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Pharmacogenetic interactions of rifapentine plus isoniazid with efavirenz or nevirapine

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Objectives **The effect of rifapentine plus isoniazid on efavirenz pharmacokinetics was characterized in AIDS Clinical Trials Group protocol A5279 (NCT01404312). The present analyses characterize pharmacogenetic interactions between these drugs, and with nevirapine.**

Methods **A subset of HIV-positive individuals receiving efavirenz- or nevirapine-containing antiretroviral therapy in A5279 underwent pharmacokinetic evaluations at baseline, and again weeks 2 and 4 after initiating daily rifapentine plus isoniazid. Associations with polymorphisms relevant to efavirenz, nevirapine, isoniazid, and rifapentine pharmacokinetics were assessed.**

Results **Of 128 participants, 101 were evaluable for associations with rifapentine and its active 25-desacetyl metabolite, 87 with efavirenz, and 38 with nevirapine. In multivariable analyses, *NAT2* slow acetylators had greater week 4 plasma concentrations of rifapentine ($P = 2.6 \times 10^{-3}$) and 25-desacetyl rifapentine ($P = 7.0 \times 10^{-5}$) among all participants, and in efavirenz and nevirapine subgroups. *NAT2* slow acetylators also had greater plasma efavirenz and nevirapine concentration increases from baseline to week 4, and greater decreases from baseline in clearance. *CYP2B6* poor metabolizers had greater efavirenz concentrations at all weeks and greater nevirapine concentrations at baseline. None of 47 additional polymorphisms in 11 genes were significantly associated with pharmacokinetics.**

Conclusions **Among HIV-positive individuals receiving efavirenz or nevirapine, and who then initiated rifapentine plus isoniazid in A5279, *NAT2* slow acetylators had greater rifapentine and 25-desacetyl rifapentine concentrations, and greater increases from baseline in plasma efavirenz and nevirapine concentrations. These associations are likely mediated by greater isoniazid exposure in *NAT2* slow acetylators. *Pharmacogenetics and Genomics* 31: 17–27** **Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Tuberculosis and HIV are major causes of death worldwide [1]. Isoniazid is a cornerstone of latent tuberculosis infection (LTBI) treatment, but because of difficulties with adherence [2], shorter regimens for LTBI have been studied. A 3-month regimen of once-weekly rifapentine plus isoniazid was as effective as 9 months of daily isoniazid in HIV-negative individuals [3,4]. A subsequent randomized trial in HIV-positive persons showed that 3 months of weekly rifapentine and isoniazid was as effective and better tolerated than 9 months of daily isoniazid [5].

Protocol A5279 (NCT01404312) of the AIDS Clinical Trials Group was a randomized, open-label trial comparing 1 month of daily rifapentine (300, 450, or 600 mg depending on weight) plus isoniazid (300 mg) with 9 months of daily isoniazid (300 mg alone) in HIV-positive patients [6]. Of 3000 enrolled, half were receiving antiretroviral therapy, which included efavirenz or nevirapine.

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The 1-month regimen was noninferior to the 9-month regimen for preventing tuberculosis and had a higher completion percentage [6].

Efavirenz and nevirapine are P450 (CYP) substrates [7,8], and rifapentine induces cytochrome CYP isoforms [9], raising concern that rifapentine might lower efavirenz and nevirapine exposure. An analysis involving a subset of 87 A5279 participants showed that rifapentine plus isoniazid did not meaningfully reduce efavirenz mid-dosing concentrations [10], but increased nevirapine clearance by 30% [11].

Genetic polymorphisms predict increased plasma exposure and toxicity with isoniazid, efavirenz, and nevirapine. Isoniazid is acetylated by *N*-acetyltransferase 2 [12], and *NAT2* loss-of-function alleles are frequent [12–15]. One or two copies of such alleles confer intermediate or slow acetylator phenotypes, respectively, and progressively greater isoniazid exposure [12–15]. Slow acetylator alleles increase risk for isoniazid hepatotoxicity [16–18] and possibly neuropathy [19,20].

Plasma efavirenz exposure is predicted by *CYP2B6* polymorphisms [21], especially *CYP2B6* 516G →T (rs3745274) [22–24], 983T→C (rs28399499) [24–26], and 15582C→T (rs4803419) [24]. Studies have associated *CYP2B6* poor metabolizer genotypes with efavirenz adverse events [21] including central nervous system symptoms [22,27,28] and suicidality [29]. Plasma nevirapine clearance also occurs through CYP2B6, less so through CYP3A and other isoforms, and increased nevirapine exposure is also associated with these *CYP2B6* loss-of-function polymorphisms [23,30–33]. Risk of rash with nevirapine is increased in *CYP2B6* poor metabolizers [34].

The rifamycin antibiotic, rifampicin, potently induces hepatic CYP isoforms, and in a study of 11 healthy, HIV-negative volunteers modestly and variability reduced efavirenz plasma exposure [35]. However, some patients receiving tuberculosis therapy that includes isoniazid with rifampicin, and who have *CYP2B6* or *NAT2* loss-of-function polymorphisms, experience increased efavirenz exposure [36–38]. This is likely mediated by isoniazid, as isoniazid without rifamycins also reduces efavirenz clearance among *CYP2B6* poor metabolizers [37]. The mechanism may involve isoniazid inhibition of CYP2A6, a minor pathway for efavirenz elimination [37–40]. Less is known about rifapentine, but in healthy volunteers, rifapentine decreased midazolam area under the concentration-time curve (AUC) by 92%, suggesting that rifapentine may induce CYP3A4 more than does rifampin [41].

There are fewer data regarding nevirapine interactions with antituberculous drugs. Among 164 newborns given nevirapine following delivery from HIV-positive mothers, concomitant rifampicin plus isoniazid was associated with 33% lower nevirapine trough concentrations [42]. Conversely, among 21 patients randomized to placebo or isoniazid while receiving antiretroviral therapy, isoniazid was associated with a 24% increase in median nevirapine AUC [43].

The present study characterized the pharmacogenetics of interactions between isoniazid plus rifapentine with efavirenz and nevirapine in a subgroup of A5279 participants, an *a priori* objective of A5279.

