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Authors

Pettit, April C
Phillips, Patrick PJ
Kurbatova, Ekaterina
et al.

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Rifapentine With and Without Moxifloxacin for Pulmonary Tuberculosis in People With Human Immunodeficiency Virus (S31/A5349)

April C. Pettit,[1,a] Patrick P. J. Phillips,[2,a] Ekaterina Kurbatova,[3] Andrew Vernon,[3] Payam Nahid,[2] Rodney Dawson,[4] Kelly E. Dooley,[5] Ian Sanne,[6] Ziyaad Waja,[7] Lerato Mohapi,[7] Anthony T. Podany,[8] Wadzanai Samaneka,[9] Rada M. Savic,[2] John L. Johnson,[10,11] Grace Muzanyi,[11] Umesh G. Lalloo,[12] Kia Bryant,[3] Erin Sizemore,[3] Nigel Scott,[3] Susan E. Dorman,[13] Richard E. Chaisson,[5] and Susan Swindells[14]; for the Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 study team

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, California, USA; [3]Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [4]Center for TB Research Innovation, University of Cape Town Lung Institute, Cape Town, South Africa; [5]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; [6]Clinical HIV Research Unit, University of Witwatersrand, Johannesburg, South Africa; [7]Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa; [8]Department of Pharmacy Practice and Science, University of Nebraska Medical Center, Omaha, Nebraska, USA; [9]Department of Medicine, University of Zimbabwe College of Health Sciences, Harare, Zimbabwe; [10]Tuberculosis Research Unit, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; [11]Uganda-Case Western Reserve University Research Collaboration, Kampala, Uganda; [12]Enhancing Care Foundation, Durban University of Technology, Durban, South Africa; [13]Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA; and [14]Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

Background. Tuberculosis (TB) Trials Consortium Study 31/AIDS Clinical Trials Group A5349, an international randomized open-label phase 3 noninferiority trial showed that a 4-month daily regimen substituting rifapentine for rifampin and moxifloxacin for ethambutol had noninferior efficacy and was safe for the treatment of drug-susceptible pulmonary TB (DS-PTB) compared with the standard 6-month regimen. We explored results among the prespecified subgroup of people with human immunodeficiency virus (HIV) (PWH).

Methods. PWH and CD4+ counts ≥100 cells/μL were eligible if they were receiving or about to initiate efavirenz-based antiretroviral therapy (ART). Primary endpoints of TB disease-free survival 12 months after randomization (efficacy) and ≥ grade 3 adverse events (AEs) on treatment (safety) were compared, using a 6.6% noninferiority margin for efficacy. Randomization was stratified by site, pulmonary cavitation, and HIV status. PWH were enrolled in a staged fashion to support cautious evaluation of drug–drug interactions between rifapentine and efavirenz.

Results. A total of 2516 participants from 13 countries in sub-Saharan Africa, Asia, and the Americas were enrolled. Among 194 (8%) microbiologically eligible PWH, the median CD4+ count was 344 cells/μL (interquartile range: 223–455). The rifapentine-moxifloxacin regimen was noninferior to control (absolute difference in unfavorable outcomes −7.4%; 95% confidence interval [CI] −20.8% to 6.0%); the rifapentine regimen was not noninferior to control (+7.5% [95% CI, −7.3% to +22.4%]). Fewer AEs were reported in rifapentine-based regimens (15%) than the control regimen (21%).

Conclusions. In people with HIV-associated DS-PTB with CD4+ counts ≥100 cells/μL on efavirenz-based ART, the 4-month daily rifapentine-moxifloxacin regimen was noninferior to the 6-month control regimen and was safe.

Clinical Trials Registration. NCT02410772.

Keywords. phase 3 clinical trial; rifapentine; moxifloxacin; tuberculosis; human immunodeficiency virus.

Human immunodeficiency virus (HIV)-associated tuberculosis (TB) remains a significant public health challenge worldwide. In 2020, an estimated 787 000 people with HIV (PWH) developed TB disease and 214 000 PWH died from TB globally. Overall TB treatment success was estimated at 86% in 2019, whereas it was only 77% among PWH [1]. Shortening TB treatment duration could lead to improved treatment completion and success with fewer adverse events (AEs) [2].

National and international guidelines recommend a 6-month rifampin-based regimen for drug-susceptible pulmonary TB (DS-PTB) [3–5]. TB Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (S31/A5349) was the first randomized trial to demonstrate a 4-month regimen had noninferior efficacy and comparable safety to the standard 6-month regimen among adults and adolescents with DS-PTB [6, 7]. The World Health Organization (WHO) [8] and US Centers for Disease Control and Prevention (CDC) recommend the 4-month rifapentine-moxifloxacin regimen, including for people with HIV-associated DS-PTB with CD4+ counts

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[a]A. C. Pettit and Patrick P. J. Phillips contributed equally.

Correspondence: A. Pettit, Vanderbilt University Medical Center, 1161 21st Ave South, Nashville, TN 37232, USA (april.pettit@vumc.org).

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≥100 cells/μL receiving or planning to initiate efavirenz-based antiretroviral therapy (ART) [9].

Importantly, S31/A5349 pharmacokinetic studies among PWH showed that rifapentine resulted in increases in efavirenz exposure and that virologic response remained excellent, so that daily rifapentine can be safely coadministered with efavirenz without dose adjustment [10, 11]. We, therefore, explored the efficacy and safety of the 4-month regimens vs control in a prespecified subgroup of PWH.

