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Authors

Podany, Anthony T
Pham, Michelle
Sizemore, Erin
et al.

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Efavirenz Pharmacokinetics and Human Immunodeficiency Virus Type 1 (HIV-1) Viral Suppression Among Patients Receiving Tuberculosis Treatment Containing Daily High-Dose Rifapentine

Anthony T. Podany,[1,*] Michelle Pham,[1] Erin Sizemore,[2] Neil Martinson,[3] Wadzanai Samaneka,[4] Lerato Mohapi,[3] Sharlaa Badal-Faesen,[5] Rod Dawson,[6] John L. Johnson,[7] Harriet Mayanja,[8] Umesh Lalloo,[9] William C. Whitworth,[2] April Pettit,[10] Kayla Campbell,[1,11] Patrick P. J. Phillips,[12] Kia Bryant,[2] Nigel Scott,[2] Andrew Vernon,[2] Ekaterina V. Kurbatova,[2] Richard E. Chaisson,[13] Susan E. Dorman,[14] Payam Nahid,[12] Susan Swindells,[1] Kelly E. Dooley,[13] Courtney V. Fletcher[1]; and the AIDS Clinical Trials Group and Tuberculosis Trials Consortium

[1]University of Nebraska Medical Center, Omaha, Nebraska, USA; [2]Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [3]Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Johannesburg, South Africa; [4]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe; [5]University of Witwatersrand Helen Joseph CRS, Johannesburg, South Africa; [6]University of Cape Town Lung Institute, Cape Town, South Africa; [7]Case Western Reserve University, Cleveland, Ohio, USA; [8]Uganda- Case Western Reserve University Research Collaboration, Kampala, Uganda; [9]Durban International Clinical Research Site, Durban, South Africa; [10]Vanderbilt University, Nashville, Tennessee, USA; [11]University of Colorado, Denver, Colorado, USA; [12]University of California, San Francisco Center for Tuberculosis, San Francisco, California, USA; [13]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and [14]Medical University of South Carolina, Columbia, South Carolina, USA

Background. A 4-month regimen containing rifapentine and moxifloxacin has noninferior efficacy compared to the standard 6-month regimen for drug-sensitive tuberculosis. We evaluated the effect of regimens containing daily, high-dose rifapentine on efavirenz pharmacokinetics and viral suppression in patients with human immunodeficiency virus (HIV)-associated tuberculosis (TB).

Methods. In the context of a Phase 3 randomized controlled trial, HIV-positive individuals already virally suppressed on efavirenz--containing antiretroviral therapy (ART) (EFV1), or newly initiating efavirenz (EFV2) received TB treatment containing rifapentine (1200 mg), isoniazid, pyrazinamide, and either ethambutol or moxifloxacin. Mid-interval efavirenz concentrations were measured (a) during ART and TB cotreatment (Weeks 4, 8, 12, and 17, different by EFV group) and (b) when ART was taken alone (pre- or post-TB treatment, Weeks 0 and 22). Apparent oral clearance (CL/F) was estimated and compared. Target mid-interval efavirenz concentrations were > 1 mg/L. Co-treatment was considered acceptable if > 80% of participants had mid-interval efavirenz concentrations meeting this target.

Results. EFV1 and EFV2 included 70 and 41 evaluable participants, respectively. The geometric mean ratio comparing efavirenz CL/F with vs without TB drugs was 0.79 (90% confidence interval [CI] .72–.85) in EFV1 and 0.84 [90% CI .69–.97] in EFV2. The percent of participants with mid-interval efavirenz concentrations > 1mg/L in EFV1 at Weeks 0, 4, 8, and 17 was 96%, 96%, 88%, and 89%, respectively. In EFV2, at approximately 4 and 8 weeks post efavirenz initiation, the value was 98%.

Conclusions. TB treatment containing high-dose daily rifapentine modestly decreased (rather than increased) efavirenz clearance and therapeutic targets were met supporting the use of efavirenz with these regimens, without dose adjustment.

