4)	0/119	1/119	1.0
Potassium high (grade 3)	0/119	1/119	1.0
Creatinine (grade 3)	2/119	4/119	0.69
Creatinine (grade 4)	3/119	2/119	1.0
ALT high (grade 3)	2/119	5/119	0.45
ALT high (grade 4)	3/119	1/119	0.62
Alkaline phosphatase high (grade 3)	4/119	2/119	0.68
Total bilirubin high (grade 3)	1/119	4/119	0.37
Glucose high (grade 3)	2/119	1/119	1.0
Hemoglobin low (grade 3)	2/119	7/119	0.17
Hemoglobin low (grade 4)	2/119	1/119	1.0
White cell count low (grade 3)	0/119	1/119	1.0
Neutrophil count low (grade 3)	4/119	1/119	0.37
Neutrophil count low (grade 4)	0/119	1/119	1.0

Table S18: Line listing of clinical adverse events (using MedDRA coding and classification)
There were 1762 clinical ACTG grade 1, 2, 3, or 4 adverse events (only the highest grade counted for a given adverse event) in 228 participants after week 0 (760 in the prednisone arm; 1002 in the placebo arm). Two participants who did not take ART or study medication are excluded from this listing. One participant was unwilling to continue participation in the trial after week 0 and therefore has no adverse events recorded. Nine participants completed the trial without any clinical adverse events recorded (6 in the prednisone arm, 3 in the placebo arm). This table lists each clinical adverse event recorded during the trial and occurring after week 0. An event that occurred twice in the same participant was counted once.

MedDRA term (PT)	Prednisone arm	Placebo arm
Blood and lymphatic system disorders		
Anemia	2	5
Lymph node pain	6	10
Lymphadenopathy	2	6
Cardiac disorders		
Pericardial effusion	0	1
Ear and labyrinth disorders		
Dysacusis	0	1
Ear congestion	0	1
Ear discomfort	2	1
Ear pain	1	1
Otorrhoea	0	2
Tinnitus	1	0
Eye disorders		
Conjunctival haemorrhage	1	0
Eye inflammation	0	1
Eye irritation	1	0
Eye pain	0	1
Eye pruritus	3	2
Eye swelling	0	1

Lacrimation increased	0	1
Photophobia	0	1
Ulcerative keratitis	0	1
Uveitis	0	1
Vision blurred	0	1
Visual acuity reduced	0	1
Gastrointestinal disorders		
Abdominal discomfort	2	2
Abdominal distension	2	0
Abdominal pain	20	23
Abdominal pain lower	2	0
Abdominal pain upper	10	8
Anal fissure	1	1
Anorectal discomfort	1	1
Aphthous ulcer	0	1
Ascites	0	1
Constipation	0	2
Diarrhoea	16	39
Dry mouth	0	1
Dyspepsia	4	4
Dysphagia	1	4
Epigastric discomfort	1	0
Gastrointestinal disorder	1	0
Gingival pain	0	1
Glossodynia	0	1
Haemorrhoids	1	4
Lip blister	1	0

Mouth ulceration	1	0
Nausea	23	34
Noninfective sialoadenitis	1	0
Odynophagia	2	1
Proctalgia	0	1
Rectal haemorrhage	0	1
Sensitivity of teeth	0	1
Toothache	3	0
Vomiting	28	51
General disorders and administration site conditions		
Asthenia	20	27
Chest discomfort	3	1
Chest pain	12	20
Chills	0	1
Discomfort	0	1
Early satiety	0	1
Fatigue	4	10
Feeling cold	4	3
Feeling hot	4	5
Feeling of body temperature change	2	5
Injection site pain	1	0
Oedema	0	3
Oedema peripheral	2	0
Pain	4	3
Peripheral swelling	1	3
Puncture site pain	0	2