METHODS

Study Design and Oversight

S31/A5439 was an international multicenter randomized open-label phase 3 three-arm noninferiority trial comparing two 4-month investigational anti-TB regimens to the standard 6-month regimen. Both investigational arms included substitution of rifapentine for rifampin; 1 investigational arm additionally included a substitution of moxifloxacin for ethambutol. Design details and results of the trial were published previously [6, 7]. Here, we report results among the prespecified subgroup of PWH. The study was approved by the CDC institutional review board (IRB) and ethics committees at participating sites that did not formally rely on the CDC IRB. All participants provided written informed consent.

Study Population

Full eligibility criteria are in the attached study protocol. In brief, participants were ≥12 years of age with suspected DS-PTB plus a sputum specimen positive for either acid-fast bacilli on smear microscopy or *Mycobacterium tuberculosis* by Xpert MTB/RIF testing with a semiquantitative result of "medium" or "high" and rifamycin resistance not detected [6]. HIV testing was required and PWH were required to have CD4+ counts ≥100 cells/μL. Individuals with suspected or documented TB involving the central nervous system, bone and joint TB, miliary TB, or pericardial TB were excluded; patients with pleural or lymphatic TB were permitted.

PWH were enrolled in a conservative staged approach to study drug–drug interactions between rifapentine and efavirenz. In stage 1, PWH on efavirenz-based ART >30 days before enrollment with viral load (VL) <200 copies/mL were eligible. After stage 1 data analysis, stage 2 enrollment began with expansion to include PWH not on ART, but with planned efavirenz-based ART initiation within 8 weeks of TB treatment initiation based on national and international guidelines [12, 13]. Local site clinicians were encouraged to follow ART initiation guidelines, but PWH were not withdrawn if ART was not initiated within 8 weeks of enrollment.

Study Procedures

Randomization was stratified by site, cavitation on baseline chest radiograph, and HIV status. The control regimen (24 weeks) included 8 weeks of once-daily isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E), followed by 18 weeks of once-daily HR. The rifapentine (P) regimen (17 weeks) included 8 weeks of once-daily HPZE, followed by 9 weeks of once-daily HP. The rifapentine-moxifloxacin regimen (17 weeks) was 8 weeks of once-daily HPZM, followed by 9 weeks of once-daily HPM. Rifapentine and moxifloxacin daily doses were 1200 mg and 400 mg, respectively; other drugs were administered at standard doses. All regimens were administered 7 days/wk, including at least 5 days/wk by directly observed therapy. Different food guidance by arm and concerns about the placebo pill burden led to the open-label design; further rationale can be found in the protocol.

Follow-up and Data Collection

At each visit, sputum for mycobacterial stains and culture, and blood for safety analyses were obtained. Phenotypic drug susceptibility testing for isoniazid, rifampin, and fluoroquinolones was performed on the baseline *M. tuberculosis* isolate, and on the first of any *M. tuberculosis* isolates obtained at or after week 17. Full details on study visits and procedures can be found in the protocol. Mid-dosing interval efavirenz concentrations were measured during ART and TB cotreatment within 4 weeks of enrollment as previously described [11, 14].

Study Outcomes

The primary efficacy outcome was TB disease-free survival 12 months after randomization. For each participant, a primary outcome of "favorable," "unfavorable," or "not assessable" was assigned; unfavorable outcomes were further classified as TB-related or not TB-related [6]. The primary safety outcome was the proportion with ≥ grade 3 AEs during treatment (within 14 days after last study medication dose). AEs were graded by site investigators according to Common Terminology Criteria for AEs [15]. Tolerability was defined as premature discontinuation for reasons other than microbiological ineligibility.

Analysis Populations

The primary microbiologically eligible population included those with culture-confirmed TB and documented to be free of resistance to isoniazid, rifampin, or fluoroquinolones. The primary assessable population included those with an assessable outcome (Table 2). Important secondary analysis populations included participants who completed ≥75% and ≥95% of treatment doses (per protocol) and all participants randomized (intention to treat).

Statistical Analysis

Repeating the primary analysis among the PWH subgroup was prespecified in the analysis plan. The primary efficacy comparison was the absolute between-group difference (test arm minus control arm, with 95% confidence interval [CI]) in the proportion of favorable outcomes adjusted for cavitation and HIV status using Cochran–Mantel–Haenszel weights [16]; efficacy analyses among PWH were unadjusted from low event rates. Noninferiority criteria were met if the upper bound of the 95%

CI of the difference was <6.6% in both the microbiologically eligible and assessable analysis populations. Justification for the noninferiority margin was published previously [6]. Although the noninferiority margin was determined for the overall study population, we used the same margin in PWH, recognizing that noninferiority determinations in PWH are exploratory.

Logistic regression was used to estimate the odds ratio (OR) for the association of ART initiation (before enrollment, within 8 weeks of enrollment, >8 weeks from enrollment, or not during study follow-up), baseline CD4+ counts (<200, 200–499, ≥500 cells/μL), baseline HIV-1 viral load values (quantifiable or below limit of quantification via local site assay), or efavirenz concentrations (above vs below therapeutic breakpoint 1000 ng/mL [17]) with the proportion of unfavorable outcomes, adjusted for treatment arm. All tests were 2-sided and *P* values <.05 were considered statistically significant.

Time to stable culture conversion on liquid or solid media was defined as time to the second of 2 negative sputum cultures without an intervening positive culture. Cox regression was used to estimate a hazard ratio (HR) and 95% CI for time to stable culture conversion. Schoenfeld residuals tested the proportional-hazards assumption and HRs were presented if there was no evidence of nonproportional hazards. Cox regression models were not adjusted for baseline or time-varying covariates. The log-rank test was used to compare time to stable culture conversion between groups.

Safety analyses included all randomized participants who started study treatment; tolerability analyses included the microbiologically eligible population. Comparisons of safety outcomes were calculated as absolute differences from control, with 95% CIs.

