Daily vs Intermittent Antituberculosis Therapy for Pulmonary Tuberculosis in Patients With HIV
A Randomized Clinical Trial

Narendran Gopalan, DNB, DTCD; Ramesh Kumar Santhanakrishnan, MB, BS, MPH; Alangudi Natarajan Palaniappan, MB, BS, PhD;
Pradeep Aravindan Menon, DPM, MPH; Sekar Lakshman, PhD; Padmapriyadarsini Chandrasekaran, DNB; Gomathi Narayan Sivaramakrishnan, PhD;
Devarajulu Reddy, MB, BS; Bhavani Perumal Kannabiran, MPH; Hemanth Kumar Kupparam Agiboth, PhD; Vijay Krishnamoorthy, MB, BS;
Sridhar Rathinam, MD, DTCD; Chandrasekar Chockalingam, MD, DTCD; Tamizhselvan Manoharan, PhD; MahilMaran Ayyamperumal, MD, DTCD;
Nalini Jayanthi, MD, DTCD; Kumar Satagopan, MD, DTCD; Ravichandran Narayanan, MD, DCH; Raja Krishnaraja, MD; Sekar Sathiyavelu, DCH;
Bhanu Kesavamurthy, DM; Chandra Suresh, MSc; Murugesan Selvachitiram, MSc; Gunasundari Arasan, MSc; Stella Susaimuthu, Dip Nur;
Prabhakaran Rathinam, MD; Prabhakar Angamuthu, DTCD; Lavanya Jayabal, DTCD; Lakshmi Murali, MD; Ranjani Ramachandran, MD;
Srikanth Prasad Tripathy, MD; Soumya Swaminathan, MD, DNB

+ Supplemental content

IMPORTANCE The benefit of daily over thrice-weekly antituberculosis therapy among HIV-positive patients with pulmonary tuberculosis (TB) who are receiving antiretroviral therapy remains unproven.

OBJECTIVE To compare the efficacy and safety of daily, part-daily, and intermittent antituberculosis therapy regimens in the treatment of HIV-associated pulmonary TB.

DESIGN, SETTING, AND PARTICIPANTS This open-label, randomized clinical trial was conducted by the National Institute for Research in Tuberculosis, south India. Adults infected with HIV with newly diagnosed, culture-positive, pulmonary TB were enrolled between September 14, 2009, and January 18, 2016.

INTERVENTIONS Patients were randomized to daily, part-daily, and intermittent antituberculosis therapy regimens, stratified by baseline CD4 lymphocyte count and sputum smear grade. Antiretroviral therapy was initiated as per national guidelines. Clinical and sputum microbiological examinations of patients were performed monthly until 18 months after randomization. Adverse events were recorded using standard criteria.

MAIN OUTCOMES AND MEASURES The primary outcome was favorable response, defined as treatment completion with all available sputum cultures negative for *Mycobacterium tuberculosis* during the last 2 months of treatment. Unfavorable responses included treatment failures, dropouts, deaths, and toxic effects among regimens.

RESULTS Of 331 patients (251 [76%] male; mean [SD] age, 39 [9] years; mean [SD] HIV viral load, 4.9 [1.2] $\log_{10}$ copies/mL; and median [interquartile range] CD4 lymphocyte count, 138 [69-248] cells/μL), favorable responses were experienced by 91% (89 of 98), 80% (77 of 96), and 77% (75 of 98) in the daily, part-daily, and intermittent regimens, respectively. With the difference in outcome between daily and intermittent regimens crossing the O'Brien-Fleming group sequential boundaries and acquired rifampicin resistance emergence (n = 4) confined to the intermittent group, the data safety monitoring committee halted the study. A total of 18 patients died and 18 patients dropped out during the treatment period in the 3 regimens. Six, 4, and 6 patients in the daily, part-daily, and intermittent regimens, respectively, had TB recurrence.

CONCLUSIONS AND RELEVANCE Among HIV-positive patients with pulmonary TB receiving antiretroviral therapy, a daily anti-TB regimen proved superior to a thrice-weekly regimen in terms of efficacy and emergence of rifampicin resistance.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Soumya Swaminathan, MD, DNB, Indian Council of Medical Research, Ansari Nagar, New Delhi, India 110029 (doctorsoumya@yahoo.com).

Globally, tuberculosis (TB) remains the leading cause of morbidity and mortality among individuals infected with HIV.[1] When this trial commenced in 2009, World Health Organization (WHO) guidelines recommended daily or part-daily (daily in the intensive phase alone) antituberculosis therapy (ATT) for TB, while the Revised National TB Control Program in India used the thrice-weekly regimen until 2016.[2,3] With few trial data from head-to-head comparison of these regimens among HIV-positive patients with TB, there was no evidence to guide treatment. Trials using intermittent (thrice-weekly) ATT, conducted at the National Institute for Research in Tuberculosis (NIRT) in India, reported cure rates of 83%[4] and 90%[5] among HIV-positive patients with TB, before and after the era of antiretroviral therapy (ART), compared with 96% among HIV-negative patients with TB in similar settings.[6,7]

