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

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Abstract

Objective—Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a frequent complication of antiretroviral therapy in resource-limited countries. We aimed to assess whether a 4 week course of prednisone would reduce morbidity in patients with paradoxical TB-IRIS without excess adverse events.

Design—A randomised double blind placebo-controlled trial of prednisone (1.5mg/kg/day for 2 weeks then 0.75mg/kg/day for 2 weeks). Patients with immediately life-threatening TB-IRIS manifestations were excluded.

Methods—The primary combined endpoint was days of hospitalization and outpatient therapeutic procedures, which were counted as one hospital day.

Results—110 participants were enrolled (55 to each arm). The primary combined endpoint was more frequent in the placebo than the prednisone arm (median hospital days 3 (IQR 0-9) and 0 (IQR 0-3) respectively; $p=0.04$). There were significantly greater improvements in symptoms, Karnofsky score, and quality of life (MOS-HIV) in the prednisone versus the placebo arm at 2 and

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Authors' contributions. GMeintjes, GMaartens and RJW designed and co-ordinated the study. GMeintjes, DJP, KR, MXR and TO were involved in patient recruitment and follow-up and collected clinical outcomes data. Data management and analysis were performed by CM and GMeintjes. GMeintjes wrote the manuscript which all authors critically reviewed.

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4 weeks, but not at later timepoints. Chest radiographs improved significantly more in the prednisone arm at weeks 2 ($p=0.002$) and 4 ($p=0.02$). Infections on study medication occurred in more participants in prednisone than placebo arm (27 vs 17 respectively; $p=0.05$), but there was no difference in severe infections (2 vs 4 respectively; $p=0.40$). Isolates from 10 participants were found to be resistant to rifampicin after enrollment.

Conclusions—Prednisone reduced the need for hospitalisation and therapeutic procedures, and hastened improvements in symptoms, performance and quality of life. It is important to investigate for drug-resistant tuberculosis and other causes for deterioration before administering glucocorticoids.

Keywords

Immune reconstitution inflammatory syndrome; IRIS; tuberculosis; HIV; glucocorticoids; prednisone; antiretroviral therapy

INTRODUCTION

The roll-out of antiretroviral therapy (ART) in resource-limited countries has been associated with dramatic improvements in survival and quality of life. In these settings a high proportion of patients commence ART while on treatment for active tuberculosis resulting in a range of management challenges [1]. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is increasingly recognized as an early complication of ART [2,3]. Paradoxical TB-IRIS is thought to result from restoration of tuberculosis-specific immune responses resulting in inflammation at disease sites of tuberculosis where antigen persists despite antitubercular treatment [4,5]. Typically, there is initial improvement on antitubercular therapy, then, after commencing ART, new, recurrent or worsening tuberculosis symptoms, signs or radiographic manifestations occur. Paradoxical TB-IRIS occurs in 8-43% patients starting ART while on antitubercular therapy [3,6-13]. Paradoxical TB-IRIS causes substantial morbidity, often resulting in hospitalization and/or the need for diagnostic and therapeutic procedures [13].

Glucocorticoids have been recommended for the treatment of paradoxical TB-IRIS [14,15], but there is little evidence for this recommendation, the largest study being a retrospective report of 9 patients [7]. In tuberculous meningitis glucocorticoids reduce mortality [16], in tuberculous pericarditis glucocorticoids reduce mortality and the need for repeat aspiration [17,18], and in pulmonary tuberculosis glucocorticoids cause modest clinical and radiographic improvement [19]. However, there is potential for harm when prescribing glucocorticoids in HIV-infected patients. Increased risk or progression of herpes zoster and Kaposi's sarcoma [20-22] have been reported. We have recently reported that a substantial proportion of patients presenting with suspected paradoxical TB-IRIS have undiagnosed drug-resistant *Mycobacterium tuberculosis* [23], another situation in which glucocorticoids may potentially cause harm.

We therefore conducted a randomized controlled trial of glucocorticoid therapy for patients with paradoxical TB-IRIS with the hypothesis that a 4 week course of prednisone would reduce morbidity without an excess of adverse events.