Pyrexia	13	33
Swelling	0	3
Thirst	1	1
Unevaluable event	0	1
Hepatobiliary disorders		
Drug-induced liver injury	1	1
Immune system disorders		
Seasonal allergy	1	0
Infections and infestations		
Abdominal sepsis	0	1
Acarodermatitis	0	4
Angular cheilitis	0	3
Bacteraemia	1	0
Body tinea	4	3
Bronchitis	0	1
Clostridium difficile colitis	0	1
Conjunctivitis	3	1
Conjunctivitis bacterial	0	1
Dysentery	1	0
Folliculitis	1	0
Fungal skin infection	0	2
Gastroenteritis	0	1
Genital herpes	2	2
Genital herpes simplex	6	2
Helminthic infection	1	0
Hepatic amoebiasis	1	0
Herpes dermatitis	0	1

Herpes ophthalmic	0	1
Herpes simplex	6	1
Herpes virus infection	2	1
Herpes zoster	2	3
Lower respiratory tract infection	2	2
Meningitis cryptococcal	0	1
Molluscum contagiosum	1	0
Nematodiasis	1	0
Oesophageal candidiasis	4	7
Ophthalmic herpes zoster	1	0
Oral candidiasis	22	21
Oral hairy leukoplakia	0	1
Oral herpes	6	7
Otitis media	0	1
Pneumonia	1	3
Pneumonia bacterial	1	0
Proctitis herpes	0	1
Pseudomembranous colitis	0	1
Pulmonary sepsis	0	1
Rash pustular	0	1
Rhinitis	5	5
Salmonella sepsis	1	0
Sepsis	3	3
Subcutaneous abscess	1	0
Tinea cruris	1	2
Tinea infection	0	1
Tinea versicolour	1	0

Upper respiratory tract infection	7	6
Urinary tract infection	0	4
Vaginal infection	1	0
Viral infection	1	0
Vulvovaginal candidiasis	3	3
Injury, poisoning and procedural complications		
Contusion	1	0
Rib fracture	0	1
Investigations		
Alanine aminotransferase increased	3	7
Blood bilirubin increased	2	1
Blood calcium decreased	0	1
Blood creatinine increased	5	9
Blood glucose decreased	0	1
Blood glucose increased	2	0
Blood magnesium decreased	1	3
Blood potassium decreased	3	8
Blood potassium increased	0	1
Blood pressure diastolic increased	0	2
Blood pressure increased	4	6
Blood urine present	1	0
Body temperature increased	0	2
Cardiac murmur	1	0
Clostridium test positive	0	1
Cryptococcus test positive	0	1
Eosinophil count increased	0	1

Haemoglobin decreased	1	1
Neutrophil count decreased	0	2
Urine output increased	0	1
Weight decreased	35	55
White blood cell count decreased	1	0
White blood cell count increased	1	0
Metabolism and nutrition disorders		
Decreased appetite	40	56
Polydipsia	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	10	10
Back pain	8	11
Flank pain	5	6
Joint swelling	2	0
Limb mass	0	1
Muscle spasms	4	5
Muscular weakness	0	3
Musculoskeletal pain	3	4
Musculoskeletal stiffness	1	0
Myalgia	1	0
Neck pain	2	4
Pain in extremity	4	11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Anogenital warts	1	0
Vulvovaginal warts	1	0

Nervous system disorders		
Ataxia	0	1
Balance disorder	0	1
Depressed level of conciousness	1	0
Dizziness	14	11
Dizziness exertional	1	0
Dizziness postural	1	0
Head discomfort	0	1
Headache	19	22
Hypoaesthesia	1	0
Loss of consciousness	1	0
Nervous system disorder	1	0
Paraesthesia	15	15
Primary cough headache	1	0
Seizure	1	0
Psychiatric disorders		
Abnormal dreams	1	0
Confusional state	1	3
Depressed mood	1	0
Depression	1	0
Emotional distress	0	1
Hypomania	0	2
Insomnia	8	7
Intentional self-injury	1	0
Nervousness	0	1
Nightmare	1	2
Renal and urinary disorders		