Acquired rifampicin resistance (ARR), a phenomenon observed in HIV-positive patients with TB treated with once-weekly,[8] twice-weekly,[9,10] and thrice-weekly[4] rifampicin-based intermittent regimens, was rarely encountered in HIV-negative patients with TB.[11] A cross-protocol analysis[12] studying the impact of HIV and ART on ARR among patients with pulmonary TB receiving intermittent ATT revealed that HIV infection per se (odds ratio [OR], 2.02) and pretreatment isoniazid resistance (OR, 9.97) significantly contributed to ARR, with ART reducing but not eliminating the trend. Li et al[13] demonstrated that intermittent ATT dosing after the intensive phase in HIV-TB coinfection did not contribute to ARR, making a part-daily regimen a feasible alternative to a fully daily regimen. The meta-analysis by Khan et al[14] concluded that a daily intensive phase of ATT could reduce TB failures and prevent ARR in HIV-positive patients with TB. However, they noted the absence of any randomized clinical trial (RCT) addressing the question of dosing schedules on TB treatment outcomes in HIV.[15] Hence, an RCT was conducted comparing the efficacy of daily, part-daily, and intermittent (thrice-weekly) TB regimens in reducing failures and emergence of ARR among HIV-positive patients from south India newly diagnosed with sputum culture-confirmed, rifampicin-sensitive TB.

Methods

Study Design and Overview

This open-label, parallel-group, active comparator RCT was conducted at centers of NIRT in Chennai, Vellore, and Madurai, south India, between September 14, 2009, and January 18, 2016, after obtaining Institutional Ethics Committee approval and written informed consent from all study participants (full protocol in Supplement 1). Interim analysis was planned when 33%, 66%, and 100% of enrolled patients had their outcomes available, applying the O'Brien-Fleming stopping rules.

Participants

Adults 18 years or older who were HIV positive and newly diagnosed with pulmonary TB by either a smear test or Xpert MTB/RIF test (Cepheid) were enrolled. Patients taking protease inhibitor–based ART, with known hypersensitivity or resistance to rifampicin, pregnant or lactating women, those with

Key Points

Question Is daily antituberculosis therapy superior to thrice-weekly dosing in reducing failures and acquired rifampicin resistance among HIV-positive patients with culture-confirmed pulmonary tuberculosis in the era of antiretroviral therapy?

Findings In this randomized clinical trial including 331 patients, favorable responses were 91% vs 77%, while hepatotoxic effects occurred in 9% vs 2% with daily and intermittent antituberculosis therapy regimens, respectively. Acquired rifampicin resistance emerged only in the group receiving intermittent antituberculosis therapy, despite antiretroviral therapy.

Meaning Daily administration of antituberculosis therapy resulted in higher cure rates and prevented acquired rifampicin resistance compared with a thrice-weekly regimen, but with slightly higher hepatotoxicity, which was manageable under trial conditions.

major psychiatric illness, and those who were moribund or had significant liver or renal function abnormalities at baseline were excluded (eAppendix in Supplement 2).

Investigations

Testing for HIV (2 separate third-generation rapid tests) was performed at baseline, adhering to national guidelines.[16] Four sputum samples collected before treatment, 3 during treatment, and 2 during follow-up were examined for acid-fast bacilli by fluorescence microscopy, processed by the modified Petroff method, and cultured on Lowenstein-Jensen medium for *Mycobacterium tuberculosis* detection.[17] Drug susceptibility testing was performed using the minimal inhibitory concentration method for isoniazid, rifampicin, and ethambutol and the resistance ratio method for streptomycin.[17,18] High-performance liquid chromatography was used for mycobacterial species identification.[19] Baseline cultures were stored for subsequent DNA fingerprinting, for comparison of strains at the time of failure (eAppendix in Supplement 2). Chest radiographs were interpreted by a panel of at least 2 chest physicians and a consensus opinion taken.

Complete blood cell count (automated hematology analyzer; ABX; HORIBA), liver and renal function tests, random plasma glucose (automated analyzer; Olympus Corp), CD4 lymphocyte count (FACScount flow cytometer; Becton Dickinson), and plasma HIV RNA load (Amplicor automated viral load monitor; Roche) measurements were done before treatment, at the end of the intensive phase, at treatment completion, and whenever clinically indicated.

Randomization

Patients fulfilling the clinical and laboratory criteria were randomly allocated 1:1:1 to the 3 ATT regimens, using a permuted block randomization scheme, with the treatment assignment list contained in concealed envelopes (eAppendix in Supplement 2). Stratification was based on a baseline CD4 lymphocyte count of less than 150 cells/μL vs greater than or equal to 150 cells/μL and sputum smear grading of 0 and 1+ vs 2+ and 3+.

Intervention

The 3 ATT regimens were (1) daily (daily in both intensive and continuation phases)—$2EHRZ_7/4HR_7$; (2) part-daily (daily

intensive phase and intermittent continuation phase)—$2EHRZ_7/4HR_3$; and (3) intermittent (thrice weekly throughout)—$2EHRZ_3/4HR_3$ (eAppendix in Supplement 2).

