MAJOR ARTICLE

Immunoadjuvant Prednisolone Therapy for HIV-Associated Tuberculosis: A Phase 2 Clinical Trial in Uganda

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Background. Human immunodeficiency virus (HIV)–infected patients with tuberculosis (TB) respond to effective antituberculous therapy, but their prognosis remains poor. Mounting evidence from clinical studies supports the concept of copathogenesis in which immune activation that is triggered by TB and mediated by cytokines stimulates viral replication and worsens HIV infection, especially when immune function is preserved.

Methods. We performed a phase 2, randomized, double-blind, placebo-controlled clinical trial in Kampala, Uganda, to determine whether immunoadjuvant prednisolone therapy in HIV-infected patients with TB who have $CD4^+$ T cell counts $\geqslant$200 cells/μL is safe and effective at increasing $CD4^+$ T cell counts.

Results. Short-term prednisolone therapy reduced levels of immune activation and tended to produce higher $CD4^+$ T cell counts. Although prednisolone therapy was associated with a more rapid clearance of *Mycobacterium tuberculosis* from the sputum, it was also associated with a transient increase in HIV RNA levels, which receded when prednisolone therapy was discontinued. The intervention worsened underlying hypertension and caused fluid retention and hyperglycemia.

Conclusion. The benefits of prednisolone therapy on immune activation and $CD4^+$ T cell counts do not outweigh the risks of adverse events in HIV-infected patients with TB and preserved immune function.

Tuberculosis (TB) is a common and serious complication of HIV-1 infection in the developing world, especially in sub-Saharan Africa [1]. Since the emergence of the HIV epidemic in Africa, the incidence rates of TB have increased dramatically, overwhelming national TB control programs across Africa. More than one-half of patients with TB presenting to TB clinics are infected with HIV, and these patients often present at early stages of HIV infection.

Although HIV-infected patients with TB respond to effective antituberculous therapy [2–4], their prognosis remains poor [3, 5–8]. Deaths early during treatment are often attributable to TB [3, 6], whereas deaths late during treatment are attributable to complications of HIV infections other than TB. Epidemiologic observations indicate that TB may increase the rate of opportunistic infections in HIV-infected patients [9, 10] and may reduce survival [9, 11, 12], especially among patients with $CD4^+$ T cell counts $\geqslant$200 cells/μL [13, 14]. Mounting evidence from immunologic and virologic studies supports the concept of copathogenesis in which TB triggers cellular immune activation [15, 16], mediated by cytokines such as tumor necrosis factor (TNF)–α, which, in turn, stimulates HIV replication, leading to higher viral load and accelerating HIV infection.

One point of attack in efforts to stop this cascade is to attenuate expression of cytokines and thereby reduce the stimulus for HIV replication in latently infected cells [17]. Phase 1 and 2 clinical trials of selective TNF-α inhibitors—such as thalidomide, pentoxifylline, and etanercept—in HIV-associated TB have shown that these

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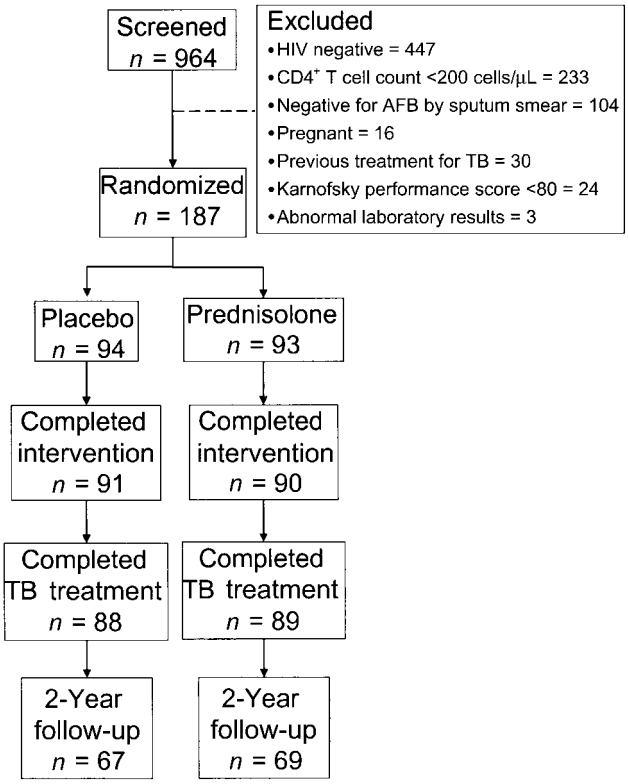

Figure 1. Study flow profile. AFB, acid-fast bacilli; TB, tuberculosis.

inhibitors offer short-term clinical benefits and reduce viral load despite only partial inhibition of TNF-α [18–20]. Since the immune activation of TB is mediated through a network of cytokines, less selective and more potent agents, such as glucocorticoids, may be more effective at interrupting the effects of TB on HIV than are selective cytokine inhibitors. In an observational study of HIV-infected patients without AIDS, the use of corticosteroids was associated with sustained increases in $CD4^+$ T cell counts, with a minimum of adverse events [21, 22].