Methods

Study population

Study A5279 was a multicenter, randomized, open-label clinical trial comparing a 4-week daily rifapentine and isoniazid regimen with a standard 9-month daily isoniazid regimen to prevent tuberculosis in HIV-positive participants [6]. Pharmacokinetic evaluations were planned for the first 90 participants each on efavirenz-containing and nevirapine-containing antiretroviral therapy for at least 4 weeks before entry, and who were randomized to rifapentine plus isoniazid. Institutional review boards of the participating institutions approved the study, and participants gave written informed consent.

Procedures

Rifapentine dosing was weight-based (300, 450, or 600 mg). Isoniazid dosing was 300 mg daily with pyridoxine 25 mg. Isoniazid and rifapentine were taken together with food. Efavirenz dosing was 600 mg once daily, and nevirapine 200 mg twice daily. Plasma was collected for pharmacokinetic evaluations at entry (week 0, before starting rifapentine and isoniazid) and at weeks 2 and 4 (with rifapentine and isoniazid). For pharmacologic evaluation of efavirenz, mid-dosing interval plasma was collected. For nevirapine, trough plasma samples were collected at weeks 0, 2, and 4. Efavirenz and nevirapine were quantified by ultra-performance liquid chromatography [44]. Rifapentine and 25-desacetyl rifapentine were quantified by liquid chromatography/tandem mass spectrometry [45]. Pharmacokinetic parameter estimation was accomplished using maximum a posteriori probability–Bayesian estimation implemented in ADAPT II (Biomedical Simulations Resource at the University of Southern California, Los Angeles) [46]. Plasma concentrations from weeks 2 and 4 were taken together to estimate the apparent oral clearance (CL/F) of efavirenz and nevirapine with concomitant rifapentine and isoniazid.

Genetic polymorphisms

Human DNA was extracted from whole blood. We genotyped 59 polymorphisms of interest, in *CYP2B6*, *CYP2A6*, *CYP3A4*, *CYP3A5*, *HNF4A*, *NAT2*, *NR1I2*, *NR1I3*, *SLCO1B1*, *TRIM4*, *UGT1A1*, and intergenic. These included *CYP2B6* polymorphisms that predict efavirenz exposure and *NAT2* polymorphisms that predict isoniazid exposure. Genotyping was done in VANTAGE (Vanderbilt Technology for Advanced Genomics) using MassARRAY

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iPLEX Gold (Agena Bioscience, California, USA) and Taqman (ThermoFisher Scientific, Massachusetts, USA). Assay design is available upon request. We excluded 11 polymorphisms with minor allele frequencies less than 5%. Polymorphisms that define *CYP2B6* or *NAT2* metabolizer status were not excluded. Genotyping efficiency exceeded 96% for all polymorphisms, and 100% for 45 of 48 polymorphisms. All were in Hardy–Weinberg equilibrium among self-identified Blacks, Asians, and Hispanics analyzed separately after correcting for multiple comparisons, except *NR1I2* rs3732360 (Hardy–Weinberg $P = 6.1 \times 10^{-6}$ among Blacks) which was excluded from analyses. Several polymorphisms with nominal Hardy–Weinberg *P*-values <0.05 were not excluded (rs11045819, rs11045872, and rs4149032 in Blacks, $P > 0.04$ for each). Analyses ultimately included 47 polymorphisms (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

Statistical analysis

Associations were assessed using linear regression models. Associations between pharmacokinetic parameters, *CYP2B6* metabolizer group, and *NAT2* acetylator group were assessed using STATA version 15.1 (StataCorp, College Station, Texas, USA). Associations with the 47 polymorphisms were assessed using PLINK version 1.07 [47]. Efavirenz and nevirapine concentrations were $\log_{10}$ transformed. For concentration associations, we included efavirenz values between 9 and 30 h postdose, nevirapine values between 10 and 15 h postdose, and rifapentine and 25-desacetyl rifapentine values between 10 and 36 h postdose. Individuals without baseline body mass index (BMI) data were excluded.

Composite *CYP2B6* metabolizer genotype was defined based on combinations of three polymorphisms as follows: normal (1: 15582CC-516GG-983TT or 2: 15582CT-516GG-983TT); intermediate (3: 15582TT-516GG-983TT; 4: 15582CC-516GT-983TT; 5: 15582CC-516GG-983CT; 6: 15582CT-516GT-983TT; or 7: 15582CT-516GG-983CT); and poor (8: 15582CC-516TT-983TT; 9: 15582CC-516GT-983CT; 10: 15582CC-516GG-983CC [24]. For *NAT2*, genotypes were categorized based on combinations of rs1801280 (*NAT2*5*), rs1799930 (*NAT2*6*), rs1799931 (*NAT2*7*), and rs1801279 (*NAT2*14*), as slow if homozygous for the variant allele at any locus or heterozygous at 2 or more loci; intermediate if heterozygous at a single locus; or rapid if no variant allele [48]. Analyses with *CYP2B6* and *NAT2* genotype groups did not correct for multiple comparisons. For the 47 polymorphisms and 6 phenotype comparisons (i.e. two phenotypes, $\log_{10}$ absolute concentration and CL/F, each with three time considerations, week 0, week 4, and change from week 0 to week 4) we used Bonferroni correction (significance threshold $P = 1.9 \times 10^{-4}$). Two-sided tests were used.

Results

Participant characteristics

Analyses included 128 participants evaluable for pharmacogenetics associations during at least one study week, including 87 for efavirenz, 38 for nevirapine, and 106 for both rifapentine and 25-desacetyl rifapentine. Black participants were overrepresented in the efavirenz group, and females and Thai participants in the nevirapine group. Overall, 14 (11%) of participants were *CYP2B6* poor metabolizers, and 46 (36%) were *NAT2* slow acetylators (Table 1).