METHODS

Study Participants

Patients were recruited at GF Jooste Hospital, a secondary level university-affiliated hospital in the Western Cape Province of South Africa serving communities with an antenatal HIV

seroprevalence of up to 33% [24]. In 2006, the annual tuberculosis case notification rate in the province was 1031/100 000 [25]. Most patients initiate antitubercular treatment and ART in primary care clinics. We have previously described the ART and antitubercular therapy regimens used in these clinics [23]. In accordance with national guidelines antitubercular drug susceptibility testing (DST) is not routinely performed for new tuberculosis cases, but is performed in patients receiving retreatment or not responding to antitubercular treatment. Clinicians at the primary care ART clinics were informed of the study and encouraged to refer all patients with suspected paradoxical TB-IRIS for assessment.

Consecutive patients were screened using standardized case definitions for paradoxical TB-IRIS [23]. We limited enrollment to four TB-IRIS manifestations to reduce clinical heterogeneity and allow longitudinal radiographic comparison. Only patients with new or recurrent tuberculosis symptoms and ≥ 1 of the following TB-IRIS manifestations were enrolled: (1) infiltrate on chest radiograph, (2) enlarging lymph node/s, (3) serous effusion or (4) cold abscess. Each participant underwent full clinical evaluation and chest radiography. Further investigations were conducted to exclude alternative reasons for clinical deterioration, according to presentation.

Exclusion criteria were: age < 18 years, known rifampicin-resistant tuberculosis, previous glucocorticoid therapy during this tuberculosis episode, prior ART exposure, pregnancy, uncontrolled diabetes mellitus, Kaposi's sarcoma and immediately life-threatening TB-IRIS (defined as: respiratory failure with arterial $pO_2 < 8$ kPa, altered level of consciousness, new focal neurological sign/s, or compression of a vital structure).

The study was approved by the University of Cape Town Research Ethics Committee (337/2004). Written informed consent was provided by all participants. The trial was registered on 17 August 2005 with the International Standard Randomised Controlled Trial Number Register (ISRCTN 21322548). The trial was conducted in accordance with the Helsinki Declaration.

Laboratory Investigations

One or more clinical specimens (e.g. sputum, lymph node aspirate) were sent for tuberculosis microscopy, culture and drug susceptibility testing. Specimens were also sent for rapid rifampicin resistance determination using a mycobacteriophage reporter system (FASTPlaque™) [26]. Repeat samples were sent if deterioration occurred during follow up.

Baseline investigations included electrolytes, urea and creatinine, random glucose, full blood count, liver function tests, calcium and albumin, random cortisol, C-reactive protein (CRP), CD4⁺ lymphocyte count (CD4 count) and hepatitis B surface antigen. Arterial blood gas determination was performed in patients with respiratory distress. Routine follow-up investigations included CRP and glucose at each visit. CD4 count was repeated at week 4.

Treatment

Study medication consisted of prednisone tablets (5 mg) or matching placebo. Prior to the study, a randomization sequence assigning participants in a 1:1 ratio was generated using Excel by the study statistician and given to an independent pharmacist. Study medication was packaged according to sequence by the independent pharmacist off-site. The study medication was then transferred to the GF Jooste Hospital pharmacy. The hospital pharmacists, study clinicians and participants remained blind to sequence and randomization throughout the trial. Participants were enrolled by the study clinicians and consecutive participants received the next study medication container from number 1 to 110. Participants received study medication 1.5mg/kg/day for 2 weeks followed by 0.75mg/kg/day for 2 weeks. The initial high dose of prednisone (1.5 mg/kg/day) was chosen because rifampicin

induces prednisone metabolism [27]. Follow up was at weeks 1, 2, 4, 8 and 12 with a full clinical assessment at each visit.

If significant clinical deterioration occurred after 2 weeks of follow up, the study protocol allowed participants to be switched to open label prednisone. If life-threatening deterioration occurred before 2 weeks, participants could be switched earlier. Unblinding, after switch to open label prednisone, was considered only if this information influenced clinical management. Participants with significant relapse of TB-IRIS symptoms after completing 4 weeks of study medication could also receive open-label prednisone. Initiation of open-label prednisone required agreement between at least two senior clinical investigators. Participants were re-investigated at deterioration for alternative diagnoses.

Most patients with respiratory presentations were prescribed broad-spectrum antibiotics prior to enrollment. If such patients experienced symptom resolution on antibiotics, the diagnosis of TB-IRIS was reconsidered and the patient was not enrolled. Non-steroidal anti-inflammatory drugs were not prescribed.

