УДК 616.98:578.828.6
http://dx.doi.org/10.22328/2077-9828-2022-14-3-65-76

PHARMACOGENETIC EFFECTS OF SINGLE NUCLEOTIDE POLYMORPHISMS COMMONLY ASSOCIATED WITH ANTIRETROVIRAL THERAPY METABOLISM

A. Bazhenova[*], *K. Mironov, A. Kravchenko, V. Akimkin*
Central Research Institute of Epidemiology, Moscow, Russia

Introduction. Identification of pharmacogenetic effects on antiretroviral therapy (ART) has become an important milestone to reach in the advancement of personalised treatment for HIV-positive patients. The therapy schemes are accompanied by multiple side effects. Therapy effectiveness and adverse reactions can be dictated by individual genetic predisposition factors, which should be taken into account for an optimal prescription. Some genetic markers (HLA-B*57:01 and UGT1A1*28), were already proven to improve discontinuation rates, and efforts are allocated to expand the range of clinically-relevant genetic tests.
Objective. In this review, an updated summary of genetic polymorphisms and their effects defining patients' tolerability to ART is presented. The aim of this research is to assess single nucleotide polymorphisms (SNPs) present in the genes that encode proteins involved in ART metabolism and transport. This review will be used to develop a PCR-based testing methodology for the detection and confirmation of risk alleles in the Caucasian population.
Materials and methods. Data from 46 original research papers and reviews was analysed. Allele frequencies of the most relevant polymorphisms were checked against the data for European population.
Results. As an outcome of this review, a few most promising SNPs were selected for future research. Firstly, *ABCC4* rs1751034 and rs3742106 and *ABCC10* rs9349256 and rs2125739 were associated with an increased risk of renal impairment, higher plasma concentration, and toxicity when treated with tenofovir. Parallel analysis of *ABCC4* and *ABCC10* SNP effects on renal impairment together with *CYP24A1* rs2248359 that was recently reported as a potential renal toxicity marker might be more informative. Secondly, *CYP2B6* rs3745274 that was associated with an increased efavirenz plasma concentration, and increased risk of liver and CNS toxicity should be evaluated. SNPs in *CYP2B6*, *CYP2A6* (rs28399433), and *CYP3A4* (rs4646437) should be evaluated in parallel since possession of all three variants might put patients at a much higher risk.
Conclusion. Identified alleles could become new markers used in drug prescription protocols if significant effect in Caucasian population will be found. The most relevant SNPs should be tested in in supporting future studies to evaluate the significance for patients with HIV in Russia.

Keywords: HIV, genetic polymorphisms, toxicity, personalised medicine

[*]Contact: *Alexandra Ya. Bazhenova, bazhenovaaleksandra@gmail.com*

ФАРМАКОГЕНЕТИЧЕСКИЕ ЭФФЕКТЫ ОДНОНУКЛЕОТИДНЫХ ПОЛИМОРФИЗМОВ, ВЛИЯЮЩИХ НА МЕТАБОЛИЗМ АНТИРЕТРОВИРУСНЫХ ПРЕПАРАТОВ

А. Я. Баженова[*], *К. О. Миронов, А. В. Кравченко, В. Г. Акимкин*
Центральный научно-исследовательский институт эпидемиологии, Москва, Россия

Введение. Определение фармакогенетических особенностей при назначении антиретровирусной терапии (АРТ) является важной составляющей персонализированного лечения ВИЧ-позитивных пациентов. АРТ может приводить к развитию различных нежелательных явлений (НЯ). Эффективность терапии и возникновение НЯ могут быть обусловлены генетической предрасположенностью, которую следует учитывать при выборе схемы АРТ. Некоторые известные аллели (HLA-B*57:01 и UGT1A1*28) связаны с развитием НЯ и прекращением приема АРТ. В настоящее время важной клинической задачей является расширение спектра клинически значимых генетических тестов.
Цель. В обзоре представлены данные об эффектах генетических полиморфизмов, влияющих на переносимость АРТ. Проведен анализ данных об однонуклеотидных полиморфизмах (SNP) в генах, участвующих в метаболизме и транспорте

АРТ. Результаты обзора предполагается использовать для разработки основанных на полимеразной цепной реакции методик определения аллелей риска в европейской популяции.

Материалы и методы. Проанализированы данные 46 публикаций. При анализе учитывались данные о частотах аллелей SNP в европейской популяции.

