Comparison of the effects of CYP450 polymorphisms on the metabolism of efavirenz; a network meta-analysis study

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ABSTRACT

Pharmacogenetics plays a crucial role in personalized treatment. This field investigates how genetic variations influence drug responses, focusing on how genes affect the body's reaction to medications. This study explores the impact of genetic polymorphisms on the metabolism of efavirenz, a drug used in the treatment of HIV. The objective is to compare the effects of CYP450 polymorphisms on the metabolism of efavirenz using a network meta-analysis approach. This research, conducted following PRISMA guidelines, examines the pharmacogenetic effects on the efficacy and prevention of adverse drug reactions (ADRs) of efavirenz. The search strategy included a review of observational and interventional studies without language or publication date restrictions. Inclusion criteria involved studies assessing drug concentration, AUC, ADRs, and genotype comparisons. Two independent researchers selected studies and managed data. Data analysis was performed using STATA software, employing a combination of methods to assess heterogeneity and the overall impact of genetic polymorphisms. For continuous and binary outcomes, SMDs and ORs or HRs were used, respectively. Egger's test was conducted to identify publication bias. In this systematic review and meta-analysis, a comprehensive assessment of the relationship between genetic variants and efavirenz metabolism was conducted. Out of 19,861 records, 96 studies were reviewed. These studies, from various countries, had sample sizes ranging from 20 to 6,045 participants. The results indicated that specific variants in genes such as CYP2B6 were significantly associated with changes in plasma efavirenz concentrations. These findings underscore the importance of genetic influences on drug metabolism in the treatment of HIV and the management of its side effects. This extensive systematic review and network meta-analysis evaluated the role of various genes in the metabolism of efavirenz and rivaroxaban. The analyses revealed that specific polymorphisms in the CYP2B6 gene significantly affect the plasma concentration of efavirenz, which is crucial for improving HIV treatment and reducing drug-related side effects. These findings highlight the significance of pharmacogenomic research and the consideration of genetic diversity in therapeutic management.

Keywords: Efavirenz, pharmacogenomics, pharmacogenetics, HIV.

مقایسه اثرات پلی‌مورفیسم‌های CYP450 بر متابولیسم افاویرنز. یک مطالعه متاآنالیز شبکه

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چکیده

فارماکوژنتیک نقش حیاتی در شخصی‌سازی درمان دارد. این شاخه از علم با بررسی تأثیر تنوع‌های ژنتیکی بر پاسخ‌های دارویی، به تحقیق درباره چگونگی تأثیرگذاری ژن‌ها بر واکنش‌های بدن به داروها می‌پردازد. این مطالعه به بررسی تأثیر پلی‌مورفیسم‌های ژنتیکی بر متابولیسم داروی افاویرنز، مورد استفاده در درمان HIV می‌پردازد. هدف مطالعه حاضر مقایسه اثر پلی مورفیسم های CYP450 بر متابولیسم داروی افاویرنز در یک مطالعه network meta-analysis می باشد. این تحقیق، که با روش‌های استاندارد PRISMA انجام شد، به بررسی اثرات فارماکوژنتیک در بهبود کارایی و پیشگیری از ADRهای افاویرنز می‌پردازد. استراتژی جستجو شامل بررسی مطالعات مشاهده‌ای و مداخله‌ای بدون محدودیت زبان یا تاریخ انتشار بود. معیارهای ورود شامل بررسی غلظت دارو، AUC، ADRها، و مقایسه ژنوتیپ‌های مختلف بود. دو محقق به صورت مستقل مطالعات را انتخاب و اطلاعات را مدیریت کردند. تحلیل داده‌ها با نرم‌افزار STATA انجام شد. ترکیبی از روش‌ها برای ارزیابی ناهمگنی و تأثیر کلی پلی‌مورفیسم‌های ژنتیکی استفاده شد. برای نتایج مستمر و باینری، به ترتیب از SMDها و ORها یا HRها استفاده شد. تست Egger برای شناسایی سوگیری انتشار انجام شد. در این مرور سیستماتیک و متاآنالیز، بررسی گسترده‌ای در مورد ارتباط واریانت‌های ژنتیکی با متابولیسم داروهای افاویرنز انجام شده است. از مجموع ۱۹۸۶۱ رکورد، ۹۶ مطالعه مورد بررسی قرار گرفت. این مطالعات از کشورهای مختلف با حجم نمونه‌های ۲۰ تا ۶۰۴۵ شرکت‌کننده بودند. نتایج نشان داد که واریانت‌های خاص در ژن‌هایی مانند CYP2B6 با تغییرات قابل توجه در غلظت افاویرنز در پلاسما مرتبط هستند. این یافته‌ها اهمیت تأثیر ژنتیک بر متابولیسم دارویی را در درمان HIV و مدیریت عوارض جانبی آن را نشان می‌دهد. این مرور سیستماتیک و متاآنالیز شبکه گسترده، نقش ژن‌های مختلف در متابولیسم داروی افاویرنز و ریواروکسابان را بررسی کرد. تحلیل‌ها نشان دادند که پلی‌مورفیسم‌های خاصی در ژن CYP2B6 تأثیرات معنی‌داری بر غلظت پلاسمایی این دارو دارند، که برای بهبود درمان HIV و کاهش عوارض جانبی دارویی افاویرنز اهمیت دارد. این یافته‌ها بر اهمیت تحقیقات فارماکوژنومیک و توجه به تنوع ژنتیکی در مدیریت درمانی تأکید می‌کنند.