RESULTS

Study Population

From January 2016 through October 2018, 2516 participants were randomized (planned enrollment 2500) in 13 countries

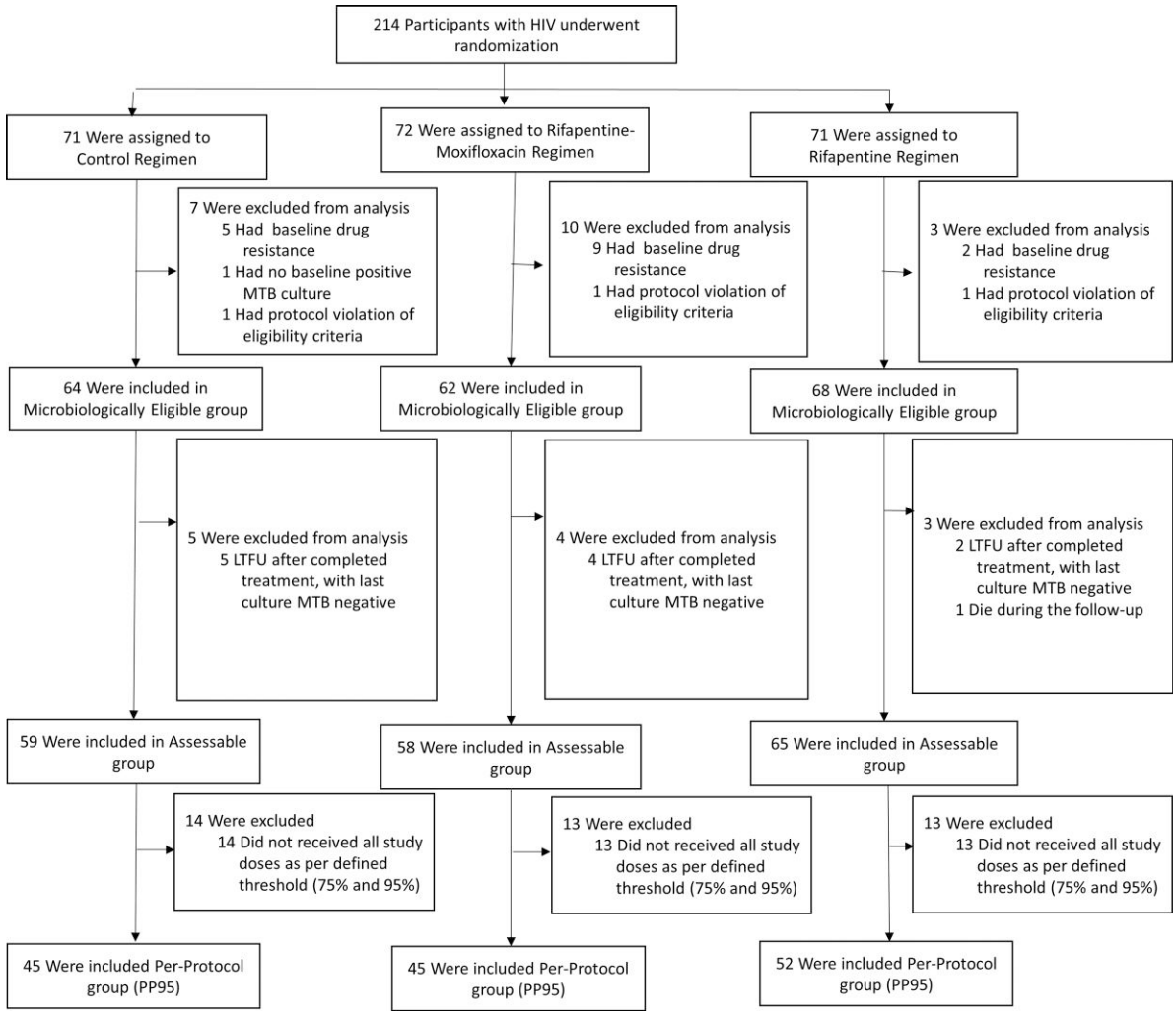

Figure 1. CONSORT flow diagram. Abbreviations: HIV, human immunodeficiency virus; LTFU, loss to follow-up; MTB, *Mycobacterium tuberculosis*; PP95, per-protocol 95%.

Table 1. Baseline Demographic Characteristics of Participants in S31/A5439 Microbiologically Eligible Population

Characteristic	People With HIV N = 194	HIV-negative N = 2148	Overall N = 2342[a]
Male, N (%)	120 (62)	1549 (72)	1669 (71)
Age, median (IQR)	35 (30–43)	30 (24–41)	31 (24–41)
Age group, N (%)			
12–17 y	0	63 (3)	63 (3)
18–34 y	92 (47)	1281 (60)	1373 (59)
≥ 35 y	102 (53)	804 (37)	906 (39)
Race, N (%)			
Asian	0	268 (12)	268 (11)
Black or African American	180 (93)	1495 (70)	1675 (71)
White	2 (1)	34 (2)	36 (1)
More than 1 race	12 (6)	346 (16)	358 (15)
Baseline cavitation, N (%)			
Absent	55 (28)	585 (27)	640 (27)
< 4 cm	68 (35)	706 (33)	774 (33)
≥ 4 cm	71 (37)	857 (40)	928 (40)
Sputum smear grade			
Negative	5 (2.6%)	72 (3.4%)	77 (3.3%)
Scanty	44 (22.7%)	337 (15.7%)	381 (16.3%)
1+	55 (28.4%)	448 (20.9%)	503 (21.5%)
2+	44 (22.7%)	586 (27.3%)	630 (26.9%)
3+	43 (22.2%)	519 (24.2%)	562 (24.0%)
Missing	3 (1.5%)	186 (8.7%)	189 (8.1%)
Weight in kg, median (IQR)	54.5 (49.1–61.8)	53.0 (48.0–59.0)	53.2 (48.0–59.1)
Body mass index, kg/m^2, median (IQR)	19.4 (17.4–22.1)	18.9 (17.4–20.7)	18.9 (17.4–20.8)
Current smoker, N (%)	41 (21)	500 (23)	541 (23)
Diabetes mellitus, N (%)	1 (0.5)	76 (3)	77 (3)

Abbreviation: IQR, interquartile range.