Efavirenz pharmacokinetics

In analyses that controlled for BMI and sex, higher efavirenz concentrations and slower CL/F were most strongly associated *CYP2B6* poor metabolizer genotype at all weeks. At baseline, the geometric mean efavirenz concentration was 5.9-times greater in *CYP2B6* poor (9863 ng/mL) than in normal metabolizers (1680 ng/mL). At week 4, *NAT2* genotype was also associated with efavirenz pharmacokinetics. In contrast, changes in both efavirenz concentrations and CL/F from baseline to week 4 were more strongly associated with *NAT2* acetylator status. For change in efavirenz concentration, the *NAT2* $P = 9.7 \times 10^{-6}$ (β coefficient = 0.42) while *CYP2B6* $P = 0.029$ (β coefficient = 0.12). Lower BMI and female sex were independently associated with higher efavirenz concentrations and slower efavirenz CL/F at each week (Table 2). Associations with efavirenz concentrations at week 2, and with change from baseline to week 2, were similar to associations at week 4 (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

Relationships between *CYP2B6* genotype, *NAT2* genotype, and efavirenz concentrations at weeks 0, 2, and 4 are shown in Fig. 1. Among all participants, efavirenz concentrations increased from week 0 to week 2 in 33 (39%) of 85. Among *NAT2* rapid acetylators, efavirenz concentrations increased from week 0 to week 2 in 1 (7%) of 14, whereas among *NAT2* slow acetylators, efavirenz concentrations increased from week 0 to week 2 in 23 (74%) of 31. Among *NAT2* intermediate acetylators, change in efavirenz concentrations varied by *CYP2B6* genotype, with increased efavirenz concentrations in 0 (0%) of 12 *CYP2B6* normal metabolizers, and increased efavirenz concentrations in 9 (32%) of 28 *CYP2B6* intermediate or poor metabolizers. Findings were similar for change from week 0 to week 4. Relationships between *CYP2B6* genotype, *NAT2* genotype, and efavirenz CL/F at week 0 and week 2/4 mirrored concentration data (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

The only individual to experience grade 3 alanine transaminase (ALT) or aspartate transaminase (AST) elevation was an Asian female in the efavirenz group, with a BMI of 19.9 kg/m^2, and both *CYP2B6* poor metabolizer and *NAT2* slow acetylator genotypes. From week 0 to week 2 her efavirenz concentration increased from

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Table 1 Baseline characteristics of A5279 participants included in genetic association analyses

	Total (n=128)[a]	Efavirenz group (n=87)[b]	Nevirapine group (n=38)[b]	Rifapentine/isoniazid group (n=106)[b]
Age in years, median (range)	35 (13–61)	35 (13–61)	38 (13–53)	36 (13–61)
Sex				
Female; *n* (%)	74 (58)	43 (49)	27 (71)	59 (56)
Male; *n* (%)	54 (42)	44 (51)	11 (29)	47 (44)
Race/ethnicity; *n* (%)				
Asian, Pacific Islander	59 (46)	33 (38)	26 (68)	54 (51)
Black	58 (45)	44 (51)	11 (29)	43 (41)
Hispanic	10 (8)	9 (10)	1 (3)	8 (8)
White	1 (1)	1 (1)	0 (0)	1 (1)
Country; *n* (%)				
Thailand	58 (45)	32 (37)	26 (68)	53 (50)
South Africa	35 (27)	34 (39)	0 (0)	26 (25)
USA	14 (11)	13 (15)	0 (0)	11 (10)
Botswana	12 (9)	5 (6)	6 (16)	8 (8)
Kenya	5 (4)	0 (0)	5 (13)	5 (5)
Peru	4 (3)	3 (3)	1 (3)	3 (3)
BMI in kg/m^2, median (range)	22.6 (15,3–41.7)	23.2 (15.4–41.7)	20.5 (15.3–35.4)	22.5 (15.3–41.7)
CYP2B6 metabolizer genotype; *n* (%)				
Normal	43 (34)	25 (29)	17 (45)	36 (34)
Intermediate	71 (55)	51 (59)	18 (47)	58 (55)
Poor	14 (11)	11 (13)	3 (8)	12 (11)
NAT2 metabolizer genotype; *n* (%)				
Rapid	22 (17)	15 (17)	7 (18)	16 (15)
Intermediate	59 (46)	40 (46)	17 (45)	50 (47)
Slow	46 (36)	32 (37)	14 (37)	40 (38)

[a]Includes 128 participants with both *CYP2B6* genotype data and week 0 efavirenz or nevirapine concentration data.
[b]For efavirenz, nevirapine, and rifapentine, we included only individuals with available data for *CYP2B6* genotype, *NAT2* genotype, and sex. For efavirenz and rifapentine, we also required data for BMI.

Table 2 Multivariable models of efavirenz and nevirapine pharmacokinetic parameter associations with *CYP2B6* genotype, *NAT2* genotype, sex, and BMI