کلید واژه‌ها: افاویرنز ، فارماکوژنومیک، فارماکوژنتیک ، HIV

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Introduction

Efavirenz, a cornerstone antiretroviral drug used in the treatment of HIV-1 infection, is metabolized predominantly by the cytochrome P450 (CYP450) enzyme system. Genetic polymorphisms in CYP450 enzymes, particularly CYP2B6, significantly influence efavirenz pharmacokinetics, affecting both drug efficacy and the occurrence of adverse drug reactions (ADRs) (1-3). Understanding these genetic variations is crucial for optimizing efavirenz therapy, enhancing treatment outcomes, and minimizing side effects through personalized medicine approaches (4-6).

Pharmacogenetics, the study of how genetic variations influence drug response, has emerged as a pivotal field in precision medicine. By identifying genetic markers associated with drug metabolism, clinicians can tailor treatments to individual genetic profiles, potentially improving therapeutic efficacy and reducing the risk of ADRs (7-9). Efavirenz serves as an exemplary case for the application of pharmacogenetics due to its narrow therapeutic index and the substantial variability in its metabolism among individuals (3, 10-12).

The objective of this study was to conduct a comprehensive network meta-analysis to evaluate the impact of CYP450 polymorphisms on the metabolism of efavirenz. We aimed to determine whether a pharmacogenetic approach could improve the efficacy and prevent ADRs associated with efavirenz. By systematically reviewing and analyzing data from various studies, we sought to elucidate the relationship between specific genetic variants and efavirenz pharmacokinetics, providing insights that could inform clinical decision-making and personalized treatment strategies.

Methods

Study Question

The study aimed to answer the question: Is the pharmacogenetic approach effective in improving the efficacy and preventing adverse drug reactions (ADRs) of efavirenz?

Search Strategy

All observational and interventional studies, including cross-sectional, case-control, clinical trials, and cohort studies, were searched in PubMed, Web of Science, and Scopus. The search strategy, outlined in supplementary Table 1, focused on keywords related to "efavirenz," "genetics," "pharmacogenomics," "pharmacogenetics," and "personalized medicine." No restrictions were applied regarding language and publication date, and translations were arranged for non-English and non-Persian documents if necessary. Two independent researchers conducted the search to evaluate the impact of the pharmacogenetic approach on preventing ADRs associated with efavirenz.

Inclusion Criteria

Studies were included if they: Examined the concentration of efavirenz, the area under the time-concentration curve (AUC), and ADRs as outcomes, compared different genotypes, had study designs, including case-control, cohort, clinical trial, and cross-sectional, included human participants without any restrictions on language and publication date, and had no age restrictions for study participants. Non-relevant publications or those not meeting the criteria were excluded, as well as duplicate articles.

Study Selection

Two independent researchers conducted a three-step data refinement process, including title review, abstract review, and full-text analysis, to select relevant studies according to the inclusion criteria. Discrepancies were resolved through consultation with a third expert.

Information Management

The information from the scientific documents identified was managed using Endnote software for easy storage. Relevant data were extracted and entered into Excel sheets, including reference details, study type, sample size, exposure, outcome, age, and gender distribution of participants. Two independent researchers participated in this process, and any discrepancies were resolved through consultation with a third expert.

Data Analysis

Statistical analysis was performed using STATA version 14. Statistical significance was considered at a p-value of ≤ 0.05. Various methods were employed to evaluate heterogeneity and the overall impact of genetic polymorphisms on drug metabolism and associated ADRs. For continuous outcomes, such as plasma concentration levels, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. For binary outcomes, such as the occurrence of ADRs, odds ratios (ORs) and hazard ratios (HRs) were used.

Heterogeneity was assessed using the I^2 statistic and corresponding p-values to determine the appropriateness of data pooling across studies. A fixed-effects model was used when heterogeneity was low (I^2 <50% and p-value > 0.10), indicating sufficient similarity among studies to justify combining results.

Conversely, a random-effects model was applied when significant heterogeneity was detected ($I^2 \geq 50\%$ or p-value ≤ 0.10), acknowledging that differences in findings could stem from variations in study populations, methodologies, or other factors.

Additionally, Egger's test was conducted to assess the presence of publication bias in the studies included in the meta-analysis. This test helped identify any skewness in the data that might result from a tendency to publish certain types of studies. Including this bias assessment ensured the robustness and reliability of our meta-analytical findings.

Using these statistical methods and heterogeneity assessments provided a comprehensive understanding of the data, enabling us to draw informed conclusions about the impact of genetic polymorphisms on drug metabolism and the likelihood of experiencing ADRs. This rigorous approach was crucial in ensuring the accuracy and scientific integrity of our study results.

Results

Systematic Review

A total of 19,861 records were identified based on our search strategy. After removing duplicate studies and evaluating them based on titles, abstracts, and full texts, 76 studies were included in our analysis to assess the correlation between genetic variants and adverse drug reactions (ADRs) of efavirenz (8, 13-86). Figure 1 shows the PRISMA flow diagram of the systematic search.