[a]One participant in the microbiologically eligible population had a missing HIV status and is not included in any analyses.

in sub-Saharan Africa, Asia, and the Americas; 213 (8%) PWH were enrolled from 17 sites in Brazil, Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe (Figure 1). There were 2342 microbiologically eligible participants with baseline HIV status, including 194 (8%) PWH. Among microbiologically eligible PWH, median age was 35 years (interquartile range: 30–43 years), 62% were male, 93% were Black, and 72% had baseline cavitary disease (Table 1). The median CD4 + cell count among microbiologically eligible PWH was 344 cells/μL (interquartile range: 223–455); 96 (49%) were on efavirenz-based ART at enrollment, 79 (41%) initiated ART within 8 weeks of enrollment, 10 (5%) initiated ART >8 weeks after enrollment, and 9 (5%) did not initiate ART during study follow-up (Table 3). Full details on longitudinal CD4+ counts and HIV VL were published previously [11]. Baseline characteristics were similar by arm among the intention-to-treat population (Supplementary Table 1).

Efficacy

For both primary analysis populations, unfavorable outcomes were less common among PWH receiving the rifapentine-moxifloxacin regimen than control, and the upper bound of the 95% CI for the difference in proportion of unfavorable events was <6.6%, the prespecified margin of noninferiority (Figure 2, upper panel). In the microbiologically eligible population, an unfavorable outcome occurred in 14.5% in the rifapentine-moxifloxacin arm and 21.9% in the control arm (unadjusted absolute difference −7.4% [95% CI, −20.8 to 6.0]). In the assessable population, an unfavorable outcome occurred in 8.6% and 15.3% for the rifapentine-moxifloxacin and control arms, respectively (absolute difference −6.6% [95% CI, −18.3 to 5.0]).

In contrast, 95% CIs for the comparison of the proportion of unfavorable events between rifapentine and control arms among PWH included the 6.6% noninferiority margin in both primary analysis populations. An unfavorable outcome occurred in 29.4% microbiologically eligible PWH in the rifapentine arm (absolute difference from control arm 7.5% [95% CI, –.3 to 22.4]) and 26.2% of assessable PWH (absolute difference from control arm 10.9% [95% CI, –3.2 to 25.0]) (Figure 2, lower panel). A prespecified comparison of the two 4-month regimens demonstrated benefit of moxifloxacin in reducing the proportion of unfavorable outcomes among PWH, with absolute differences of −14.9% (95% CI, −28.8 to −1.0) and −17.5% (95% CI, −30.4 to −4.6) for microbiologically eligible and assessable populations, respectively.

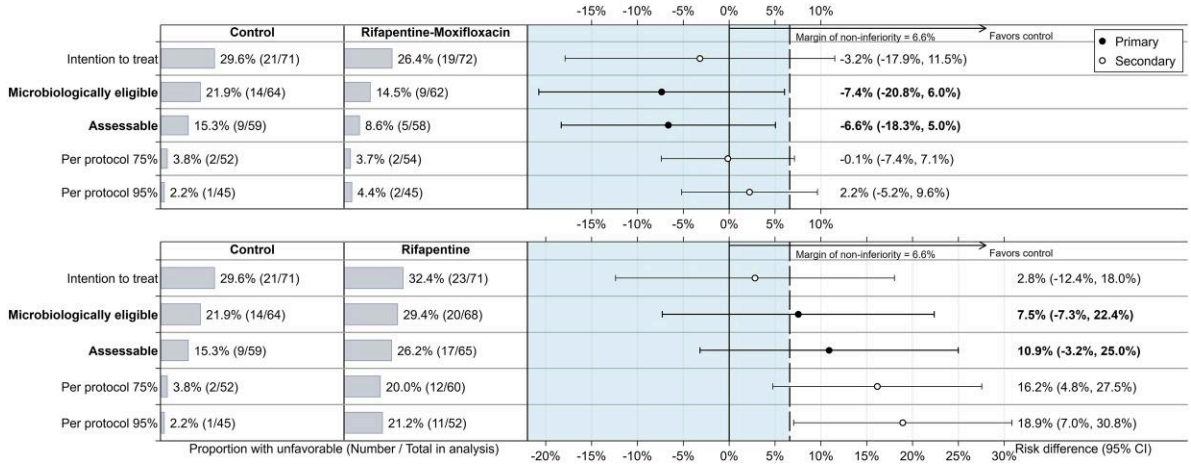

Figure 2. Unadjusted differences in unfavorable outcomes in each analysis population among PWH. Figure 2 shows the results of the primary efficacy results in all 4 analysis populations (top, rifapentine–moxifloxacin regimen vs control regimen; bottom, rifapentine regimen vs control regimen). The noninferiority margin of 6.6% is designated by the dashed vertical line.