Clinical Trials Registration. NCT 02410772.

Keywords. HIV/AIDS; tuberculosis; rifapentine; efavirenz; pharmacokinetics.

Approximately 800 000 individuals living with human immunodeficiency virus (HIV) develop tuberculosis (TB) yearly, and more than 200 000 die of HIV-associated TB [1]. Treatment of HIV-associated TB is complicated by interactions between antiretroviral drugs and rifamycins, the backbone of TB therapy. Multiple studies have shown reductions in morbidity and mortality among people living with HIV (PLWH) when antiretroviral therapy (ART) is initiated early in the course of TB treatment [2, 3]. For individuals newly diagnosed with HIV and TB, current guidelines recommend initiating HIV treatment within the first 2 weeks of TB treatment for those with CD4 counts of < 50 cells/mm^3 and within 8 weeks for those with CD4 counts ≥ 50 cells/mm^3 [4–6].

Current treatment guidelines for drug-susceptible TB (DS-TB) recommend 6 months of daily rifampin-based treatment [4, 5]. Substitutions of more potent drugs for TB have been shown to speed the killing of *Mycobacterium tuberculosis* in sputum cultures, but until recently novel regimens failed to reduce treatment durations in Phase 3 trials [7–9]. Tuberculosis Trials

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*Correspondence: A. T. Podany, Omaha, NE (apodany@unmc.edu).

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Consortium (TBTC) Study 31/ AIDS Clinical Trials Group (ACTG) Study A5349 (S31/ A5349) was a phase 3 noninferiority trial comparing 2 of the 4-month regimens using higher daily doses of rifapentine, with or without moxifloxacin, to the current standard 6-month rifampin-based regimen for DS-TB [10, 11]. The primary efficacy analysis of S31/A5349 showed noninferiority of the 4-month rifapentine and moxifloxacin arm, the first major shortening of a DS-TB regimen in over 40 years [11].

Rifamycin antibiotics have potent induction effects on drug metabolizing enzymes and transporters [12, 13]. Our knowledge of the interaction potential of rifapentine with commonly-used antiretrovirals is limited. We nested a pharmacokinetic (PK) and safety study into S31/A5349 to investigate effects of the highest dose (1200 mg) and longest duration (17 weeks) of rifapentine ever used on efavirenz PK. The goal was to ensure a safe and effective ART option for PLWH was available with the 4-month rifapentine based TB treatment regimen. The results of this efavirenz PK substudy are reported here.

METHODS

Study Population

S31/A5349 was an international, multicenter, open-label, randomized controlled trial comparing 2 of the 4-month regimens with the standard 6-month regimen for drug-susceptible pulmonary TB in both HIV-negative and positive individuals [10, 11]. Each of the 4-month investigational regimens substituted rifapentine, at a dose of 1200 mg, for rifampin. All TB regimens were administered daily. Details regarding study population and conduct have been published elsewhere [11]. For PLWH, a CD4 T-cell count of ≥ 100 cells/mm^3 within 30 days of study entry was required. Participants were randomly assigned 1:1:1 to treatment arm, and randomization was stratified by site, lung cavitation, and HIV status.

The Institutional Review Boards or Ethics Committees of the US Centers for Disease Control (CDC) as well as the participating institutions approved the study. Each participant gave written informed consent.

Substudy Design

A secondary objective of S31/A5349 was to evaluate the PK of efavirenz-based ART among participants with TB/HIV randomized to one of the rifapentine-containing arms. Because the effects of high-dose daily rifapentine on efavirenz concentrations were not known and subtherapeutic concentrations could adversely impact HIV treatment outcomes, a conservative approach was taken. Initially, only PLWH already receiving an efavirenz regimen who had a viral load < 200 copies/mL were enrolled into "EFV1." If prespecified safety metrics were met, then "EFV2", which included treatment-naïve PLWH, could open (see below). The overall target sample size was 90 participants per group.