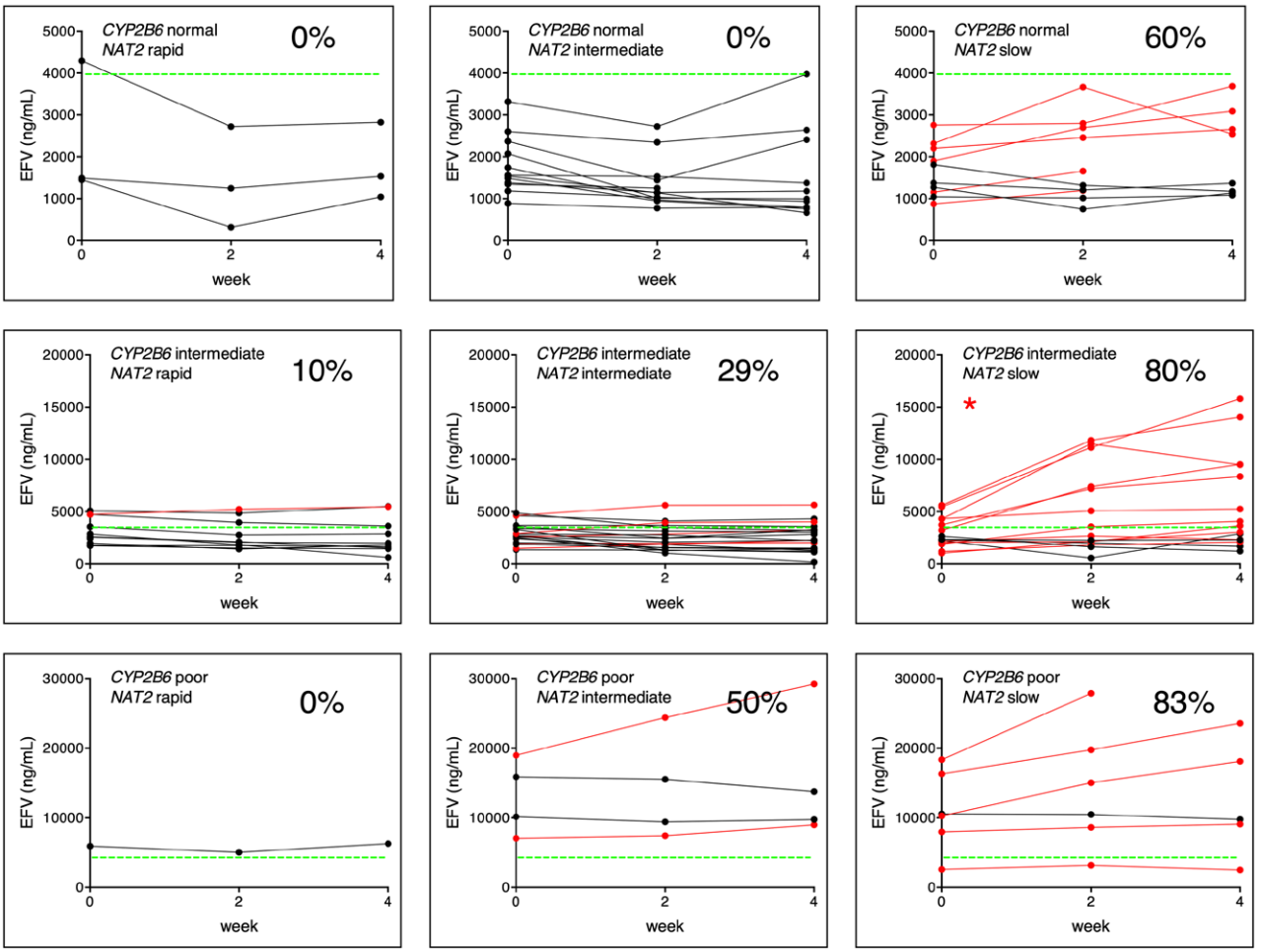
	n	Plasma concentration β coefficient, P value	n	Plasma clearance[d] β coefficient, P value
Efavirenz[c]				
Week 0 (without isoniazid/rifapentine)	87		82	
CYP2B6 genotype[b]		$0.63, 2.0\times10^{-14}$		$-0.60, 2.9\times10^{-11}$
NAT2 genotype		0.01, 0.89		0.15, 0.061
BMI		$-0.29, 8.9\times10^{-5}$		$0.30, 5.2\times10^{-5}$
Female sex		0.19, 0.015		$-0.21, 8.0\times10^{-3}$
Week 4 (with isoniazid/rifapentine)	80		80	
CYP2B6 genotype		$0.53, 5.9\times10^{-12}$		$-0.57, 6.2\times10^{-18}$
NAT2 genotype		$0.22, 1.2\times10^{-3}$		$-0.22, 2.0\times10^{-4}$
BMI		$-0.37, 2.3\times10^{-7}$		$0.39, 9.4\times10^{-8}$
Female sex		$0.27, 6.4\times10^{-4}$		$-0.39, 5.6\times10^{-8}$
Change, week 0 to week 4	80		80	
CYP2B6 genotype		0.12, 0.029		−0.14, 0.15
NAT2 genotype		$0.42, 9.7\times10^{-6}$		$-0.44, 5.9\times10^{-6}$
BMI		$-0.25, 2.3\times10^{-3}$		0.18, 0.010
Female sex		$0.30, 5.0\times10^{-3}$		$-0.29, 3.9\times10^{-3}$
Nevirapine[c]				
Week 0 (without isoniazid/rifapentine)	36		36	
CYP2B6 genotype		$0.46, 1.7\times10^{-3}$		$-0.50, 8.6\times10^{-4}$
NAT2 genotype		−0.11, 0.39		−0.04, 0.79
Female sex		0.38, 0.010		−0.16, 0.17
Week 4 (with isoniazid/rifapentine)	36		35	
CYP2B6 genotype		0.24, 0.027		−0.16, 0.11
NAT2 genotype		$0.48, 2.9\times10^{-4a}$		$-0.38, 6.9\times10^{-3}$
Female sex		0.39, 0.013		−0.46, 0.012
Change, week 0 to week 4	34		35	
CYP2B6 genotype		−0.05, 0.66		0.08, 0.45
NAT2 genotype		$0.61, 3.7\times10^{-5a}$		−0.36, 0.037[a]
Female sex		0.20, 0.24		−0.43, 0.014

[a]These associations with *NAT2* genotype persisted at $P<0.05$ in analyses limited to self-identified Asian, Pacific Islanders.
[b]There were no significant interactions between *NAT2* genotype and *CYP2B6* genotypes (at $P<0.05$) identified in any of these analyses.
[c]$\log_{10}$ transformations were used for absolute efavirenz and nevirapine concentrations.
[d]Clearance data ('week 4') were generated using concentration data from both week 2 and week 4.

18 340 to 27 874 ng/mL (the highest value in the entire cohort), ALT increased from 19 to 140 IU/L, AST increased from 24 to 69 IU/L, and her week 2 rifapentine and 25-desacetyl rifapentine concentrations were 23 646 and 36 161 ng/mL, respectively (among the highest in the cohort). She discontinued study before week 4.

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Fig. 1



Relationships between *CYP2B6* metabolizer genotype, *NAT2* acetylator genotype, and plasma efavirenz (EFV) concentrations among 85 efavirenz group participants. Each panel indicates which *CYP2B6* metabolizer genotype and *NAT2* acetylator genotype is represented. The percentages in each panel represent individuals in whom efavirenz concentrations increased from baseline (week 0) to week 2. Red lines and markers represent individuals in whom efavirenz concentrations increased from baseline to week 2. Note that *Y*-axes differ among the graphs. The graphs only include individuals who also had data for BMI, sex, and efavirenz concentration data between 9 and 30 h postdose. *Not represented is one individual with nevirapine concentrations of 38 061 and 58 589 ng/mL at baseline and week 2, respectively. Green dashed lines represent an efavirenz concentration of 4000 ng/mL, the suggested threshold for increased toxicity [21].