The regimens were given under direct observation during weekdays and self-administered on weekends and holidays, supplemented with pyridoxine, 100 mg, and a tablet of co-trimoxazole double strength daily unless clinically contraindicated. Patients who had never received ART were initiated on lamivudine and efavirenz along with 1 of 3 drugs (zidovudine, stavudine, or tenofovir) between 2 and 8 weeks after ATT (eAppendix in Supplement 2), as per prevailing guidelines.[16,20]

Outcome Measures

The primary outcome measure was proportion of patients with a favorable response at the end of ATT, defined as treatment completion accompanied by negative sputum cultures (n = 6) collected during the last 2 months of treatment. Unfavorable responses included (1) bacteriological failures (with or without emergence of ARR) and clinical failures (mandating change or restart of regimen), (2) deaths (all-cause mortality), except unnatural death, (3) toxic effects necessitating permanent substitution of allocated regimen, and (4) patients who dropped out (irretrievable >6 weeks). Surveillance for the primary outcome was done through a detailed clinical and sputum examination, performed monthly or when clinically indicated, for either persistence or recrudescence of TB symptoms or signs. The team performed appropriate evaluation and management, and outcomes were classified accordingly (eAppendix in Supplement 2). Treatment-emergent adverse drug reactions were reported as per modified Division of AIDS criteria.[21] Similarly, recurrences were classified as bacteriological or clinical (eAppendix in Supplement 2). Retrieval mechanisms were inbuilt for effective case holding (eAppendix in Supplement 2). An independent end point review committee, blind to the assigned regimen, adjudicated the outcomes after scrutinizing patient details.

Statistical Analysis

Sample Size

We hypothesized that a daily and a part-daily regimen would have a 95% rifampicin resistance–free survival compared with 80% with the intermittent regimen (superiority design). With a power of 80%, a type I error of 5%, and increasing the sample size by 20% to compensate for loss due to death, default, and exclusions after randomization, we arrived at a sample size of 420 (140 patients in each group).

Comparisons and Analyses

The primary comparisons for efficacy were between daily vs intermittent regimens and part-daily vs intermittent regimens; the contrast was fixed prior to trial initiation. The modified intent-to-treat analysis was used, including all randomized patients except those with pretreatment cultures that were negative for *M tuberculosis*, were rifampicin resistant, or grew nontuberculous mycobacteria. To adjust for multiple comparisons, the Bonferroni correction was applied, taking a two-sided *P* value of .025 as the significance level. The per-protocol analysis was simultaneously performed, including

patients in modified intent-to-treat analysis, but with an adherence of greater than 80% of scheduled drug intake. The χ^2 test was used for proportions, and the *t* test and Wilcoxon test were used for analyzing continuous variables. Kaplan-Meier mean survival estimates for time to an unfavorable event were calculated, and the log-rank test was used for significance testing between regimens. A Cox hazards model was built, taking into account all potential risk factors for an unfavorable response, that could simultaneously analyze categorical and continuous variables, accounting for individual period of observation, and provide the hazard rates and ratios for each of the risk factors. Furthermore, the γ frailty model was used to measure heterogeneity of baseline parameters among patients allocated to the 3 regimens. We used SPSS statistical software, version 20.0 (IBM) for all analyses.

Results

The data safety monitoring committee, after careful deliberation of the findings of the second interim analysis, when 331 patients had been recruited, halted the trial and permitted publication of the findings; preliminary results were presented at the AIDS 2016 conference.[22]
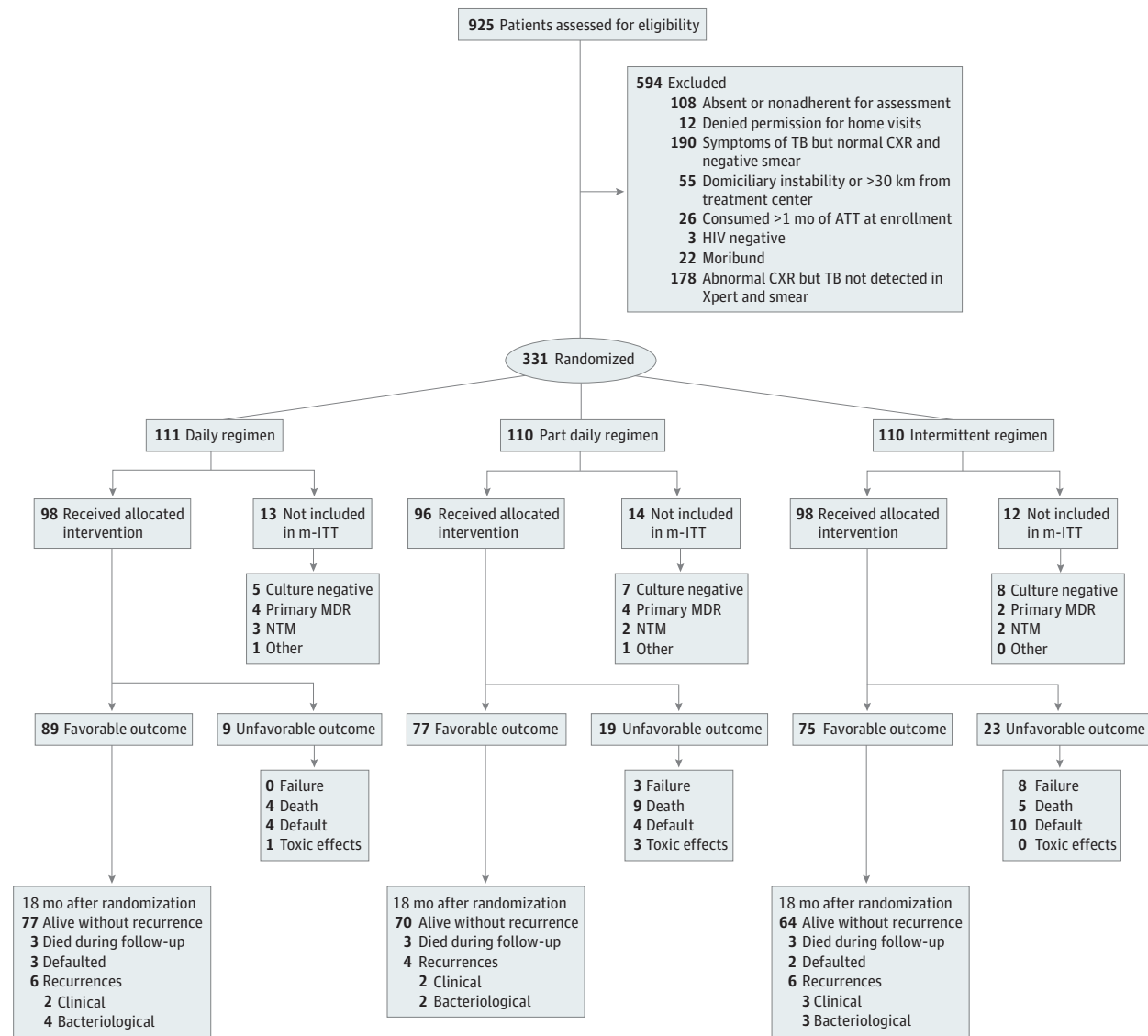
Between September 14, 2009, and January 18, 2016, 925 patients were screened and 331 were randomly allocated to daily (n = 111), part-daily (n = 110), and intermittent (n = 110) ATT regimens (Figure 1). Of the 331 patients allocated, 251 (76%) were male; mean (SD) age was 39 (9) years; mean (SD) HIV viral load was 4.9 (1.2) $\log_{10}$ copies/mL; and median (interquartile range [IQR]) CD4 lymphocyte count was 138 (69-248) cells/μL. Baseline characteristics were comparable across the 3 groups of patients (Table 1).