Study Procedures

All participants in the rifapentine arms received daily 1200mg rifapentine, isoniazid 300 mg, weight-based pyrazinamide (<55 kg 1000 mg, 55–75 kg 1500 mg, >75 kg 2000 mg) and either weight-based ethambutol (<55 kg 800 mg, 55-75 kg 1200 mg, >75 kg 1600 mg) or moxifloxacin 400 mg. All participants in the efavirenz PK study received 600 mg efavirenz daily, plus 2 nucleoside reverse transcriptase inhibitors (NRTI).

Plasma samples for mid-interval efavirenz concentration determination were collected at entry (week 0), and weeks 4, 8, and 17 during TB treatment in EFV1. Week 0 values were with efavirenz alone, whereas week 4, 8, and 17 values were efavirenz taken together with TB treatment. Participants in EFV2 had plasma samples collected approximately 4 and 8 weeks after efavirenz initiation, and again at study week 22 after TB treatment completion. Efavirenz initiation in EFV2 participants could occur up until study week 8. Efavirenz sampling points were aligned to the closest study week visit which may occur at weeks 4, 8, 12, or 17. For example, a participant starting efavirenz at study week 4 would have a 4 and 8 week post efavirenz initiation plasma sample collected at study week 8 and 12. A detailed schedule of events for the study has been previously published [10]. Plasma samples were collected at an efavirenz mid-dosing interval timepoint, corresponding to 12–20 hours post efavirenz administration. Efavirenz concentrations in plasma were quantified with a validated, quality-controlled LC/MS assay as previously described [14].

Plasma for HIV viral load determination was collected at study screening in all participants with HIV. HIV viral load was also measured at weeks 8, 17, and 22 in EFV1. For EFV2 participants, HIV viral load testing was performed at 8 weeks following initiation of efavirenz and at study week 22. If a follow-up viral load result was > 200 copies/mL then 2 to 4 weeks after that test, a repeat HIV viral load test was performed.

Cohort Management and Stopping Rules

Pharmacokinetic data were evaluated after 9, 21, 31, and 90 individuals had enrolled into each group (EFV1 or EFV2). Participants were not allowed to enroll into EFV2 until after PK data from 31 EFV1 participants were deemed acceptable. Efavirenz PK were judged to acceptable if ≤ 20% of participants had mid-interval efavirenz concentrations < 1 mg/L at both time points during TB treatment.

Outcomes

The primary outcome of the efavirenz PK studies was the proportion of participants receiving efavirenz with mid-interval efavirenz plasma concentrations ≥ 1 mg/L, a commonly

accepted threshold for virologic efficacy, at 2 time points during TB treatment [15].

Analyses

Continuous variables including patient-specific demographics (age, weight, treatment duration) and efavirenz PK data were summarized with descriptive statistics. Categorical data were summarized with frequency distributions. Participants with missing data were not included in specific variable summaries where data were incomplete. Median and interquartile range were used to describe efavirenz sampling times and efavirenz plasma concentrations by week. Any participant who had a mid-interval efavirenz concentration < 1 mg/L either pre (EFV1) or post (EFV2) TB treatment (ie, when not on TB treatment) was deemed nonevaluable and excluded from PK analysis, assuming adherence challenges in these individuals. Additionally, participants with missing samples, or samples collected outside of the timepoints specified in the protocol were deemed nonevaluable for PK analysis. Efavirenz concentrations that were below the limit of quantitation (BLQ) were handled as follows: any EFV1 participant with baseline BLQ sample was nonevaluable, any EFV2 participant with a week 22 concentration reported as BLQ was nonevaluable, and any participant EFV1 or EFV2 with 2 or more BLQ values during TB treatment was considered nonevaluable. Viral load data were summarized as percent of participants with detectable HIV RNA, and median (interquartile range [IQR]) where measurable. The limits of detection of HIV RNA assays varied by clinical site/ country.

