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Systematic or Test-Guided Treatment for Tuberculosis in HIV-Infected Adults

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ABSTRACT

BACKGROUND

In regions with high burdens of tuberculosis and human immunodeficiency virus (HIV), many HIV-infected adults begin antiretroviral therapy (ART) when they are already severely immunocompromised. Mortality after ART initiation is high in these patients, and tuberculosis and invasive bacterial diseases are common causes of death.

METHODS

We conducted a 48-week trial of empirical treatment for tuberculosis as compared with treatment guided by testing in HIV-infected adults who had not previously received ART and had CD4+ T-cell counts below 100 cells per cubic millimeter. Patients recruited in Ivory Coast, Uganda, Cambodia, and Vietnam were randomly assigned in a 1:1 ratio to undergo screening (Xpert MTB/RIF test, urinary lipoarabinomannan test, and chest radiography) to determine whether treatment for tuberculosis should be started or to receive systematic empirical treatment with rifampin, isoniazid, ethambutol, and pyrazinamide daily for 2 months, followed by rifampin and isoniazid daily for 4 months. The primary end point was a composite of death from any cause or invasive bacterial disease within 24 weeks (primary analysis) or within 48 weeks after randomization.

RESULTS

A total of 522 patients in the systematic-treatment group and 525 in the guided-treatment group were included in the analyses. At week 24, the rate of death from any cause or invasive bacterial disease (calculated as the number of first events per 100 patient-years) was 19.4 with systematic treatment and 20.3 with guided treatment (adjusted hazard ratio, 0.95; 95% confidence interval [CI], 0.63 to 1.44). At week 48, the corresponding rates were 12.8 and 13.3 (adjusted hazard ratio, 0.97 [95% CI, 0.67 to 1.40]). At week 24, the probability of tuberculosis was lower with systematic treatment than with guided treatment (3.0% vs. 17.9%; adjusted hazard ratio, 0.15; 95% CI, 0.09 to 0.26), but the probability of grade 3 or 4 drug-related adverse events was higher with systematic treatment (17.4% vs. 7.2%; adjusted hazard ratio 2.57; 95% CI, 1.75 to 3.78). Serious adverse events were more common with systematic treatment.

CONCLUSIONS

Among severely immunosuppressed adults with HIV infection who had not previously received ART, systematic treatment for tuberculosis was not superior to test-guided treatment in reducing the rate of death or invasive bacterial disease over 24 or 48 weeks and was associated with more grade 3 or 4 adverse events. (Funded by the Agence Nationale de Recherches sur le Sida et les Hépatites Virales; STATIS ANRS 12290 ClinicalTrials.gov number, NCT02057796.)

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Tuberculosis is the 10th leading cause of death worldwide and the main cause of death from a single infectious agent.[1] In 2019, the World Health Organization (WHO) estimated that 251,000 annual deaths due to tuberculosis occurred in persons with human immunodeficiency virus (HIV) infection.[1] Coinfection with tuberculosis and HIV still represents a "cursed duet,"[2] especially in sub-Saharan Africa and Asia.[3,4] The WHO recommends that people living with HIV infection should be systematically screened for active tuberculosis and that those who report current cough, fever, weight loss, or night sweats should be evaluated for tuberculosis and other diseases.[5,6] However, because of variations in the appearance of chest radiographs and the decrease in the performance of sputum-smear microscopy as the CD4+ T-cell count declines,[7] a diagnosis of tuberculosis remains challenging in HIV-infected adults, especially when they are severely immunosuppressed.

Despite increasing access to antiretroviral therapy (ART) in regions with high burdens of tuberculosis and HIV, many HIV-infected adults still present for care when they are already severely immunocompromised.[8,9] Among these adults, mortality after the initiation of ART is high, and tuberculosis and invasive bacterial diseases are common causes of death.[10-17] Persons with active tuberculosis may report no or few symptoms. The use of the urinary lipoarabinomannan (LAM) test and Xpert MTB/RIF test (a rapid nucleic acid amplification test to detect *Mycobacterium tuberculosis* and resistance to rifampin) increases the chance of correctly diagnosing tuberculosis.[18] However, physicians commonly initiate empirical treatment for tuberculosis without using these tests.[19,20] One potential benefit of empirical treatment for tuberculosis is that rifampin is active against several common pathogens that can be fatal in patients with advanced HIV infection. We conducted a randomized, clinical trial to compare the benefits and risks of a tuberculosis-screening strategy involving a combination of investigations (urinary LAM test, Xpert MTB/RIF test, and chest radiography) and targeted treatment with those of a strategy of systematic empirical treatment for tuberculosis in HIV-infected patients with severe immunosuppression.

Methods

Trial Design and Oversight

This research was sponsored and funded by the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS). The funding agency had no role in the trial design, the collection and analysis of the data, or the decision to submit the manuscript for publication. The STATIS (Systematic vs. Test-Guided Antituberculosis Treatment Impact in Severely Immuno-suppressed HIV-Infected Adults Initiating Antiretroviral Therapy with CD4 Cell Counts <100/mm^3) ANRS 12290 trial was a multicenter, randomized, open-label, superiority trial that compared the efficacy of two strategies in reducing mortality and the risk of invasive bacterial diseases among ambulatory HIV-infected adults with no overt evidence of tuberculosis, whose CD4+ T-cell count was less than 100 cells per cubic millimeter, and who were ready to start ART (see Section 1.2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were recruited between September 29, 2014, and May 3, 2017, in Abidjan, Ivory Coast (two centers); Mbarara, Uganda (two centers); Phnom Penh, Cambodia (one center); and Ho Chi Minh City, Vietnam (one center).