Результаты. Выбрано несколько наиболее перспективных SNP. Полиморфизмы в генах *ABCC4* (rs1751034, rs3742106) и *ABCC10* (rs9349256, rs2125739) связаны с повышенным риском нарушения функции почек, обусловленного более высокой концентрацией в плазме крови препарата тенофовир. Показана эффективность одновременного исследования SNP в этих генах и *CYP24A1* (rs2248359) как потенциального маркера нефротоксичности. Полиморфизм в гене *CYP2B6* (rs3745274) связан с повышением концентрации эфавиренца в плазме крови, повышенным риском гепатотоксичности и развития НЯ со стороны ЦНС. SNP в *CYP2B6*, *CYP2A6* (rs28399433) и *CYP3A4* (rs4646437) следует исследовать вместе, поскольку все три SNP ассоциированы с высоким риском развития НЯ.

Заключение. Описанные аллели SNP являются новыми диагностическими маркерами, которые могут быть использованы при назначении АРТ. Для оценки их клинической значимости и перспектив практического применения у пациентов с ВИЧ-инфекцией в России требуется проведение дополнительных исследований.

Ключевые слова: ВИЧ, полиморфизмы, токсические осложнения, персонализированная медицина

*Контакт: *Баженова Александра Ярославна, bazhenovaaleksandra@gmail.com*

Conflict of interest: the authors stated that there is no potential conflict of interest.

For citation: Bazhenova A., Mironov K., Kravchenko A., Akimkin V. Pharmacogenetic effects of single nucleotide polymorphisms commonly associated with antiretroviral therapy metabolism // *HIV Infection and Immunosuppressive Disorders*. 2022. Vol. 14, No. 3. P. 65–76, doi: http://dx.doi.org/10.22328/2077-9828-2022-14-3-65-76.

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Баженова А.Я., Миронов К.О., Кравченко А.В., Акимкин В.Г. Фармакогенетические эффекты однонуклеотидных полиморфизмов, влияющих на метаболизм антиретровирусных препаратов // *ВИЧ-инфекция и иммуносупрессии*. 2022. Т. 14, № 3. С. 65–76, doi: http://dx.doi.org/10.22328/2077-9828-2022-14-3-65-76.

Introduction.

The trend of in-clinic uses of antiretroviral therapies. Modern European and American guidelines suggest that Tenofovir Disoproxil fumarate (Tenofovir, TDF); Lamivudine (3TC); Emtricitabine (FTC); Dolutegravir (DTG); Efavirenz (EFV); and Abacavir (ABC) should be the most prescribed drugs as initial antiretroviral therapy (ART)[1] [1]. Most recently included newer drugs, Bictegravir (BIC) and Tenofovir Alafenamide (TAF) are consistently mentioned but expected to be less prevalent in clinical use due to such recent adoption. Clinical guidelines in Russia aim to adhere to global standards, and there are established prescription plans in place[2]. According to the 2020 ART monitoring report issued by Treatment Preparedness Coalition (ITPC), by far the most popular first-line drugs in Russia are 3TC, TDF, and EFV An additional first-line treatment scheme was included that contains DTG (substitutes EFV in combination with 3TC (or FTC)+TDF), but its use is not as high, comparatively. ABC and Zidovudine (ZDV) are the most prevalent among the rest of the available options. For example, first-line alternative schemes have either TDF substituted for ABC, or DTG substituted for EFV. Nevirapine (NVP) is now classed as a second-line treatment option, further reducing its use. The recent update now includes TAF, which is less toxic than TDF, and despite its inclusion, TAF use is still very limited even on a global scale, while in Russia it has only recently been listed as an essential drug. EFV remains the most purchased «third agent», followed by DTG, 3TC/Ritonavir (RTV), Atazanavir (ATV), and others[3]. It is not advised to prescribe EFV in the regions with a high prevalence of primary drug

[1] https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines?view=full (дата обращения: 16.06.2022).

[2] https://cr.minzdrav.gov.ru/schema/79_1 (дата обращения: 16.06.2022).