The final PK analysis was planned after 90 individuals had enrolled into each of the efavirenz groups, or when full parent study enrollment had been reached should that occur prior to fully enrolling each of the efavirenz groups. In the final efavirenz PK evaluation, the proportion of individuals in each group (EFV1 and EFV2) who maintained mid-interval efavirenz plasma concentrations above 1 mg/L at both time points during TB treatment was determined. A 95% confidence interval (CI) around these proportions was then calculated. The final evaluation deemed efavirenz PK data acceptable if the lower bound of the 95% CI did not fall below 80%. This evaluation occurred for EFV1 and EFV2 independently.

Pharmacokinetic parameter estimation was implemented in ADAPT software (Biomedical Simulations Resource at the University of Southern California). Bayesian maximum a posteriori probability estimates were used to estimate efavirenz apparent oral clearance (CL/F) during and pre/post TB treatment. Efavirenz concentrations obtained during TB treatment were combined to model the during-TB-treatment efavirenz CL/F. The pre-TB treatment efavirenz concentration was used to model the "off" TB treatment efavirenz CL/F in EFV1, while the week 22 efavirenz concentration was used to model a similar value in EFV2. A population estimate of efavirenz CL/F of 8.0 ± 4 L/hour (mean, standard deviation) was used in the model [16].

The geometric mean ratio (GMR) of the efavirenz CL/F when efavirenz was given together with TB treatment was compared with that when efavirenz was given alone for both EFV1 and EFV2. The 90% CI around the GMR was obtained using a nonparametric bootstrap. Statistical analysis was conducted in R software, version 4.0.2 (R Core Team, 2020) [17] using stats, boot [18, 19], tidyverse [20], and ggbeeswarm [21] packages.

RESULTS

A total of 214 PLWH were enrolled into S31/A5349, of whom 133 were enrolled in the efavirenz PK substudy (80 and 53 in EFV1 and EFV2, respectively) from January 2016 to October 2018. The target sample size of 180 participants was not met owing to low numbers of individuals on ART with undetectable viral load being diagnosed with TB at study sites and, therefore, late opening of EFV2. One hundred and eleven of the 133 participants (EFV1 n = 70, EFV2 n = 41) had complete PK sampling and met the criteria for evaluable participants. Two EFV1 participants were missing baseline PK samples, whereas another 8 were deemed nonevaluable due to BLQ or insufficient/ incorrect sampling. Seven EFV1 participants were missing a post-treatment PK sample, whereas another 5 were deemed nonevaluable due to BLQ or insufficient/incorrect sampling. Evaluable participants' demographics are in Table 1.

EFV1

In EFV1, 265 PK samples (70, 67, 66, and 62 samples for weeks 0, 4, 8, and 17, respectively) were available (Figure 1). Median (IQR) mid-interval efavirenz concentrations were 2.41 (IQR, 1.64 – 3.64) mg/L at week 0, 2.99 (IQR, 1.95 – 5.14) mg/L at week 4, 2.71 (IQR, 1.67 – 4.57) mg/L at week 8, and 2.45 (IQR. 1.75 – 4.45) mg/L at week 17. At week 0, 67/70 (95.7%) participants had mid-interval efavirenz concentrations ≥ 1 mg/L, and 64/67 (95.5%) participants at week 4. At weeks 8 and 17, these proportions were 58/66 (87.9%) and 55/62 (88.7%), respectively. EFV1 efavirenz concentrations by week are summarized in Table 2. Median efavirenz CL/F values were: 9.82 L/hour (IQR, 6.82 –13.03 L/hr) and 7.73 L/hour (IQR, 5.10 –11.49 L/hr) at baseline and during TB treatment, respectively (GMR, 0.79 [90% CI .72–.85]). Sixty-two of 67 (92.5% [95% CI lower bound: 83.7%]) EFV1 participants maintained plasma efavirenz concentrations ≥ 1 mg/L during TB treatment.