Outcome Analysis

The CONSORT diagram summarizes the flow of patients from screening until 18 months after randomization (Figure 1). At the end of the intensive phase, sputum smear results were negative for 117 of 181 patients (65%) receiving daily ATT vs 52 of 90 patients (58%) receiving intermittent ATT (difference, 6.9%; 95% CI, −5.2% to −19.1%; *P* = .33), while culture results were negative for 177 of 183 patients (97%) receiving daily ATT vs 77 of 89 patients (87%) receiving intermittent ATT (difference, 10.2%; 95% CI, 3.5%-19.0%; *P* = .002) (eFigure 1 in Supplement 2).

In the modified intent-to-treat analysis, favorable responses at the end of TB treatment occurred in 89 of 98 patients (91%), 77 of 96 patients (80%), and 75 of 98 patients (77%) in the daily, part-daily, and intermittent regimens, respectively. The difference in favorable response between the daily and the intermittent regimen (14%; 95% CI, 3.9%-25%) attained statistical significance at the second interim analysis stage, crossing the O'Brien-Fleming group sequential boundaries (calculated χ^2 = 7.32 vs required χ^2 = 5.67; *P* = .006; with Bonferroni correction, *P* = .009), whereas the difference between part-daily and intermittent remained insignificant (difference, 9.2%; 95% CI, 0.6%-18.3%; *P* = .53). Similarly, favorable responses in the per-protocol analysis occurred in

Figure 1. Flow of Patients From Screening Until 18 Months After Randomization

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                        │ 925 Patients assessed for eligibility │
                        └──────────────────────────────────────┘
                                         │
                                         │        ┌─────────────────────────────────────────────────────┐
                                         │        │ 594 Excluded                                         │
                                         ├───────▶│   108 Absent or nonadherent for assessment           │
                                         │        │    12 Denied permission for home visits              │
                                         │        │   190 Symptoms of TB but normal CXR and              │
                                         │        │       negative smear                                 │
                                         │        │    55 Domiciliary instability or >30 km from         │
                                         │        │       treatment center                               │
                                         │        │    26 Consumed >1 mo of ATT at enrollment            │
                                         │        │     3 HIV negative                                   │
                                         │        │    22 Moribund                                       │
                                         │        │   178 Abnormal CXR but TB not detected in            │
                                         │        │       Xpert and smear                                │
                                         │        └─────────────────────────────────────────────────────┘
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                                ┌─────────────────┐
                                │ 331 Randomized  │
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	111 Daily regimen	110 Part daily regimen	110 Intermittent regimen
Received allocated intervention	98	96	98
Not included in m-ITT	13	14	12
Culture negative	5	7	8
Primary MDR	4	4	2
NTM	3	2	2
Other	1	1	0
Favorable outcome	89	77	75
Unfavorable outcome	9	19	23
Failure	0	3	8
Death	4	9	5
Default	4	4	10
Toxic effects	1	3	0

18 mo after randomization (Daily)
77 Alive without recurrence
3 Died during follow-up
3 Defaulted
6 Recurrences
  2 Clinical
  4 Bacteriological