Assessment of Outcome

The primary endpoint was cumulative days of hospital admission during the 12 week study period, combined with outpatient therapeutic procedures (including aspiration of lymph nodes, cold abscesses and serous effusions) which were assigned a value of one hospital day. Procedures performed prior to or at enrollment were not included.

There were several secondary outcome measures. At each study visit participants were asked about the TB-IRIS symptoms they had presented with and the study clinician enquired about any new TB-IRIS symptoms. The study clinician, blinded to treatment allocation, graded TB-IRIS symptom response at week 2 and 4 visits in relation to the symptoms described at study entry. Symptom response was graded in 1 of 3 categories: deteriorated, no change, or improved/resolved. All patients who developed new TB-IRIS symptoms were graded as “deteriorated”. Participants who switched to open label prednisone within 2 weeks or between 2-4 weeks had their symptoms scored at the time of switching for their 2 and 4 week score respectively.

Symptoms of participants who switched to open label prednisone at or before week 2 were not scored at week 4. The Medical Outcomes Study-HIV (MOS-HIV) Health Survey [28] and Karnofsky performance score were performed at each visit. Participants were assessed for glucocorticoid adverse drug reactions and new infections. Mortality and interruption of antitubercular therapy or ART were other outcomes measured.

Two radiologists, blinded to study allocation, compared chest radiographs at weeks 2 and 4 with baseline (week 0). They utilized a 3-point scale (deteriorated, no change, or improved/resolved). Where there was disagreement they met to agree a final consensus score. Ultrasound scans (measuring lymph node diameter or pericardial effusion width) were also scored at the same time points using a 3-point scale: > 25% increase, < 25% increase or decrease, and > 25% decrease in size.

Statistical Analysis

Defervescence in paradoxical TB-IRIS is reported to occur in 50% by 2 weeks [6]. We based our sample size calculation on the assumption that spontaneous resolution of paradoxical TB-IRIS at 2 weeks would occur in 50% of participants who received placebo. We estimated resolution in 80% of participants by 2 weeks on prednisone. A sample size of 90 would be required to detect these rates of resolution for an α of 0.05 and β of 0.2. Therefore we planned recruitment of 100 patients assuming a 10% drop out rate. Sample

size was subsequently increased to 110 as we found that approximately 10% of our participants had unsuspected rifampicin-resistant tuberculosis [23].

A data and safety monitoring board (DSMB) of 3 clinical researchers and an independent statistician reviewed the study results after 50 participants had completed study follow up. They advised continuing based on predetermined stopping rules.

The analysis of the primary endpoint included all participants, according to the intention to treat principle. Analysis of the primary combined endpoint was performed using the Wilcoxon ranksum test. Other comparisons between the two groups were made using Wilcoxon ranksum, chi-square and Fisher's exact tests, as appropriate. Quantile regression was performed to adjust the primary endpoint for baseline differences between the two groups in duration from start of antitubercular therapy to initiation of ART and random cortisol level. Kaplan Meier methods were used to construct time to event curves for the two groups, and the Gehan-Breslow-Wilcoxon test was used for comparison. Reported p-values are two-sided.

RESULTS

Two hundred and eighty-seven patients were screened and 110 were enrolled (55 to prednisone, 55 to placebo). Progress of participants through the trial is shown in Figure 1.

Seventy (64%) were female and the median age was 31.6 years (range 19-56). Median CD4 count prior to ART was 53 cells/ μ L, and at enrolment 116 cells/ μ L. Table 1 shows baseline characteristics comparing the two arms. Median duration from antitubercular therapy to ART initiation was significantly longer in the prednisone arm. Random cortisol was significantly lower in the prednisone arm, but no participant had a value below reference range. Otherwise the arms were evenly matched. Forty-four participants received antibiotics prior to enrollment.

Initial tuberculosis diagnosis was made by culture of *Mycobacterium tuberculosis* in 46 (42%), a positive smear for acid fast bacilli in 26 (24%), and was empiric based on clinical and radiographic findings in 38 (35%). Fourteen of the 38 participants with an initial empiric tuberculosis diagnosis had microbiologic confirmation at some stage during the study (7 culture positive and 7 smear positive).

Outcomes are shown in Table 2 and Figure 2. The median cumulative number of hospital days (with outpatient therapeutic procedures counted as one additional day) was 0 (interquartile range, IQR 0-3) in the prednisone arm and 3 (IQR 0-9) in the placebo arm ($p=0.04$). In a multivariate regression model controlling for baseline differences between the two arms, this difference remained significant ($p=0.009$).