After written informed consent was obtained, the patients were randomly assigned in a 1:1 ratio to undergo screening to guide treatment for tuberculosis (guided-treatment group) or to receive systematic empirical treatment for tuberculosis (systematic-treatment group). A sequentially numbered block-randomization list was computer-generated and included in a software tool that allowed access to the next available trial identification number and treatment group. Randomization was stratified according to country (Ivory Coast, Uganda, Cambodia, or Vietnam) and baseline CD4+ T-cell count (≤50 cells per cubic millimeter or 51 to 99 cells per cubic millimeter). The trial was conducted in compliance with current international regulations, including the Declaration of Helsinki[21] and the Good Clinical Practice guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[22] and was approved by ethics and regulatory authorities in each country. The authors vouch for the accuracy and completeness

of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

TRIAL INTERVENTIONS

The patients were evaluated by on-site physicians on the day of enrollment and randomization (day 0) and then at weeks 2, 4, 8, 12, 16, 20, 24, 36, and 48. Between these visits, the patients were asked to come to the clinic if they had any symptoms or concerns about treatment. On day 0, the patients assigned to the guided-treatment group underwent systematic tuberculosis screening by means of the Xpert MTB/RIF test, the Alere Determine TB LAM Ag urinary test, and chest radiography, regardless of reported symptoms. Only the patients who met the criteria for confirmed or probable tuberculosis, as determined by these tests, started treatment for tuberculosis in this group (see Section 1.4.4 in the Supplementary Appendix). The patients assigned to the systematic-treatment group underwent chest radiography but no other tuberculosis test, even if they reported tuberculosis symptoms; all the patients in this group started treatment for tuberculosis immediately.

During follow-up, the patients in the guided-treatment group who had not received treatment for tuberculosis were systematically screened for tuberculosis symptoms with the use of the 2010 WHO questionnaire[5] at each visit. Those who answered "yes" to any of the four questions or who had any other clinical manifestations suggestive of tuberculosis underwent repeated screening with the Xpert MTB/RIF test, the urinary LAM test, and chest radiography, as well as any other appropriate symptom-driven investigation. Treatment for tuberculosis was initiated in the case of confirmed, probable, or possible tuberculosis. In the systematic-treatment group, patients whose condition had deteriorated before week 24 underwent symptom-driven investigations, including tuberculosis tests when immune reconstitution inflammatory syndrome (IRIS), drug resistance, or poor adherence was suspected. After week 24, the patients in the systematic-treatment group were screened for tuberculosis with the use of the same procedures that were used in the guided-treatment group.

In both groups, treatment for tuberculosis consisted of a daily oral regimen of isoniazid, rifampin, ethambutol, and pyrazinamide in doses recommended by the WHO, as summarized in the protocol, for 2 months, followed by daily administration of isoniazid and rifampin for 4 months. All the patients received counseling regarding adherence and were offered prophylaxis with trimethoprim–sulfamethoxazole. ART consisted of efavirenz, plus lamivudine or emtricitabine, plus tenofovir or zidovudine, in accordance with the national guidelines from each country. In the guided-treatment group, ART was initiated immediately after randomization in the patients who did not receive a diagnosis of tuberculosis and 2 weeks later in the patients who did. In the systematic-treatment group, all the patients started ART 2 weeks after randomization.

TRIAL END POINTS

The primary end point was a composite of death from any cause or invasive bacterial disease within 24 weeks (primary analysis) or within 48 weeks (secondary analysis) after randomization. Invasive bacterial disease was defined as a bacteremia or clinical, biologic, or radiologic signs compatible with a bacterial infection of any solid organ or sterile space (standardized definitions of probable and confirmed invasive bacterial diseases are provided in Section 1.4.4.2 in the Supplementary Appendix). Secondary end points included death from any cause; serious adverse events (defined as invasive bacterial diseases, incident tuberculosis, other acquired immunodeficiency syndrome [AIDS]–defining diseases, and other grade 3 or 4 adverse events, as classified according to the Division of AIDS)[23]; IRIS[24]; HIV-1 virologic suppression success (defined as a viral load of <50 copies per milliliter); change in CD4+ T-cell count from baseline; and adherence to treatment. These end points were classified according to standardized criteria (see Section 1.4 in the Supplementary Appendix) and were assessed at 24 and 48 weeks.

Adherence to ART was assessed by calculating the medication possession ratio (the number of daily doses of antiretroviral drugs dispensed by the pharmacy to each patient, divided by that patient's total follow-up time in days since the initiation of ART). Adherence to antituberculous drugs was assessed according to the patient's recall of the number of pills missed over the previ-

ous 4 days. All primary and secondary clinical end points were reviewed by two event-documentation committees, one at the trial center level and one at the international level. Members of the committees were aware of the treatment-group assignments.