18 mo after randomization (Part daily)
70 Alive without recurrence
3 Died during follow-up
4 Recurrences
  2 Clinical
  2 Bacteriological

18 mo after randomization (Intermittent)
64 Alive without recurrence
3 Died during follow-up
2 Defaulted
6 Recurrences
  3 Clinical
  3 Bacteriological

Adults aged 18 years or older who were HIV positive and newly diagnosed with pulmonary tuberculosis (TB) were enrolled. Patients fulfilling the clinical and laboratory criteria were randomly allocated to 1 of 3 regimens. ATT indicates antituberculosis therapy; CXR, radiograph of the chest; MDR, multidrug-resistant; mITT, modified intent-to-treat analysis; NTM, nontuberculous mycobacteria; Xpert, Xpert MTB/RIF test (Cepheid).

86 of 90 patients (95%), 76 of 88 patients (86%), and 74 of 87 patients (85%) in the daily, part-daily, and intermittent regimens, respectively. Kaplan-Meier estimates are provided in **Figure 2**.

Results of the Cox proportional hazards regression analysis are provided in **Table 2**. The γ frailty model incorporating the potential confounders showed no heterogeneity among the regimens with respect to baseline parameters. A lower CD4 lymphocyte count (<150 cells/μL compared with ≥150 cells/μL) at 2 months rather than at baseline forecasted an unfavorable outcome (eFigure 2 in Supplement 2). Trends in various laboratory parameters during the treatment period are provided in eFigure 3 in Supplement 2.

Failures and ARR

In the intermittent regimen, 6 patients experienced bacteriological failures of treatment, with 4 of these patients developing ARR. Two patients experienced clinical failures (1 persistent bronchopleural fistula and 1 TB pontine abscess). Treatment failed in 3 patients in the part-daily regimen, but the patients did not develop ARR. The daily regimen had no failures (eTable 1 in Supplement 2). While none of the 16 patients with pretreatment isoniazid resistance (eTable 1 in Supplement 2) treated with a daily intensive phase developed ARR, 3 of 11 patients in the intermittent group developed ARR, and treatment failed subsequently.

Table 1. Baseline Characteristics of Patients Randomized to 3 Antituberculosis Therapy Regimens

Characteristic	Regimen		
	Daily (n = 111)	Part-Daily (n = 110)	Intermittent (n = 110)
Demographic characteristics			
Age, mean (SD), y	38 (9)	39 (9)	40 (9)
Male, No. (%)	86 (77)	81 (74)	84 (76)
Weight, mean (SD), kg	42.78 (8.28)	42.60 (7.54)	44.50 (7.47)
BMI, mean (SD)	16.79 (2.71)	16.87 (2.66)	17.36 (2.74)
Site of lesion, No.			
Pulmonary	70	77	68
Pulmonary with extrapulmonary	41	33	42
Opportunistic infections at baseline, No.	37	36	32
Pneumocystitis carinii pneumonia	8	2	4
Oral candidiasis	15	23	19
Herpes zoster or herpes simplex	6	8	7
Hepatitis B and C	8	2	3
Mycobacterium avium intracellulare	2	1	1
History of alcohol intake, No.	54	46	52
Smoker, No.	40	37	47
Transmission, No.			
Heterosexual	90	87	88
Homosexual	1	2	3
Intravenous drug user	7	2	3
Others	7	8	8
Biochemical and hematological parameters			
RBC count, median (range), $\times10^6$ cells/µL	3.55 (3.01-4.12)	3.54 (2.98-4.13)	3.62 (3.14-4.15)
WBC count, median (range), $\times10^3$ cells/µL	6.4 (4.4-8.9)	6.7 (4.7-9.5)	6.8 (4.9-8.3)
Platelets, median (IQR), $\times10^3$ cells/µL	3.09 (2.36-4.07)	3.12 (1.94-4.24)	3.15 (2.44-4.23)
Hemoglobin, mean (SD), g/dL	9.81 (2.14)	9.43 (2.08)	9.88 (2.05)
Hematocrit, mean (SD), %	30.07 (9.97)	28.96 (8.8)	29.66 (6.66)
Plasma glucose, median (IQR), mg/dL	102 (92-120)	105 (96-124)	102 (90-125)
Serum creatinine, mean (SD), mg/dL	0.77 (0.19)	0.73 (0.21)	0.73 (0.18)
Blood urea, mean (SD), mg/dL	21.40 (8.90)	20.91 (9.18)	21.35 (7.67)
Serum bilirubin, median (IQR), mg/dL	0.5 (0.4-0.7)	0.4 (0.4-0.7)	0.5 (0.4-0.7)
Serum AST, median (IQR), IU/L	37 (24-66)	35 (23-61)	34 (25-52)
Serum ALT, median (IQR), IU/L	24 (16-43)	22 (13-33)	20 (14-35)
Serum AP, median (IQR), IU/L	123 (86-218)	108 (74-189)	125 (82-240)
Immunological parameters			
Receiving ART at ATT initiation, No.	23	16	22
Not receiving ART during ATT, No.	11	22	13
Stavudine, lamivudine, efavirenz or zidovudine, lamivudine, efavirenz regimen, No.	60	51	54
Tenofovir, lamivudine, efavirenz regimen, No.	40	37	43
CD4 lymphocyte count, median (IQR), cells/µL	130 (65-226)	144 (71-261)	137 (68-258)
CD8 lymphocyte count, median (IQR), cells/µL	600 (334-957)	573 (337-1048)	707 (356-1018)
CD4/CD8 ratio, median (range)	0.23 (0.11-0.4)	0.23 (0.16-0.40)	0.20 (0.11-0.38)
Viral load, mean (SD), $\log_{10}$ copies/mL	4.91 (1.29)	5.00 (1.14)	4.93 (1.26)
ATT-ART interval, median (IQR), d	16 (2-36)	17 (5-47)	15 (1-34)
CD4 lymphocyte count <100 cells/µL, No. (%)	45 (41)	38 (34)	43 (39)