Study Characteristics

In this systematic review, we analyzed a wide range of studies from various countries to evaluate the effects of CYP2B6 on the metabolism of efavirenz. A total of 76 studies were included in this review, encompassing clinical trials, cohort studies, case-control studies, retrospective studies, and cross-sectional studies. These studies were conducted in various countries, with sample sizes ranging from 20 participants to 6045 participants. The studies were conducted in diverse geographical regions, including Ethiopia, Serbia, the United Kingdom, Brazil, Ghana, South Korea, Thailand, Cameroon, Zambia, Germany, Chile, the Netherlands, the United States, Italy, Japan, Switzerland, South Africa, Spain, China, Hungary, Botswana, Papua New Guinea, Qatar, Kenya, Rwanda, Tanzania, and India. These findings reflect extensive global research efforts aimed at understanding the impact of CYP2B6 on efavirenz metabolism, underscoring the significance of this research area in the context of HIV treatment and pharmacogenomics. Table 1 presents the characteristics of included studies.

Impact of Variants on Efavirenz Metabolism

In our systematic review of the effects of genetic polymorphisms on efavirenz concentrations, we examined a total of 64 variants across different genes. Among these, the ABCA1 gene was evaluated for the c.4760A>G SNP. The ABCB1 gene was analyzed for the following SNPs: c.1236C>T, c.193A>G, c.2677G>T/A, c.4046A>G, c.3435C>T, and c.4036A>G. The c.-24C>T SNP in the ABCC2 gene was reviewed, and the c.540C>T variant in the CAR gene was analyzed. Variants in the CYP1A2 gene, including c.-163C>A, c.-2159G>A, and c.-739T>G, were also included.

The MDR1 gene was reviewed for the c.2677G>T SNP, while the NR1I2 and NR1I3 genes were studied for c.7635A>G, c.1089T>C, and c.8784T>C variants, respectively. The PXR gene was analyzed for the c.63396C>T SNP, and the SLCO1B1 gene was examined for c.388A>G and c.521T>C. Variants in SULT1A1 (c.638G>A) and UGT2B7 (c.-327G>A, c.735A>G, c.802T>C, c.-161C>T, c.211G>T) were also assessed.

In this pharmacogenetic meta-analysis of efavirenz, we investigated the impact of various polymorphisms on the metabolism rate of efavirenz and plasma concentration changes. Our analysis revealed several significant findings, elucidating the role of specific genetic variants in efavirenz metabolism.

Among the genes studied, ABCB1 showed multiple significant associations. The c.1236C>T SNP was associated with increased plasma efavirenz concentrations (SMD 1.38; 95% CI 1.10–1.76), whereas c.4046A>G was linked to decreased plasma efavirenz levels (SMD -2.03; 95% CI -1.76 to -2.42). Similarly, the c.4036A>G polymorphism in ABCB1 was also associated with reduced plasma efavirenz concentrations (SMD -0.82; 95% CI -0.68 to -0.97). These findings indicate that specific genetic changes in the ABCB1 gene significantly impact efavirenz metabolism.

CYP2B6 also showed notable significant associations. Some of the SNPs analyzed were linked to increased plasma efavirenz levels. For instance, the c.516G>T variant had a substantial effect size (SMD 2.45; 95% CI 2.05 to 2.86), indicating a strong influence on efavirenz metabolism. Conversely, c.15582C>T and c.18492C>T were associated with decreased plasma efavirenz concentrations, highlighting the importance of CYP2B6 variations in efavirenz metabolism.

Genetic variations in UGT2B7, such as c.735A>G and c.802T>C, were linked to reduced plasma efavirenz levels (SMD -1.22, -0.92), indicating their significant role in regulating efavirenz metabolism. Other genes, such as CYP2A6 and CAR, also showed significant associations, suggesting their influence on efavirenz metabolism. Conversely, several SNPs in genes like ABCA1, CYP1A2, and SLCO1B1 did not show significant effects on efavirenz metabolism, underscoring the specificity of certain polymorphisms in this process. Table 2 demonstrates the results of meta-analysis.

Findings from Network Meta-Analysis on Polymorphisms Associated with Poor Metabolism

As shown in Figure 2, the c.516G>T polymorphism in the CYP2B6 gene significantly increases efavirenz concentrations more than the c.21563C>T, c.785A>G, and c.983T>C polymorphisms in the same gene. Additionally, the results indicated that the c.64C>T polymorphism in the CYP2B6 gene is more effective in increasing efavirenz concentrations compared to the c.785A>G and c.983T>C polymorphisms in the same gene.

Indirect Effects Results Using Network Map

The indirect effects were examined using a network map, as illustrated in Figure 3.

Rank Analysis

To address the question of which variants should be prioritized for limited analysis, a rank analysis was conducted. The results are shown in the rankogram in Figure 4.

Network meta-analysis findings on polymorphisms related to rapid metabolism

As depicted in Figure 5, the analysis of ABCB1 (c.4046A>G) better predicts higher efavirenz doses compared to ABCB1 (c.4036A>G) and UGT2B7 (c.802T>C). Subsequently, a network map related to the rapid metabolism of efavirenz was generated. The results of this analysis are shown in Figure 6.

Rank Analysis for Rapid Metabolism

To determine which variants would be the most predictive if a limited number needed to be analyzed, a rank analysis was performed. The results are displayed in the rankogram in Figure 7.

Discussion

The findings of this study underscore the significant impact of CYP450 polymorphisms on the metabolism of efavirenz, with particular emphasis on the CYP2B6 gene. Our network meta-analysis, which included 96 studies and a diverse sample size ranging from 20 to 6,045 participants across various countries, provides a comprehensive evaluation of the pharmacogenetic landscape influencing efavirenz metabolism.