Prednisolone is an attractive choice for immunoadjuvant therapy in HIV-associated TB because it reduces expression of cytokines [23, 24], is effective in managing inflammatory complications of extrapulmonary TB [25], and is an inexpensive and widely available glucocorticoid agent. Like all corticosteroids, however, prednisolone can produce serious adverse events that may limit its use, even if shown to be effective. The balance of benefit and risk for prednisolone therapy has not been established for patients with HIV-associated TB. The aim of the present study was to assess the safety and biological effect of oral, self-administered prednisolone therapy as an immunoadjuvant treatment for HIV-associated TB among patients with $CD4^+$ T cell counts $\geqslant$200 cells/μL.

SUBJECTS AND METHODS

Study design and population. The present study was a phase 2, randomized, double-blind, placebo-controlled clinical trial of oral prednisolone therapy during standard treatment for HIV-associated pulmonary TB. The study protocol was approved by the institutional review board at Case Western Reserve University and by the Ugandan AIDS Research Committee. All subjects gave informed consent for the study. In 2001, the study was reviewed by the data safety and monitoring board of the Division of AIDS, National Institutes of Health, and the decision was made to not expand the study to include mortality as the main outcome, because surrogate markers for HIV disease progression were similar between the 2 treatment arms at the end of the intervention period.

Between October 1998 and August 2000, 187 HIV-infected patients >18 years of age with initial episodes of acid fast smear–positive pulmonary TB who presented to the National Tuberculosis Program in Kampala, Uganda, were enrolled in the trial. The exclusion criteria were the following: previous treatment for TB, advanced HIV infection (World Health Organization stage IV), Karnofsky performance score <80, peripheral blood $CD4^+$ T cell count <200 cells/μL, Kaposi sarcoma, active herpes zoster, glucose level >160 mg/dL or diabetes mellitus by history, serum aminotransferase level >65 IU/L, potassium level >5.5 mmol/L, positive β-urinary human chorionic gonadotrophin test, previous use of immunomodulators, presence or history of hypertension, psychiatric disease, peptic ulcer disease, or pancreatitis.

Intervention and randomization. A phase 1 clinical trial of 30 HIV-infected patients with TB was performed to determine the weight-adjusted dose of prednisolone required to reduce expression of TNF-α by 50%, as measured in whole-blood cultures stimulated with culture filtrate of *Mycobacterium tuberculosis*. In a pilot pharmacokinetic study, we determined the oral bioavailability of prednisolone to be 51% and that a daily dose of 2.75 mg/kg prednisolone was needed to achieve a 50% reduction in expression of TNF-α. The intervention consisted of prednisolone tablets (Berk Pharmaceuticals) given at a dose of 2.75 mg/kg daily for 4 weeks and tapered over the course of the next 4 weeks to complete an 8-week course. Placebo was an inactive, inert tablet manufactured to be identical in appearance to the active prednisolone tablets. Placebo tablets were given in the same quantity as were prednisolone tablets, within the same weight category. All patients were treated with standard treatment for TB, which consisted of weight-adjusted doses of isoniazid, rifampin, pyrazinamide, and ethambutol [26].

Eligible patients were randomly assigned in blocks of 6 to receive either prednisolone or placebo. The randomization schedule was developed before the trial by use of computer-generated random numbers with corresponding treatment assignments. These assignments were placed in sealed envelopes and drawn sequentially by a study nurse who was not involved with patient care. The clinic dispensary supplied prelabeled drug packs according to assigned treatment and gave instructions for proper dosing and health education. Medications were

Table 1. Baseline clinical and demographic characteristics, by treatment arm.