STATISTICAL ANALYSIS

We estimated that the risk of death or invasive bacterial disease in the guided-treatment group would be 14% at 24 weeks.[4] A sample size of 1050 patients was estimated to provide the trial with 80% power to show a 40% lower risk of death or invasive bacterial disease in the systematic-treatment group than in the guided-treatment group, with a two-sided type I error rate of 5% and a 4.5% loss to follow-up.

The main analyses of the primary and secondary end points were performed at week 24 on an intention-to-treat basis. The same analyses were performed at week 48 (end of the trial). We used the Kaplan–Meier method to estimate the cumulative probability of the occurrence of an event. Follow-up data were censored when patients were lost to follow-up. Multivariate Cox proportional-hazards models were used to compare the treatment groups with respect to event rates, with adjustment for country and baseline CD4+ T-cell count category. The proportional-hazards assumption was examined. All the patients who underwent randomization were included in the analysis, including the patients who died, were lost to follow-up, or withdrew from the trial. Patients who did not attend the last scheduled visit at 48 weeks, who were not known to have died, and who could not be found after intensive tracing were considered lost to follow-up. There was no imputation for missing data. Because the 95% confidence intervals of the between-group differences with respect to the secondary end points have not been adjusted for multiple comparisons, inferences cannot be made from the results.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 1050 patients were randomly assigned to a treatment group. Three patients were excluded from the analysis because they had previously received ART (Fig. 1). Data were obtained from 525 patients in the guided-treatment group and 522 patients in the systematic-treatment group (Table 1). The median age of the patients was 35 years (interquartile range, 29 to 41), 436 (41.6%) were women, and the median CD4+ T-cell count was 30 cells per cubic millimeter (interquartile range, 12 to 56). At the time of enrollment, 94.7% of the patients had a Karnofsky performance-status score of at least 80 (on a scale from 0 to 100, with lower scores indicating greater disability), and 354 patients (67.4%) in the guided-treatment group and 346 (66.3%) in the systematic-treatment group reported no symptoms or one tuberculosis symptom. A total of 886 patient-years of follow-up (444 in the guided-treatment group and 442 in the systematic-treatment group) were completed. At trial termination, 24 patients (2.3%) were lost to follow-up (11 patients in the guided-treatment group and 13 patients in the systematic-treatment group). The percentage of patients who attended the scheduled trial visits through week 24 was 96.7%, and 95.3% attended the scheduled trial visits through week 48; the percentages in the two treatment groups did not differ meaningfully (Table S1 in the Supplementary Appendix). A total of 521 of 522 patients (99.8%) in the systematic-treatment group started treatment for tuberculosis, of whom 497 (95.4%) completed the 6-month treatment period (Table 1). In this group, the percentage of patients who reported having missed at least one antituberculous pill during the 4 days preceding a trial visit varied between 1% and 2% during follow-up (Fig. S4).

CLINICAL END POINTS

During follow-up, 90 patients died (69 before week 24) (Tables S16 and S17), and 42 cases of invasive bacterial disease occurred in 41 patients (34 cases occurred in 33 patients before week 24) (Table S18). The cases of invasive bacterial disease included 13 cases of bacteremia, 12 cases of pneumonia, 6 cases of severe sepsis, 5 cases of pyelonephritis, 2 cases of necrotizing fasciitis, 1 case of salpingitis, 1 cases of skin abscess, 1 case of bacterial enteritis, and 1 case of appendicitis. The proportional-hazards assumption was fulfilled. With respect to the primary outcome, the rate of death from any cause or invasive bacterial disease (calculated as the number of first