The symptom score showed more rapid improvement in the prednisone arm at 2 weeks ($p=0.001$) and 4 weeks ($p=0.03$) (Figure 2a). The chest radiograph score demonstrated greater improvement in the prednisone arm at 2 and 4 weeks (figure 2b). The ultrasound score ($n=29$) demonstrated no significant difference at either time point (data not shown). There were significantly greater improvements in MOS-HIV physical and mental health summary scores, Karnofsky performance score and CRP at weeks 2 and 4 in the prednisone arm, but not at later time points.

Five participants switched to open label prednisone during the period of study medication (first 4 weeks) in the prednisone arm and 18 in the placebo arm ($p=0.002$) (Figure 3). Three such participants had study allocation unblinded. There was concern of hepatitis B flare in one, oesophagitis due to herpes virus (not confirmed) in another and pancreatitis in a third.

All 3 had been allocated placebo. 10 participants in the prednisone arm and 2 in the placebo arm were started on open-label prednisone after completing the 4 weeks of study medication ($p=0.01$) due to ongoing deterioration or, more frequently, relapse after having improved on study medication. Participants who initiated open label prednisone were weaned according to response. Median duration of open label prednisone was 84 days (IQR 60-126).

Eight participants in the prednisone arm and 3 in the placebo arm had events that could potentially be attributed to a glucocorticoid adverse drug reaction while on study medication ($p=0.11$). Infections while on study medication occurred in 27 participants in the prednisone arm and 17 in the placebo arm ($p=0.05$). The majority of these infections were mild, mainly oral and vaginal candidiasis, and uncomplicated herpes simplex. Severe infections, defined as invasive bacterial infections or new World Health Organisation stage 4 conditions, occurred in 2 participants in the prednisone arm and 4 in the placebo arm during the 12 week study period ($p=0.40$). These severe infections were a *Klebsiella* wound infection complicated by fatal sepsis syndrome, oesophageal candidiasis, pneumocystis pneumonia and cryptococcal meningitis in the placebo arm. The participant who developed oesophageal candidiasis was on open label prednisone when this occurred. In the prednisone arm the severe infections were fatal pneumonia and cytomegalovirus retinitis.

There were 3 deaths in the prednisone arm and 2 in the placebo arm ($p=0.70$). Six participants defaulted follow up for more than 7 days (all in the placebo arm; $p=0.01$). Five subsequently returned to care.

Drug resistance

Ten cases of rifampicin-resistant tuberculosis were diagnosed after study enrollment. In 8, it was diagnosed after completion of study medication. Three received open label prednisone. In the placebo arm there were 6 cases (5 multidrug-resistant (MDR) and 1 rifampicin-mono-resistant) and in the prednisone arm 4 (2 MDR, 1 rifampicin mono-resistant and 1 rifampicin resistant on FASTplaque™ assay but other drug susceptibility testing could not be done due to contamination) ($p=0.50$). INH-mono-resistant tuberculosis was present in 1 participant in the placebo arm (diagnosed at tuberculosis diagnosis) and 1 in the prednisone arm (diagnosed at TB-IRIS presentation).

DISCUSSION

We found that a 4 week course of prednisone reduced the primary combined endpoint of days hospitalized and outpatient therapeutic procedures in patients presenting with paradoxical TB-IRIS. Mortality was not chosen as a primary outcome as death due to paradoxical TB-IRIS is infrequent in reported series [3,12,13,29]. Furthermore, exclusion of patients with immediately life-threatening manifestations reduced the likelihood that we would demonstrate a significant difference. Additional benefits of prednisone were seen across a range of secondary outcome measures including symptom and Karnofsky performance scores, quality of life assessments, radiographic response, and reduction in CRP. The greatest effects were seen at the 2 week visit. Thereafter the effect size and significance diminished, likely due to the combined effect of crossovers from placebo to open label prednisone for symptom deterioration and the self-limiting nature of most cases of paradoxical TB-IRIS in placebo group.

Switching to open label prednisone while on study medication occurred significantly more frequently in the placebo arm. This is further evidence of the benefit of prednisone. The fact that 10 participants in the prednisone arm needed to restart prednisone after 4 weeks suggests that for a subset this course was too short. Some participants were treated with open label prednisone for several months. Paradoxical TB-IRIS is a heterogeneous condition

with variable natural history and the glucocorticoid regime should in clinical practice be tailored to severity and response.