[3] https://www.itpcru.org/monitoring/ (дата обращения 21.06.2022).

resistance to NNRTIs (more than 10%) and a resistance test is recommended prior to treatment[1]. It is recommended to lower EFV treatment dose to 400mg due to its better tolerability, a lower risk of side effects, and treatment discontinuation, while a previous standard 600mg dose is recommended in special cases or as a «third agent», and thus, the future proportions of these medicines in use are expected to be adjusted accordingly. Expansion of DTG and FTC use in the clinic is also stated as desired. In summary, the most prescribed treatments include lamivudine (3TC), tenofovir (TDF), and efavirenz (EFV). Abacavir (ABC) and dolutegravir (DTG) share second place, with potentially increasing use of DTG in the near future[2].

Although personalised approach to ART prescription is currently limited and remains a medium to a long-term goal for clinical application, it is important to evaluate the influence of genetic factors on treatment outcomes to improve treatment efficacy and safety. Population-focused pharmacogenetic research benefits the identification of exclusive high-risk genotypes and the development of more individualised standards of care.

Materials and methods. Publications for this review were sourced from PubMed, Google Scholar, and Ensembl between July and September 2021 (n=46, original studies and reviews published from 2008 to 2021). Sourced publications primarily covered the most commonly researched pharmacogenetic associations for TDF, EFV, DTG, and 3TC. Allele frequencies of the most relevant polymorphisms were checked against the data from dbSNP for European population. Associations of relevant polymorphisms with possible effects of these and other drugs were summarised in Table. The search included combinations of terms: HIV, polymorphisms, pharmacogenetics, antiretroviral therapy and antiretroviral drug names. Inclusion criteria concerned the indication of defined SNPs and their pharmacogenetic effect in the context of popular ART regimens. Selected papers described associations of SNPs and ART drugs and their direct or indirect effects. Caucasian and Asian adult populations were included in the analysis. To meet suitability criteria for future research, studies of African population and of uncommon SNPs for Caucasian population were excluded due to pharmacogenetic discrepancies. Subsequent analysis of reported genes and their impact on individual pharmacological responses and the risk of side effects was carried out. Based on this evaluation, a recommendation for molecular marker detection kits was concluded.

Results and discussion.

Paving the path to HIV pharmacogenetics. Parameters of successful treatment are not limited to effective viral load suppression and good immune recovery in patients. High tolerability and high barrier of resistance drive the expedient therapy allocation strategies. Response to a drug can be negatively affected by individual genetic predisposition factors, which differently affect drug disposition, activity, and consequently, tolerability. Therefore, pharmacogenetic research plays a central role to achieve therapy personalisation.

Presently, the only molecular genetic test approved for clinical guidelines for HIV treatment is the HLA-B*57:01 test. It checks for the presence of the human leukocyte antigen allele, HLA-B*57:01, which is strongly associated with a hypersensitivity reaction (HSR) to ABC (NRTI). The assay tends to be more informative for non-black ethnicities with negative and positive predictive values of up to 100% and 70%, respectively [2, 3]. Currently, a test is recommended for every patient to be prescribed ABC. The effectiveness of the test stimulates researchers to seek the most adaptable methods with similar predictiveness. Recent research confirmed a possibility to substitute HLA-B*57:01 genotyping by qPCR screening for an SNP in the HLA complex protein 5 gene [4,5]. In the Spanish patient cohort (n=226) results demonstrated absolute concordance between HLA-B*57:01 and the *HCP5* rs2395029 G allele [5]. Antibody-based mononuclear cell screening method was also recently suggested [6]. A novel rapid PCR-based method may also benefit many patients if it gets validated [7]. The sensitivity, utility, and lower cost of rapid PCR-based approaches should allow to rise the rate of risk-allele screening globally.

Another genetic association was drawn between variations in thymine–adenine (TA) repeats within the promoter region of the *UGT1A1* gene and the risk of hyperbilirubinemia when ATV is administered [8,9]. In Caucasians, UGT1A1*28 is a prevalent risk allele, and it even was investigated as a diagnostic test in Russia and included as a supporting test for hyperbilirubinemia correction in patients taking ART. Consideration of UGT1A1*28 (rs8175347) homozygosity was unveiled to lower ATV discontinuation rate in patients

[1] http://rushiv.ru/klinicheskie-rekomendatsii-vich-infektsiya-u-vzroslyh-2020/ (дата обращения: 21.06.2022).

[2] https://www.itpcru.org/monitoring/ (дата обращения 21.06.2022).

