R E V I E W

Effect of Genetic Variations in Drug-Metabolizing Enzymes and Drug Transporters on the Pharmacokinetics of Rifamycins: A Systematic Review

Tesemma Sileshi [1,2], Gosaye Mekonen [1], Eyasu Makonnen [2,3], Eleni Aklillu [4]

[1]Department of Pharmacy, Ambo University, Ambo, Ethiopia; [2]Department of Pharmacology and Clinical Pharmacy, Addis Ababa University, Addis Ababa, Ethiopia; [3]Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, Addis Ababa, Ethiopia; [4]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence: Tesemma Sileshi, Department of Pharmacy, Ambo University, P.O Box 19, Ambo, Ethiopia, Tel +2510911550975, Email tesemmasileshi@gmail.com

Background: Rifamycins are a novel class of antibiotics clinically approved for tuberculosis chemotherapy. They are characterized by high inter-individual variation in pharmacokinetics. This systematic review aims to present the contribution of genetic variations in drug-metabolizing enzymes and transporter proteins to the inter-individual variation of rifamycin pharmacokinetics.

Method: We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The search for relevant studies was done through PubMed, Embase, Web of Science, and Scopus databases. Studies reporting single nucleotide polymorphism in drug transporters and metabolizing enzymes' influence on rifamycin pharmacokinetics were solely included. Two reviewers independently performed data extraction.

Results: The search identified 117 articles of which 15 fulfilled the eligibility criteria and were included in the final data synthesis. The single nucleotides polymorphism in the drug transporters *SLCO1B1* rs4149032, rs2306283, rs11045819, and *ABCB1* rs1045642 for rifampicin, drug metabolizing enzyme *AADAC* rs1803155 for rifapentine and *CES2 c.-22263A>G (g.738A>G)* for rifampicin partly contributes to the variability of pharmacokinetic parameters in tuberculosis patients.

Conclusion: The pharmacokinetics of rifamycins is influenced by genetic variation of drug-metabolizing enzymes and transporters. Controlled clinical studies are, however, required to establish these relationships.

Keywords: rifamycin, pharmacokinetics, pharmacogenetics, enzymes, transporters

Introduction

Tuberculosis (TB) is an infectious disease, which remains a major public health problem globally. In the year 2020, the estimated number of people who died from tuberculosis is 1.3 million among HIV-negative people and 214,000 among HIV-positive.[1] Current pharmacotherapy of tuberculosis involves a combination of at least four drugs. Rifamycins are key components of pharmacotherapy for both active and latent TB.

Rifamycins are a class of antibiotics isolated from Amycolatopsis in 1957. Four distinct semi-synthetic rifamycin analogs (rifampicin, rifabutin, rifapentine, and rifaximin) are approved for clinical use. Rifampicin, rifabutin, and rifapentine are used for the treatment of TB and chronic staphylococcal infections.[2] Rifapentine given once weekly for 12 weeks with isoniazid is effective and well tolerated in the treatment of latent TB.[3] Rifaximin is poorly absorbed from the gastrointestinal tract and is indicated for the treatment of traveler's diarrhea, functional bloating, irritable bowel syndrome, and small bowel bacterial overgrowth.[4]

Variable exposure to anti-TB drugs may be associated with unfavorable treatment outcomes.[5] Factors associated with drug exposure variability of anti-TB drugs, such as age, gender nutritional status, human immune-deficiency virus, diabetes, and genetic polymorphism, were described in various previous studies.[6–9] There has been a notable development in recent years on how genetic variations in drug-metabolizing enzymes and transporters contribute to variation in

exposure and response to the drugs.[10,11] As the local and systemic concentrations of anti-TB drugs are affected by genetic variations in drug-metabolizing enzymes and transporters, pharmacokinetic and pharmacogenetic studies are increasingly performed to optimize TB treatments.[12,13]

Rifamycins are thought to be metabolized by microsomal hepatic carboxylesterases (CES), and serine esterase arylacetamide deacetylase (AADAC) to 25-deacetylrifamycins.[14,15] The uptake, distribution, and excretion of rifampicin are mediated by membrane drug transporters. There are two transporters superfamilies; the solute carrier (SLC) transporters and the adenosine triphosphate (ATP)-binding cassette (ABC) transporters.[16] SLC superfamily consists of more than 400 membrane-bound family proteins. Multiple studies revealed that the *SLCO1B1* sinusoidal influx transporter influences rifampicin influx,[17,18] and the *SLCO1B1 *15* haplotype is associated with rifampin-induced liver injury.[19] Most ABC transporters in eukaryotic cells mediate the efflux of the substrate from the cells. ABC transporters influence the hepatocellular concentration of rifampicin.[20–23] Rifamycins are substrates of P glycoprotein (P-gp), coded for by the polymorphic *ABCB1* gene.[24] Rifampicin also induces *ABCB1* gene expression.[25] Although *SLCO1B1* and *ABCB1* gene products have been reported to influence rifamycins pharmacokinetics, there is no candidate gene identified so far for therapeutic drug monitoring.

Recently, advances in technology and scientific discoveries in the medical arena have enabled the practitioner to individualize drug therapy. The keen interest to personalize TB treatment has been a point of discussion over the last decade.[26–29] The use of pharmacokinetics and pharmacogenetics of anti-tubercular drugs as tools for TB treatment optimization has been discussed previously.[13,18] However, there is a scarcity of comprehensive data on the pharmacogenetics of rifamycins. This systematic review was, therefore, designed to evaluate the influence of genetic polymorphism in rifamycins metabolizing enzymes and transporters on their pharmacokinetics.

Methods
This systematic review was carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Table S1). The protocol has been registered at PROSPERO with registration number CRD42020206029.

Search Strategy
Relevant studies were identified through a search of PubMed, Web of Science, Embase, and Scopus databases. The following combination of words was used: pharmacokinetics OR concentration OR "drug concentration" AND rifamycins OR rifampin OR rifampicin OR rifabutin OR rifapentine OR rifaximin AND *SLCO1B1* OR *ABCB1* OR carboxylesterase OR *CES* OR Arylacetamide deacetylase OR *AADAC* AND "Genetic polymorphism" OR pharmacogenetics OR pharmacogenomics OR "single nucleotide polymorphisms" OR SNP. Further, a hand-search was done from reference lists of studies included to identify eligible studies. There was no limitation on the dates of publication or publication status. Publications available only in the English language were included. The search was refined to studies of human participants.