Exploratory analyses beyond *CYP2B6* and *NAT2* groups included 47 polymorphisms. Each polymorphism was included separately in the above models, adjusting for *CYP2B6* metabolizer genotype, *NAT2* acetylator genotype, BMI, and sex. There were no consistent associations, and none withstood correction for multiple comparisons. At week 0, the lowest *P*-values for $\log_{10}$ efavirenz concentration and CL/F were *NR1I2* rs4688040 ($P=0.05$) and *NAT2* rs4646244 ($P=0.0041$), respectively. At week 2, the lowest *P*-values for $\log_{10}$ efavirenz concentration and CL/F were *HNF4A* rs2071197 ($P=0.06$) and *CYP3A5* rs776746 ($P=0.0033$), respectively. The lowest *P*-values for change from week 0 to week 2 in $\log_{10}$ efavirenz concentration and CL/F were *SLCO1B1* rs4363657, rs4149081, rs11045879 (for each, $P=0.0024$), and *NAT2* rs1208 ($P=0.015$), respectively. Associations with each polymorphism are in Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*.

Nevirapine pharmacokinetics

In analyses that controlled for sex, higher nevirapine concentrations, and slower CL/F at week 0 were associated with *CYP2B6* poor metabolizer genotypes. At baseline, the geometric mean nevirapine concentration was 1.85-times greater in *CYP2B6* poor (9885 ng/mL) than in normal metabolizers (5334 ng/mL). In contrast, higher nevirapine concentrations and slower CL/F at week 4 were more strongly associated with *NAT2* slow acetylator genotype. Change from baseline to week 4 in nevirapine

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concentrations and CL/F were associated with *NAT2* genotype but not *CYP2B6* genotype. For change in nevirapine CL/F from baseline to week 4, *NAT2* $P = 3.7 \times 10^{-5}$ (β coefficient = 0.61) while *CYP2B6* $P = 0.66$ (β coefficient = –0.05). At week 4, geometric mean nevirapine concentrations were 2.3-times higher in *NAT2* slow (6173 ng/mL) than in rapid acetylators (2749 ng/mL). Female sex was associated with nevirapine concentrations and CL/F in some models (Table 2). BMI was not significantly associated with nevirapine pharmacokinetics in multivariable models, so was not included. Genetic associations with nevirapine concentrations at week 2, and change from baseline to week 2, were similar to associations at week 4 (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

Analyses were repeated among just the 26 Asian participants in the nevirapine group. Results were similar to those for all participants. For $\log_{10}$ nevirapine concentration at week 4 among Asian participants, *NAT2* $P = 1.3 \times 10^{-4}$ (β coefficient = 0.59) and *CYP2B6* $P = 0.22$ (β coefficient = 0.16). At week 4, geometric mean nevirapine concentrations among Asians were 3.1-times higher in *NAT2* slow (6958 ng/mL) than in rapid acetylators (2259 ng/mL) (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

Temporal relationships between *CYP2B6* genotype, *NAT2* genotype, and nevirapine concentrations at weeks 0, 2, and 4 are shown in Fig. 2. Among *NAT2* rapid and intermediate acetylators, nevirapine concentrations decreased from week 0 to week 2 in 21 (95%) of 22 participants, whereas among *NAT2* slow acetylators, nevirapine concentrations increased from week 0 to week 2 in 8 (62%) of 13 participants. Temporal relationships between *CYP2B6* genotype, *NAT2* genotype, and nevirapine CL/F at week 0 and week 2/4 mirrored concentration results (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*).

For exploratory analyses, each of 47 polymorphisms was included separately in the above models, adjusting for *CYP2B6* metabolizer genotype, *NAT2* acetylator genotype, and sex. There were no consistent associations, and none withstood correction for multiple comparisons. At week 0, the lowest *P*-values for $\log_{10}$ nevirapine concentration and CL/F were *NAT2* rs1799930 ($P = 0.030$) and *NAT2* rs4271002 ($P = 0.035$), respectively. At week 2, the lowest *P*-values for $\log_{10}$ nevirapine concentration and CL/F were *NR1I2* rs4688040 ($P = 0.003$) and *SLCO1B1* rs10841753 ($P = 7.2 \times 10^{-4}$), respectively. The lowest *P*-values for change from week 0 to week 2 in $\log_{10}$ nevirapine concentration and CL/F were *NR1I2* rs7643645 ($P = 0.0037$) and *SLCO1B1* rs10841753 ($P = 0.0056$), respectively. Associations with each polymorphism are in Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*.