Acute kidney injury	0	2
Dysuria	1	3
Nocturia	1	0
Pollakiuria	1	0
Renal failure	0	2
Renal impairment	3	0
Reproductive system and breast disorders		
Perineal pain	1	0
Vaginal discharge	0	1
Vulvovaginal pruritus	0	1
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	1	1
Cough	30	33
Dysphonia	0	1
Dyspnoea	8	16
Dyspnoea exertional	2	3
Epistaxis	0	1
Haemoptysis	0	1
Nasal congestion	1	3
Oropharyngeal pain	4	4
Oropharyngeal plaque	1	0
Pleuritic pain	8	9
Pneumothorax	1	0
Rhinorrhoea	2	0
Sneezing	1	0
Sputum retention	1	0

Throat irritation	0	1
Upper-airway cough syndrome	1	0
Wheezing	1	0
Skin and subcutaneous tissue disorders		
Dry skin	1	4
Exfoliative rash	0	1
Hyperhidrosis	1	0
Night sweats	46	36
Pruritus	8	8
Pruritus allergic	1	0
Pruritus generalised	5	3
Rash	2	4
Rash erythematous	0	1
Rash generalised	2	1
Rash maculo-papular	1	2
Rash papular	13	23
Rash pruritic	5	2
Swelling face	1	0
Urticaria	1	1
Vascular disorders		
Deep vein thrombosis	6	5
Diastolic hypertension	1	2
Hypertension	18	16
Hypotension	1	1
Total	**703**	**920**
Participants with 1 or more clinical adverse event recorded	**112**	**116**

Table S19: Pre-specified corticosteroid adverse events

Adverse events that could potentially be attributed to corticosteroids were pre-specified. 24 corticosteroids adverse events occurred in 24 participants in the first 4 weeks; and 41 corticosteroid adverse events in 38 participants during 12 weeks of follow-up.

	Up to and including week 4		**Up to and including week 12**	
	Prednisone arm	**Placebo arm**	**Prednisone arm**	**Placebo arm**
New hypertension > 160/100	2	3	2	3
New poor blood pressure control > 160/100	1	0	1	0
Hyperglycaemia (random glucose > 11.1 mmol/l)	2	3	2	3
Hypomania or mania	1	2	1	2
Depression	0	0	1	0
Acne	0	0	0	0
Epigastric pain	6	4	9	11
Upper gastro-intestinal tract bleed	0	0	0	1
Cushingoid features	0	0	0	0
New oedema	1	0	2	3
Avascular necrosis	0	0	0	0
Total	**12**	**12**	**18**	**23**
Participants with 1 or more corticosteroid adverse event	**12**	**12** **(p=1.0)**	**15**	**23** **(p=0.22)**

Table S20: IRIS events that were not TB-IRIS

All newly diagnosed herpes infections (simplex and zoster), molluscum contagiosum, genital warts, fungal skin infections within 12 weeks of ART initiation were considered as IRIS. Cryptococcosis was considered IRIS if there was severe inflammation in the CSF or paradoxical reaction. Uveitis, inflammation of the eye and conjunctivitis were considered IRIS, with the exception of one case of conjunctivitis that was clearly allergic. (Poly)arthralgia, although this could be attributed to IRIS, was not considered IRIS, because there are several differential diagnoses including drug side-effects. There were 73 events in 54 participants: 29 participants in the prednisone arm and 25 in the placebo arm.

Other IRIS	**Prednisone arm**	**Placebo arm**
Conjunctivitis	3 (2.5%)	2 (1.7%)
Cryptococcal meningitis	1 (0.8%)	0 (0%)
H. simplex infection	24 (20.1%)	16 (13.4%)
H. zoster infection	4 (3.4%)	2 (1.7%)
Inflammation of eye	0 (0%)	1 (0.8%)
IRIS folliculitis	1 (0.8%)	0 (0%)
Molluscum contagiosum	1 (0.8%)	0 (0%)
Uveitis	0 (0%)	1 (0.8%)
Tinea	7 (5.9%)	8 (6.7%)
Genital warts	2 (1.7%)	0 (0%)
Total	**43**	**30**
Participants with 1 or more episodes of IRIS other than TB-IRIS	**29 (24.4%)**	**25 (21.0%)**