All EFV1 participants had an HIV viral load < 200 copies/mL at screening. HIV RNA was detectable in 15 of 70 (21%) with a median (IQR) HIV RNA of 54 (20 123) copies/mL. A week 17 or 22 viral load was available for 60/70 (86%) EFV1 participants; 59 of 60 (98%) week 17 or 22 viral loads were < 50 copies/mL. One EFV1 participant had a week 17 HIV RNA of 364 copies/mL; this participant had mid-interval efavirenz concentrations > 1 mg/L at all PK study visits (weeks 0, 4, 8, and 17).

Table 1. Baseline Demographic and Clinical Characteristics

Participant Characteristics	EFV1 N = 70	EFV2 N = 41	Total N = 111
Male sex, no. (%)	39 (55.7)	27 (65.9)	66 (59.5)
Age, median (IQR)	41 (36–48)	37 (30—43)	39 (35–47)
Age group, no. (%)			
18-35 y	12 (17.1)	16 (39.0)	28 (25.2)
>35 y	58 (82.9)	25 (61.0)	83 (74.8)
Race, no. (%)			
Black	66 (94.3)	37 (90.2)	103 (92.8)
Multiple	3 (4.3)	4 (9.8)	7 (6.3)
White	1 (1.4)	0 (0.0)	1 (0.9)
CD4 + count (cells/mL^3), baseline, median (IQR)	355 (227–446)	331 (210–410)	343 (219–440)
HIV viral load (copies/mL), baseline, median (IQR)[a] [in persons with detectable HIV]	54 (20–123)	221 548 (714–1 200 684)	157 655 (20–1 200 684)
ART status, no. (%)	70 (100.0) 0 (0.0)	0 (0.0) 41 (100.0)	70 (63.1) 41 (36.9)
On ART before or at enrollment			
Started ART after enrollment			
Cavitation (CXR), baseline, no. (%)			
Absent	18 (25.7)	15 (36.6)	33 (29.7)
< 4 cm	24 (34.3)	13 (31.7)	37 (33.3)
≥ 4 cm	28 (40.0)	13 (31.7)	41 (36.9)
Weight (kg), baseline, median (IQR)	56 (51-65)	55 (49-62)	55 (51-63)
Body mass index, baseline, median (IQR)	19.7 (18.0—23.1)	20.4 (17.4–22.8)	19.9 (17.5–22.9)
Current smoker, baseline, no. (%)	21 (30.0)	13 (31.7)	34 (30.6)
Prior tuberculosis treatment, no. (%)	21 (30.0)	9 (22.0)	30 (27.0)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]In total, 52/111 (46.8%) participants had detectable levels of HIV RNA within 30 d of study entry (15 EFV1, 37 EFV2).