(continued)

Deaths

Overall, 18 deaths occurred during therapy (daily group, 4; part-daily group, 9; and intermittent group, 5). The baseline median (IQR) CD4 lymphocyte count of patients who died was 58 (45-136) cells/µL compared with 145 (78-259) cells/µL among patients who survived (*P* = .04) (eTable 2 in Supplement 2).

Treatment-Emergent Adverse Drug Reactions

Adverse reactions related to ATT occurred in 30 of 111 patients (27%), 23 of 110 patients (21%), and 19 of 110 patients (17%) in the daily, part-daily, and intermittent regimens, respectively (difference, 9.8%; 95% CI, −1.2% to −20.5%; *P* = .08), with no drug-induced deaths. Four patients (1 with jaundice;

Table 1. Baseline Characteristics of Patients Randomized to 3 Antituberculosis Therapy Regimens (continued)

Characteristic	Regimen		
	Daily (n = 111)	Part-Daily (n = 110)	Intermittent (n = 110)
Chest radiograph characteristics			
>3 Zones, No./total No. (%)	71/111 (64)	82/110 (75)	67/110 (61)
Bilateral lesions, No.	71	71	65
Lower lung TB, No.	69	66	57
Cavitation, No.	23	18	16
Pleural, No.	24	18	17
Military, No.	13	9	10
Mediastinal adenitis, No.	31	30	25
Others, No.	2	3	2
Microbiological characteristics			
Sputum smear grade 2+, No./total No.	52/111	52/110	52/110
Culture grade ≥2+, No./total No.	79/111	68/110	66/110
Sensitive to all first-line drugs, No./total No. (%)	92/99 (93)	82/97 (85)	85/97 (88)
Isoniazid resistance, No.	5	11	11
MDR TB at baseline (isoniazid and rifampicin resistance), No.	4	4	2

Abbreviations: ALT, alanine transaminase; AP, alkaline phosphatase; ART, antiretroviral therapy; AST, aspartate transaminase; ATT, antituberculosis therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; MDR, multidrug-resistant; RBC, red blood cell; TB, tuberculosis; WBC, white blood cell.

SI conversion factors: To convert RBC count to ×10^{12}/L, multiply by 1.0. To convert WBC count to ×10^9/L, multiply by 0.001. To convert platelet count to ×10^9/L, multiply by 1.0. To convert hemoglobin to g/L, multiply by 10.0. To convert hematocrit to proportion of 1, multiply by 0.01. To convert plasma glucose to mmol/L, multiply by 0.0555. To convert serum creatinine to μmol/L, multiply by 76.25. To convert blood urea to mmol/L, multiply by 0.357. To convert serum bilirubin to μmol/L, multiply by 17.104. To convert serum AST to μkat/L, multiply by 0.0167. To convert serum ALT to μkat/L, multiply by 0.0167. To convert serum AP to μkat/L, multiply by 0.0167.

2, thrombocytopenia; and 1, Stevens-Johnson syndrome) had their study regimen permanently modified (**Table 3**). Jaundice occurred in 21 patients (daily group, 11; part-daily group, 8; and intermittent group, 2), with 16 of 21 events occurring while the patient was receiving concomitant ART (eFigure 4 in Supplement 2). Seven patients developed jaundice as part of the immune reconstitution inflammatory syndrome (IRIS) spectrum. Hepatotoxic effects were experienced by 19 of 221 patients (9%) receiving treatment daily vs 2 of 110 patients (2%) receiving intermittent treatment during the intensive phase. Median (range) time of occurrence of jaundice was 19 (6-80), 27 (9-56), and 20 (18-23) days after ATT. All cases of jaundice resolved by 28 days in the daily and part-daily regimens, and by 20 days in the intermittent regimen. These 21 patients with jaundice, however, attained bacteriological quiescence at the end of 6 months.

Recurrences

Six patients (7.21/100 person-years), 4 patients (5.33/100 person-years), and 6 patients (9.01/100 person-years) in the daily, part-daily, and intermittent regimens, respectively, had TB recurrence (Figure 1). There was no statistically significant difference in recurrences when the daily regimen (1.6/100 person-years; 95% CI, −0.7 to −10.2; P = .71) or part-daily regimen (0.8/100 person-years; 95% CI, −8.2 to −9.9; P = .42) were compared with the intermittent regimen.