Eligibility Criteria
The following were the eligibility criteria for the inclusion of studies: 1. Human participant studies; 2. Studies that reported on pharmacokinetic parameters of rifamycins; 3. Studies in which study participants were genotyped for rifamycins metabolizing enzyme or transporters gene; and 4. Studies that reported on the pharmacokinetic parameters of rifamycins and the effect of genetic variation on pharmacokinetics.

Quality Assessment
Validated tools exist for genetic association studies methodological quality assessment. We used the quality of genetic association studies (Q-Genie)[30] tool to assess the quality of included studies. Using the checklist adopted (Table S2) from Q-Genie TS assessed the quality of selected studies.

Data Extraction

Two (TS and GM) independently extracted data from all included publications using a pre-prepared data extraction format which included items as follows: first author, publication year, study drug, sample size, type of pharmacokinetic parameters assessed, a country in which the study was conducted, participant characteristics, genetic polymorphism investigated, pharmacokinetic parameter results and its association with genetic polymorphism. The disparity between the two reviewers during data extraction was resolved through discussion.

No contact with the authors was done for missing data and the data presented in this review were extracted from the articles.

Results

Included and Excluded Study

A total of 115 articles related to genetic polymorphism of drug-metabolizing enzymes and drug transporters with the pharmacokinetics of rifamycins were retrieved from PubMed, Web of Science, Scopus, and Embase databases. Hand search identified two additional articles which were not obtained during the database search. As shown in the PRISMA flowchart (Figure 1) 51 duplicates were removed. The remaining 66 articles were screened by title and abstract for predefined criteria, and 47 were excluded. The reasons for exclusion of studies from titles and abstracts were (1) review articles (N=3); (2) studies focusing on drugs other than rifamycins (N=26); (3) studies that did not have information on the pharmacokinetics of rifamycins but only genetic information reported (N=8); and (4) studies in which only pharmacokinetics data were reported without genetic information (N=10). Furthermore, four articles were excluded after reading them fully. Of the four articles excluded; one article did not contain rifamycins data, one study was done on healthy participants and the other two articles did not contain pharmacokinetic parameters.

Characteristics of Included Studies

Of the 15 articles selected for qualitative data synthesis, most of the studies (N=14) focused on *SLCO1B1* gene polymorphism association with the pharmacokinetics of rifamycins (Table S3). Specifically, seven studies evaluated
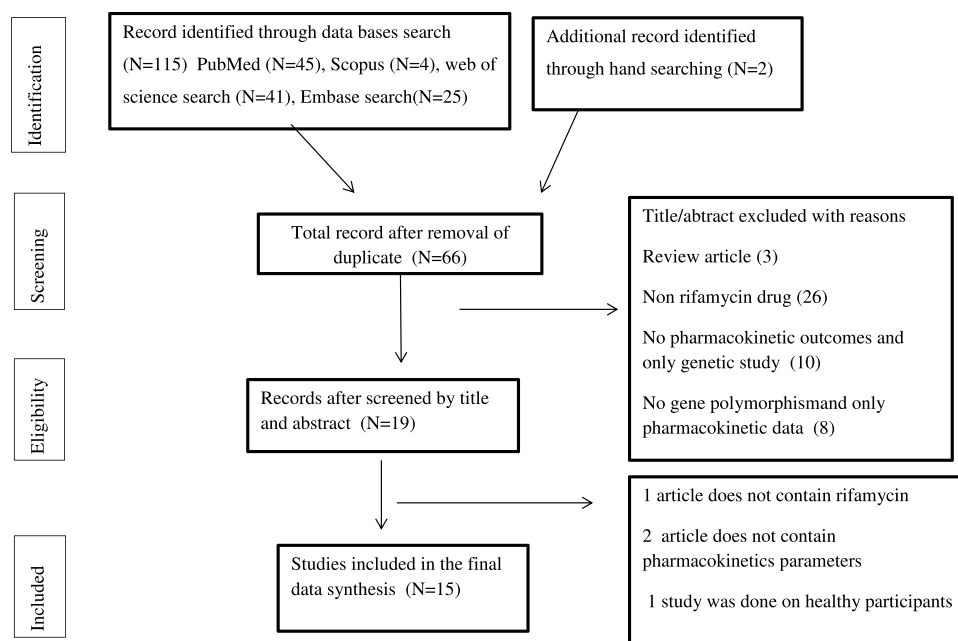

Figure 1 PRISMA flow diagram showing the literature search for studies that investigated the effect of genetic variations in drug metabolizing enzymes and drug transporters on the pharmacokinetics of rifamycins.
Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.

the association of *SLCO1B1* gene polymorphism and pharmacokinetics,[31–37] three studies *SLCO1B1* and *ABCB1* gene polymorphism with pharmacokinetics,[38–40] one study *SLCO1B1* and AADAC gene polymorphism with pharmacokinetics,[41] one study *SLCO1B1*, and CES gene polymorphism with pharmacokinetics,[42] and two studies *SLCO1B1, AADAC*, and *CES* gene polymorphism with pharmacokinetics.[43,44] Only one study investigated the association between *CES* gene polymorphism with pharmacokinetics.[45] The most studied rifamycins are rifampicin (thirteen studies) and rifapentine (two studies). No study is available that reported the pharmacokinetic-pharmacogenetic association for rifabutin and rifaximin.

There was variation among studies in sample size, the type of study participants, and the pharmacokinetics parameter compared with gene polymorphism. The smallest sample size was 34,[39] while the largest was 256.[34] The study participants were TB patients from 13 different countries and races. The majority of the studies were done on adults, but one study data were obtained from children.[42] In some studies, participants were TB-HIV co-infected patients. The pharmacokinetics parameters commonly compared with gene polymorphism were maximum concentration (Cmax), AUC (area under the curve), and clearance. However, methods for blood sample collection and pharmacokinetic parameter determination varied among studies.