Table 2. Primary Efficacy Analysis in the HIV Microbiologically Eligible and Assessable Analysis Populations

	Microbiologically Eligible Analysis Population				Assessable Analysis Population			
	Control	RPT-MOX	RPT	All	Control	RPT-MOX	RPT	All
Total in the analysis population	64	62	68	194	59	58	65	182
Favorable outcome, N (%)	50 (78.1)	53 (85.5)	48 (70.6)	151 (77.8)	50 (84.7)	53 (91.4)	48 (73.8)	151 (83.0)
Culture negative at month 12	49 (76.6)	53 (85.5)	47 (69.1)	149 (76.8)	49 (83.1)	53 (91.4)	47 (72.3)	149 (81.9)
Seen at month 12, sputum not evaluable	1 (1.6)	0	1 (1.5)	2 (1.0)	1 (1.7)	0	1 (1.5)	2 (1.1)
Unfavorable outcome, N (%)	14 (21.9)	9 (14.5)	20 (29.4)	43 (22.2)	9 (15.3)	5 (8.6)	17 (26.2)	31 (17.0)
TB-related unfavorable outcome	1 (1.6)	3 (4.8)	11 (16.2)	15 (7.7)	1 (1.7)	3 (5.2)	11 (16.9)	15 (8.2)
Two consecutive positive cultures at or after week 17	1 (1.6)	3 (4.8)	10 (14.7)	14 (7.2)	1 (1.7)	3 (5.2)	10 (15.4)	14 (7.7)
Clinical TB recurrence and treatment restarted	0	0	1 (1.5)	1 (0.5)	0	0	1 (1.5)	1 (0.5)
Not TB-related unfavorable outcome	8 (12.5)	2 (3.2)	6 (8.8)	16 (8.2)	8 (13.6)	2 (3.4	6 (9.2)	16 (8.8)
Treatment changed because of AE	1 (1.6)	2 (3.2)	2 (2.9)	5 (2.6)	1 (1.7)	2 (3.4)	2 (3.1)	5 (2.7)
Consent withdrawn during treatment; no AE reported	2 (3.1)	0	3 (4.4)	5 (2.6)	2 (3.4)	0	3 (4.6)	5 (2.7)
Death during treatment	2 (3.1)	0	1 (1.5)	3 (1.5)	2 (3.4)	0	1 (1.5)	3 (1.6)
Consent withdrawn during treatment, after the occurrence of AE	1 (1.6)	0	0	1 (0.5)	1 (1.7)	0	0	1 (0.5)
Lost to follow-up during treatment	1 (1.6)	0	0	1 (0.5)	1 (1.7)	0	0	1 (0.5)
Treatment changed or restarted for other reasons	1 (1.6)	0	0	1 (0.5)	1 (1.7)	0	0	1 (0.5)
Not assessable	5 (7.8)	4 (6.5)	3 (4.4)	12 (6.2)	N/A	N/A	N/A	N/A
Not seen at month 12; last culture negative	5 (7.8)	4 (6.5)	2 (2.9)	11 (5.7)	N/A	N/A	N/A	N/A
Death during follow-up, not TB-related	0	0	1 (1.5)	1 (0.5)	N/A	N/A	N/A	N/A
Retreatment after exogenous reinfection (WGS-confirmed)	0	0	0	0	N/A	N/A	N/A	N/A
Unadjusted difference from control in percentage with favorable outcome (95% CI)	N/A	–7.4% (–20.8 to 6.0)	7.5% (–7.3 to 22.4)	N/A	N/A	–6.6 to (–18.3 to, 5.0)	10.9% (–3.2 to 25.0)	N/A

Abbreviations: AE, adverse event; CI, confidence interval; MOX, moxifloxacin; N/A, not applicable; RPT, rifapentine; TB, tuberculosis; WGS, whole-genome sequencing.

All unfavorable outcomes were classified as TB-related or not TB-related. In the microbiologically eligible analysis population, most unfavorable outcomes were not TB-related on the control arm (13 of 14, 92.9%); a lower proportion of unfavorable outcomes were not TB-related in the rifapentine-moxifloxacin (6 of 9, 66.7%) and the rifapentine arms (9 of

Table 3. Unfavorable Outcomes in PWH Overall and by Baseline HIV Characteristics

	Control N (% of total)	Rifapentine-Moxifloxacin N (% of total)	Rifapentine N (% of total)	Total N (% of total)	Odds Ratio (95% CI) for Unfavorable Outcome (Adjusted for Treatment Arm Unless Otherwise Noted)
Total	64	62	68	194	…
Timing of start of ART	…	…	…	…	$P = .174$[a]
Before enrollment	24 (38%)	33 (53%)	39 (57%)	96 (49%)	Reference
Within 8 wk of enrollment	30 (47%)	25 (40%)	24 (35%)	79 (41%)	1.23 (0.51–2.96)
More than 8 wk from enrollment but before the end of study follow-up	2 (3%)	4 (6%)	4 (6%)	10 (5%)	4.07 (0.81–20.45)
Not during study follow-up	8 (13%)	0 (0%)	1 (1%)	9 (5%)	4.46 (0.83–24.07)
CD4+ count at enrollment	…	…	…	…	$P = .115$[a]
100–199 cells/μL	13 (20%)	10 (16%)	14 (21%)	37 (19%)	Reference
200–499 cells/μL	37 (58%)	41 (66%)	44 (65%)	122 (63%)	0.61 (0.12–3.00)
≥500 cells/μL	14 (22%)	11 (18%)	10 (15%)	35 (18%)	1.90 (0.60–6.03)
Median (IQR)	333 (248, 484)	345 (253, 458)	350 (220, 437)	343 (223, 445)	…
Viral load at enrollment[c]	…	…	…	…	$P = .200$[a]
Below limit of quantification (BLQ)	25 (39%)	32 (52%)	30 (44%)	87 (45%)	Reference
Quantifiable	37 (58%)	27 (44%)	38 (56%)	102 (53%)	0.58 (0.25–1.35)[d]
Missing	2 (3%)	3 (5%)	0 (0%)	5 (3%)	N/A
Median (IQR)	70 (BLQ, 42 806)	BLQ (BLQ, 26 612)	40 (BLQ, 27 827)	40 (BLQ, 28 999)	…
Efavirenz Concentration at enrollment[e]	…	…	…	…	$P = .391$[b]
≤1000 ng/L	N/A	4 (6%)	7 (10%)	11 (6%)	Reference
>1000 ng/L	N/A	29 (47%)	35 (51%)	64 (33%)	2.25 (0.39–13.13)
Missing	64 (100%)	29 (47%)	26 (38%)	119 (61%)	N/A
Median (IQR)	N/A	2407 (1673, 3641)	1762 (1312, 2679)	2003 (1355, 2945)	…