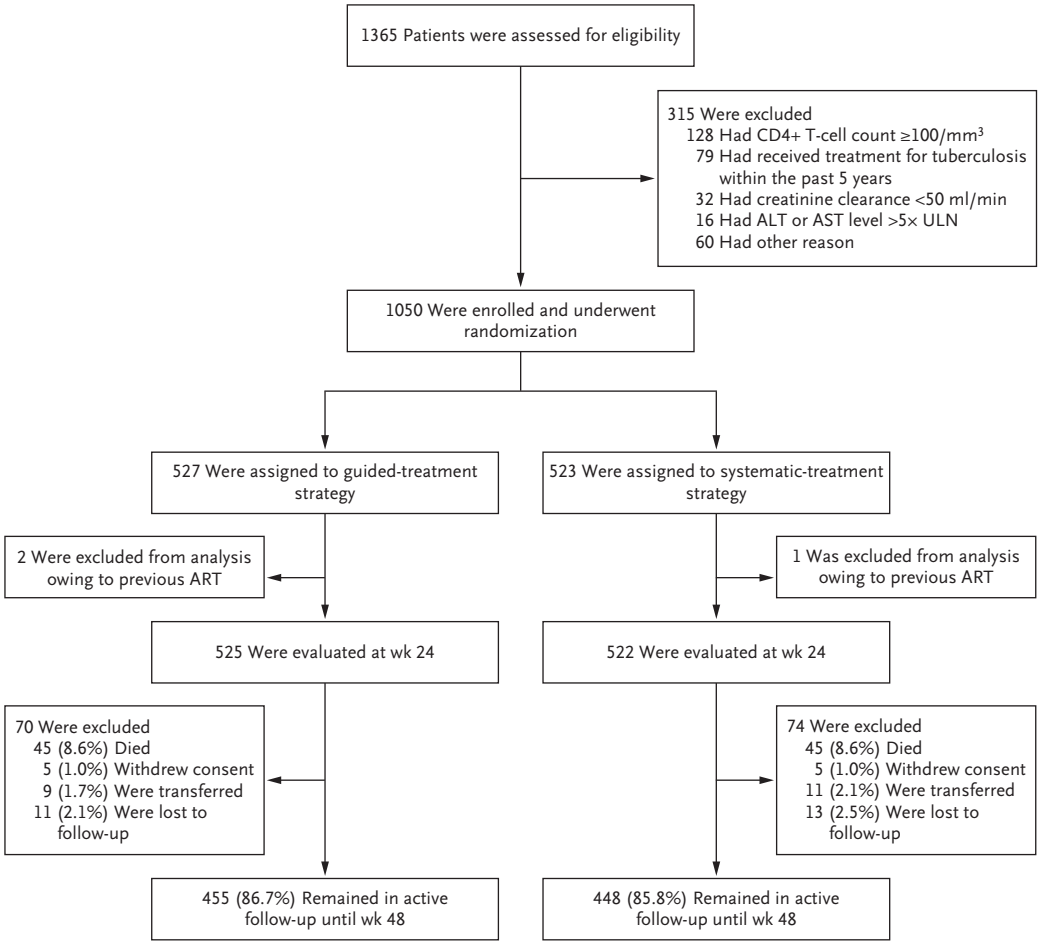


Figure 1. Screening, Randomization, and Follow-up.

The patients assigned to the guided-treatment group underwent tuberculosis screening by means of the Xpert MTB/RIF test, urinary lipoarabinomannan test, and chest radiography to determine whether treatment for tuberculosis should be implemented, and the patients assigned to the systematic-treatment group received empirical treatment for tuberculosis with the World Health Organization–recommended regimen of rifampin, isoniazid, ethambutol, and pyrazinamide daily for 2 months, followed by rifampin and isoniazid daily for 4 months. ALT denotes alanine aminotransferase, ART antiretroviral therapy, AST aspartate aminotransferase, and ULN upper limit of the normal range.

events per 100 patient-years) was 19.4 in the systematic-treatment group and 20.3 in the guided-treatment group at week 24 (adjusted hazard ratio, 0.95; 95% confidence interval [CI], 0.63 to 1.44) (Table 2 and Fig. 2). The most common causes of death were tuberculosis (17 patients in the guided-treatment group and 4 in the systematic-treatment group), invasive bacterial disease (3 patients and 6 patients, respectively), and AIDS-defining illnesses (7 patients in each group). Six deaths in the guided-treatment group and 15 deaths in the systematic-treatment group were of unknown cause (Table S19).

Overall, tuberculosis occurred in 117 patients (99 patients in the guided-treatment group and 18 patients in the systematic-treatment group), but this total includes 50 prevalent cases of tuberculosis that were diagnosed at baseline (49 cases in the guided-treatment group, including 3 cases of rifampin-resistant tuberculosis, according to Xpert MTB/RIF testing) and 67 cases of incident tuberculosis (50 cases in the guided-treatment group and 17 cases in the systematic-

Table 1. Characteristics of the Patients at Baseline and during Follow-up.*

Characteristic	Guided Treatment (N = 525)	Systematic Treatment (N = 522)
Baseline		
Female sex — no. (%)	221 (42.0)	215 (41.2)
Median age (IQR) — yr	35 (29–41)	35 (29–41)
Median body-mass index (IQR)†	19.6 (17.9–21.9)	19.7 (17.8–21.9)
Karnofsky performance-status score — no. (%)‡		
<80	27 (5.1)	27 (5.2)
≥80	497 (94.7)	494 (94.6)
Missing data	1 (0.2)	1 (0.2)
WHO clinical stage — no. (%)		
Stage 1	152 (29.0)	146 (28.0)
Stage 2	132 (25.1)	148 (28.4)
Stage >2	240 (45.7)	227 (43.5)
Missing data	1 (0.2)	1 (0.2)
Median CD4+ T-cell count (IQR) — cells/mm^3	28 (12–56)	32 (13–55)
CD4+ T-cell count — no. (%)		
≤50/mm^3	370 (70.5)	370 (70.9)
51–99/mm^3	155 (29.5)	152 (29.1)
Median plasma HIV-1 RNA level (IQR) — $\log_{10}$ copies/ml	5.5 (5.2–5.8)	5.4 (5.1–5.8)
Median hemoglobin level — g/dl	11.5 (9.9–13.4)	11.7 (9.9–13.2)
Positive plasma HBV surface antigen — no. (%)	47 (9.0)	48 (9.2)
Positive plasma HCV antibodies — no. (%)	36 (6.9)	35 (6.7)
Plasma ALT >2.5× ULN — no. (%)	49 (9.3)	36 (6.9)
Patients with tuberculosis symptoms according to WHO criteria — no. (%)§		
No symptoms	199 (37.9)	196 (37.5)
1 Symptom	155 (29.5)	150 (28.7)
2 Symptoms	90 (17.1)	103 (19.7)
3 Symptoms	62 (11.8)	58 (11.1)
4 Symptoms	18 (3.4)	15 (2.9)
Missing data	1 (0.2)	0
Follow-up		
Lost to follow-up — no. (%)	11 (2.1)	13 (2.5)
Follow-up time — person-yr	444	442
Initiated ART — no. (%)	523 (99.6)	510 (97.7)
First-line regimen		
Tenofovir + lamivudine or emtricitabine + efavirenz	490 (93.7)	473 (92.7)
Zidovudine + lamivudine + efavirenz	32 (6.1)	35 (6.9)
Other¶	1 (0.2)	2 (0.4)
Medication possession ratio >95%‖	445 (85.1)	434 (85.1)
Initiated treatment for tuberculosis — no. (%)	93 (17.7)	521 (99.8)
Completed 6 mo of treatment	85 (91.4)	497 (95.4)

Table 1. (Continued.)