Associations with rifapentine and 25-desacetly rifapentine concentrations

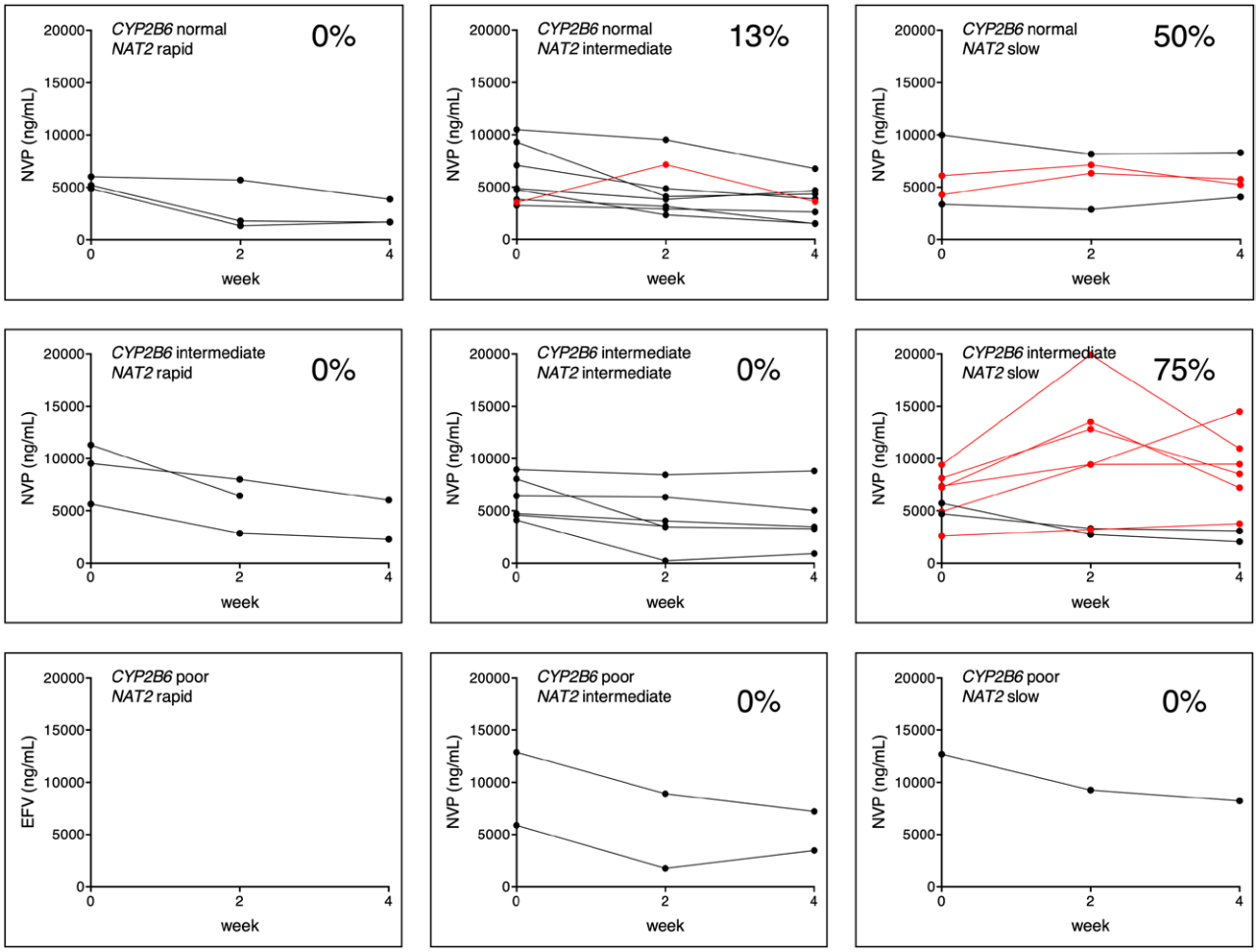
In analyses that controlled for BMI, sex, and time since prior rifapentine dose, *NAT2* slow acetylator genotype was associated with higher concentrations of rifapentine and 25-desacetyl rifapentine, more so at week 4 than at week 2. Among all participants at week 4, *NAT2* genotype was associated with concentrations of rifapentine ($P = 2.6 \times 10^{-3}$, $\beta = 0.25$) and 25-desacetyl rifapentine ($P = 7.0 \times 10^{-5}$, $\beta = 0.33$). This was also seen in efavirenz and nevirapine groups analyzed separately. Lower BMI, female sex, and shorter time since prior rifapentine dose were also associated with higher rifapentine and 25-desacetyl rifapentine concentrations. There were no associations between *CYP2B6* genotype and rifapentine or 25-desacetyl rifapentine concentrations (Table 3). Results were similar among 26 Asian participants in the nevirapine group (Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*). Relationships between *NAT2* genotype and week 4 rifapentine and 25-desacetyl rifapentine concentrations among all participants, and stratified by efavirenz and nevirapine group, are shown in Fig. 3.

For exploratory analyses, each of 47 polymorphisms was included separately in the above models, while adjusting for *NAT2* acetylator genotype, BMI, sex, and time since prior rifapentine dose (we did not adjust for BMI in nevirapine subgroup analyses). There were no consistent associations, and none withstood correction for multiple comparisons. At week 4 among all participants, the lowest *P*-values for rifapentine and 25-desacetyl rifapentine concentrations were *UGT1A1* rs887829 ($P = 0.0068$) and *SLCO1B1* rs4149056 ($P = 0.0045$), respectively. At week 4 in the efavirenz group, the lowest *P*-values for rifapentine and 25-desacetyl rifapentine concentrations were *NAT2* rs1799929 ($P = 0.0085$) and *NAT2* rs1041983 ($P = 0.083$), respectively. At week 4 in the nevirapine group, the lowest *P*-values for rifapentine and 25-desacetyl rifapentine concentrations were *SLCO1B1* rs2291075 ($P = 0.029$) and *NR1I2* rs1523130 ($P = 0.044$), respectively. Of note, *SLCO1A1* 521T→C (rs4149056) that predicts decreased organic anion transporting polypeptide 1B1 (OATP1B1) activity was nominally associated in all participants with lower 25-desacetyl rifapentine concentrations at week 2 ($P = 0.043$) and week 4 ($P = 0.0045$), and in the efavirenz group with lower week 4 rifapentine ($P = 0.043$) and 25-desacetyl rifapentine ($P = 0.018$) concentrations. Associations of rifapentine and 25-desacetyl rifapentine with each polymorphism are provided in Supplemental Material, supplement digital content 1, *http://links.lww.com/FPC/B379*.

The geometric mean rifapentine concentration at week 4 was 1.34-times higher in *NAT2* slow (12 224 ng/mL) than in rapid acetylators (9126 ng/mL), while 25-desacetyl

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Fig. 2



Relationships between *CYP2B6* metabolizer genotype, *NAT2* acetylator genotype, and plasma nevirapine (NVP) concentrations among 35 nevirapine group participants. Each panel indicates which *CYP2B6* metabolizer genotype and *NAT2* acetylator genotype is represented. The percentages in each panel represent individuals in whom nevirapine concentrations increased from baseline (week 0) to week 2. Red lines and markers represent individuals in whom nevirapine concentrations increased from baseline to week 2. Note that *Y*-axes differ among the graphs. The graphs only include individual who also had data for sex, and nevirapine concentration data between 10 and 15 h postdose.