Characteristic	Placebo (n = 94)	Prednisolone (n = 93)
Men, no. (%) of patients	58 (62)	55 (59)
BCG scar present, no. (%) of patients	42 (46)	40 (44)
PPD induration ⩾5 mm, no. (%) of patients	79 (84)	83 (89)
Karnofsky performance status, no. (%) of patients		
90	21 (22)	28 (30)
80	68 (72)	60 (65)
70	5 (5)	5 (5)
Age, mean (SD), years	31 (7.2)	31 (7.1)
Body mass index, mean (SD), kg/m^2	19 (2.6)	19 (2.8)
Hemoglobin level, mean (SD), g/dL	11 (1.8)	11 (1.8)
WBC count, mean (SD), cells/mm^3	7.8 (2.8)	8.0 (2.8)
Lymphocyte count, mean (SD), cells/mm^3	2.0 (0.9)	1.9 (0.8)
AST level, mean (SD), IU/L	24 (12)	26 (12)
Glucose level, mean (SD), mg/dL	88 (24)	85 (24)
Potassium level, mean (SD), mmol/dL	4.8 (0.5)	4.7 (0.4)
PPD induration, mean (SD), mm	15 (6.4)	16 (5.4)
Symptoms, no. (%) of patients		
Cough	94 (100)	93 (100)
Chest pain	55 (59)	53 (57)
Hemoptysis	11 (12)	5 (5)
Dyspnea	31 (33)	36 (40)
Fever[a]	46 (49)	62 (67)
Weight loss	76 (81)	78 (84)
Purulent sputum	81 (86)	76 (82)
Night sweats[a]	50 (53)	60 (65)
Physical examination, no. (%) of patients		
Respiratory		
Consolidation	93 (99)	90 (97)
Wheezing or rhonchi	1 (1)	2 (2)
Pleural effusion	1 (1)	0
Lymph node enlargement	4 (4)	6 (6)
Sputum smear		
Scanty	7 (7)	7 (8)
1	17 (18)	22 (24)
2	26 (28)	13 (14)
3	44 (47)	49 (54)
Cavitary	74 (79)	80 (86)
Chest radiograph finding		
Normal	0	2 (1)
Minimal	4 (4)	3 (3)
Moderately advanced	25 (27)	23 (25)
Far advanced	65 (69)	66 (71)

NOTE. AST, aspartate aminotransferase; BCG, Bacille Calmette-Guérin; PPD, purified protein derivative; WBC, white blood cell.

[a] $P < .05$, χ^2 test.

self-administered, and adherence was monitored by self-report, pill count, and urinary isoniazid metabolite testing (DynaGen).

Assessment of outcome. The main study outcomes were the safety of prednisolone therapy and the effect of prednisolone therapy on CD4$^+$ T cell counts and HIV RNA levels during treatment for HIV-associated pulmonary TB. The safety of prednisolone therapy was assessed by mortality and the incidence rate of grade 3 or 4 adverse events, as defined by standard toxicity tables used by the AIDS Clinical Trials Group. Deaths occurring within 1 year of the intervention were reviewed by 2 of the authors, to determine the relation to the study intervention; deaths occurring after 1 year were considered unlikely

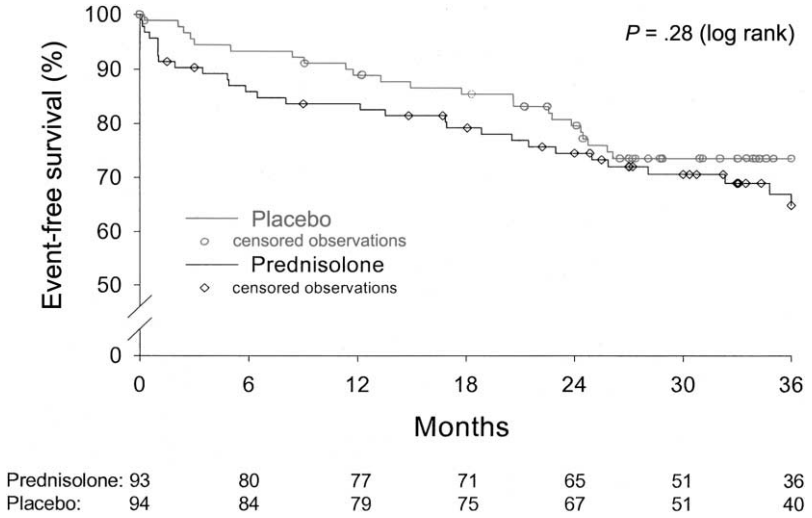

Figure 2. Event-free survival to first grade 3 or 4 adverse event or death in the prednisolone arm *(dark line)* and the placebo arm *(light line)*

to be affected by the study intervention. Serum TNF-α (Medgenic; BioSource), serum TNF-α type II receptor (TNF-αRII; Medgenic; BioSource), *M. tuberculosis* culture filtrate–induced TNF-α (TNF-α–CF; R&D Systems), and serum neopterin (ICN) were used to measure immune activation at baseline and 1 and 4 months. To evaluate the effects of prednisolone therapy on the response to antituberculous therapy, sputum samples obtained at 1 and 2 months were examined for clearance of microorganisms. Treatment failure was defined as the failure to clear acid-fast bacilli (AFB) from the sputum after 5 consecutive months of antituberculous therapy to which the organism was susceptible. TB relapse was defined as the recurrence of active TB after the establishment of cure.