Association Between Drug Transporter and Rifamycins Pharmacokinetics
Association Between Polymorphism of *SLCO1B1* and Rifamycins Pharmacokinetics

SLCO1B1 gene encodes for an Organic Anion Transport Proteins 1B1 (OATP1B1). It is located on chromosome 12. OATP1B1 is a transmembrane protein involved in the uptake of various drugs including rifamycins from the blood into the hepatocyte.[46] Currently, 191 clinical variants have been reported. *SLCO1B1*c.521T>C (rs4149056), where the valine amino acid changed to alanine at position 174, was reported to affect drug response.[47] Eight studies assessed the effect of rs4149056 SNPs on rifamycin pharmacokinetic parameters. Among these studies, only Huerta-García et al reported increased AUC among heterozygous CT for *SLCO1B1* 521T>C than the other genotypes. However, the observed increase in AUC was not statistically significant.[39] A summary of specific transporters influence on pharmacokinetics is presented in Table 1.

SLCO1B1 g.38664C>T (rs4149032) was reported in twelve studies. rs4149032 is an intronic SNP most common in the African population.[48,49] Gengiah et al reported high frequency in the *SLCO1B1* (rs4149032) gene polymorphism and its association with low median rifampicin C2.5hr in the heterozygous and homozygous variant carriers.[32] Similarly, Chigutsa et al reported high allelic frequency of the *SLCO1B1* rs4149032 polymorphism and 28% reductions in the bioavailability of rifampin for homozygous variants.[40] No statistically significant increase in the rifampicin exposure for the homozygous TT of *g.38664 C > T* (rs4149032) was observed in the study of Kim et al.[37] However, the large number of studies reviewed here did not report any observed significant effect of *SLCO1B1* rs4149032 SNP polymorphism with rifamycin pharmacokinetic variation.

SLCO1B1 c.388A>G (rs2306283) is another SNP in the *SLCO1B1* gene. This SNP causes a change of asparagine amino acid to aspartic at 130, but the effect of this change on the transporter function is not clear yet. Huerta-García et al reported the AG genotype derived from SNP *SLCO1B1 c.388A>G* was associated with lower rifampicin AUC0–24 h values compared to those with AA genotype.[39] In post hoc analysis, Dompreh et al observed that the *SLCO1B1 c.388AA* genotype was associated with low rifampin concentrations compared to those with *c.388GG*.[42] The five remaining studies did not report any association between rs2306283 SNP and rifamycin pharmacokinetics. The SNP *SLCO1B1 c.463 C>A* (rs11045819) is another variant allele of the *SLCO1B1* gene reported to affect rifamycin pharmacokinetics. According to Weiner et al, patients with *SLCO1B1c.463C>A* variant allele had 42% lower rifampin exposure, 34% lower peak concentration levels, and 63% greater apparent oral clearance compared with *SLCO1B1 c.463CC*.[36] However, the remaining five studies did not report any association between rs11045819 SNPs and rifamycin pharmacokinetics.

Association Between Polymorphism of *ABCB1* and Pharmacokinetics

ABCB1 (ATP-binding cassette sub-family B member 1) genes encode for P-gp also known as multidrug resistance protein 1 (MDR1). P-gp is a transmembrane protein, which acts as an energy-dependent drug efflux pump. It decreases intracellular drug accumulation, thereby decreasing the effectiveness of many drugs.[50] The *ABCB1*c.3435 C>T

Table 1 Summary of the Studies Reported the Drug Transporter (*SLCO11* and *ABC1B*) Gene Polymorphisms Association with Rifamycins Pharmacokinetics Variation

Reference	Gene	SNPs	Characteristics of Study Participant	Rifamycins PK Change Observed
[31]	*SLCO1B1*	rs2306283 rs4149032 rs4149056 rs4149015	Tuberculosis recurrent black South African of which 127 (73.8) are HIV positive	No significant association between rifampicin pharmacokinetic and all variants of *SLCO1B1* gene SNPs studied was observed
[43]	*SLCO1B1*	rs11045819 rs4149032	174 Malawian adults with pulmonary TB of which 98 are HIV-infected patients	No association was reported for both variants of *SLCO1B1* gene SNPs studied and the pharmacokinetics of rifampicin
[32]	*SLCO1B1*	rs4149032	57 newly diagnosed TB-HIV co-infected South African patients	Lower median concentration of rifampicin at 2.5hr; 3.7 μg/mL in heterozygous and 3.4μg/mL in homozygous variants
[38]	*SLCO1B1*	rs4149056 rs2306283	Adult tuberculosis patients 57 study group of 30% are diabetics and 27 validation group of 27% are diabetics	No variation of rifampicin volume of distribution or clearance was observed for both *SLCO1B1* gene *A388T* (rs2306283) and *T521C* (rs4149056).
	ABCB 1	rs1045642		No effect of rs1045642 SNP on rifampicin pharmacokinetics was observed
[33]	*SLCO1B1*	rs4149032	100 tuberculosis patients where 50 are HIV positive	No effect of SLCO1B1 rs4149032 genotype on rifampin Median Cmax and Median AUC0–24 was observed
[34]	*SLCO1B1*	rs4149032 rs4149033 rs11045819	256 adult tuberculosis patients from India	No significant difference in 2 hr rifampicin plasma concentration for all SNPs studied was observed
[39]	*SLCO1B1*	rs4149056	34 tuberculosis patients of which 41.2% are diabetics and some are taking other drugs	AG genotype of SLCO1B1 388A>G had lower rifampicin AUC0–24 h compared to AA genotype (83.42 mcg.h/mL versus 108.31 mcg.h/mL) respectively
	ABCB 1	rs1045642 (3435C>T)		Patients with CC or CT genotypes showed lower values in Cmax, and AUC0–24 h compared to those with a TT genotype (Cmax = 9.1 6 mcg/mL versus 15.8 6 mcg/mL; AUC0–24 h = 72.83mcg.h/mL versus 130.35 6 29.5 mcg.h/mL respectively)
[42]	*SLCO1B1*	rs2306283 rs11045819 rs4149056 rs4149032	113 children aged 3 months to 14 years and 59 (52.2%) were HIV co-infected	In post hoc analysis, the rare SLCO1B1 c.388AA genotype was associated with lower rifampicin Cmax (1.81μg/mL versus 7.11 μg/mL) and AUC0–8h (9.33 μg.h/mL versus 29.50 μg.h/mL) and higher CL/F and V/F compared to those with c.388GG
[40]	*SLCO1B1*	rs4149032 rs4149056 rs11045819	60 adult tuberculosis patients aged from 18 to 55 years and 16% were HIV infected.	Patients heterozygous and mutant homozygous for rs4149032 had 18% and 28% reductions in the bioavailability of rifampicin respectively.
	ABCB 1	rs1045642 rs2032582 rs1128503 rs3842		The *ABCB1 G2677T* (rs2032582) showed no statistically significant increase (19%) in the CL/F and a 19% increase in the mean transit time
[41]	*SLCO1B1*	rs2306283 rs4149032	162 pulmonary tuberculosis from two clinical studies receiving rifapentine in South Africa	No effect on oral clearance, apparent volume of distribution, and F was detected

(Continued)

Table 1 (Continued).