Table

Genetic polymorphisms and their effects on ART metabolism in the selected populations

Таблица

Генетические полиморфизмы и их влияние на метаболизм антиретровирусных препаратов в выбранных популяциях

Type	Gene	Variant	Risk allele	Population studied	Allele freq. in Europe, %	Effect	Drug	Class	Reference
1	2	3	4	5	6	7	8	9	10
HLA complex	*HLA-B*	N/A	57:01	Global	≈6	Predictive factor for hypersensitivity reaction	ABC	NRTI	[6, 7]
HLA complex	*HCP5*	rs2395029	G	Caucasian, Hispanic	5	Predictive factor for hypersensitivity reaction	ABC	NRTI	[8, 9]
UDP-glucuronosyltransferase	*UGT1A1*	rs887829	T	Caucasian	≈30	Risk of hyperbilirubinemia, 3x higher risk for heterozygotes, 34 times higher risk for homozygotes	ATV	PI	[12, 16]
		Rs8175347	(TA)7	Caucasian	Varies	Risk of hyperbilirubinemia and early treatment discontinuation	ATV	PI	[14, 15, 41]
Pregnane X Receptor	*NR1I2*	rs2472677	T	Caucasian	66	Higher DTG plasma C_{max} especially in combination with UGT1A1*28 (rs8175347) homozygosity (79% increase in AUC_{0-24}; 27% if analysed individually) and with ABCG2 rs2231142 homozygosity (43% increase in C_{max} and 39% increase in AUC_{0-24})	DTG	INSTI	[44]
Constitutive Androstane Receptor	*NR1I3*	rs2307424	C*	Caucasian	65	Risk of early EFV discontinuation in Caucasian populations with homozygous genotypes Significantly higher EFV concentrations	EFV	NNRTI	[45, 46]
ATP Binding Cassette Transporters; Multidrug resistance-associated proteins (MRPs)	*ABCC2*	rs717620	C	Thai, UK, Japanese, Spanish, Italian, Caucasian	79	Risk of lower glomerular filtration rate Association with KTD yielded conflicting results in different studies CC genotype may be a predictor of elevated parathyroid hormone levels, but not associated with Caucasian population No association with TDF discontinuation was observed	TDF	NRTI	[18–20, 22, 23, 41, 47]
		rs2273697	A	Italian, Japanese, Caucasian	20	No association with KTD found Possible risk of higher TDF discontinuation rates for AA genotype	TDF	NRTI	[22, 23, 41]
	ABCC4	rs1059751	G	Thai, n=150	48	Influence plasma concentrations, which could be associated with tenofovir-induced renal toxicity. Low body weight, low eGFR, and concomitant use of RTV-boosted PI, increased risk of a higher plasma TDF concentration.	TDF	NRTI	[24]

Продолжение таблицы

1	2	3	4	5	6	7	8	9	10
		rs1751034	G	Caucasian, n=158	19	GG genotype associated with KTD in univariate analysis	TDF	NRTI	[22, 24, 27, 28]
						Higher risk of bone disease observed in patients with KTD (54,8 vs 27,6%; p=0.002), but study population with prevalent bone disease may influence this result			
						*c.3348G>A (AA genotype associated with higher TDF plasma concentrations, but some studies refer to G allele at c.3463 position			
		rs3742106	G*	Italian, n=179	38	Annual eGFR decrement >25% and TDF discontinuation for toxicity	TDF	NRTI	[22, 24, 26]
				Thai, n=342 / n=150		Increase in mean TDF plasma concentration, but conflicting results with Thai group			
	ABCC10	rs9349256	G	Italian, n=179	54	GG genotype may impose a higher risk of KTD when exposed to TDF versus AA genotype	TDF	NRTI	[22]
		rs2125739	C	Madrid (not reported), n=115	23	Marginally significantly higher % in the KTD group when treated with TDF versus allele T (23.4% vs 38.8%)	TDF	NRTI	[30]
				Caucasian, n=158		ABCC10 not associated with KTD	TDF	NRTI	[28]
				USA, n=160; White n=98		Significantly associated with NVP plasma concentration in Whites, which can lead to reduced viral suppression	NVP	NNRTI	[29]
						CC homozygotes resulted in significantly lower NVP concentration			
Cytochrome P450	*CYP2B6*	rs3745274	T	Caucasian	24	T allele is associated with higher EFV plasma drug levels and more frequent CNS-related symptoms and toxicity	EFV	NNRTI	[15, 37]
				Chilian, n=67					
				North American women, n=95		Better virologic suppression in intermediate (GT) and slow (TT) metabolizers (2.90 and 13.44 times as likely) when compared to extensive metabolizers	EFV	NNRTI	[34]
		rs2279345	C	Thai, n=139	62	Low EFV concentration independently associated with C allele and high body weight. Compromised EFV concentration in patients with haplotype *1/*1 and are coinfected with HIV and tuberculosis.	EFV	NNRTI	[38]
						Increased EFV metabolism			