Follow-up and measurements. Study patients in both treatment arms were seen weekly during the first month, twice during the second month, monthly up to 6 months, and quarterly thereafter. Home visitors contacted subjects who missed scheduled appointments and encouraged them to return to the clinic.

Demographic and clinical information was obtained through standardized interviews and physical examinations performed by medical officers. At the time of screening, chest radiographs and sputum smears for AFB (by the Ziehl-Neelsen method) were performed. Blood was collected for HIV testing, complete blood and differential counts (Coulter T540 system), $CD4^+$ T cell counts (EPICS Profile 2 Flow Cytometry), and determination of glucose, potassium, and liver enzyme levels. A urine pregnancy test (β-HCG) was performed for women. Quantitative plasma HIV RNA levels were determined (Cambridge BioScience) and whole-blood cytokine assays were performed at baseline and 1 and 4 months. $CD4^+$ T cell counts were determined at baseline and 1, 2, and 6 months. Sputum samples were collected at baseline, monthly until 6 months, and then at every visit thereafter. Sputum samples were concentrated and stained for AFB at the Uganda Tuberculosis Investigations Bacteriologic Unit in Wandegeya. Sputum smears were graded according to the number of acid-fast organisms seen by light microscopy. Samples were cultured for *M. tuberculosis* on Lowenstein-Jensen medium by use of standard methods. Posteroanterior chest radiography was performed at baseline and 2, 6, and 18 months and was graded [27] by reviewers blinded to treatment assignment.

Statistical analysis. Cumulative incidence (95% confidence interval) was estimated as the number of events per population at risk, at baseline. Distributions of time to first event were summarized by use of the Kaplan-Meier method [28] and were compared between treatment arms by use of the log rank test [29]. The safety of corticosteroids was determined by comparing the cumulative proportion of grade 3 or 4 adverse events between treatment arms by use of the χ^2 or Fisher's exact test. Means for $CD4^+$ T cell counts and HIV RNA levels were compared by use of the Student's *t* test or mixed effects linear regression models [30]. The response to antituberculous therapy was evaluated by comparing the treatment-failure and disease-recurrence rates and the proportion of subjects in each treatment arm with negative smears or cultures at 1 and 2 months.

RESULTS

Between October 1998 and August 2000, 964 patients were screened for entrance into the study, of whom 202 were considered to eligible for the study (figure 1). Screened patients ($n = 762$) were excluded for 1 or more of the following reasons: HIV negativity ($n = 447$), $CD4^+$ T cell count <200 cells/μL ($n = 233$), AFB-negative sputum smear ($n = 104$), previous treatment for TB ($n = 30$), Karnofsky performance score <80 ($n = 24$), and pregnancy ($n = 16$). Of the 202 patients with TB

Table 2. Highest grade experienced for selected adverse events in patients, by treatment arm.

Adverse event, grade	Placebo (n = 94)	Prednisolone (n = 93)	P
Candidiasis, moderate	34 (36)	30 (32)	
Hyperglycemia			.036
Mild	1 (1)	0	
Moderate	2 (2)	5 (5)	
Severe	0	4 (4)	
Abdominal pain			.47
Mild	0	1 (1)	
Moderate	12 (13)	15 (16)	
Hepatitis			.09
Mild	2 (2)	6 (6)	
Moderate	1 (1)	5 (5)	
Severe	1 (1)	1 (1)	
Life threatening	2 (2)	0	
Fluid retention			<.001
Mild	4 (4)	22 (24)	
Moderate	0	3 (3)	
Severe	0	1 (1)	
Pruritis			.95
Mild	5 (5)	6 (6)	
Moderate	26 (28)	25 (27)	
Herpes simplex, moderate	4 (4)	9 (10)	
Herpes zoster			.99
Mild	1 (1)	0	
Moderate	15 (16)	14 (15)	
Severe	0	1 (1)	
Kaposi sarcoma	2 (2)	0	.49
Pneumonia			.93
Moderate	9 (10)	8 (9)	
Severe	4 (4)	6 (6)	
Life threatening	2 (2)	1 (1)	
Urinary tract infection			.19
Moderate	7 (7)	12 (13)	
Severe	0	1 (1)	
Hypertension			.039
Mild	2 (2)	9 (10)	
Moderate	1 (2)	1 (1)	
Life threatening	0	1 (1)	