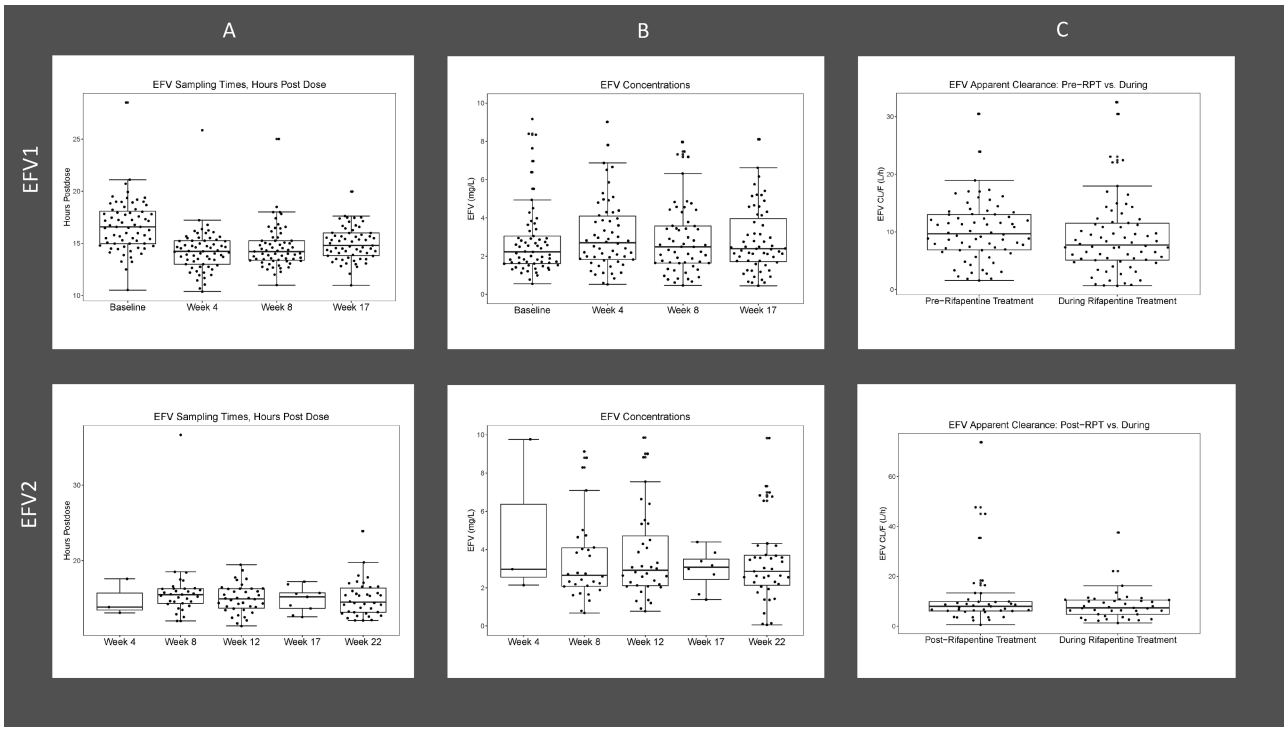

Figure 1. Efavirenz (EFV) sampling times (hours post dose) by week (*A*), EFV concentrations by week (*B*), EFV apparent oral clearance (CL/F) pre/post rifapentine (RPT) and isoniazid (H) and during RPT/H treatment (*C*), shown for EFV1 (*top row*) and EFV2 (*bottom row*).

Table 2. Mid-Dosing Interval Efavirenz Concentrations by Study Week for EFV1 and EFV 2

EFV1						
	Week 0	Week 4	Week 8	Week 12	Week 17	Week 22
Efavirenz concentration, median (IQR) mg/L	2.41 (1.64–3.64)	2.99 (1.95–5.14)	2.71 (1.67–4.57)		2.45 (1.75–4.45)	
No. (%) participants with EFV concentrations > 1 mg/L	67/70 (96%)	64/67 (96%)	58/66 (88%)		55/62 (89%)	
EFV2						
	Week 0	Week 4	Week 8	Week 12	Week 17	Week 22
Efavirenz concentration, median (IQR) mg/L		2.98 (2.56–6.37)	2.74 (2.10–4.74)	3.04 (2.14–5.35)	3.17 (2.70–3.84)	2.99 (2.20–4.21)
No. (%) participants with EFV concentrations > 1 mg/L		3/3 (100%)	31/33 (94%)	36/38 (95%)	9/9 (100%)	37/41 (90%)

Abbreviations: EFV, efavirenz; IQR, interquartile range.

At study month 15 this participant had an undetectable viral load.

EFV2

There were 124 PK samples available for EFV2 (3, 33, 38, 9, and 41 samples for weeks 4, 8, 12, 17, and 22, respectively) (Figure 1). Median (IQR) mid-interval efavirenz concentrations were 2.98 (IQR, 2.56 – 6.37) mg/L at week 4, 2.74 (2.10 – 4.74) mg/L at week 8, 3.04 (IQR, 2.14 – 5.35) mg/L at week 12, 3.17 (IQR, 2.70 – 3.84) mg/L at week 17 and 2.99 (IQR, 2.20 – 4.21) mg/L at week 22.