Characteristic	Guided Treatment (N=525)	Systematic Treatment (N=522)
Chest radiography performed — no. of patients/no. of tests		
At day 0	519/519	514/516
After day 0 and before wk 24	192/313	488/870
After wk 24	81/108	156/180
Urinary LAM test performed — no. of patients/no. of tests		
At day 0	524/524	1/1
After day 0 and before wk 24	146/183	24/26
After wk 24	43/54	14/17
Xpert MTB/RIF test performed on sputum sample — no. of patients/no. of tests		
At day 0	472/475	0/0
After day 0 and before wk 24	154/227	37/49
After wk 24	51/70	19/30

* None of the baseline characteristics differed significantly between strategies. Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, ART antiretroviral therapy, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, IQR interquartile range, LAM lipoarabinomannan, ULN upper limit of the normal range, and WHO World Health Organization.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.
§ Tuberculosis symptoms according to the WHO criteria[5] include cough, fever, weight loss, and night sweats.
¶ All 3 patients received tenofovir, lamivudine, and lopinavir–ritonavir.
‖ The medication possession ratio is the number of daily doses of antiretroviral drugs dispensed by the pharmacy to each patient, divided by that patient's total follow-up time in days since the initiation of ART.

treatment group). Among the 199 patients (37.9%) in the guided-treatment group who reported no tuberculosis symptoms at baseline, 10 (5.0%) received a diagnosis of prevalent tuberculosis. In the guided-treatment group, 29 cases of incident tuberculosis occurred before week 4, 9 cases between week 4 and week 8, 1 case between week 8 and week 12, 5 cases between week 12 and week 24, and 6 cases between week 24 and week 48. The 1 case of prevalent tuberculosis in the systematic-treatment group was documented according to a positive urinary LAM test that was incorrectly performed at enrollment. The 17 cases of incident tuberculosis in the systematic-treatment group included 11 cases of paradoxical tuberculosis-associated IRIS that occurred 3 to 70 days after the initiation of ART, 3 cases of tuberculosis that were diagnosed before week 24 (including 1 that occurred before the initiation of ART and 2 that occurred after an untimely discontinuation of treatment for tuberculosis 2 months after enrollment), and 3 cases that were diagnosed after week 24. All strains of *M. tuberculosis* that were isolated in the systematic-treatment group were fully susceptible to antituberculosis drugs. The cumulative probability of receiving a diagnosis of incident or prevalent tuberculosis was 3.0% in the systematic-treatment group and 17.9% in the guided-treatment group at week 24 (adjusted hazard ratio, 0.15; 95% CI, 0.09 to 0.26) and 3.6% and 19.2%, respectively, at week 48 (adjusted hazard ratio, 0.17; 95% CI, 0.10 to 0.28).

ART, Virologic Response, and Immune Reconstitution

In the guided-treatment group, ART was initiated in 523 patients (99.6%): 477 (91.2%) started ART during the first week of the trial, and 40 (7.6%) started ART during the second week. In the systematic-treatment group, ART was initiated in 510 patients (97.7%): 447 (87.6%) started ART at week 2, and 32 (6.3%) started ART between week 2 and week 4. The ART medication possession ratio did not differ significantly between the two treatment groups (Table 1). The