NOTE. Data are no. (%) of patients, unless otherwise noted. Categories without observations were omitted from the table but included in the statistical analysis.

initially considered to be eligible for the study, 15 were confirmed to be ineligible after enrollment and were not included in the analysis, for the following reasons: TB-negative sputum smear ($n = 5$), $CD4^+$ T cell count <200 cells/μL ($n = 4$), abnormal levels of liver enzymes or potassium ($n = 3$), Karnofsky performance score <80 ($n = 1$), and HIV negativity ($n = 2$). Thus, a total of 187 subjects were eligible for analysis: 93 in the prednisolone arm and 94 in the placebo arm. Of the patients in the prednisolone arm, 90 (96%) completed the study intervention, and 89 (95%) completed antituberculosis treatment and 6 months of follow-up. Of the 94 patients in the placebo arm, 91 (94%) completed the study intervention, and 88 (95%) completed 6 months of follow-up. The median follow-up time for both treatment arms was 34 months.

The baseline clinical and demographic characteristics were similar in the 2 treatment arms, except for fever and night sweats, which were both more common in the prednisolone arm ($P = .05$) (table 1). The mean age of patients was 31 years (SD, 7.2 years), with males composing 59% of the study population. Cough and consolidation were present in all patients. All patients had mycobacterial cultures growing *M. tuberculosis,* and 92% had AFB smears of grade 1–3. Most patients had advanced disease, by chest radiography, and cavitary lesions were common in both treatment arms.

During the study, 17 patients (18%) in the prednisolone arm died, compared with 14 patients (15%) in the placebo arm. The event-free survival to either a severe or life-threatening event or death did not differ between treatment arms ($P = .28$, log rank test) (figure 2). The overall survival distributions between the 2 treatment arms did not differ ($P = .75$, log rank test). Three deaths occurred during the first 90 days after enrollment, and all occurred in the prednisolone arm. One death resulted from a sickle cell crisis on study day 3, 1 death resulted from hypertensive encephalopathy on study day 35, and 1 death resulted from meningitis on study day 64. Of the 17 deaths in the prednisolone arm, 1 was classified as probably related and 2 were classified as possibly related to the study intervention.

Of the 93 patients receiving prednisolone therapy, 87 (94%) experienced $\geqslant$1 adverse event, a proportion comparable to that in the placebo arm, in which 82 patients (87%) experienced any adverse event ($P = .38$, χ^2 test). During 36 months of follow-up, $\geqslant$1 severe or life-threatening event occurred in 22 patients (29.2%) receiving prednisolone therapy and 18 patients (21.2%) receiving placebo ($P = .19$, log rank test). Of the 31 individuals who died during the study, 12 in the prednisolone arm and 8 in the placebo arm experienced serious adverse events that preceded death. Of the adverse events related to prednisolone therapy, hyperglycemia, fluid retention, and hypertension were significantly more common in the prednisolone arm than in the placebo arm (table 2). When hyperglycemia occurred it tended to be moderate to severe. For fluid retention and hypertension, excess cases occurred in the mild category.

At baseline, the median levels of TNF-α–CF, serum TNF-α, TNF-αRII, and neopterin did not differ between treatment arms (table 3). When evaluating changes in immune activation within individuals, the level of TNF-α–CF decreased at 1 month in the prednisolone arm, whereas it remained unchanged in the placebo arm, but, by 4 months, the differences between treatment arms had resolved (figure 3*A*). The other markers of immune activation followed a similar pattern. This pattern of change was seen at the treatment-arm level—median levels of TNF-α–CF, serum TNF-α, TNF-αRII, and neopterin were

Table 3. Median CD4⁺ T cell counts, plasma HIV RNA levels, and immune activation markers, by treatment arm.