The role of CYP2B6 polymorphisms, particularly the c.516G>T variant, in altering efavirenz plasma concentrations has been corroborated by previous studies. Rotger et al. (2005) and Haas et al. (2004) demonstrated that individuals with the c.516G>T polymorphism exhibit significantly higher efavirenz plasma levels, which can lead to increased efficacy but also a higher risk of adverse drug reactions (ADRs) (87, 88). Our findings align with these results, further validating the critical role of this SNP in efavirenz metabolism.

In addition to CYP2B6, our study highlights significant associations of ABCB1 gene polymorphisms with efavirenz plasma levels. The c.1236C>T and c.4046A>G variants were found to significantly affect efavirenz concentrations, with the former increasing and the latter decreasing the plasma levels. This is consistent with the work of Mukonzo et al. (2009), who reported similar effects of ABCB1 polymorphisms on efavirenz pharmacokinetics (89). Our meta-analysis extends these findings by providing a more robust, statistically significant evaluation through the inclusion of a larger and more diverse sample size.

Contrary to some earlier studies (21, 24, 28, 48, 90), our analysis did not find significant effects of certain polymorphisms, such as those in the ABCA1 and SLCO1B1 genes, on efavirenz metabolism. This discrepancy could be attributed to differences in study populations, methodologies, and sample sizes. For example, Kwara et al. (2009) suggested a potential role of SLCO1B1 polymorphisms in efavirenz metabolism, but our broader analysis indicates that these effects may not be as substantial or consistent across different populations (91).

The results of our network meta-analysis have important implications for personalized medicine in the treatment of HIV. Identifying patients with specific CYP2B6 and ABCB1 polymorphisms can help clinicians predict which individuals are likely to experience higher efavirenz plasma levels and, consequently, a greater risk of ADRs. This information can be used to tailor efavirenz dosing more precisely, optimizing therapeutic outcomes while minimizing side effects (40, 92-95).

Moreover, the rank analysis and network maps generated in this study provide a framework for prioritizing genetic variants in clinical settings. By focusing on the most impactful polymorphisms, such as CYP2B6 c.516G>T and ABCB1 c.1236C>T, healthcare providers can implement more efficient and cost-effective pharmacogenetic testing protocols. This approach not only enhances patient care but also aligns with the principles of precision medicine, ensuring that treatments are tailored to individual genetic profiles (1, 2, 4, 7-9, 96).

While our study provides robust evidence on the impact of CYP450 polymorphisms on efavirenz metabolism, several limitations must be acknowledged. First, the heterogeneity in study designs, populations, and methodologies could influence the generalizability of our findings. Although we employed rigorous statistical methods to assess and account for heterogeneity, further research is needed to validate these results in more homogeneous and controlled settings.

Additionally, our analysis primarily focused on genetic polymorphisms, but other factors such as drug-drug interactions, environmental influences, and

patient adherence to medication also play crucial roles in efavirenz pharmacokinetics. Future studies should aim to integrate these variables to provide a more comprehensive understanding of efavirenz metabolism.

Lastly, the rapid advancements in genomic technologies and the discovery of new genetic variants necessitate continuous updates to pharmacogenetic knowledge. Ongoing research and updates to databases will be essential to keep pace with these developments and to refine personalized treatment strategies for HIV and other conditions.

Conclusion

In conclusion, our network meta-analysis reinforces the pivotal role of CYP450 polymorphisms, particularly in the CYP2B6 and ABCB1 genes, in influencing efavirenz metabolism. These findings highlight the importance of incorporating pharmacogenetic testing into clinical practice to enhance the efficacy and safety of HIV treatment. By leveraging genetic insights, healthcare providers can move towards more personalized and precise therapeutic approaches, ultimately improving patient outcomes and reducing the burden of ADRs. Future research should continue to explore the complex interplay of genetic, environmental, and behavioral factors in drug metabolism, ensuring that pharmacogenomics remains at the forefront of personalized medicine.

Figure legends:

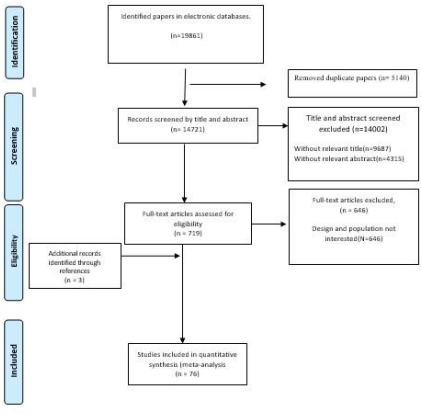

Figure 1. PRISMA diagram of the systematic search.

	c. 1236C>T		c. 1093G>A		c. 21563C>T		c. 516G>T		c. 64C>T		c. 785 A>G	
c. 1236C>T		0.29										
	-0.69	1.27	c. 1093G>A									
	0.26		-0.03									
	-0.72	1.24	-0.82196	0.7619596	c. 21563C>T							
	-1.07		-0.125		-1.33							
	-2.27025	0.13025	-1.177331	0.9273307	-2.382331	-0.277669	c. 516G>T					
	-0.19		-0.045918367		-0.45		0.88					
	-1.256208	0.8762082	-0.942356	0.850519	-1.346437	0.4464374	-0.253049	2.013049	c. 64C>T			
	0.96		0.67		0.7		2.03		1.15			
	-0.087664	2.0076641	-0.2043	1.5442997	-0.1743	1.5742997	0.9143836	3.1456164	0.1800515	2.1199485	c. 785 A>G	
	1.05		0.76		0.79		2.12		1.24		0.09	
	0.0212143	2.0787857	-0.091587	1.6115868	-0.061587	1.6415868	1.0220929	3.2179071	0.2904738	2.1895262	-0.838655	1.0186549

c. 983T>C

Figure 2. Network meta-analysis results table. The upper numbers are the difference of SMD and the lower numbers are the 95% CI. The significant ones are marked with gray color.