Reference	Gene	SNPs	Characteristics of Study Participant	Rifamycins PK Change Observed
[37]	SLCO1B1	rs2306283 rs11045819 rs4149056 rs4149032	105 adult patients were newly diagnosed with active pulmonary TB, and Twenty (19%) patients had diabetes mellitus	rs4149032 wild type (TT) had lower oral clearance and higher AUC but no statistically significant differences were detected
[35]	SLCO1B1	rs4149032 rs2306283	A cohort of 50 HIV negative patients 25 with rifampicin sensitive pulmonary TB and 25 patients with rifampicin-resistant	When adjusted for all covariates no significant effect of the two SLCO1B1 genotypes on rifampicin pharmacokinetics parameters was identified
[36]	SLCO1B1	rs11045819 rs4149056 rs59502379 rs2306283 rs4149015	72 TB patients (37 from Africa and 35 from the United States and Spain) and 16 healthy controls from USA	Patients with the SLCO1B1 c.463C>A (rs11045819) polymorphism had 42% lower rifampicin AUC0–24, 34% lower Cmax, and 63% CL/F
[44]	SLCO1B1	rs2239751 rs2306283 rs11045819 rs4149014 rs4149032 rs4149056	173 adults of different races and countries of origin of which 12 are HIV positive	None of the SLCO1B gene polymorphism investigated were associated with rifapentine exposure (AUC 24hour)

Abbreviations: AUC, area under curve; PK, pharmacokinetic; SNP, single nucleotide polymorphism; Cl, clearance; F, bioavailability; Cmax, maximum concentration; CL/F, apparent oral clearance; V/F, apparent predicted volume of distribution.

(rs1045642), *ABCB1c.G2677 T/A* (rs2032582) and *ABCB1c*.1236C>T (rs1128503) SNPs are the most common non-synonymous and synonymous SNPs studied.[51] Rifamycins are a substrate and inducer of the *ABCB1* gene.[52] The decrease in rifampicin exposure with the time of treatment is partly explained by the induction of the *ABCB1* gene. Three studies assessed the effect of four *ABCB1*, rs1045642 rs2032582, rs1128503, and rs3842 (*ABCB1c.4036A>G*) SNPs. Huerta-García et al demonstrated that the rs1045642 TT genotype is a predictor that explains 34.8% of the variability in rifampicin Cmax and 48.5% of the variability in AUC0–24 h.[39] However, the other two studies did not replicate this observed result of Huerta-García et al.[38,40]

Association Between Drug-Metabolizing Enzyme and Pharmacokinetics

Rifamycins are metabolized by esterase enzymes. The esterase enzymes implicated in the metabolism of rifamycins are hepatic carboxylesterases (CES), and serine esterase arylacetamide deacetylase (AADAC). Two carboxylesterases, CES1 and CES2, are recognized to play major roles in drug metabolism. These enzymes metabolize rifamycins to their respective deacetylrifamycins.[14,15,53] Polymorphism of the *CES1* and *CES2* genes have been shown to influence the metabolism of several drugs.[54] However, few studies investigated the effect of *CES1* and *CES2* gene variants on rifamycin metabolism (Table 2).

Sloan et al investigated *CES1* rs12149368 SNP effect on rifampicin pharmacokinetics in Malawian tuberculosis patients. The rs12149368 variant does not affect the plasma rifampicin concentration[43] (Table 2). Song et al identified 10 variations in *CES2* in Korean TB patients. Among the ten variants three closely linked SNPs, *c.-2263A>G* (rs3759994, *g.738A>G), c.269–965A>G* (rs4783745, *g.4629A>G*), and *c.1612+136G>A (g.10748G > A)*, may alter the metabolism of rifampicin by affecting the efficiency of transcription of the gene. In particular, the *CES2 c.-2263A>G* variant, which is found in the promoter region is associated with increased plasma concentrations of rifampicin.[45]

Shimazu et al reported that microsomes from a liver sample genotyped as *AADAC*3/AADAC*3* showed decreased enzyme activities, compared with others. However, the allelic frequency is low, 1.3% European American, and 2.0% African American. The *AADAC*2* (rs1803155) allele, which has a higher frequency has also shown reduced enzyme

Table 2 Summary of the Studies Reported the Drug-Metabolizing Enzyme (*AADAC* and *CES*) Gene Polymorphisms Association with Rifamycins Pharmacokinetics Variation

Reference	Gene	SNPs	Characteristics of Study Participant	Rifamycins Pharmacokinetics
[43]	CES 1	rs12149368	174 Malawian adults with pulmonary tuberculosis of which 98 are HIV-infected patients	No associations between rifampicin AUC, Cmax, (CL/F), or V/F and AADAC or CES-1 SNPs polymorphism were identified
	AADAC	rs1803155 rs61733692		
[42]	CES2	rs3759994	113 children aged 3 months to 14 years and 59 (52.2%) were HIV co-infected	No significant effect of studied CES2 SNPs on rifampicin Cmax, AUC, and CL/F was observed
[41]	AADAC	rs1803155	162 pulmonary tuberculosis patients from two clinical studies receiving rifapentine in South Africa	Patients carrying the AA variant of *AADAC* rs1803155 were found to have a 10.4% lower rifapentine clearance
[45]	CES2	c.-2548C>T c.-2263A>G c.269–965A>G c.474–152T>C c.615+120G>A c.1612+136G>A c.1613–87G>A c.1872*69A>G c.1872*302_304delGAA c.1872*445C>T	35 patients with tuberculosis receiving a first-line antituberculosis treatment and 100 healthy individuals for analysis of the frequency of genetic variations in CES2 in the general population	The plasma rifampicin concentration increased with the number of risk alleles at c.2263A>G, c.269–965A>G and c.1612+136G>A, for example for c.2263A>G 8.9 mg/L versus 13.9mg/L for GG and AA respectively, while the plasma concentration decreased along with an increase in the number of risk alleles at c.1872*302_304delGAA
[44]	AADAC	rs1803155	173 adults of different races and countries of origin of which 12 are HIV positive	Rifapentine exposure (AUC 24) decreased by 10.2% in black participants for AADAC rs1803155 G versus A allele
	CES2	rs8045523 rs8192925 rs4783745		17.2% increase in rifapentine AUC0-24 for rs8192925 G versus A was observed