Measurement, time of determination	Placebo (n = 94)	Prednisolone (n = 93)	P[a]
TNF-α–CF level, pg/mL			
Baseline	2377 (1571–3985)	2343 (1531–3546)	.77
1 Month	1944 (1274–3069)	692 (325–1770)	<.001
4 Months	2154 (1430–3196)	1715 (1081–3003)	.19
Serum TNF-α level, pg/mL			
Baseline	56.4 (40.2–70.2)	54.7 (41.0–76.6)	.91
1 Month	61.9 (37.4–89.2)	25.3 (17.1–38.1)	<.001
4 Months	53.9 (37.9–85.8)	45.8 (32.8–72.9)	.06
TNF-αRII level, ng/mL			
Baseline	19.3 (13.4–30.8)	21.1 (16.2–28.7)	.25
1 Month	17.5 (11.4–29.8)	10.2 (7.1–14.9)	<.001
4 Months	16.9 (11.5–22.6)	19.8 (12.6–25.1)	.16
Neopterin level, ng/mL			
Baseline	7.0 (4.5–10.7)	5.9 (4.1–10.1)	.54
1 Month	5.6 (3.2–10.5)	3.7 (2.3–5.3)	<.001
4 Months	4.7 (2.9–7.4)	4.0 (2.6–7.5)	.37
CD4⁺ T cell count, cells/μL			
Baseline	354 (264–507)	360 (287–478)	.76
1 Month	387 (297–572)	416 (261–604)	.66
2 Months	440 (295–585)	417 (328–573)	.57
6 Months	385 (292–569)	389 (284–568)	.89
HIV RNA level, $\log_{10}$ copies/mL			
Baseline	4.9 (4.5–5.4)	5.0 (4.4–5.4)	.89
1 Month	4.9 (4.4–5.4)	5.4 (4.9–5.7)	<.001
4 Months	4.9 (4.3–5.4)	4.9 (4.2–5.4)	.46

NOTE. Data are median (interquartile range). TNF, tumor necrosis factor; TNF-α–CF, culture filtrate–induced TNF-α; TNF-αRII, TNF-α type II receptor.

[a] Wilcoxon rank sum test.

lower in the prednisolone arm than in the placebo arm at 1 month but not at 4 months (table 3). The median levels of TNF-α–CF, serum TNF-α, and TNF-αRII decreased by at least 50% from baseline values.

At baseline, median CD4⁺ T cell counts and HIV RNA levels did not differ between the treatment arms (table 3). To evaluate within-individual changes for CD4⁺ T cell counts and HIV RNA levels, for each measure, we examined the change from baseline at 1 month. The mean increase in CD4⁺ T cell count tended to be higher in the prednisolone arm than in the placebo arm (69 vs. 17 cells/μL; $P = .09$) (figure 3*B*), and the variance in the change in CD4⁺ T cell counts was higher in the prednisolone arm (259 vs. 129 cells/μL; $P < .001$, analysis of variance). Of the patients in the prednisolone arm, 26% achieved an increase in CD4⁺ T cell count ⩾200 cells/μL, and 35% achieved an increase >100 cells/μL, compared with 10% and 18%, respectively, of the patients in the placebo arm. For HIV RNA levels, the mean increase within individuals was greater in the prednisolone arm than in the placebo arm (0.48 ± 0.61 vs. 0.02 ± 0.58 $\log_{10}$ copies/mL; $P < .001$) (figure 3*C*). The median CD4⁺ T cell count increased in each treatment arm but did not differ between them at 1 month; in contrast, the median HIV RNA level was higher in the prednisolone arm than in the placebo arm ($P < .001$) (table 3). At 6 months, the differences in median CD4⁺ T cell counts had resolved, as had the differences in median HIV RNA levels.

Among patients in the placebo arm, during the first month of treatment, HIV RNA levels increased as levels of culture-filtrate induced expression of TNF increased (Pearson correlation coefficient, 0.25; $P = .02$); this effect was mitigated in the prednisolone arm (Pearson correlation coefficient, −0.04; $P = .71$). HIV RNA levels also increased directly as levels of neopterin increased, in both the placebo arm (Pearson correlation coefficient, 0.25; $P = .02$) and the prednisolone arm (Pearson correlation coefficient, 0.22; $P = .04$). Changes in immune activation markers were not associated with changes in CD4⁺ T cell counts, in either treatment arm.

Sputum culture conversion occurred earlier in the prednisolone arm than in the placebo arm. At 1 month, a greater proportion of patients receiving prednisolone had a negative mycobacterial culture, compared with those receiving placebo (62% vs. 37%; $P = .001$). At 2 months, between the 2 treatment arms, there was no difference in the proportion of patients with negative cultures (86% vs. 85%). A similar pattern was observed