Table 2. Clinical End Points at 24 and 48 Weeks.*

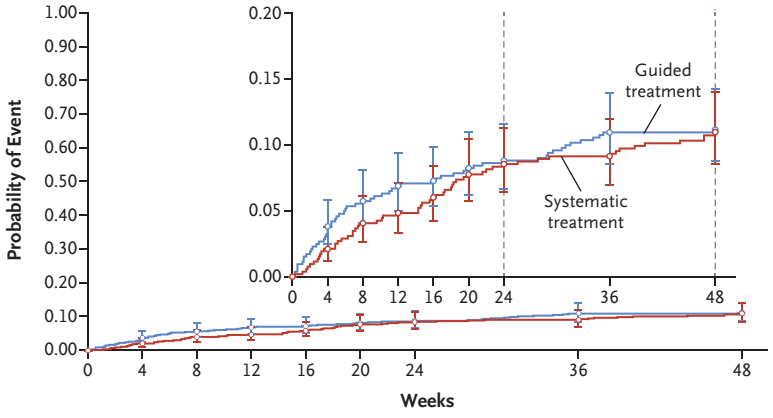
Clinical End Points	Guided Treatment		Systematic Treatment		Adjusted Hazard Ratio (95% CI)†
	No. of First Events	Rate (95% CI)‡	No. of First Events	Rate (95% CI)‡	
Primary end point at 24 wk: composite of death from any cause or invasive bacterial disease	46	20.3 (14.5–26.2)	44	19.4 (13.7–25.1)	0.95 (0.63–1.44)§
Secondary end points at 24 wk¶					
Death from any cause	36	15.6 (10.5–20.8)	33	14.4 (9.5–19.3)	0.92 (0.57–1.47)
Invasive bacterial disease	15	6.7 (3.7–11.0)	18	8.0 (4.7–12.6)	1.19 (0.60–2.36)
Tuberculosis‖	93	47.2 (37.6–56.8)	15	6.7 (3.7–11.0)	0.15 (0.09–0.26)
IRIS	57	26.8 (19.8–33.7)	17	7.6 (4.4–12.1)	0.39 (0.22–0.69)
AIDS-defining events	62	29.3 (22.0–36.5)	46	21.3 (15.1–27.5)	0.73 (0.50–1.06)
Grade 3 or 4 adverse events**	125	65.5 (54.0–76.9)	166	94.3 (80.0–108.7)	1.39 (1.11–1.76)
Grade 3 or 4 drug-related adverse events**	37	16.9 (11.5–22.3)	89	44.7 (35.4–54.0)	2.57 (1.75–3.78)
Secondary end points at 48 wk¶					
Composite of death from any cause or invasive bacterial disease	58	13.3 (9.9–16.7)	56	12.8 (9.5–16.2)	0.97 (0.67–1.40)
Death from any cause	45	10.1 (7.4–13.5)	45	10.2 (7.4–13.6)	1.01 (0.67–1.52)
Invasive bacterial disease	19	4.4 (2.7–6.9)	22	5.1 (3.2–7.7)	1.15 (0.62–2.13)
Tuberculosis‖	99	26.2 (21.0–31.3)	18	4.2 (2.5–6.6)	0.17 (0.10–0.28)
IRIS	59	14.4 (10.7–18.1)	17	3.9 (2.3–6.3)	0.27 (0.16–0.47)
AIDS-defining events	72	17.7 (13.6–21.8)	52	12.6 (9.2–16.0)	0.71 (0.49–1.01)
Grade 3 or 4 adverse events**	143	39.8 (33.3–46.4)	179	54.7 (46.7–62.8)	1.32 (1.06–1.65)
Grade 3 or 4 drug-related adverse events**	39	9.3 (6.4–12.2)	94	24.9 (19.9–30.0)	2.59 (1.78–3.76)

* AIDS denotes acquired immunodeficiency syndrome, and IRIS immune reconstitution inflammatory syndrome.
† The hazard ratios are for the systematic-treatment group as compared with the guided-treatment group and were adjusted for country (Ivory Coast, Uganda, Cambodia, or Vietnam) and baseline CD4+ T-cell count (≤50 per cubic millimeter or 51 to 99 per cubic millimeter).
‡ Rate was calculated as the number of first events per 100 patient-years.
§ P=0.82.
¶ Because the trial protocol did not include a plan for adjustment for multiple comparisons, the results of the analyses of secondary end points are reported with point estimates and 95% confidence intervals, without P values, and the results cannot be used to infer effects.
‖ The end point of tuberculosis includes prevalent and incident cases. Of the 117 cases of tuberculosis, 54 included pulmonary involvement only, 18 included pulmonary and extra pulmonary involvement, and 45 included extrapulmonary involvement only.
** Adverse events were graded according to the criteria of the Division of AIDS.[23]

HIV viral load was below 50 copies per milliliter in 576 of the 935 patients (61.6%) with available data on viral load at week 24 (298 of 466 patients [63.9%] in the guided-treatment group and 278 of 469 patients [59.3%] in the systematic-treatment group) and in 646 of the 885 patients (73.0%) with available data on viral load at week 48 (324 of 446 patients [72.6%] in the guided-treatment group and 322 of 439 patients [73.3%] in the systematic-treatment group). The median gain in the CD4+ T-cell count was 94 cells per cubic millimeter (interquartile range, 51 to 147)

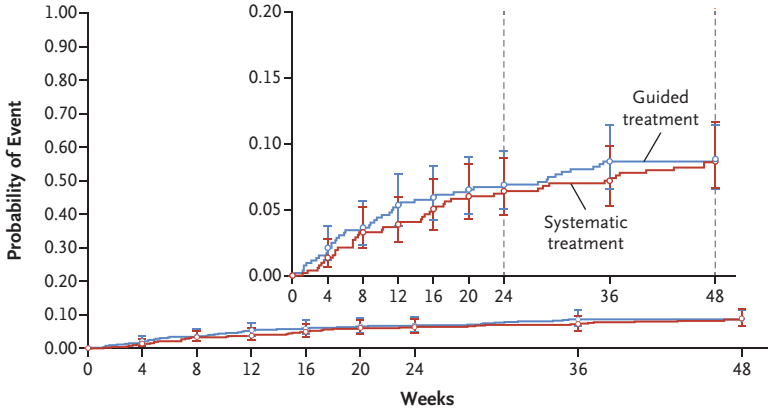
Figure 2 (facing page). Kaplan–Meier Analysis of the Primary Composite End Point and End-Point Components.
Shown are the Kaplan–Meier curves for the probability of the primary composite end point of death from any cause or invasive bacterial disease (Panel A) and the probability of the end-point components of death from any cause (Panel B) and invasive bacterial disease (defined as a bacteremia or clinical, biologic, or radiologic signs compatible with a bacterial infection of any solid organ or sterile space). In each panel, the inset shows the same data on an enlarged y axis. I bars represent 95% confidence intervals.