Abbreviations: AUC, area under the curve; CES, carboxylesterases; AADAC, arylacetamide deacetylase; Cmax, maximum concentration; CL/F, apparent oral clearance; V/F, apparent predicted volume of distribution.

activity. The recent report of Francis et al and Weiner et al revealed that rs1803155 SNP has a significant effect on rifapentine exposure in tuberculosis patients. The mean AUC-24 of rifapentine decreased by 10.2% in black tuberculosis patient carriers of *AADAC* rs1803155 G versus A allele.[44] The odds increase for GG allele carriers. A similar result was reported by Francis et al. Patients carrying the AA variant of *AADAC* rs1803155 were found to have a 10.4% lower clearance of rifapentine.[41] However, another study from Malawi showed that *AADAC* rs1803155 SNP did not affect rifampicin pharmacokinetics.[43]

Discussion

This systematic review provides current updates on the impact of genetic polymorphisms of drug transporters and drug-metabolizing enzymes on the pharmacokinetics of rifamycins. The overall finding suggests that the polymorphism in the drug transporter *SLCO1B1* rs4149032, rs2306283, rs11045819, and *ABCB1* rs1045642 and metabolizing enzyme AADACrs1803155 and CES2 c.-22263A>G (g.738A>G) of rifamycins partly contributes to the variability of pharmacokinetic parameters in tuberculosis patients.

The *SLCO1B1* gene is located on chromosome 12. Fifteen exons and many variants have been identified in the *SLCO1B1* gene. The missense mutation of rs4149056 (*c.521T>C*) where the wild type T is substituted with variant C causes a change in amino acid of OATP1B1 protein from valine to alanine at 174 positions. This change has been

implicated in reduced OATP1B1 protein function and is associated with an increased risk for statin-induced muscle toxicity.[55] However, an increase in the exposure to rifamycins was not reported in seven studies, and the one study, which reported an increase in AUC for the heterogeneous variant is also statistically non-significant. Lower frequency of rs4149056 CC variant in African populations[56] where the majority of studies were done and small sample size may contribute to no difference in the pharmacokinetics. rs2306283 (*388A>G*) SNP causes a change of asparagine amino acid to aspartic at 130 positions. The consequence of this change on the transporter function is not well elucidated. The patients who were homozygous wild type (AA)[42] and heterozygous (AG)[39] were reported to have lower rifampicin exposure. Similarly, no myopathy was observed with rs2306283 polymorphism which was observed in other *SLCO1B1* genes in patients taking statins suggesting no effect or increased activity of the mutant variant.[57]

rs11045819, which is located on exon 4, is another missense variant known in *SLCO1B1* gene. Of the four studies that assessed the impact of rs11045819 SNPs on rifampicin pharmacokinetics, only Weiner et al reported lower rifampicin exposure, lower peak concentration levels and greater apparent oral clearance with the *SLCO1B1* rs11045819 variant allele (CA) compared to the wild-type allele (CC).[36] This is consistent with a previous report that rs11045819 polymorphism increases OATP1B1 transporter activity and decreases systemic exposure of the OATP1B1 substrate.[58,59]

The well-studied *SLCO1B1* gene SNPs believed to affect rifamycin pharmacokinetics is rs4149032. The rs4149032 is an intron-located SNP and is reported to have a high allelic frequency. The effect of *SLCO1B1* rs4149032 on gene expression and OATP1B1 protein transporter function is not clear yet. Nevertheless, *SLCO1B1* rs4149032 polymorphism was found to be associated with lower rifampicin exposures. Emmanuel et al and Gengiah et al reported that patients who are homozygous mutant and heterozygous for rs4149032 polymorphism have lower bioavailability and Cmax respectively of rifampicin.[32,40] In addition, Kim et al observed lower oral clearance and higher rifampicin exposure for rs4149032 homozygous wild type (TT).[37]

Rifampicin significantly increases gene expression, protein levels, and efflux activity of *ABCB1*.[25,60] It is also a substrate for P-glycoprotein.[61] Huerta-García et al demonstrated that the rs1045642 SNPs, which is a silent mutation, is associated with rifampicin pharmacokinetics. Patients with CC or CT genotypes showed lower values of Cmax and AUC 24 compared to those with a TT genotype.[39] Although the rs1045642 SNPs is a silent mutation, previous studies have shown that rs1045642 affects the P-gp protein either by being in linkage disequilibrium with other functional SNPs or by allele-specific differences in the codon usage affecting the protein folding and function.[62,63] The observed change in the rifampicin pharmacokinetics with rs1045642 SNPs may be attributed to the above explanation.

Rifamycins are metabolized by the esterase enzyme family; microsomal hepatic carboxylesterases (CES), and serine esterase arylacetamide deacetylase (AADAC) to 25-deacetylrifamycins.[14] Three esterase enzymes AADAC, CES1, and CES2 have been reported as enzymes responsible for rifamycin deacetylation. Several genetic polymorphisms of the *CES1* and *CES2* genes have been shown to affect drug metabolism. For example, variations of the *CES1* gene have been reported to affect the metabolism of dabigatran oseltamivir, imidapril, and clopidogrel. Similarly, CES2 gene polymorphisms have been found to affect aspirin and irinotecan.[54] Few studies are available that report the association of *CES1* and *CES2* variants and rifamycin pharmacokinetics. Song et al evaluated 10 SNPs of *CES2* and found increased plasma rifampicin concentrations with the *CES2 c.-22263A>G (g.738A>G)* variants.[45] Although Dompreh et al did not report similar results,[42] the higher frequency of this variant allele warrants further investigation.