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; N/A, not applicable.

[a]Likelihood ratio test, comparing models adjusted for treatment arm.

[b]Likelihood ratio test, comparing models not adjusted for treatment arm because of small numbers in some subgroups when split by treatment; 95% CI, 1.20–12.23.

[c]Level of quantification differs based on the assay used at each site.

[d]Participants with missing viral load excluded from calculation of odds ratio.

[e]Measurement closest to enrollment, up to 4 weeks after enrollment.

20, 45%). TB-related unfavorable outcomes occurred among 1 (1.6%), 3 (4.8%), and 11 (16.2%) in the control, rifapentine-moxifloxacin, and rifapentine arms, respectively, in the microbiologically eligible population (Table 2). One PWH randomized to the rifapentine arm had resistance to isoniazid and rifampicin detected during treatment, but not by phenotypic and molecular tests at baseline. Subsequent whole-genome sequencing of baseline and recurrence isolates demonstrated presence of multidrug-resistant TB at baseline.

Initiation of ART and Baseline CD4 and Viral Load

When considering ART initiation timing, there was no difference in the odds of an unfavorable outcome ($P = .174$). There were 9 PWH who did not initiate ART during the study period (8 in control arm, 1 in rifapentine arm). Among these, 6 (67%) had favorable outcomes and 3 (33%) had unfavorable outcomes, none of which was TB-related. Two unfavorable outcomes occurred within 2 weeks of study enrollment (1 death from hemoptysis, 1 withdrawal; the latter on the rifapentine arm) and 1 participant was lost to follow-up. The proportion of participants with unfavorable outcomes did not differ significantly by CD4+ count ($P = .115$), HIV VL ($P = .200$), or efavirenz concentration ($P = 0.391$) (Table 3). In a sensitivity analysis excluding the 9 PWH who did not initiate ART during the study period, primary efficacy outcomes were similar (Supplementary Table 2).

Time to Culture Conversion

Among microbiologically eligible PWH, culture conversion in liquid media occurred by 8 weeks (≤70 days) among 74.2% in the rifapentine-moxifloxacin, 68.9% in the rifapentine, and 69.3% in the control arms, respectively. Time to stable culture conversion was shorter for the 4-month regimens than control in liquid and solid media regardless of HIV status (both $P <$ .001 for the log-rank test, Figure 3). HRs are not presented because the proportional hazards assumption was not met for