rifapentine concentration was 1.62-times higher in *NAT2* slow (12 356 ng/mL) than in rapid acetylators (7612 ng/mL). In the efavirenz group, the geometric mean rifapentine concentration at week 4 was 1.33-times higher in *NAT2* slow (10 003 ng/mL) than in rapid acetylators (7530 ng/mL), while 25-desacetyl rifapentine concentration was 1.66-times higher in *NAT2* slow (9772 ng/mL) than in rapid acetylators (5874 ng/mL). In the nevirapine group, the geometric mean rifapentine concentration at week 4 was 1.48-times higher in *NAT2* slow (17 489 ng/mL) than in rapid acetylators (11 794 ng/mL), while 25-desacetyl rifapentine concentration was 1.75-times higher in *NAT2* slow (18 786 ng/mL) than in rapid acetylators (10 754 ng/mL). Among Asians in the nevirapine group, the geometric mean rifapentine concentration at week 4 was 1.86-times higher in *NAT2* slow (19 609 ng/mL) than in rapid acetylators (10 529 ng/mL), while 25-desacetyl rifapentine concentration was 2.16 times higher in *NAT2* slow (21 404 ng/mL) than in rapid acetylators (9889 ng/mL).

Discussion

Protocol A5279 showed that 1 month of rifapentine plus isoniazid was noninferior to 9 months of isoniazid for preventing tuberculosis, and had a higher treatment completion percentage [6]. The present analysis involving a subset of 128 efavirenz or nevirapine recipients from the rifapentine plus isoniazid arm of A5279 who underwent pharmacokinetic evaluations provides novel observations. We report that *NAT2* slow acetylators had significantly

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Table 3 Multivariable models of rifapentine and desacetyl-rifapentine concentration associations with *CYP2B6* genotype, *NAT2* genotype, sex, BMI, and rifapentine dose

	n	Plasma rifapentine β coefficient, *P* value	Plasma des-rifapentine β coefficient, *P* value
All participants			
Week 2	101		
NAT2 genotype		0.12, 0.095	$0.24, 5.0\times10^{-3}$
CYP2B6 genotype		0.0005, 0.99	−0.01, 0.3091
BMI		−0.13, 0.046	−0.16, 0.026
Female sex		$0.31, 3.4\times10^{-4}$	$030, 1.0\times10^{-3}$
Hours since rifapentine dose		$-0.56, 9.4\times10^{-11}$	$-0.44, 2.5\times10^{-6}$
Week 4	101		
NAT2 genotype		$0.25, 2.6\times10^{-3}$	$0.33, 7.0\times10^{-5}$
CYP2B6 genotype		0.05, 0.55	0.07, 0.37
BMI		−0.17, 0.04	−0.21, 0.011
Female sex		$0.34, 9.6\times10^{-5}$	$0.37, 2.6\times10^{-5}$
Hours since rifapentine dose		$-0.46, 3.0\times10^{-8}$	$-0.29, 3.8\times10^{-4}$
Efavirenz group[a]			
Week 2	63		
NAT2 genotype		0.097, 0.36	0.20, 0.075
CYP2B6 genotype		0.003, 0.96	0.07, 0.51
BMI		−0.14, 0.081	−0.17, 0.069
Female sex		0.25, 0.031	0.26, 0.036
Hours since rifapentine dose		$-0.60, 1.1\times10^{-6}$	$-0.52, 2.7\times10^{-5}$
Week 4	65		
NAT2 genotype		0.24, 0.024	$0.32, 8.0\times10^{-3}$
CYP2B6 genotype		0.12, 0.25	−0.10, 0.28
BMI		−0.07, 0.3951	−0.15, 0.17
Female sex		0.25, 0.024	0.25, 0.018
Hours since rifapentine dose		$-0.50, 2.3\times10^{-6}$	$-0.37, 2.0\times10^{-4}$
Nevirapine group[a]			
Week 2	38		
NAT2 genotype[b]		0.16, 0.21	0.31, 0.028
CYP2B6 genotype		0.06, 0.70	0.046, 0.76
Female sex		$0.36, 8.5\times10^{-3}$	0.26, 0.067
Hours since rifapentine dose		$-0.45, 1.3\times10^{-3}$	−0.29, 0.045
Week 4	35		
NAT2 genotype[b]		0.31, 0.063	$0.41, 1.7\times10^{-3}$
CYP2B6 genotype		0.012, 0.50	0.19, 0.30
Female sex		$0.38, 9.1\times10^{-3}$	$0.46, 5.9\times10^{-3}$
Hours since rifapentine dose		−0.27, 0.099	−0.020, 0.90

[a]Rifapentine dose was not included in efavirenz and nevirapine subgroup analyses to avoid overfitting the models.
[b]These associations with *NAT2* genotype persisted at $P<0.05$ in analyses limited to self-identified Asian, Pacific Islanders (data not shown).

higher rifapentine and 25-desacetyl rifapentine concentrations among all participants, and in efavirenz and nevirapine subgroups. This was most pronounced among Asians in the nevirapine group, in whom the geometric mean rifapentine and 25-desacetyl rifapentine concentration at week 4 were approximately two times higher in *NAT2* slow acetylators than in rapid acetylators.