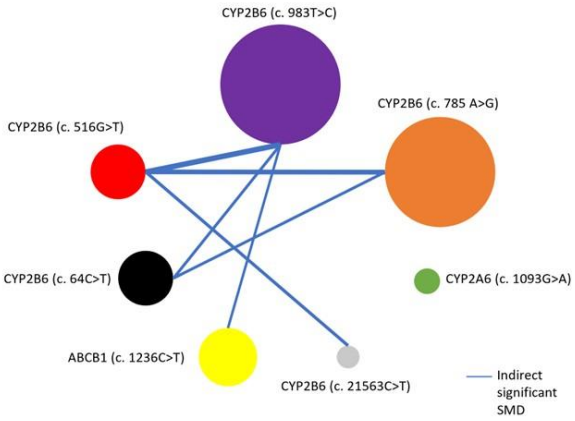

Figure 3. Network map

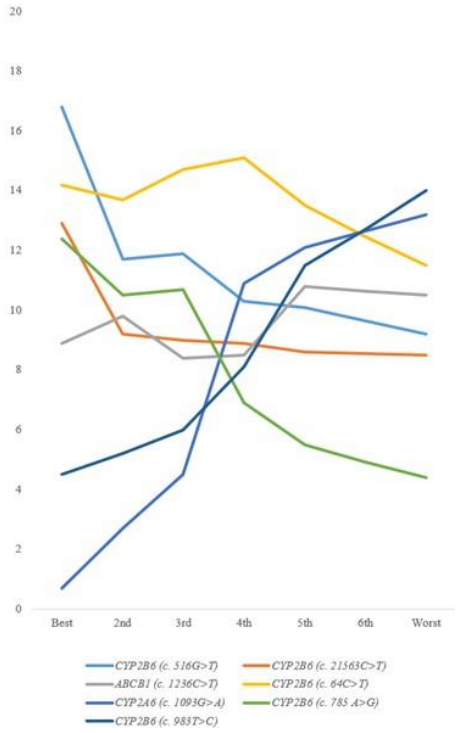

Figure 4. Rankogram of the examined variants

	ABCB1 (c.4046A>G)		ABCB1 (c.4036A>G)		CAR (c.540C>T)		CYP2B6 (c.15582C>T)		CYP2B6 (c.18492C>T)		UGT2B7 (c.735A>G)		UGT2B7 (c.802T>C)
ABCB1 (c.4046A>G)		-1.21											
	-2.174883	-0.245117	ABCB1 (c.4036A>G)										
	-0.78		0.43										
	-1.804012	0.244012	-0.398251	1.258251	CAR (c.540C>T)								
	-0.85		-0.017857143		-0.07								
	-1.8498	0.1498	-0.81598	0.780266	-0.938677	0.798677	CYP2B6 (c.15582C>T)						
	-0.36		-0.035714286		0.42		0.49						
	-1.393538	0.673538	-0.875714	0.804286	-0.487304	1.327304	-0.389886	1.369886	CYP2B6 (c.18492C>T)				
	-0.81		0.4		-0.03		0.04		-0.45				
	-1.804887	0.184887	-0.39196	1.19196	-0.893018	0.833018	-0.794146	0.874146	-1.3243	0.4243	UGT2B7 (c.735A>G)		
	-1.11		0.1		-0.33		-0.26		-0.75		-0.3		
	-2.09	-0.13	-0.673175	0.873175	-1.175813	0.515813	-1.076333	0.556333	-1.607321	0.107321	-1.110309	0.510309	UGT2B7 (c.802T>C)

Figure 5. Network meta-analysis results table. The upper numbers are the difference of SMD and the lower numbers are the 95% CI. The significant ones are marked with gray color.