At weeks 4, 8, 12, 17, and 22, 100%, 94%, 95% 100% and 90% of participants had efavirenz mid-interval concentrations ≥ 1 mg/L. EFV2 efavirenz concentrations are summarized in Table 2. Median efavirenz CL/F values were: 7.35 L/hour (IQR, 4.75 –10.5 L/hour) and 7.94 L/hr (IQR, 6.09–9.86 L/hour) during HIV-TB cotreatment and during HIV treatment alone, respectively (GMR, 0.84 [90% CI .69–.97]). Thirty-six of 37 participants (97.2% [95% lower bound: 86.2%]) EFV2 participants maintained mid-interval efavirenz concentrations ≥ 1 mg/L during TB treatment.

HIV RNA was detectable in 37 of 41 (90%) EFV2 participants at screening with a median (IQR) HIV RNA of 221 548 (IQR, 714–1 200 684) copies/mL. Three of the 41 had undetectable HIV RNA at enrollment, while one was missing an enrollment HIV RNA. A week 17 or 22 viral load was available for 38/41 (93%) of EFV2 participants. All values were < 200 copies/mL; 36 of 38 (95%) available week 17 or 22 viral loads were undetectable. Two EFV2 participants had a week 22 HIV RNA of 79 and 85 copies/mL, respectively. One participant had 3/3 mid-interval efavirenz concentrations ≥ 1mg/mL while on study, whereas the other had 3/3 below 1 mg/L while on study. One of these 2 participants had a follow-up viral load at month 15, reported as "undetectable," the other participant had no further HIV RNA available in the study database.

DISCUSSION

High-dose rifapentine-containing TB therapy decreased efavirenz clearance modestly among patients with HIV-associated TB receiving efavirenz-based ART. We found that > 80% of participants maintained mid-interval efavirenz plasma concentrations above the commonly cited threshold for virologic efficacy, 1 mg/L [15], and HIV virologic response was excellent.

The rifamycin antibiotics broadly induce drug metabolizing enzymes and transporters [13]. The end effect of this induction is often decreased plasma concentrations of companion drugs that are substrates for those drug metabolizing enzymes and transporters, when taken with rifamycins. Thus, we hypothesized that if high-dose rifapentine had any effect on efavirenz PK it would be to increase clearance and thereby reduce plasma concentrations. Previous clinical studies of efavirenz 600mg in combination with rifampin-based TB treatment have shown mixed results. Lopez-Cortes et al found roughly a 25% reduction in efavirenz exposures whether measured by area under the concentration-time curve (AUC), or peak and trough concentrations, although Luetkemeyer et al found a paradoxical increase in efavirenz trough concentrations when given with rifampin [22, 23]. Similarly, studies of efavirenz 400mg daily in combination with rifampin, ~10 mg/kg, showed a minimal effect (<25%) on efavirenz exposures as measured by $AUC_{0\text{-}24}$, C_{max} and C_{24h} [24]. Current FDA labeling allows clinicians to increase efavirenz doses to 800 mg to compensate for a reduction in EFV concentrations as a result of an increase in EFV CL/F when given with rifampin in individuals weighing more than 60kg; however, current treatment guidelines state dose adjustment of efavirenz with rifampin is not needed [6, 25].

Both daily and weekly rifapentine use in TB prevention has been studied in combination with efavirenz. When rifapentine was given at a dose of 900 mg once weekly for 3 weeks, efavirenz $AUC_{0\text{-}24}$ was decreased 14% versus when given without rifapentine [26]. Similarly, in a study of daily rifapentine at a dose of ~10 mg/kg (max 60 0mg) for 4 weeks as part of a TB prevention regimen (1HP), mid-dosing interval efavirenz concentrations were decreased only 2% after 4 weeks of daily rifapentine [27]. Until now, there have been no studies of efavirenz PK when used with rifapentine

at the higher treatment dose of 1200 mg (~20 mg/kg) daily for any duration of time. Interestingly, in our present study of efavirenz concentrations during rifapentine treatment, efavirenz concentrations did not decrease with time during TB treatment.