A Death or Invasive Bacterial Disease



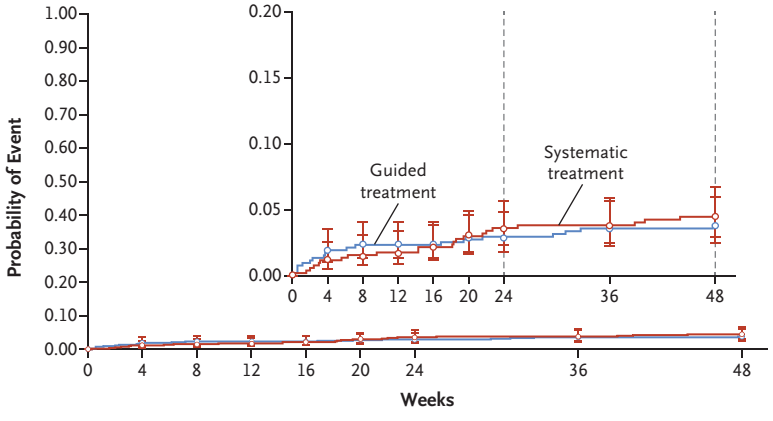
No. at Risk									
Guided treatment	525	502	491	484	481	476	472	454	360
Systematic treatment	522	506	494	490	482	472	466	459	359

B Death



No. at Risk									
Guided treatment	525	511	502	492	488	485	482	466	371
Systematic treatment	522	510	498	495	487	480	476	468	366

C Invasive Bacterial Disease



No. at Risk									
Guided treatment	525	498	486	480	477	472	469	449	352
Systematic treatment	522	505	491	486	478	469	463	454	354

Table 3. Distribution of Serious Adverse Events According to Treatment Group.

Serious Adverse Event	All Events (495 Events)*		Drug-Related Events (150 Events)†	
	Guided Treatment	Systematic Treatment	Guided Treatment	Systematic Treatment
	number of events			
Invasive bacterial infections	20	22	—	—
Isolated bacteremia	4	9	—	—
Bacterial pneumonia	8	4	—	—
Severe sepsis	2	4	—	—
Pyelonephritis	4	1	—	—
Necrotizing fasciitis	2	0	—	—
Bacterial enteritis	0	1	—	—
Salpingitis	0	1	—	—
Skin abscess	0	1	—	—
Appendicitis	0	1	—	—
Incident tuberculosis‡	50	17	—	—
Other AIDS-defining illnesses	31	39	—	—
Cryptococcosis	6	10	—	—
Nontuberculous mycobacteriosis	5	2	—	—
Pneumocystis pneumonia	5	6	—	—
Esophageal candidiasis	3	8	—	—
Cytomegalovirus retinitis	2	1	—	—
Isosporiasis	2	2	—	—
Cryptosporidiosis	1	3	—	—
Microsporidiosis	1	0	—	—
Progressive multifocal leukoencephalopathy	1	1	—	—
Kaposi's sarcoma	1	1	—	—
Solid tumors other than Kaposi's sarcoma	1	1	—	—
Wasting syndrome	3	4	—	—
Other grade 3 or 4 adverse events	119	197	45	105
Noninfectious transaminitis	26	43	17	39
Pruritus, rash, mucous ulcerations	8	35	8	34
Stevens–Johnson syndrome	2	3	2	3
Neutropenia	16	17	5	10
Anemia	7	14	1	4
Thrombopenia	0	3	0	1
Bicytopenia or pancytopenia	6	3	2	1
Neuropsychiatric disorders	5	6	4	3
Nonspecific acute fever	5	13	0	1
Nonspecific kidney failure	7	5	5	4
Vomiting	0	2	0	2
Hyperuricemia	0	1	0	1
Gynecomastia	1	2	1	2

Table 3. (Continued.)

Serious Adverse Event	All Events (495 Events)*		Drug-Related Events (150 Events)†	
	Guided Treatment	Systematic Treatment	Guided Treatment	Systematic Treatment
	number of events			
Other	36	50	0	0
Total	220	275	45	105

* During follow-up, 495 serious adverse events occurred in 322 patients. Serious adverse events were defined as invasive bacterial diseases, incident tuberculosis, other AIDS-defining diseases, and other grade 3 or 4 events (classified according to the Division of AIDS[23]).

† The 150 serious drug-related adverse events are included with the 495 serious adverse events. Drug-relatedness was first assessed by an adjudication committee at the national level and was then reviewed by an international adjudication committee. The two committees were aware of the treatment-group assignments. A dash indicates that an event cannot be caused by medications.

‡ Overall, 117 patients had tuberculosis: 50 cases were diagnosed at baseline (prevalent tuberculosis) and 67 were diagnosed during follow-up as new cases (incident tuberculosis). Only the 67 incident cases are shown in this table.

at week 24 (105 cells per cubic millimeter in the guided-treatment group and 86 cells per cubic millimeter in the systematic-treatment group) and 140 cells per cubic millimeter (interquartile range, 91 to 207) at week 48 (147 cells per cubic millimeter and 133 cells per cubic millimeter in the two groups, respectively).