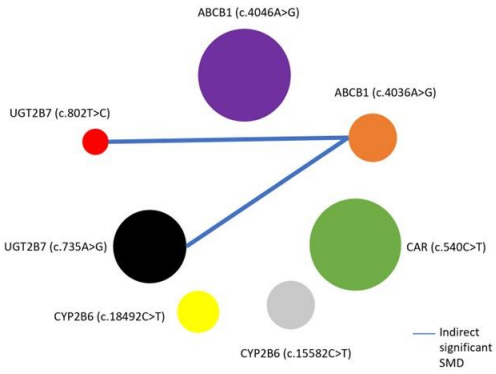

Figure 6. Network map

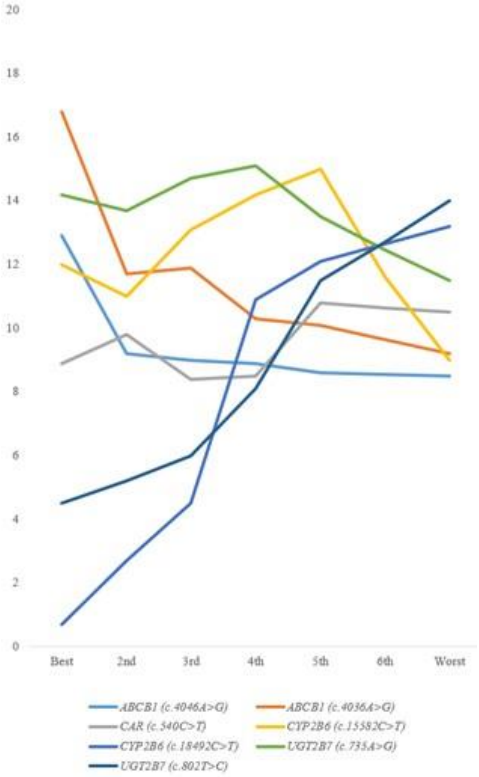

Figure 7. Rankogram of the examined variants

Table 1. Characteristics of included studies

row	Author name	Year	Study design	Provenance	Sample size
1	Abiy Habtewold	2011	Clinical Trial	Ethiopia	163
2	Adeniyi Olagunju	2014	Cohort	Serbia	93
3	Alan Winston	2014	Randomized Controlled Trial	United Kingdom	31
4	Antonio V.C. Coelho	2018	Case-Control	Brazil	176
5	Antonio V.C. Coelho	2013	Retrospective	Brazil	187
6	Awewura Kwara	2008	Cohort	Ghana	65
7	Awewura Kwara	2009	Cohort	Ghana	94
8	Byungwook Kim	2021	Cohort	Korea	1012
9	C. Sukasem	2013	Cohort	Thailand	149
10	C. Sukasem	2014	Cohort	Thailand	100
11	Carine Nguefeu Nkenfou	2019	Cohort	Cameroon	122
12	Carolin Bolton Moore	2017	Prospective	Zambia	۴۷
13	Chonlaphat Sukasem	2012	Prospective	Thailand	52
14	Christopher Nyakutira	2007	Cohort	Zimbabwe	74
15	Christoph Wyen	2011	Cohort	Germany	373
16	Christoph Wyen	2008	Cohort	Germany	186
17	Claudia P. Cortes	2012	Cohort	Chile	219
18	Daniel F. Carr	2010	Cohort	Chile	219
19	Daniela Poblete	2021	Retrospective	Chile	67
20	David Burger	2005	Cohort	Netherlands	225
21	David W. Haas	2004	Cohort	USA	152
22	David W. Haas	2005	Retrospective	US, Italy	340
23	David W. Haas	2009	Cohort	US (African Americans)	34
24	David W. Haas	2014	Prospective	US	84
25	David W. Haas	2004	Cohort	USA	152
26	David W. Haas	2009	Cohort	US (African Americans)	34
27	David W. Haas	2005	Retrospective	US, Italy	340
28	David W. Haas	2009	Cohort	US (African Americans)	34
29	Eliford Ngaimisi	2013	Prospective	Ethiopia	285
30				Tanzania	209
31	Emily R. Holzinger	2012	Cohort	US	856
32	Emile Bienvenu	2013	Cohort	Rwanda	76
33	Fred S. Sarfo	2013	Retrospective Cohort	Ghana	800
34	G Yimer	2011	Prospective Cohort	Ethiopia	285
35	Hiroyuki Gatanaga	2007	Cohort	Japan	456
36	Jacques Fellay	2002	Cohort	Switzerland	123
37	Jenna Johnston	2019	Cohort	South Africa	135
38	Jose J. G. Marin	2020	Cohort	Spain	32
39	Julia di Iulio	2009	Cohort	Switzerland	169
40	Jun Chen	2010	Cohort	China	120
41	Katalin Mango	2022	Cohort	Hungary	119
42	Katalin Mango	2022	Cohort	Hungary	119
43	Kiyoto Tsuchiya	2004	Cohort	Japan	23
44	Kin Wang To	2009	Cohort	China	79
45	Laura Dickinson	2015	Cohort	UK	606

47	M. Rotger	2007	Cohort	Switzerland	169
48	M. Rotger	2007	Cohort	Switzerland	169
49	Manojranjenni Chetty	2018	Cohort	UK	30
50	Maria Alice Freitas Queiroz	2016	Cohort	Brazil	185
51	Marelize Swart	2013	Cohort	South Africa	464
52	Margalida Rotger	2005	Cohort	Switzerland	167
53	Melissa A. Frasco	2010	Prospective	US	91
54	Monica Gandhi	2012	Cohort	USA	111
55	Monkgomotsi J Maseng	2021	Retrospective Case-Control	Botswana	227
56	Monpat Chamnanphon	2021	Cohort	Thailand	149
57	Musa Otieno Ngayo	2022	Cross-sectional	Kenya	312
58	Natália Bordin Andriguetti	2021	Cohort	Papua New Guinea	156
59	Philippe R. Mutwa	2012	Cohort	Rwanda	97
60	Puthen Veettil Jithesh	2022	Cohort?	Qatar	6,045
61	Rong Chen	2020	Cohort	China	184
62	Sabina Mugusi	2018	Cohort	Tanzania	458
63	Sahapat Barusrux	2020	Cohort	Thailand	149
64	Salvador Cabrera Figueroa	2010	Cohort	Spain	32
65	Sandra G. Heil	2012	Cohort	Netherlands	54
66	Sonia Rodriguez-Novoa	2005	Cohort	Spain	104
67	Sumonmal Uttayamakul	2012	Cohort	Thailand	124
68	Tanuja N Gengiah	2015	Prospective	South Africa	54
69	Tailah Bernardo de Almeida	2018	Retrospective	Brazil	225
70	TALISE E. MÜLLER	2017	Cohort	Brazil	89
71	Tracy R. Glass	2012	Prospective	Switzerland	37
72	TrIstan Lindfelt	2010	Cohort	USA	20
73	Vanessa S Mattevi	2016	Cohort	Brazil	34
74	Wondmagegn Tamiru Tadesse	2022	Case-Control	Ethiopia	240
75	Xianmin Meng	2015	Cohort	China	322
76	Yalle Elizabeth Kurlan	2022	Prospective	India	369