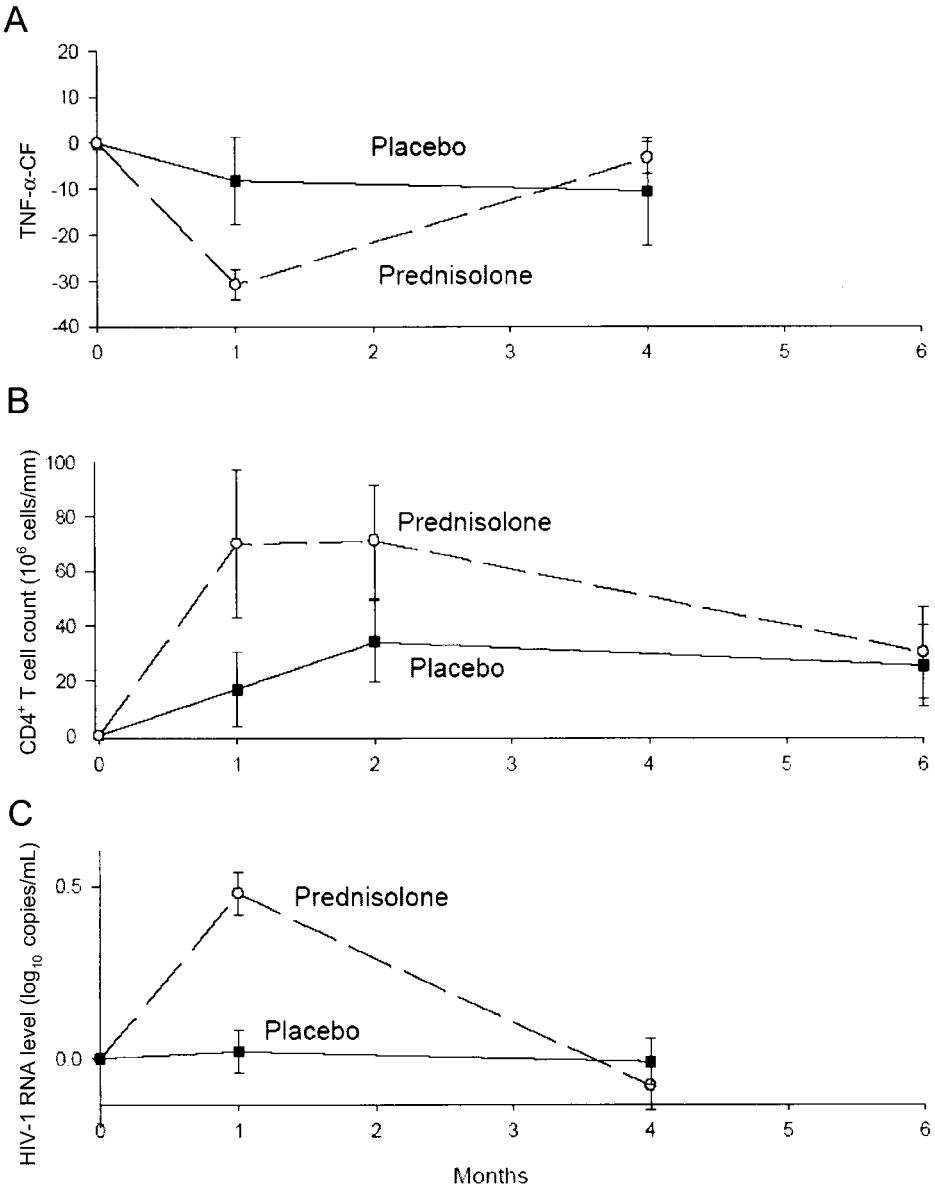

Figure 3. Changes in culture filtrate–induced levels of tumor necrosis factor (TNF)-α *(A),* $CD4^+$ T cell counts *(B),* and HIV RNA levels *(C)* in the prednisolone arm and the placebo arm. Error bars indicate 1 SE of the mean at each time point.

with sputum smears. Treatment failure occurred in only 2 patients (1 from each treatment arm); 1 treatment failure occurred in a patient with drug resistance to both isoniazid and rifampin. The cumulative proportion of recurrent cases within 2 years of starting treatment was similar between the prednisolone arm and the placebo arm (8.6% vs. 11.7%).

DISCUSSION

In this phase 2, randomized, double-blind, placebo-controlled clinical trial of oral immnoadjuvant prednisolone therapy for acid fast smear–positive pulmonary TB in HIV-infected adults, we found that short-term prednisolone therapy reduced levels of immune activation and tended to produce higher $CD4^+$ T cell counts than did placebo. Although prednisolone therapy was associated with a more rapid clearance of *M. tuberculosis* from the sputum, it was also associated with a transient increase in HIV RNA levels, which receded when prednisolone therapy was discontinued. The intervention worsened underlying hypertension and caused fluid retention and moderate to severe hyperglycemia.