Immune Reconstitution Inflammatory Syndrome

Overall, there were 82 cases of IRIS (27 of 98 patients [28%] in the daily regimen, 21 of 96 patients [22%] in the part-daily regimen, and 34 of 98 patients [35%] in the intermittent regimen). The median (IQR) interval between administration of ATT and

that of ART was 17 (4-39) days and the median (IQR) time of IRIS occurrence was 15 (7-22) days after ART. Immune reconstitution inflammatory syndrome lesions were pulmonary in 26 of 82 patients (32%) and extrapulmonary in 56 of 82 patients (68%), requiring steroids for amelioration of symptoms in 59 of 82 patients (72%). Antiretroviral therapy was temporarily withheld in 4 cases (2 with brain tuberculomas and 2 with obstructive jaundice).

Discussion

This study addresses the vital issue of optimal frequency of anti-TB drug administration among HIV-positive patients with TB by comparing the efficacy of daily, part-daily, and intermittent ATT regimens in a pure group of patients newly diagnosed with culture-positive, rifampicin-sensitive, pulmonary TB. Not only did the daily regimen prove superior to a 6-month intermittent regimen, but it also prevented ARR, prompting the data safety monitoring committee to halt the study at the stage of second interim analysis. The per-protocol analysis yielded similar results. In the Cox proportional hazards model, significant risk factors leading to an unfavorable response were intermittent administration of ATT and pretreatment isoniazid resistance, confirming the hypotheses raised by previous analyses of observational cohorts.[15,23] The meta-analysis by Khan et al[14,15] among HIV-positive patients with TB showed that the odds of treatment failure increased by 2.0 times (95% CI, 0.8-5) and the odds of ARR increased by 3.7 times (95% CI, 0.7-18.9) when an intermittent rather than a daily intensive phase of ATT was used. In an observational cohort study[24] among 1460 HIV-positive patients with TB from south India, higher mortality was noted with

supervised intermittent ATT compared with unsupervised daily ATT, with similar default rates in both groups. This study by Alvarez-Uria et al[24] had its own limitation, which was that only one-third of patients had access to ART.

Clinical trials among HIV-negative patients with TB have not shown any significant difference in treatment responses between daily and intermittent regimens.[7,25] The meta-analysis by Kasozi et al[26] of HIV-negative patients newly diagnosed with drug-susceptible TB revealed similar cure rates with intermittent (88%) and daily (90%) ATT. Additionally, the meta-analysis by Menzies et al[23] done in a predominantly HIV-negative population of patients with TB revealed an increased adjusted risk of ARR with a thrice-weekly intensive phase with no difference in relapse or failure.

Interestingly, in our study a lower CD4 lymphocyte count at the end of the intensive phase, rather than at baseline, was associated with an unfavorable outcome. Even among patients with advanced immunodeficiency that persisted (CD4 lymphocyte count <150 cells/μL at the end of 2 months), patients receiving the daily regimen exhibited better survival

compared with those who received the part-daily or intermittent regimens (eFigure 2 in Supplement 2). Three of 4 patients who developed ARR in the intermittent group had lower CD4 lymphocyte counts repeatedly, despite timely ART and effective viral suppression (eTable 1 in Supplement 2). Furthermore, the part-daily regimen conferred no added advantage over the intermittent regimen in terms of efficacy or toxic effects, but prevented ARR.[27] Even though there seem to be more patients with isoniazid-resistant disease or advanced immunodeficiency at baseline in the part-daily regimen group, this was not statistically different, and the γ frailty model failed to reveal any heterogeneity among regimens with respect to these baseline parameters. Comparing previous trials conducted at NIRT, ART initiation within the intensive phase of ATT augmented cure rates, reduced mortality, and prevented ARR but contributed to higher incidence of toxic effects and IRIS.[4,5] Significant increases in weight, CD4 lymphocyte count, hemoglobin, red blood cells, and hematocrit and decline in HIV viral load that were uniformly observed across all 3 groups confirmed the advantage of early ART initiation and good clinical management of HIV (eFigure 3 in Supplement 2).

Figure 2. Mean Survival Estimates for Time to an Unfavorable Event Among Antituberculosis Therapy Regimens
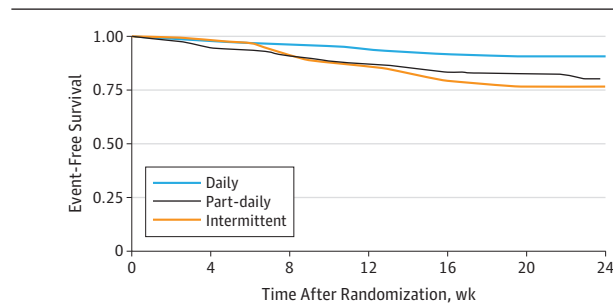
No. at risk												
Daily	98	(2)	96	(1)	95	(2)	93	(1)	92	(2)	90	(1)	89
Part-daily	96	(3)	93	(4)	89	(5)	84	(1)	83	(3)	80	(3)	77
Intermittent	98	(1)	97	(5)	92	(5)	87	(4)	83	(5)	78	(3)	75

The numbers given within parentheses reflect the number of individuals who experienced the event at that particular week after randomization (censored at 24 weeks after randomization). Event-free survival was 22.76 (95% CI, 21.91-23.61) in the daily regimen, 21.34 (95% CI, 20.11-22.57) in the part-daily regimen, and 21.07 (95% CI, 19.91-22.22) in the intermittent regimen, results that were significant according to the log-rank test (P = .03).