Окончание таблицы

1	2	3	4	5	6	7	8	9	10
	CYP2A6	rs28399433	G*	Swiss HIV Cohort Study, 80% Caucasian, n=272	7	Higher risk of discontinuation, especially in women	EFV	NNRTI	[41]
	CYP3A4	rs4646437	T*	Swiss HIV Cohort Study, n=169	9	Reduce EFV clearance, higher risk of discontinuation	EFV	NNRTI	[43]
	CYP24A1	rs2248359	T	Italy, n=377	41	Tubular dysfunction defined by abnormally high uRBP/Cr; TT genotype may be a predictor of toxic RBP levels	TDF	NRTI	[47]
	ABCG2	rs2231142	A*	UK, London, n=93	9	Higher C_{max} observed in homozygote type, especially in combination with NR1I2 rs2472677 homozygote type	DTG	INSTI	[44]
Solute carrier (SLC) membrane-associated transporters	*SLC22A2*	rs316019	A	Not reported, n=203	11	Abnormal general severity index, anxiety, hostility and with moderate to severe headache DTG C_{trough} associated with hostility and psychoticism no association with pharmacokinetic exposure	DTG	INSTI	[49]
	SCLO1B1	rs4149056	C	Mostly Caucasian	16	Higher lopinavir concentrations, especially high $C_{through}$ observed in patients homozygous for SCLO1B1 521CC and CYP3A4*22 522–191C>T rs35599367	3TC	NRTI	[48]

Footnote key: ABC: abacavir; ATV: atazanavir; DTG: dolutegravir; EFV: efavirenz; 3TC: lamivudine; NRTI: nucleoside reverse transcription inhibitor; NNRTI: non-nucleoside reverse transcription inhibitor; PI: protease inhibitor; INSTI: integrase strand transfer inhibitor.

Allele marked with an asterisk (*): allele indicated in accordance with publication, but allele frequency is in correspondence with a complementary nucleotide information through ensembl.org.

C_{trough}: plasma trough concentration. C_{max}: plasma maximum concentration. AUC_{0-24}: area under the plasma concentration-time curve over the last 24-h dosing interval.

down to 4,7%, and it was recommended for patients with high bilirubin levels detected prior to, or in the duration of treatment [10]. ATV-associated hyperbilirubinemia is also linked with UGT1A1*80 rs887829 allele (which is in very strong linkage disequilibrium (LD) with UGT1A1*28), baseline bilirubin levels, and baseline haemoglobin level, while is best predicted using all these factors combined [11, 12]. Clinical Pharmacogenetics Implementation Consortium (CPIC) reported a 60% positive predictive value of rs887829 T/T for bilirubin-associated ATV discontinuation in White patients, which supports its use as a potential marker [8]. Multidrug-resistance protein-coding genes are associated with toxicity of a popular NRTI (TDF).

Polymorphisms in multidrug-resistance protein-coding genes are associated with TDF-induced toxicity. Multidrug-resistance proteins (MRP) are the members of ATP-binding cassette efflux transporters, which interact and influence ART distribution and excretion [13]. While MRP 4 often acts as the main transporter, polymorphisms in other MRP genes may alter pharmacokinetics of different ART drugs, especially TDF, where certain mutations lead to an increased risk of renal toxicity (TDF imposes a compound risk of kidney disease and osteoporosis, and is avoided in patients with these conditions, according to USA clinical guidelines). Most associations were linked with SNPs in the genes coding for MRP2 (*ABCC2*), MRP4 (*ABCC4*), and MRP7 (*ABCC10*).