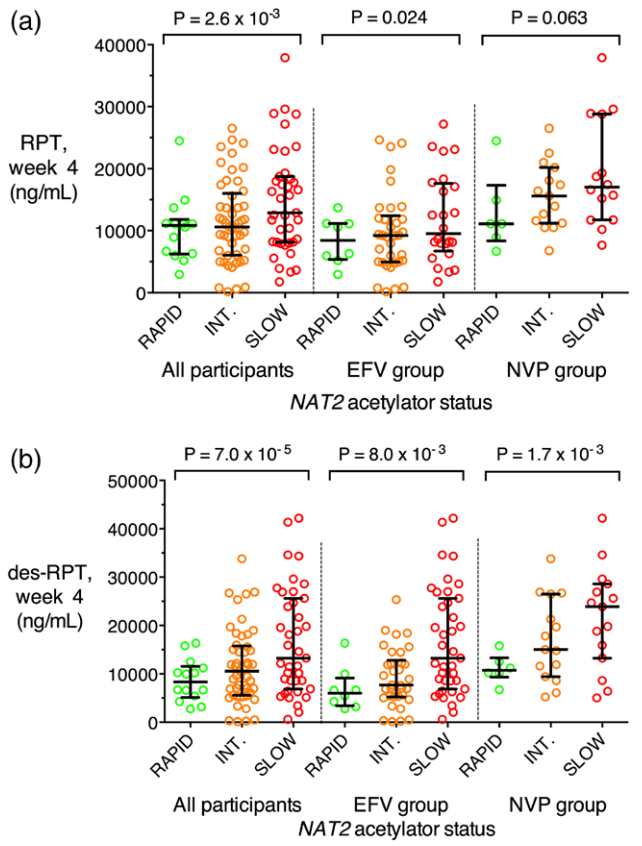
We also report that *NAT2* slow acetylator genotype, but not *CYP2B6* genotype, was associated with higher nevirapine concentrations, slower nevirapine CL/F at week 4, and greater change from baseline to week 4 among all participants, and among Asians analyzed separately. At week 4, geometric mean nevirapine concentrations were 2.3 times higher in *NAT2* slow acetylators than in rapid acetylators. Both *CYP2B6* poor metabolizer genotype and *NAT2* slow acetylator genotype were associated with higher efavirenz concentrations and slower efavirenz CL/F at week 4, with *CYP2B6* genotype having a stronger association. In contrast, change from baseline to week 4 in efavirenz concentrations and CL/F were associated with *NAT2* genotype, but little if any with *CYP2B6* genotype. Increased efavirenz concentrations from baseline to week 4 were most frequent among *NAT2* slow acetylators, but were also found in *NAT2* intermediate acetylators with *CYP2B6* intermediate or poor metabolizer genotypes.

The effect of *NAT2* genotype on rifapentine, 25-desacetyl rifapentine, nevirapine, and efavirenz pharmacokinetics is likely mediated by greater isoniazid exposure among slow acetylators [12–15]. Rifapentine, nevirapine, and efavirenz are not NAT2 substrates, while isoniazid is a mechanism-based inhibitor of CYP3A4, CYP2A6, CYP1A2, and CYP2C19 [49]. Hepatic CYP isoforms metabolize all four analytes in this study, and higher isoniazid exposure likely inhibits their metabolism, resulting in slower CL/F and higher concentrations. For efavirenz, inhibition of CYP2A6 may be important, while for rifapentine, 25-desacetyl rifapentine and nevirapine, CYP3A4 may be most important.

Increased expression of various drug-metabolizing enzymes and transporters is induced by rifapentine [50], nevirapine, and efavirenz. Resultant plasma

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Fig. 3



Relationships between *NAT2* acetylator genotype and plasma concentrations of rifapentine and 25-desacetyl rifapentine at week 4. (a) associations of rifapentine (RPT) with *NAT2* acetylator genotype among all participants, and in the efavirenz (EFV) group, and the nevirapine (NVP) group analyzed separately. (b) associations of plasma 25-desacetyl rifapentine (des-RPT) with *NAT2* acetylator genotype among all participants, and in the efavirenz group, and the nevirapine group analyzed separately. INT, intermediate metabolizers. *P*-values are from linear regression models that included *CYP2B6* genotype, BMI, sex, and hours since rifapentine dose. The graphs only include individuals who also had data for *CYP2B6* genotype, BMI, sex, and rifapentine concentration data between 10 and 36 h postdose. Error bars indicate medians and 75th percentiles.

concentrations and changes over time in the present study likely reflect competition between enzyme induction by these compounds and enzyme inhibition by isoniazid.

Female sex and lower BMI and were independently associated with higher concentrations of rifapentine, 25-desacetyl rifapentine and efavirenz, and slower efavirenz CL/F. Female sex but not lower BMI was also associated with higher nevirapine concentrations and slower nevirapine CL/F. As expected, *CYP2B6* poor metabolizers had higher baseline concentrations of efavirenz and nevirapine [21,23,30–33]. Exploratory analyses involving 47 polymorphisms found no consistent associations with pharmacokinetics of rifapentine, 25-desacetyl rifapentine, efavirenz, or nevirapine.

This study had limitations. We did not study the effect of *NAT2* slow acetylator status on rifapentine and 25-desacetyl rifapentine in the presence of isoniazid without efavirenz or nevirapine, but we anticipate that such concentrations would be increased. Isoniazid concentrations were not quantified. The sample size for genetic association analyses was modest, limiting our ability to more thoroughly interrogate associations. For the 47 exploratory polymorphisms, some nominally significant associations may be true despite notwithstanding multiple comparisons. As exploratory analyses only involved 47 selected polymorphisms, other variants may be associated with study drug pharmacokinetics. We did not genotype *CYP2B6* alleles that identify rapid metabolizers (*CYP2B6*4* and **22*) because these are infrequent and have only modest effect on efavirenz pharmacokinetics.

This study has implications. For antiretrovirals, increased plasma exposure in *NAT2* slow acetylators may increase risk for adverse events with efavirenz [21], such as central nervous system symptoms [22,27,28], suicidality [29], hepatic injury [51] or QT prolongation [52], and increase risk for rash with nevirapine [34]. For rifapentine, *NAT2* acetylator status may increase risk for microbiologic treatment failure in rapid acetylators, or toxicities such as hypersensitivity or hepatotoxicity in slow acetylators.

In summary, among HIV-positive individuals who were receiving antiretroviral therapy including either efavirenz or nevirapine, and then initiated daily rifapentine and isoniazid in protocol A5279, *NAT2* acetylator genotype was associated with interindividual differences in pharmacokinetics for rifapentine, 25-desacetyl rifapentine, efavirenz, and nevirapine. *CYP2B6* metabolizer genotype was also associated with interindividual pharmacokinetic differences for efavirenz, but not for rifapentine, 25-desacetyl rifapentine, or nevirapine. Implications of these findings for treatment of LTBI warrant study in larger cohorts.

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Rifapentine was provided by Sanofi-Aventis (France) free of charge. Isoniazid was provided by multiple manufacturers.

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Conflicts of interest

S.S. reports research grants to her institution from ViiV Healthcare. R.E.C. has consulted for Sanofi. His spouse is Merck stockholder. There are no conflicts of interest for the remaining authors.

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