Prednisone was well tolerated. There was no excess of glucocorticoid adverse drug reactions while on study medication in the prednisone arm. More infections occurred in the prednisone arm while on study drug. The majority of these were mild infections and there was no difference by study arm in the incidence of severe infections.

When considering glucocorticoid therapy for paradoxical TB-IRIS it is crucial to exclude alternative diagnoses, especially new infections or drug-resistant tuberculosis [23], because glucocorticoids may cause harm if the diagnosis of paradoxical TB-IRIS is incorrect. Most patients who had a respiratory presentation were treated with a broad-spectrum antibiotic prior to enrollment, as a bacterial chest infection is an important differential diagnosis in this context. An alternative diagnosis was made in 44 of the paradoxical TB-IRIS suspects screened, and rifampicin-resistant tuberculosis was diagnosed in a further 10 participants after enrollment, even though we excluded patients with known rifampicin-resistant tuberculosis and patients who had not symptomatically improved prior to ART. There is currently no diagnostic test for paradoxical TB-IRIS. In resource-limited settings, where most cases of paradoxical TB-IRIS occur, it is difficult to exclude alternative diagnoses and drug-resistant tuberculosis. Some caution therefore has to be exercised when prescribing glucocorticoids in resource-limited settings. In any setting, it is prudent to avoid or defer glucocorticoids until the diagnosis of paradoxical TB-IRIS is firmly established and reassess the diagnosis of paradoxical TB-IRIS should a patient further deteriorate while being treated with glucocorticoids.

A major challenge in management and research of paradoxical TB-IRIS is that there is no confirmatory diagnostic test. We [23] have previously reported that CRP is almost universally elevated in paradoxical TB-IRIS and that CRP levels are higher in paradoxical TB-IRIS suspects who are subsequently diagnosed with rifampicin-resistant TB. However, CRP is unlikely to have diagnostic utility as most of the differential diagnoses for paradoxical TB-IRIS also cause elevations of CRP. Interferon-gamma release assays (IGRAs) have been proposed as possible diagnostic tools. Certain studies [4,30] have demonstrated that IGRAs, with purified protein derivative as the antigen stimulus, differentiate paradoxical TB-IRIS cases from controls. Our own study [5] suggested that IGRAs do not sufficiently differentiate cases from controls to be considered as a diagnostic test. Other approaches being explored are the identification of a characteristic cytokine profile or gene expression signature for paradoxical TB-IRIS. In the interim diagnosis relies upon the use of clinical case definitions [2].

The development of Kaposi's sarcoma in HIV-infected patients treated with glucocorticoids has been reported [20,21]. Kaposi's sarcoma was an exclusion criterion in our study and no cases occurred in our study, possibly due to the protective effect of ART. We recommend avoidance of glucocorticoids in patients with Kaposi's sarcoma as life-threatening exacerbation may occur [22].

Our study has several limitations. It was conducted at a single site with a relatively small sample size that did not permit subgroup analyses. Radiography from the time of initial tuberculosis diagnosis and ART initiation was unavailable in some participants. In these participants the diagnosis of paradoxical TB-IRIS was made on the basis of recurrent tuberculosis symptoms and the presence of compatible radiographic tuberculosis manifestations (pulmonary infiltrates, visceral lymphadenopathy, or serous effusions), but we did not know for certain if the radiographic manifestations were worsening. Furthermore, it is possible that certain of the subjective measures of improvement (symptom score, quality

of life assessment and Karnofsky performance score) may have been influenced by the euphoric effect associated with high dose glucocorticoids. Although the treatment allocation was randomized, two characteristics were found not to be evenly matched between the two arms (random cortisol and duration of antitubercular therapy to ART). These variables could thus potentially have confounded study findings, but no such effect could be found on the primary endpoint when these two variables were included in a multivariate regression model. An additional limitation was that the tuberculosis diagnosis was confirmed by culture in only 48% of participants. This reflects the practice in a programmatic setting in South Africa where culture is limited and not routinely performed in new tuberculosis cases.