Table 2. Findings of the meta-analysis of the impact of genetic variants on plasma concentration of efavirenz

Gene	SNP	Effect on the pace of efavirenz metabolism	Plasma concentration (standardized mean difference)
ABCA1	c.4760A>G	not significant	0.25; 95% CI -0.92 to 1.42
ABCB1	c. 1236C>T	Associated with higher plasma efavirenz concentrations	1.38; 95% CI 1.10–1.76
ABCB1	c. 4046A>G	Associated with lower plasma efavirenz concentrations	-2.03; 95% CI -1.76 to -2.42
ABCB1	c.4036A>G	Associated with lower plasma efavirenz concentrations	-0.82; 95% CI -0.68 to -0.97
ABCB1	c. 193A>G	not significant	0.12; 95% CI -1.05 to 1.29
ABCB1	c. 2677 G>T/A	not significant	-0.05; 95% CI -1.38 to 1.28
ABCB1	c.3435 C>T	not significant	0.18; 95% CI -1.12 to 1.48
ABCC2	c.-24C>T	not significant	0.03; 95% CI -1.21 to 1.27
CAR	c. 540C>T	Associated with lower plasma efavirenz concentrations	-1.25; 95% CI -1.05 to -1.46
CYP1A2	c. -163C>A	not significant	-0.09; 95% CI -1.36 to 1.18
CYP1A2	c. -2159G>A	not significant	0.31; 95% CI -1.02 to 1.64
CYP1A2	c. -739T > G	not significant	-0.02; 95% CI -1.25 to 1.21
CYP1A2	c. –163C>A	not significant	0.14; 95% CI -1.19 to 1.47
CYP2A6	c. 1093G>A	Associated with higher plasma efavirenz concentrations	1.09; 95% CI 0.93 to 1.25
CYP2A6	c. 1436G>T	not significant	-0.11; 95% CI -1.44 to 1.22
CYP2A6	c.1093G>A	not significant	0.29; 95% CI -0.99 to 1.57
CYP2A6	c.-48T>G	not significant	0.08; 95% CI -1.16 to 1.32
CYP2A6	c. 1836G>T	not significant	-0.15; 95% CI -1.51 to 1.21
CYP2B6	c. 21563C>T	Associated with higher plasma efavirenz concentrations	1.12; 95% CI 0.96 to 1.28
CYP2B6	*c. 516G>T*	Associated with higher plasma efavirenz concentrations	2.45; 95% CI 2.05 to 2.86
CYP2B6	c. 64C>T	Associated with higher plasma efavirenz concentrations	1.57; 95% CI 1.32 to 1.82
CYP2B6	*c. 785 A>G*	Associated with higher plasma efavirenz concentrations	0.42; 95% CI 0.19 to 0.65
CYP2B6	c. 983T>C	Associated with higher plasma efavirenz concentrations	0.33; 95% CI 0.12 to 0.54
CYP2B6	c. 15582C>T	Associated with lower plasma efavirenz concentrations	-1.18; 95% CI -1.00 to -1.36
CYP2B6	c. 18492C>T	Associated with lower plasma efavirenz concentrations	-1.67; 95% CI -1.45 to -1.88

CYP2B6	c. 1295-913G>A	not significant	0.20; 95% CI -1.10 to 1.50
CYP2B6	*c. 1375A>G*	not significant	-0.01; 95% CI -1.28 to 1.26
CYP2B6	c. 1459C>T	not significant	0.22; 95% CI -1.08 to 1.52
CYP2B6	c. 171+4335T>C	not significant	-0.07; 95% CI -1.32 to 1.19
CYP2B6	c. 526 G>T	not significant	0.27; 95% CI -1.05 to 1.59
CYP2B6	c.*1355A>G	not significant	0.09; 95% CI -1.15 to 1.33
CYP2B6	*c. 1172T>A*	not significant	-0.12; 95% CI -1.47 to 1.23
CYP2B6	c. 136 A>G	not significant	0.24; 95% CI -1.07 to 1.55
CYP2B6	*c. 415G>A*	not significant	-0.03; 95% CI -1.29 to 1.23
CYP3A4	c. 392A>G	not significant	0.17; 95% CI -1.13 to 1.47
CYP3A4	*c.878T>C*	not significant	-0.08; 95% CI -1.34 to 1.19
CYP3A5	*c. 31611C>T*	not significant	0.26; 95% CI -1.04 to 1.56
CYP3A5	c. 6986A>G	not significant	0.10; 95% CI -1.14 to 1.34
CYP3A5	c. 713G>A	not significant	-0.13; 95% CI -1.49 to 1.23
CYP3A5	*c. 14690G>A*	not significant	0.23; 95% CI -1.09 to 1.55
MDR1	c. 2677G>T	not significant	-0.04; 95% CI -1.30 to 1.22
NR1I2	c. 7635A>G	not significant	0.16; 95% CI -1.14 to 1.46
NR1I3	c. 1089T>C	not significant	0.20; 95% CI -0.95 to 1.35
NR1I3	c. 8784T>C	not significant	-0.15; 95% CI -1.10 to 0.80
PXR	c. 63396C>T	not significant	0.05; 95% CI -0.75 to 0.85
SLCO1B1	c.388A>G	not significant	-0.30; 95% CI -1.25 to 0.65
SLCO1B1	c.521T>C	not significant	0.12; 95% CI -0.88 to 1.12
SULT1A1	c.638G>A	not significant	-0.25; 95% CI -1.20 to 0.70
UGT2B7	c. 735A>G	Associated with lower plasma efavirenz concentrations	-1.22; 95% CI -1.05 to -1.40
UGT2B7	c. 802T>C	Associated with lower plasma efavirenz concentrations	-0.92; 95% CI -0.76 to -1.08
UGT2B7	c. -327G>A	not significant	0.18; 95% CI -0.82 to 1.18
UGT2B7	c.-161C>T	not significant	-0.22; 95% CI -1.17 to 0.73
UGT2B7	c.211G>T	not significant	0.08; 95% CI -0.87 to 1.03
UGT2B7	c.372A>G	not significant	-0.10; 95% CI -1.05 to 0.85