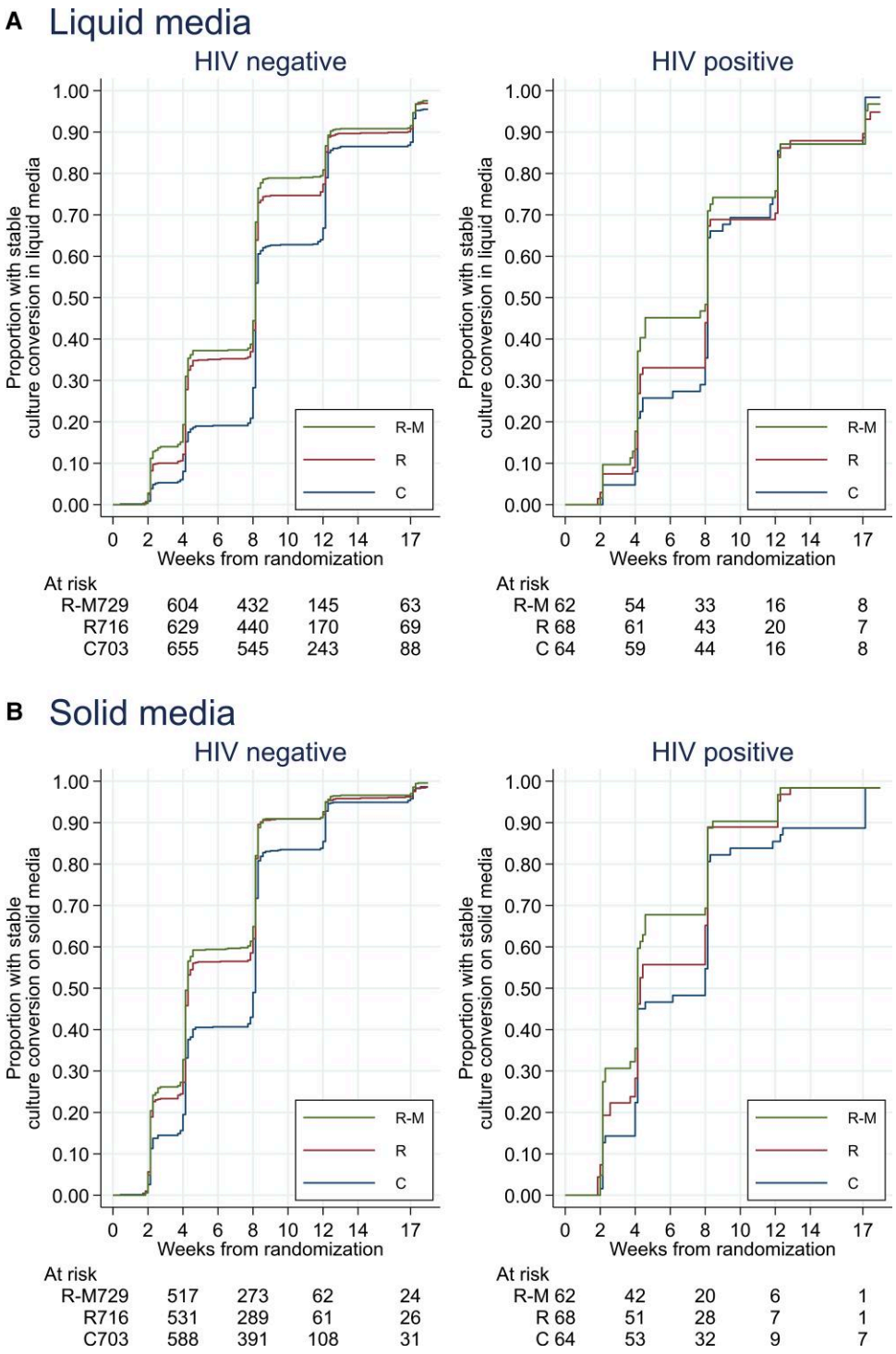

Figure 3. Time to stable culture conversion by treatment arm among microbiologically eligible participants, stratified by HIV status (*A*) in liquid media and (*B*) on solid media; shorter for the 4-month regimens than the control group in all figures ($P < .001$ for the log-rank test). Abbreviations: C, Control regimen; HIV, human immunodeficiency virus; R, rifapentine regimen; R-M, rifapentine-moxifloxacin regimen.

HIV-negative participants ($P < .001$ for both solid and liquid media). There was no evidence of lack of proportional hazards in PWH, likely because of small numbers and an underpowered test.

Safety

The proportions of PWH who had an on-treatment ≥ grade 3 AE (primary safety outcome) were 21% in the control, 14% in the rifapentine-moxifloxacin (difference vs control −7.5%

Table 4. Safety and Tolerability Outcomes During Treatment and Up to 14 Days Following Treatment Discontinuation Among PWH

Total Safety Population	Control N = 70	RPT-MOX N = 72	RPT N = 71	Overall N = 213
Primary safety outcome: Grade 3 or higher AE, N (%)	15 (21)	10 (14)	12 (17)	37 (17)
Difference in percentage (95% CI)	…	−7.5 (−20.0 to 5.0)	−4.5 (−17.5 to 8.4)	…
Secondary safety outcome: Treatment-related grade 3 or higher AE, N (%)	4 (6%)	6 (8%)	8 (11%)	18 (8%)
Difference in percentage (95% CI)	…	2.6 (−5.8 to 11.0)	5.6 (−3.6 to 14.7)	…
Other safety outcomes				
Any serious AE, N (%)	7 (10)	2 (3)	6 (8)	15 (7)
Death during treatment, N (%)	1 (1)	0 (0)	2 (3)	3 (1)
ALT or AST ≥5× ULN, N (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)
Serum total bilirubin ≥3 × ULN, N (%)[b]	0	1 (1.4)	2 (2.8)	3 (1.4)
Hy's law criteria [20] of ALT or AST ≥3× ULN plus serum total bilirubin ≥ 2-fold ULN, N (%)	0	2 (2.8)[c]	0	2 (0.9)
Tolerability (microbiologically eligible population)				
Total in microbiologically eligible population	64	62	68	194
Discontinuation of assigned treatment for any reason, N (%)	8 (12.5)	4 (6.5)	5 (7.4)	17 (8.8)
Difference in percentage (95% CI)	…	−6.0 (−16.2 to 4.1)	−5.1 (−15.4 to 5.1)	…

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST aspartate aminotransferase; CI, confidence interval; RPT, rifapentine; RPT-MOX, rifapentine-moxifloxacin; ULN, upper limit of normal.

[a]ALT or AST >5-fold upper limit of normal corresponds to grade 3 or higher.

[b]Total bilirubin >3-fold upper limit of normal corresponds to grade 3 or higher.

[c]One participant had chronic hepatitis B virus infection and was discontinued from the assigned tuberculosis treatment regimen (maximum bilirubin 8.8 ULN, maximum ALT 3.1 ULN), with a resolution of transaminitis and hyperbilirubinemia. Another participant (maximum bilirubin 2.2 ULN, maximum ALT 3.5 ULN) had no interruption in study treatment, with a resolution of transaminitis and hyperbilirubinemia.

[95% CI, −20.0 to 5.0]), and 17% in the rifapentine arms (difference vs control −4.5% [95% CI, −17.5 to 8.4]). There was no observed difference in the proportion of PWH who had a treatment-related ≥ grade 3 AE by treatment arm (secondary safety outcome). No PWH died during treatment or follow-up in the rifapentine-moxifloxacin arm (Table 4) [20]. Deaths in the rifapentine and control arms were due to pulmonary embolism (n = 2, 1 in the control arm, and 1 in the rifapentine arm) and hemoptysis (n = 1 in the control arm) [17].