In conclusion, a 4 week course of prednisone reduced days hospitalized and outpatient therapeutic procedures, and resulted in more rapid improvements in symptoms, radiography, markers of inflammation, performance, and quality of life. An important caveat is that clinicians should be certain of the diagnosis of paradoxical TB-IRIS and investigate for antitubercular drug resistance when considering glucocorticoid therapy. Knowing that there is effective symptomatic therapy for paradoxical TB-IRIS may make clinicians less reluctant to start ART early in patients with tuberculosis and advanced immunosuppression [31].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Progress of participants through the trial

^a Common alternative diagnoses were drug reaction (9), bacterial infection (8), cryptococcosis (4), diarrhoeal illness (4) and heart failure (4).

^b Among these 33 patients the most frequent immediately life threatening manifestation was neurological TB-IRIS (n=25).

a

b

Figure 2.

a: Symptom score at week 2 and 4

The distribution of symptom scores in percentage at week 2 and 4 in 3 categories (deteriorated, no change, improved/resolved) is shown. Participants who switched to open label prednisone at or before week 2 were not scored at week 4 (they are shown in a separate category together with those who died within 2 weeks on the week 4 graph). There were significant differences between the 2 arms at week 2 ($p=0.001$) and week 4 ($p=0.03$).

b: Chest radiograph score at week 2 and 4

Participants who had a pulmonary infiltrate on chest radiograph at baseline (week 0) had a chest radiograph score assigned at week 2 and 4 by 2 radiologists. Scores were allocated in 3

categories (deteriorated, no change, improved/resolved) in comparison with the week 0 chest radiograph. The distribution of scores in percentage is shown. There were significant differences between the 2 arms at week 2 ($p=0.002$) and week 4 ($p=0.02$).

Time to initiation of open label prednisone

35 patients initiated open label prednisone

20 in placebo arm; 15 in prednisone arm

Figure 3.

Thirty-five participants were started on open label prednisone (20 in the placebo arm and 15 in the prednisone arm). This Kaplan-Meier graph demonstrates the differences in the time that open label prednisone was started between the two arms. In the first 4 weeks while participants were receiving study medication, 18 in the placebo arm (33%) vs 5 in the prednisone arm (9%) were switched to open label prednisone ($p=0.002$) because of significant symptom deterioration. After 4 weeks, 2 in the placebo arm (4%) vs 10 in the prednisone arm (18%) were started on open-label prednisone ($p=0.01$) mainly because of relapse of TB-IRIS symptoms.

TABLE 1
Participant characteristics at enrollment

Values shown are medians (interquartile range) or numbers (%). Reference ranges for laboratory tests are shown in brackets.

	Placebo arm N=55	Prednisone arm N=55	P-value for comparison
Age	31.6 (19-56.9)	31.5 (19.1-46)	0.82
Female gender	32 (58%)	38 (69%)	0.23
Previous tuberculosis	10 (18%)	15 (27%)	0.26
CD4 count prior to ART (cells/ μ L)	48 (20-92)	56 (30-103)	0.15
WHO stage 4 at ART initiation	33 (60%)	29 (53%)	0.44
Duration antitubercular therapy to ART in days	43.5 (23.8-76)	66 (35-84)	0.02
Duration ART to TB-IRIS in days	10 (7-19)	14 (7-21)	0.21
Duration TB-IRIS to enrollment in days	14 (8-23.5)	12.5 (7-21)	0.24
TB-IRIS manifestations			
New/recurrent lymphadenopathy	28 (51%)	19 (35%)	0.10
New/recurrent cold abscess	1 (2%)	1 (2%)	1.0
New/worsening pulmonary infiltrate	16 (29%)	19 (35%)	0.54
New/worsening serous effusion	9 (16%)	9 (16%)	1.0
Recurrent symptoms and consistent radiography, but without baseline radiography available for comparison	14 (25%)	15 (27%)	0.83
CD4 count at enrollment (cells/ μ L) (n=97)	109 (55-190)	138 (78-243)	0.07
Random glucose, mmol/L (4.1-11.1) (n=108)	5.3 (4.8-5.7)	5.1 (4.8-6)	0.79
Haemoglobin, g/dL (M:13-17, F:12-15) (n=107)	9.2 (7.8-10.1)	9.1 (8.1-10.3)	0.79
Albumin, g/L (35-52) (n=108)	23 (19.5-26.5)	23 (20-26)	0.62
C-reactive protein, mg/L (0-10) (n=108)	106 (79-172)	104 (50-150)	0.18
Random cortisol, nmol/L (138-690) (n=97)	559.5 (405.8-774)	471 (350-614)	0.03
Hepatitis B surface antigen positive (n=94)	3/42 (7%)	3/52 (6%)	0.79
Weight, kg	52.2 (46.6-58.8)	51.6 (48.1-56.5)	0.69
Hospitalised at enrollment	19 (35%)	14 (25%)	0.30
Antibiotics prior to enrollment	19 (35%)	25 (45%)	0.24
Karnofsky performance score (n=107)	70 (30-80)	70 (30-80)	0.96
MOS-HIV Health Survey (n=106)			
Physical health summary score	37.9 (32.8-44.9)	36.3 (33.4-43.1)	0.97