The present study was based on the concept of copathogenesis in which immune activation produced by the host's response to *M. tuberculosis* may be detrimental in dually infected patients by promoting HIV replication [13, 31]. Among the

many cytokines involved in the host response to TB, TNF-α was used as the main marker of immune activation because it plays a central role in TB pathogenesis, granuloma formation [32], and containment of latent infection [33, 34]. Moreover, it is overexpressed in HIV-associated TB [35] and can activate cells latently infected with HIV to trigger productive infections [36–38]. Unlike previous interventions with specific TNF-α inhibitors, prednisolone therapy reduced levels of TNF-α by ~50%, compared with those in the placebo arm. Thus, the intervention achieved the desired pharmacological effect.

Despite achieving the desired effect on immune activation, prednisolone therapy did not alter the $CD4^+$ T cell response, compared with antituberculosis therapy alone. Prednisolone therapy induced an increase in $CD4^+$ T cell counts from baseline to 1 month (69 cells/μL), but this increase was not statistically greater than the increase observed with antituberculosis therapy alone (17 cells/μL). Furthermore, $CD4^+$ T cell counts returned to near baseline levels within 4 months of discontinuation of prednisolone therapy. The initial increase in $CD4^+$ T cell counts with prednisolone therapy has been observed in HIV-infected patients with pleural TB with $CD4^+$ T cell counts distributed over a wide range [39] and in asymptomatic HIV-infected patients with high $CD4^+$ T cell counts [22, 40]. Unlike these studies, in the present study, the initial increase in $CD4^+$ T cell count with prednisolone therapy was not sustained. This difference may result from differences in study populations, dose, or duration of prednisolone therapy. It is also possible that a subset of patients did achieve sustained benefit but that this response was masked by heterogeneity in response to prednisolone therapy.

In contrast to $CD4^+$ T cell counts, HIV RNA levels were affected by prednisolone therapy. During the first month of prednisolone therapy, HIV RNA levels increased. This increase was transient and not associated with an increase in the incidence of HIV-associated conditions or mortality. The reasons for the increase in HIV RNA levels are speculative. HIV RNA levels were consistently higher in the prednisolone arm than in the placebo arm, across all levels of immune activation. This finding is consistent with the hypothesis that prednisolone therapy increases viral production, possibly through mechanisms involving glucocorticoid response elements in the genome of HIV [41]. It is also possible that the increase in HIV RNA levels resulted from lytic effects of high-dose prednisolone therapy on lymphocytes or from a complex mass-action effect between virus and $CD4^+$ cells [42]. Of note, HIV RNA levels were directly correlated with *M. tuberculosis*–induced levels of TNF-α, but only in the placebo arm. This later effect is consistent with the underlying hypothesis that TNF-α may stimulate HIV replication.

Prednisolone therapy was associated with a more rapid clearance of *M. tuberculosis* from the sputum, as has been reported in patients with TB without HIV infection [43]. Although early clearance of organisms did not translate into reduced rates of treatment failure or disease recurrence, the present study was not designed to test this hypothesis. It is possible that, by reducing lung inflammation, prednisolone improved drug penetration into affected tissue, thereby accelerating the response to chemotherapy. Additional studies will be necessary to test this hypothesis.

As an immunoadjuvant treatment for TB, prednisolone therapy was associated with hypertension, fluid retention, and hyperglycemia. In most cases, adverse events were managed clinically, but, in 1 case, a patient with unrecognized hypertension developed accelerated hypertension after starting prednisolone therapy and died despite aggressive efforts to control blood pressure. There was no difference in short-term survival between the 2 treatment arms; the parity in survival implies that there was no excess mortality attributable to the intervention. Herpes viral infections (simplex and zoster combined) were seen more often in the prednisolone arm, but, unlike other investigators, we did not see an increase in cytolomegalovirus infections [44], Kaposi sarcoma [45, 46, 39], *Pneumocystis carinii* pneumonia, candidiasis, or other major opportunistic infections, because most patients were not severely immunosuppressed during the intervention period.

In light of the findings of the present study, we conclude that, in patients with TB with $CD4^+$ T cell counts $\geqslant$200 cells/μL, short-term prednisolone therapy reduced levels of immune activation, tended to produce higher $CD4^+$ T cell counts, and caused a transient increase in HIV RNA levels during treatment. These findings did not support further investigation for clinical efficacy of prednisolone therapy in HIV-associated TB, as was reflected in the decision to curtail enrollment for a larger study of survival. Because of the risks of short-term prednisolone therapy and the failure to prolong survival in HIV-associated TB [39], there is little to recommend its use. The next logical target for immunoadjuvant treatment in HIV-associated TB is viral replication, an event downstream from the immune activation. As international efforts enhance access to antiretroviral therapy in Africa, the next step is to determine how best to treat HIV-associated TB with antiretroviral therapy.

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