AEs of Special Interest: Hematologic and Hepatic

Frequency of grade ≥3 AEs during treatment by MedDRA preferred term can be found in Supplementary Table 3 [18]. In the safety population (n = 213), the most frequent grade ≥3 AEs were neutropenia (n = 10), anemia (n = 4), hepatitis (n = 4), and pulmonary embolism (n = 3). Neutropenia AEs were observed more frequent among the rifapentine regimens (5.6%) compared with the control regimen (2.9%) but did not differ by arm ($P = .503$). One PWH randomized to the rifapentine arm was discontinued from study treatment permanently from neutropenia. Anemia AEs were similar among the rifapentine regimens (2.1%) compared with the control regimen (1.4%).

Overall, there were no ≥ grade 3 alanine aminotransferase or aspartate aminotransferase (≥5 × upper limit of normal [ULN]) elevations among PWH. Grade 3 or higher total bilirubin levels (≥3× ULN) were more frequent among PWH treated with rifapentine (n = 3) compared with control (n = 0). Among those 3 PWH, 2 were continued on assigned treatment with resolution of hyperbilirubinemia (maximum bilirubin concentrations ≥3× ULN in both cases); the third patient had chronic hepatitis B virus infection and was discontinued from the rifapentine-moxifloxacin arm (maximum bilirubin concentration ≥8.8× ULN; maximum alanine aminotransferase concentration ≥3 × ULN, but not ≥5× ULN), with resolution of transaminitis and hyperbilirubinemia (Table 4) [15, 20].

Tolerability

A total of 8 (12.5%), 4 (6.5%), and 5 (7.4%) PWH discontinued study treatment for any reason other than microbiology eligibility in the control, rifapentine-moxifloxacin, and rifapentine arms, respectively (Table 4).

DISCUSSION

In this prespecified subgroup of PWH enrolled in Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349, the efficacy of the 4-month rifapentine-moxifloxacin regimen was noninferior to the 6-month control. Efficacy of the 4-month rifapentine regimen without moxifloxacin did not meet noninferiority criteria among PWH. These results are similar to the results of the analysis including all participants, demonstrating that the addition of moxifloxacin is requisite to the success of the 4-month regimen for PWH [7].

In the overall study, the proportion of unfavorable outcomes was lowest in the control arm (9.6%) followed by the rifapentine-moxifloxacin (11.6%) and rifapentine (14.2%) arms. In contrast, among PWH, the proportion of unfavorable outcomes was lowest in the rifapentine-moxifloxacin arm (14.5%) followed by the control (21.9%) and rifapentine (29.4%) arms. We hypothesize that the standard dose of rifampin in the control arm may lead to a suboptimal rifamycin exposure compared with the rifapentine dose in the investigational arms among PWH. Pharmacokinetic and pharmacogenomic analyses are ongoing and will be important to explore this hypothesis.

WHO guidelines recommend ART initiation within 8 weeks of TB treatment for people with HIV-associated TB [18]. However, this trial was not designed to evaluate the impact of ART initiation timing on TB treatment outcomes. Even in this setting of a well-conducted clinical trial, 10% of PWH were not started on ART within 8 weeks. And although randomization was stratified by HIV status, most PWH not started on ART during the study period were allocated to the control arm (8 of 9). Three of the 9 had unfavorable outcomes, but none had a TB-related unfavorable outcome (1 death during treatment, 1 withdrawal, 1 loss to follow-up).

The safety and AE profiles were similar among PWH compared with the overall study population. Mortality during anti-TB treatment among PWH was low (1.5%), with no deaths observed in the rifapentine-moxifloxacin arm. Mortality was similarly low (0.6%) in the overall study population. There were no cases of acquired TB drug resistance in PWH.

Our prespecified subgroup analysis of PWH in this trial has several limitations. First, few PWH were enrolled (8%) and there were few unfavorable outcomes, making it difficult to identify predictors of unfavorable outcomes in PWH. Although sites were in high TB and HIV prevalence areas, accrual of PWH was slow because of the initial requirement that participants be on stable efavirenz-based ART, which is known to decrease TB risk [19]. Second, the median baseline CD4+ was high (343 cells/μL) and PWH with CD4+ counts of <100 cells/μL were excluded, which limits generalizability to PWH with advanced immunosuppression. Third, we used the 6.6% noninferiority margin identified for the overall trial for this PWH subgroup analysis. A different maximum observable difference in unfavorable outcomes may be appropriate for individuals with HIV-associated TB given that unfavorable outcomes are expected to be more frequent for PWH.

Importantly, only PWH on efavirenz-based ART were eligible based on guidelines at the time of study development because of potential drug–drug interactions with rifamycins. However, use of regimens based on integrase inhibitors, particularly those including dolutegravir, is rising globally. The DOLPHIN study showed that once-weekly rifapentine (900 mg) can be used with once-daily dolutegravir [20]. Similarly, A5372 showed that daily rifapentine (600 mg) can be used with twice-daily dolutegravir [21], and data with once-daily dolutegravir are forthcoming. A5406 plans to study the use of daily rifapentine (1200 mg) with twice-daily dolutegravir (protocol under development) [22]. Results from these ongoing studies will be critical for making recommendations on the use of the daily rifapentine-moxifloxacin regimen for PWH on dolutegravir-based ART.

CONCLUSIONS

Results from this large, international TB treatment trial demonstrate that among people with HIV-associated DS-PTB with CD4+ counts ≥100 cells/μL and on efavirenz-based ART, a 4-month daily rifapentine-moxifloxacin regimen had noninferior efficacy compared with the standard 6-month control regimen. Moreover, the rifapentine-moxifloxacin regimen was safe and well-tolerated. Further studies are needed to ensure this important new 4-month regimen can be used among PWH with advanced immunosuppression or taking dolutegravir-based ART.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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