ADVERSE EVENTS

Overall, 495 serious adverse events (220 in the guided-treatment group and 275 in the systematic-treatment group) occurred in 322 patients (143 in the guided-treatment group and 179 in the systematic-treatment group), including 150 grade 3 or 4 drug-related adverse events (45 in the guided-treatment group and 105 in the systematic-treatment group) in 133 patients (39 in the guided-treatment group and 94 in the systematic-treatment group) (Table 3). The cumulative 24-week probability of grade 3 or 4 drug-related adverse events was 17.4% in the systematic-treatment group and 7.2% in the guided-treatment group (adjusted hazard ratio, 2.57; 95% CI, 1.75 to 3.78). Treatment for tuberculosis was stopped prematurely in 24 patients (4.6%) in the systematic-treatment group owing to adverse events. During follow-up, 79 cases of IRIS (59 in the guided-treatment group and 20 in the systematic-treatment group) occurred in 76 patients (59 in the guided-treatment group and 17 in the systematic-treatment group), including 60 cases of tuberculosis-associated IRIS (49 cases and 11 cases in the two groups, respectively).

DISCUSSION

The results of the STATIS trial showed that among severely immunosuppressed adults who had not previously received ART, systematic empirical treatment for tuberculosis was not superior to a strategy involving a combination of repeated tuberculosis screening and targeted treatment for tuberculosis. Both strategies were associated with a lower-than-expected rate of death or invasive bacterial disease at week 24, as compared with previous trials and studies. The initial systematic tuberculosis-screening strategy used at enrollment captured a high number of prevalent tuberculosis diagnoses among asymptomatic patients or those with few symptoms, and additional symptom-driven screening allowed early detection of incident tuberculosis after ART was initiated.

Empirical treatment for tuberculosis has accounted for up to 15% of instances in which treatment has been initiated in some health care settings.[20] Empirical treatment has been compared with isoniazid preventive therapy in one trial involving outpatients, which did not show a reduction in mortality at 6 months.[25] An open cluster-randomized trial also did not show a reduction in mortality or the risk of hospitalization at 6 months.[26] Another trial of empirical treatment for tuberculosis was stopped prematurely because of slow recruitment.[27] In the current trial, systematic treatment for tuberculosis was associated with a higher probability of grade

3 or 4 drug-related toxic effects than test-guided treatment, although treatment had to be stopped in only 4.6% of the patients in the systematic-treatment group because of adverse reactions. Although such drug-related toxic effects are nonfatal, they might lead physicians to avoid systematic treatment for tuberculosis if they have access to Xpert MTB/RIF and urinary LAM tests.

Our tuberculosis-screening strategy was used to detect prevalent tuberculosis, regardless of symptoms. At the time of screening, 5% of the asymptomatic patients received a diagnosis of tuberculosis. After the initiation of ART, in order to capture incident tuberculosis, these tests were repeated when the results of the WHO tuberculosis symptoms questionnaire[5] were positive. This continuous strategy was a compromise between current practice and the repeated use of simple tests that are not yet routinely used in this context, although their usefulness in detecting tuberculosis in patients with advanced immunodeficiency has been shown.[18] The use of this repeated-testing strategy identified 93 cases of tuberculosis in 525 patients (17.7%) at week 24, with the majority of patients receiving a diagnosis within the first 4 weeks — a rate similar to that in previous studies[28-30] and probably reflecting the level of background tuberculosis in this population. In the population targeted by the trial, invasive bacterial diseases are important causes of death.[31] When designing the composite primary end point, we speculated that 6 months of rifampin therapy could help to prevent some bacterial-associated illnesses. Although we cannot rule out a potential underestimation of invasive bacterial diseases in both treatment groups, our results suggest that treatment for tuberculosis did not have a detectable effect on the rate of invasive bacterial diseases.

This trial has several limitations. First, neither of the assigned strategies can be directly compared with those used in current practice. At the time the trial was designed, most clinicians used only sputum smear for tuberculosis screening before initiating ART, but we anticipated that the development of the Xpert MTB/RIF and urinary LAM tests would lead to their use in future care. Second, although isoniazid preventive therapy was known to decrease the rate of, and mortality from, tuberculosis among HIV-infected adults living in areas with a high burden of tuberculosis,[32] at the time of randomization, isoniazid preventive therapy was deliberately not given to the patients who were assigned to the guided-treatment group to avoid the potential risk of treating undiagnosed tuberculosis with isoniazid alone. Because the patients were regularly screened for tuberculosis at each trial visit, we considered that this strategy was acceptable during the 48 weeks of the trial. After completion of the trial, isoniazid preventive therapy was considered in accordance with the national tuberculosis policy at each trial site. Third, despite systematic review, causes of death remained undocumented in 21 patients (23%), particularly among the patients who died in the systematic-treatment group (15 of 45 patients). Unknown causes of death are common in such trials, even at trial sites that are familiar with clinical research involving patients who are coinfected with tuberculosis and HIV.[33-36]

In conclusion, systematic empirical treatment for tuberculosis and treatment guided by specific testing had similar effects on the rate of death or invasive bacterial disease in a population of HIV-infected adults with CD4+ T-cell counts below 100 cells per cubic millimeter.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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