AADAC is primarily expressed in the liver and metabolizes clinically important drugs including rifamycins. Three, namely, *AADAC*1* (wild-type), *AADAC*2*, and *AADAC*3,* where the latter two have decreased enzymatic activity, were reported so far.[14,15] Recently, Francis et al and Weiner et al reported *AADAC* rs1803155 SNPs to have a significant effect on rifapentine metabolism. Shortly, a mutant variant of rs1803155 (AA) has decreased activity and decreased clearance of rifapentine. On the other hand, patients who have the wild type (GG) have shown decreased rifapentine exposure.[41,44] Furthermore, Gabriele et al discovered the presence and inter-individual variation of AADAC in the human lung.[64] These findings suggest the important role of *AADAC* pharmacogenetics in tuberculosis drug therapy.

Exposure to rifamycins in particular rifampicin is a crucial variable for successful tuberculosis treatment outcomes. The high inter-individual variability in rifamycins pharmacokinetics have been associated with various factors such as

diabetes mellitus[65] and partly HIV co-infection.[66,67] The majority of studies included in this review included patients with co-morbid conditions. The sample size is also inadequate for some studies.

In conclusion, the genetic polymorphism of drug transporters and drug-metabolizing enzymes has an impact on rifamycin pharmacokinetics. However, based on the available data, it is difficult to identify candidate SNPs in the drug transporters SLCO1B1 and ABCB1 for therapeutic drug monitoring. On the other hand, the effect of drug-metabolizing enzyme SNPs on the rifamycin pharmacokinetics is promising but needs more studies. In general, further controlled clinical studies with adequate sample size are required to characterize the genetic variation influence on the pharmacokinetics of rifamycins for tuberculosis chemotherapy optimization.

Funding

Disclosure

The authors declare no conflicts of interest.

References

1. WHO. Global tuberculosis report 2021. 2021.
2. William J, Burman KG. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. 2001;40 (5):327–341. doi:10.2165/00003088-200140050-00002
3. Surey J, Stagg HR, Yates TA, et al. An open label, randomised controlled trial of rifapentine versus rifampicin based short course regimens for the treatment of latent tuberculosis in England: the HALT LTBI pilot study. *BMC Infect Dis*. 2021;21(1):90. doi:10.1186/s12879-021-05766-9
4. Shayto RH, Abou Mrad R, Sharara AI. Use of rifaximin in gastrointestinal and liver diseases. *World J Gastroenterol*. 2016;22(29):6638–6651. doi:10.3748/wjg.v22.i29.6638
5. Sileshi T, Tadesse E, Makonnen E, Aklillu E. The impact of first-line anti-tubercular drugs' pharmacokinetics on treatment outcome: a systematic review. *Clin Pharmacol*. 2021;13:1–12. doi:10.2147/CPAA.S289714
6. Ramachandran G, Hemanth Kumar AK, Bhavani PK, et al. Age, nutritional status and INH acetylator status affect pharmacokinetics of anti-tuberculosis drugs in children. *Int J Tuberc Lung Dis*. 2013;17(6):800–806. doi:10.5588/ijtld.12.0628
7. Daskapan A, Idrus LR, Postma MJ, et al. A systematic review on the effect of HIV infection on the pharmacokinetics of first-line tuberculosis drugs. *Clin Pharmacokinet*. 2019;58(6):747–766. doi:10.1007/s40262-018-0716-8
8. Alfarisi O, Mave V, Gaikwad S, et al. Effect of diabetes mellitus on the pharmacokinetics and pharmacodynamics of tuberculosis treatment. *Antimicrob Agents Chemother*. 2018;62(11):e01383–18. doi:10.1128/AAC.01383-18
9. Mtabho CM, Semvua HH, van den Boogaard J, et al. Effect of diabetes mellitus on TB drug concentrations in Tanzanian patients. *J Antimicrob Chemother*. 2019;74(12):3537–3545. doi:10.1093/jac/dkz368
10. Afsar NA, Bruckmueller H, Werk AN, Nisar MK, Ahmad HR, Cascorbi I. Implications of genetic variation of common drug metabolizing enzymes and ABC transporters among the Pakistani population. *Sci Rep*. 2019;9(1):7323. doi:10.1038/s41598-019-43736-z
11. Ahmed S, Zhou Z, Zhou J, Chen S-Q. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. *Genom Proteom Bioinform*. 2016;14(5):298–313. doi:10.1016/j.gpb.2016.03.008
12. Choi R, Jeong BH, Koh WJ, Lee SY. Recommendations for optimizing tuberculosis treatment: therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations. *Ann Lab Med*. 2017;37(2):97–107. doi:10.3343/alm.2017.37.2.97
13. Motta I, Calcagno A, Bonora S. Pharmacokinetics and pharmacogenetics of anti-tubercular drugs: a tool for treatment optimization?. *Expert Opin Drug Metab Toxicol*. 2018;14(1):59–82. doi:10.1080/17425255.2018.1416093
14. Nakajima A, Fukami T, Kobayashi Y, Watanabe A, Nakajima M, Yokoi T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: rifampicin, rifabutin, and rifapentine. *Biochem Pharmacol*. 2011;82(11):1747–1756. doi:10.1016/j.bcp.2011.08.003
15. Shimizu M, Fukami T, Kobayashi Y, et al. A novel polymorphic allele of human arylacetamide deacetylase leads to decreased enzyme activity. *Drug Metab Dispos*. 2012;40(6):1183–1190. doi:10.1124/dmd.112.044883
16. Keogh J, Hagenbuch B, Rynn C, Stieger B, Nicholls G. Chapter 1 membrane transporters: fundamentals, function and their role in ADME. Drug transporters: volume 1: role and importance in ADME and drug development. 1: the royal society of chemistry; 2016: 1–56.
17. Shugarts S, Benet LZ. The role of transporters in the pharmacokinetics of orally administered drugs. *Pharm Res*. 2009;26(9):2039–2054. doi:10.1007/s11095-009-9924-0
18. Thomas L, Sekhar Miraj S, Surulivelrajan M, Varma M, Sanju CSV, Rao M. Influence of single nucleotide polymorphisms on rifampin pharmacokinetics in tuberculosis patients. *Antibiotics*. 2020;9(6):307. doi:10.3390/antibiotics9060307
19. Li LM, Chen L, Deng GH, et al. SLCO1B1 *15 haplotype is associated with rifampin-induced liver injury. *Mol Med Rep*. 2012;6(1):75–82. doi:10.3892/mmr.2012.900