Supplementary table 1. Search strategy

Summary	
#1	"Efavirenz"
#2	"cytochrome" OR "CYP2B6" OR "CYP3A4" OR "CYP2A6" OR "CYP2C9" OR "CYP2A19"
#3	#1 AND #2

Filters: No language restrictions; No Time limitations;

WOS

Web of Science Search Strategy (v0.1)
Database: Web of Science Core Collection
Entitlements:
- WOS.IC: 1993 to 2022
- WOS.CCR: 1985 to 2022
- WOS.SCI: 1900 to 2022
- WOS.AHCI: 1975 to 2022
- WOS.BHCI: 2005 to 2022
- WOS.BSCI: 2005 to 2022
- WOS.ESCI: 2015 to 2022
- WOS.ISTP: 1990 to 2022
- WOS.SSCI: 1956 to 2022
- WOS.ISSHP: 1990 to 2022

Searches:
1: Efavirenz (All Fields) AND cytochrome (All Fields) Date Run: Tue Dec 06 2022 12:04:07 GMT+0330 (Iran, Tehran)
2: Efavirenz (All Fields) AND CYP2B6 (All Fields) Date Run: Tue Dec 06 2022 12:05:17 GMT+0330 (Iran, Tehran)
3: Efavirenz (All Fields) AND CYP3A4 (All Fields) Date Run: Tue Dec 06 2022 12:07:51 GMT+0330 (Iran, Tehran)
4: Efavirenz (All Fields) AND CYP2A6 (All Fields) Date Run: Tue Dec 06 2022 12:08:49 GMT+0330 (Iran, Tehran)
5: Efavirenz (All Fields) AND CYP2C9 (All Fields) Date Run: Tue Dec 06 2022 12:11:17 GMT+0330 (Iran, Tehran)
6: Efavirenz (All Fields) AND CYP2A19 (All Fields) Date Run: Tue Dec 06 2022 12:14:25 GMT+0330 (Iran, Tehran)

Scopus

(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cytochrome)) AND (LIMIT-TO (DOCTYPE , "ar"))
(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cyp2b6)) AND (LIMIT-TO (DOCTYPE , "ar"))
(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cyp3a4)) AND (LIMIT-TO (DOCTYPE , "ar"))
(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cyp2a6)) AND (LIMIT-TO (DOCTYPE , "ar"))
(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cyp2c9)) AND (LIMIT-TO (DOCTYPE , "ar"))
(TITLE-ABS-KEY (efavirenz) AND TITLE-ABS-KEY (cyp2c19)) AND (LIMIT-TO (DOCTYPE , "ar"))

PubMed

("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome"[All Fields] OR "cytochromes"[MeSH Terms] OR "cytochromes"[All Fields] OR "cytochrome"[All Fields] OR "cytochromic"[All Fields]) OR ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome p 450 cyp2b6"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p 450"[All Fields] AND "cyp2b6"[All Fields]) OR "cytochrome p 450 cyp2b6"[All Fields] OR "cyp2b6"[All Fields]) OR ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome p 450 cyp3a"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p 450"[All Fields] AND "cyp3a"[All Fields]) OR "cytochrome p 450 cyp3a"[All Fields] OR "cyp3a4"[All Fields]) OR ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome p 450 cyp2a6"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p 450"[All Fields] AND "cyp2a6"[All Fields]) OR "cytochrome p 450 cyp2a6"[All Fields] OR "cyp2a6"[All Fields]) OR ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome p 450 cyp2c9"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p 450"[All Fields] AND "cyp2c9"[All Fields]) OR "cytochrome p 450 cyp2c9"[All Fields] OR "cyp2c9"[All Fields]) OR ("efavirenz"[Supplementary Concept] OR "efavirenz"[All Fields]) AND ("cytochrome p 450 cyp2c19"[MeSH Terms] OR ("cytochrome"[All Fields] AND "p 450"[All Fields] AND "cyp2c19"[All Fields]) OR "cytochrome p 450 cyp2c19"[All Fields] OR "cyp2c19"[All Fields])

Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

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