One possible explanation for this unexpected lack of decrease in efavirenz concentrations could be drug metabolizing enzyme inhibition by isoniazid, which all participants received in both the induction and continuation phase of TB therapy. Isoniazid has been previously shown in vitro to inhibit CYP2B6, which is one of the main enzymes responsible for efavirenz metabolism. In both the present study, as well as the 1HP study with efavirenz, the dose of isoniazid used was 300 mg daily. Differences in efavirenz PK between the 2 studies may possibly be explained by differences in the genetic makeup of participants between the two studies. Previous studies have found an association between individuals with slow n-acetyltransferase 2 (NAT2) alleles, one of the enzymes responsible for isoniazid metabolism, and increased efavirenz concentrations in individuals receiving isoniazid and rifapentine [28]. NAT2 genotype was not considered for the present analyses, and the present PK outcomes for efavirenz may not be applicable to individuals who receive rifapentine without the combination of isoniazid.

Our study has some limitations. First, we recognize there has been a global shift toward integrase strand transfer inhibitors (INSTI)-based ART regimens. We did not study INSTI in our trial, as even the effects of standard-dose rifampin on INSTI's were not known at the time of S31/A5349 study initiation. A currently enrolling trial (ACTG A5372, NCT04272242) is evaluating once-daily rifapentine (600 mg) given for 1 month with dolutegravir-based ART. Following that, dolutegravir-based ART will be tested with the S31/A5349 regimen in ACTG study 5406. In countries where TB remains most prevalent, efavirenz is available as a second-line drug and widely used. Additionally, the generalizability of our findings may be limited in part by the inclusion criteria of the parent study, which allowed participation of individuals with a CD4 + cell count of ≥ 100 cells/mm^3 within 30 days of study entry. Whether or not these PK and viral suppression findings can be extended to individuals with CD4 counts < 100 remains to be studied. Finally, our study had a high percentage of participants with either BLQ or incomplete PK data. Reassuringly, a sensitivity analysis including all available PK data from participants with measurable efavirenz concentrations found no major differences in the primary outcomes we report from the PK evaluable group (supplemental material).

A 4-month regimen of high-dose rifapentine, moxifloxacin, isoniazid, and pyrazinamide has now been shown to be safe and effective for the treatment of pulmonary TB. The PK, safety, and virologic data described herein provide important support for co-treatment of HIV and TB with efavirenz-based ART. To date, there have been no other antiretrovirals tested in combination with rifapentine-containing regimens for pulmonary TB treatment. These PK data extend the possibility of a 4-month TB treatment to individuals with HIV on 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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Ethical approval. The trial was approved by the US CDC Institutional Review Board (IRB). Each participating institution provided for the review and approval of this protocol and its informed consent documents by a local IRB or ethics committee or relied formally on the US CDC IRB approval.

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Author contributions. A. T. P., M. P., E. S., W. C. W., A. P., K. C., K. B., N. S., A. V., J. L. J., E. V. K., R. E. C., S. D., P. N., S. S., K. E. D., and C. V. F. were involved in study design, data collection, data analysis, data interpretation.

A. T. P., R. E. C., E. V. K., S. S., and K. E. D. wrote the manuscript. N. M., W. S, L. M., S. B. F., R .D., H. M., and U. L. were site investigators and were involved in data collection and data analysis. P. P. was a study statistician and was involved in data analysis, data interpretation.

Conduct of the study was entirely the responsibility of the investigators, with regulatory oversight by the CDC and NIAID. Data collection, management, and interpretation were entirely the responsibility of the investigators. All authors had full access to all data. The corresponding author had the final responsibility to submit for publication

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC), the National Institute of Allergy and Infectious Diseases, or the US Department of Health and Human Services.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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