20. Mohammad IS, He W, Yin L. Understanding of human ATP binding cassette superfamily and novel multidrug resistance modulators to overcome MDR. *Biomed Pharmacother*. 2018;100:335–348. doi:10.1016/j.biopha.2018.02.038

21. Köck K, Grube M, Jedlitschky G, et al. Expression of adenosine triphosphate-binding cassette (ABC) drug transporters in peripheral blood cells: relevance for physiology and pharmacotherapy. *Clin Pharmacokinet*. 2007;46(6):449–470. doi:10.2165/00003088-200746060-00001

22. Marin JJG. Plasma membrane transporters in modern liver pharmacology. *Scientifica*. 2012;2012:428139. doi:10.6064/2012/428139

23. Juan-Carlos P-DM, Perla-Lidia -P-P, Stephanie-Talia -M-M, Mónica-Griselda A-M, Luz-María T-E. ABC transporter superfamily. An updated overview, relevance in cancer multidrug resistance and perspectives with personalized medicine. *Mol Biol Rep*. 2021;48(2):1883–1901. doi:10.1007/s11033-021-06155-w

24. Schuetz EG, Schinkel AH, Relling MV, Schuetz JD. P-glycoprotein: a major determinant of rifampicin-inducible expression of cytochrome P4503A in mice and humans. *Proc Nat Acad Sci*. 1996;93(9):4001–4005. doi:10.1073/pnas.93.9.4001

25. Martinec O, Biel C, de Graaf IAM, et al. Rifampicin induces gene, protein, and activity of P-glycoprotein (ABCB1) in human precision-cut intestinal slices. *Front Pharmacol*. 2021;12:684156.

26. Khan N, Das A. Can the personalized medicine approach contribute in controlling tuberculosis in general and India in particular?. *Precis Clin Med*. 2020;3(3):240–243. doi:10.1093/pcmedi/pbaa021

27. da Silva Alcobia MC, Nogueira L, Villar M, et al. Precision medicine in tuberculosis treatment – a role for pharmacogenetics?. *Eur Respir J*. 2018;52(suppl 62):PA2689.

28. Mahomed S, Padayatchi N, Singh J, Naidoo K. Precision medicine in resistant tuberculosis: treat the correct patient, at the correct time, with the correct drug. *J Infect*. 2019;78(4):261–268. doi:10.1016/j.jinf.2019.03.006

29. Lange C, Aarnoutse R, Chesov D, et al. Perspective for precision medicine for tuberculosis. *Front Immunol*. 2020;11:2442. doi:10.3389/fimmu.2020.566608

30. Sohani ZN, Meyre D, de Souza RJ, et al. Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies (Q-Genie) tool. *BMC Genet*. 2015;16(1):50. doi:10.1186/s12863-015-0211-2

31. Naidoo A, Chirehwa M, Ramsuran V, et al. Effects of genetic variability on rifampicin and isoniazid pharmacokinetics in South African patients with recurrent tuberculosis. *Pharmacogenomics*. 2019;20(4):224–240. doi:10.2217/pgs-2018-0166

32. Gengiah TN, Botha JH, Soowamber D, Naidoo K, Abdool Karim SS. Low rifampicin concentrations in tuberculosis patients with HIV infection. *J Infect Dev Countries*. 2014;8(8):987–993. doi:10.3855/jidc.4696

33. Jeremiah K, Denti P, Chigutsa E, et al.. Nutritional supplementation increases rifampin exposure among tuberculosis patients coinfected with HIV. *Antimicrob Agents Chemother*. 2014;58(6):3468–3474. doi:10.1128/AAC.02307-13

34. Ramesh K, Hemanth Kumar AK, Kannan T. *SLCO1B1* gene polymorphisms do not influence plasma rifampicin concentrations in a South Indian population. *Int J Tuberc Lung Dis*. 2016;20(9):1231–1235. doi:10.5588/ijtld.15.1007

35. Mukonzo JK, Kengo A, Kutesa B, et al. Role of pharmacogenetics in rifampicin pharmacokinetics and the potential effect on TB-rifampicin sensitivity among Ugandan patients. *Trans R Soc Trop Med Hyg*. 2020;114(2):107–114. doi:10.1093/trstmh/trz108

36. Weiner M, Peloquin C, Burman W, et al. Effects of tuberculosis, race, and human gene SLCO1B1 polymorphisms on rifampin concentrations. *Antimicrob Agents Chemother*. 2010;54(10):4192–4200. doi:10.1128/AAC.00353-10

37. Kim ES, Kwon BS, Park JS, et al. Relationship among genetic polymorphism of SLCO1B1, rifampicin exposure and clinical outcomes in patients with active pulmonary tuberculosis. *Br J Clin Pharmacol*. 2021;87(9):3492–3500. doi:10.1111/bcp.14758

38. Medellin-Garibay SE, Huerta-Garcia AP, Rodriguez-Baez AS, et al. A population approach of rifampicin pharmacogenetics and pharmacokinetics in Mexican patients with tuberculosis. *Tuberculosis*. 2020;124:101982.

39. Huerta-García AP, Medellín-Garibay SE, Salazar-González RA, et al.Anthropometric and genetic factors associated with the exposure of rifampicin and isoniazid in Mexican patients with tuberculosis. *Ther Drug Monit*. 2019;41:648–656.

40. Chigutsa E, Visser ME, Swart EC. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: dosing implications. *Antimicrob Agents Chemother*. 2011;55(9):4122–4127. doi:10.1128/AAC.01833-10

41. Francis J, Zvada SP, Denti P, et al.. A population pharmacokinetic analysis shows that arylacetamide deacetylase (AADAC) gene polymorphism and HIV infection affect the exposure of rifapentine. *Antimicrob Agents Chemother*. 2019;63(4). doi:10.1128/AAC.01964-18.

42. Dompreh A, Tang X, Zhou J, et al.. Effect of genetic variation of NAT2 on isoniazid and SLCO1B1 and CES2 on rifampin pharmacokinetics in Ghanaian children with tuberculosis. *Antimicrob Agents Chemother*. 2018;62(3). doi:10.1128/AAC.02099-17.

43. Sloan DJ, McCallum AD, Schipani A, et al.. Genetic determinants of the pharmacokinetic variability of rifampin in Malawian adults with pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2017;61(7). doi:10.1128/AAC.00210-17.