	Placebo arm N=55	Prednisone arm N=55	P-value for comparison
Mental health summary score	49.8 (39.1-56.9)	49.7 (44.5-56)	0.75

ART = antiretroviral therapy; WHO = World Health Organisation; MOS-HIV = Medical Outcomes Study.

TABLE 2
Primary and secondary outcomes^a

Values shown are medians (interquartile range) or numbers (%).

	Placebo N=55	Prednisone N=55	p-value for comparison
Cumulative days hospitalized and outpatient therapeutic procedures	3 (0-9)	0 (0-3)	0.04
Number of participants hospitalized	25 (45%)	17 (31%)	0.12
Cumulative number of days hospitalized	463	282	-
Median number of days hospitalized (all participants)	0 (0-8)	0 (0-3)	0.07
Median number of days hospitalized (among 42 participants who were hospitalized)	12 (5-30)	4 (3-29)	0.26
Number of participants who had outpatient therapeutic procedure performed	12 (22%)	12 (22%)	1.0
Cumulative number of outpatient therapeutic procedures	28	24	-
Karnofsky performance score			
Week 2 (n=92)	70 (50-90)	90 (80-90)	< 0.001
Week 4 (n=86)	80 (60-90)	90 (80-100)	< 0.001
Week 8 (n=91)	90 (75-100)	90 (90-100)	0.33
Week 12 (n=89)	90 (90-100)	100 (90-100)	0.16
MOS-HIV Health Survey			
Physical Health Summary Score			
Week 2 (n=98)	44.5 (36.7-52.4)	51.5 (44.5-54.5)	0.01
Week 4 (n=94)	48.3 (39.7-55)	51.2 (46.6-56.8)	0.04
Week 8 (n=96)	52.9 (44.2-55.5)	53.3 (42.9-56)	0.97
Week 12 (n=88)	52.4 (48.1-56.1)	52.4 (48.9-55.5)	0.93
Mental Health Summary Score			
Week 2 (n=98)	57.4 (48.8-60)	59.9 (54.2-62.1)	0.02
Week 4 (n=94)	55.5 (50.3-60)	58.5 (55.6-62.2)	0.01
Week 8 (n=96)	60.6 (55.8-62.6)	60.6 (54.4-62.7)	0.79
Week 12 (n=88)	61.7 (58.6-63)	60.7 (58.6-63.7)	0.68
CRP (mg/L)			
Week 2 (n=101)	96.5 (53.8-122.5)	35 (13.8-60.3)	<0.001
Week 4 (n=94)	63 (40.5-117.5)	34 (16.3-57)	0.001
Week 8 (n=95)	42 (20-83.5)	39 (13-84.3)	0.49
Week 12 (n=97)	36 (17-80)	25 (9-60.5)	0.12
Week 4 CD4 count (cells/ μ L) (n=75)	145 (61-224)	154 (78-248)	0.51
Glucocorticoid adverse drug reaction ^b while on study medication	3 (5%)	8 (15%)	0.11
Infections while on study medication	17 (31%)	27 (49%)	0.05

	Placebo N=55	Prednisone N=55	p-value for comparison
Death	2 (4%)	3 (5%)	0.65

IQR = Interquartile range; MOS = Medical Outcomes Study; CRP = C-reactive protein; ART = Antiretroviral therapy.

^a Symptom and radiographic scores are not shown here, but are shown in Figure 2.

^b Defined as clinical events that could potentially be attributed to glucocorticoid adverse drug reaction: blood pressure > 140/90, glucose > 11.1 mmol/L, oedema, hypomania, Cushingoid features, acne or gastritis symptoms.