Table 2. Cox Proportional Hazards Regression Analysis Evaluating the Risk of an Unfavorable Event During Treatment Period

Baseline Parameter	Hazard Ratio (95% CI)	P Value
Daily regimen[a]	0.310 (0.131-0.733)	.008
Part-daily regimen	0.834 (0.440-1.578)	.58
Baseline CD4 lymphocyte count <100 cells/μL	0.903 (0.496-1.644)	.74
Sputum culture grade >2+	1.476 (0.817-2.667)	.20
Isoniazid resistance at baseline[b]	2.340 (1.107-4.947)	.03
Baseline weight, kg	0.961 (0.924-1.000)	.05
Baseline viral load, $\log_{10}$ copies/mL	1.363 (0.995-1.866)	.05
Radiographic involvement >3 zones	0.906 (0.479-1.714)	.76
Receiving ART at initiation of ATT	1.113 (0.530-2.340)	.78

Abbreviations: ART, antiretroviral therapy; ATT, antituberculosis therapy.

[a] The hazard of an unfavorable response was reduced to one-third when a daily regimen replaced an intermittent regimen.

[b] The hazard of an unfavorable response increased 2.3 times when there was isoniazid resistance at baseline.

Table 3. Treatment-Emergent Adverse Drug Reactions Among HIV-Positive Patients With Tuberculosis Receiving 3 Antituberculosis Therapy Regimens

Toxic Effect Type	Grade of Toxic Effects	Regimen[a]		
		Daily (n = 111)	Part-Daily (n = 110)	Intermittent (n = 110)
Gastrointestinal and hepatic	1 and 2	5	1	8
	3 and 4	11	11[b]	2
Neurological	1 and 2	11	8	8
	3 and 4	1	1	0
Cutaneous	1 and 2	1	0	1
	3 and 4	1[c]	0	0
Others	1 and 2	0	0	0
	3 and 4	0	2[d]	0
Overall adverse drug reactions, No. (%)		30 (27)	23 (21)	19 (17)

[a] Four patients had permanent discontinuation or modification of antituberculosis therapy.

[b] Two patients had jaundice.

[c] One patient had Stevens-Johnson syndrome.

[d] One patient had thrombocytopenia.

Overall toxic effects were statistically similar among regimens. However, patients receiving the daily intensive phase of ATT with coadministered ART had a higher incidence of hepatotoxic effects despite normal baseline liver function. These effects were manageable under trial conditions. Studies of HIV-positive patients with TB have reported hepatotoxic effects ranging from 5% to 33%.[28] Except in 2 cases that mandated permanent modification of the regimen because of hepatotoxic effects, the study regimen was successfully reinstituted and the patients attained bacteriological quiescence at treatment completion.[29,30] Factors possibly contributing to higher incidence of hepatotoxic effects among patients in our trial were prior alcohol intake, extrapulmonary site of involvement, advanced immunodeficiency, and a shorter interval between administration of ATT and ART. Yimer et al[30] similarly reported the risk of hepatotoxic effects to be 3.6 times greater (95% CI, 1.5-8.5) with HIV, 2.7 times greater (95% CI, 1.2-5.8) with concomitant drug intake, and 5.2 times greater (95% CI, 0.6-46) when CD4 lymphocyte count was lower than 100 cells/μL. Furthermore, early hepatic injury was more common in patients with HIV-TB coinfection than in those with TB alone (33% vs 7% [$P = .004$]),[31] indicating the need for close monitoring.

Recurrences were similar in the 3 groups during the 1-year follow-up period. Dosing schedule was not associated with recurrences in our study, probably because of effective and early highly active ART therapy.[15] We believe that these results may be sustainable even over a longer follow-up period, as three-fourths of recurrences occur within the first year.[4] Analogous to toxic effects, shorter interval between administration of ATT and ART, advanced immunodeficiency, and extrapulmonary involvement coupled with active surveillance for IRIS resulted in a higher IRIS incidence reported.[32,33] Steroids were required in most of the cases.[34]

Limitations

The strengths of this study included a pure group of study participants (culture-confirmed, rifampicin-sensitive, ATT-naive, HIV-positive patients with TB) treated with quality-assured, assayed drugs and fully supervised drug intake. The bacteriology department was blinded to each patient's clinical condition and regimen. The outcomes were ratified by an independent end point review committee, reducing the bias arising out of the open-label design. The main limitations of the study were the slow recruitment rate due to stringent selection criteria and failure to stratify for isoniazid resistance at baseline, as rapid tests for resistance detection were unavailable at that time and we wanted to replicate programmatic conditions.

Conclusions

A daily ATT regimen for 6 months in HIV-positive patients with TB receiving concomitant ART proved superior to an intermittent regimen in terms of efficacy and prevention of ARR. A slightly higher incidence of hepatotoxic effects for patients receiving the daily regimen demanded closer monitoring of liver function. The part-daily regimen did not confer any advantage over an intermittent regimen with regard to efficacy or tolerability but prevented ARR. A higher CD4 lymphocyte count (≥150 cells/μL) at the end of the intensive phase, rather than at baseline, was associated with a successful outcome.

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