44. Weiner M, Gelfond J, Johnson-Pais TL, et al. Decreased plasma rifapentine concentrations associated with AADAC single nucleotide polymorphism in adults with tuberculosis. *J Antimicrob Chemother*. 2021;76(3):582–586. doi:10.1093/jac/dkaa490

45. Song SH, Chang HE, Jun SH, et al. Relationship between ces2 genetic variations and rifampicin metabolism. *J Antimicrob Chemother*. 2013;68(6):1281–1284. doi:10.1093/jac/dkt036

46. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev*. 2011;63(1):157–181. doi:10.1124/pr.110.002857

47. Al-Salameh A, Danchin N, Verstuyft C, et al. Association between rs4149056 variant in SLCO1B1 and early discontinuation of statin after acute myocardial infarction. *Pharmacogenomics*. 2020;21(3):163–172. doi:10.2217/pgs-2019-0109

48. Rajman I, Knapp L, Hanna I. Genetic diversity in drug transporters: impact in African populations. *Clin Transl Sci*. 2020;13(5):848–860. doi:10.1111/cts.12769

49. Aklillu E, Habtewold A, Ngaimisi E, et al. SLCO1B1 gene variations among Tanzanians, Ethiopians, and Europeans: relevance for African and worldwide precision medicine. *Omics*. 2016;20(9):538–545. doi:10.1089/omi.2016.0119

50. Luker GD, Flagg TP, Sha Q, et al. MDR1 P-glycoprotein reduces influx of substrates without affecting membrane potential. *J Biol Chem*. 2001;276(52):49053–49060.

51. Bosch TM, Meijerman I, Beijnen JH, Schellens JH. Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer. *Clin Pharmacokinet*. 2006;45(3):253–285. doi:10.2165/00003088-200645030-00003

52. Williamson B, Dooley KE, Zhang Y, Back DJ, Owen A. Induction of influx and efflux transporters and cytochrome P450 3A4 in primary human hepatocytes by rifampin, rifabutin, and rifapentine. *Antimicrob Agents Chemother*. 2013;57(12):6366–6369. doi:10.1128/AAC.01124-13

53. Jamis-Dow CA, Katki AG, Collins JM, Klecker* RW. Rifampin and rifabutin and their metabolism by human liver esterases. *Xenobiotica*. 1997;27 (10):1015–1024. doi:10.1080/004982597239994

54. Merali Z, Ross S, Paré G. The pharmacogenetics of carboxylesterases: CES1 and CES2 genetic variants and their clinical effect. *Drug Metabol Drug Interact*. 2014;29(3):143–151. doi:10.1515/dmdi-2014-0009

55. Linskey DW, English JD, Perry DA, et al. Association of SLCO1B1 c.521T>C (rs4149056) with discontinuation of atorvastatin due to statin-associated muscle symptoms. *Pharmacogenet Genom*. 2020;30(9):208–211. doi:10.1097/FPC.0000000000000412

56. Santos PC, Soares RAG, Nascimento RM, et al. SLCO1B1 rs4149056 polymorphism associated with statin-induced myopathy is differently distributed according to ethnicity in the Brazilian general population: Amerindians as a high risk ethnic group. *BMC Med Genet*. 2011;12(1):136. doi:10.1186/1471-2350-12-136

57. Turongkaravee S, Jittikoon J, Lukkunaprasit T, Sangroongruangsri S, Chaikledkaew U, Thakkinstian A. A systematic review and meta-analysis of genotype-based and individualized data analysis of SLCO1B1 gene and statin-induced myopathy. *Pharmacogenomics J*. 2021;21(3):296–307. doi:10.1038/s41397-021-00208-w

58. Dudenkov TM, Ingle JN, Buzdar AU, et al. SLCO1B1 polymorphisms and plasma estrone conjugates in postmenopausal women with ER+ breast cancer: genome-wide association studies of the estrone pathway. *Breast Cancer Res Treat*. 2017;164(1):189–199. doi:10.1007/s10549-017-4243-3

59. Ramsey LB, Moncrieffe H, Smith CN, et al. Association of SLCO1B1 *14 allele with poor response to methotrexate in juvenile idiopathic arthritis patients. *ACR Open Rheumatol*. 2019;1(1):58–62. doi:10.1002/acr2.1008

60. Westphal K, Weinbrenner A, Zschiesche M, et al. Induction of P-glycoprotein by rifampin increases intestinal secretion of talinolol in human beings: a new type of drug/drug interaction. *Clin Pharmacol Ther*. 2000;68(4):345–355. doi:10.1067/mcp.2000.109797

61. Sissung TM, Baum CE, Kirkland CT, Gao R, Gardner ER, Figg WD. Pharmacogenetics of membrane transporters: an update on current approaches. *Mol Biotechnol*. 2010;44(2):152–167. doi:10.1007/s12033-009-9220-6

62. Bouatou Y, Stenz L, Ponte B, Ferrari S, Paoloni-Giacobino A, Hadaya K. Recipient rs1045642 polymorphism is associated with office blood pressure at 1-year post kidney transplantation: a single center pharmacogenetic cohort pilot study. *Front Pharmacol*. 2018;9. doi:10.3389/fphar.2018.00009

63. Kimchi-Sarfaty C, Oh JM, Kim IW, et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science*. 2007;315 (5811):525–528. doi:10.1126/science.1135308

64. Gabriele M, Puccini P, Lucchi M, Aprile V, Gervasi PG, Longo V. Arylacetamide deacetylase enzyme: presence and interindividual variability in human lungs. *Drug Metab Dispos*. 2019;47(9):961–965. doi:10.1124/dmd.119.087031

65. Metwally AS, El-Sheikh E-S, Galal AAA. The impact of diabetes mellitus on the pharmacokinetics of rifampicin among tuberculosis patients: a systematic review and meta-analysis study. *Diabetes Metab Syndr*. 2022;16(2):102410. doi:10.1016/j.dsx.2022.102410

66. Chideya S, Winston CA, Peloquin CA, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis*. 2009;48(12):1685–1694. doi:10.1086/599040

67. Nardotto GHB, Bollela VR, Rocha A, Della Pasqua O, Lanchote VL. No implication of HIV coinfection on the plasma exposure to rifampicin, pyrazinamide, and ethambutol in tuberculosis patients. *Clin Transl Sci*. 2022;15(2):514–523.