***ABCC2*: rs717620 and rs2273697.** MRP 2 is not involved in the direct transport of TDF, but its variants might predispose renal toxicity issues and risk of kidney tubular dysfunction (KTD). However, results found for the associated SNPs (rs717620 and rs2273697) are conflicting, which complicates their evaluation. A study from Madrid (n=115) suggested a strong link between rs717620 CC genotype and KTD [14]. As well as that, in the Thai population (n=117) CC genotype was reported to impose a higher risk of decreased glomerular filtration rate (GFR), but this effect was also associated with high TDF plasma levels independent of the genotype [15]. A recent UK-based study (n=58) also found a link between the CC genotype and KTD. However, instead of imposing a risk, it was negatively associated with the concentration of a KTD marker, urinary Retinol-Binding Protein (RBP) [16]. There are conflicting results on whether a possession of rs717620 and rs2273697 SNPs correlates with pre-existing tubular dysfunction in patients or not [17]. Recent research of these SNPs in 179 patients in Milan reported a lack of association of *ABCC2* with TDF-induced kidney impairment [18]. Another large study on the Japanese population (n=703) carried out on treatment-naïve Japanese HIV-1-infected patients reported that rs717620 (C/C) and rs2273697 (A/A) were not associated with TDF-induced nephrotoxicity [19]. Results seem to be different partially due to divergence in clinical outcomes used as KTD markers and in sample sizes. More work is needed to better define possible predictors of TDF-associated renal disorders in the *ABCC2* gene.

***ABCC4*: rs1751034, rs3742106 and rs1059751.** Contrastingly, researched polymorphisms in the *ABCC4* gene show less dissimilarity in results. Cheli et al. found a significant association with the *ABCC4* rs3742106 G allele and decrement in estimated GFR, as well as the increase in the mean TDF plasma concentration and TDF discontinuation for toxicity, in line with a previous study by Rungtivasuwan et al. who also observed a 30% increase in the mean TDF plasma concentration in Thai HIV-infected patients with rs3742106 TG/GG genotype [18, 20]. This variant may be associated with a reduced expression and/or function of the transporter [19]. A different study in the Thai population (n=273) associated *ABCC4* rs1059751 SNP with increased TDF plasma concentrations and TDF-induced renal toxicity [21].

Cheli et al. also suggested that c. 3348 AA genotype in *ABCC4* rs1751034 was associated with higher TDF plasma concentrations, which was in line with the study result by Rungtivasuwan et al. (n=342) who showed lower oral clearance for AA genotype, but at position c. 3463 [18, 22]. This result was in disagreement with the previous study by Rungtivasuwan et al, as well as by Kiser et al. where G allele was mentioned instead, however, those studies were carried out on smaller patient groups (n=150 and n=30, respectively) [20, 23]. Nevertheless, GG genotype was also more prevalent in another cohort of Italian patients (n=158) who had TDF-associated KTD [24]. Therefore, for rs1751034 c.3348/c.3463 a conclusion needs to be drawn in terms of result heterogeneity.

***ABCC10*: rs9349256 and rs2125739.** Polymorphism in the *ABCC10* gene (encoding MRP 7) c. 1875+526G>A (rs9349256) is also a marker of renal impairment. In the same study by Cheli et al. allele G was carried more frequently by those patients who had an annual eGFR decrement >5 mL/min/1.73 m^2, and

the main risk factor resulted to be body mass index (BMI), eGFR, and concurrent use of protease inhibitors (PIs) [18]. *ABCC10* rs2125739 C allele has been associated with significantly lower plasma concentrations of NVP in White HIV+ patients, and therefore, lower effectiveness [25]. This SNP was not associated with renal toxicity of HIV-infected patients [24]. However, an earlier study in Madrid confirmed a link of this SNP to KTD, and another single patient case linked this SNP to TDF-induced KTD [26, 27]. *ABCC10* rs9349256 A allele and *ABCC10* rs2125739 C allele could be potential risk factors for renal impairment for patients treated with TDF.

Nonetheless, a recent randomised controlled trial in Europeans reported no significant association between *ABCC10* or *ABCC2* SNPs and TDF oral clearance or renal failure, probably because previous renal function parameters were not replicated. Instead, they found the risk of decreased glomerular function to be linked with higher AUC_{0-24} and plasma maximum concentration but based on 2.9% of patients only [28]. The *ABCC4* and *ABCC10* variants should be tested and evaluated as predictors of TDF-induced toxicity. *ABCC10* rs2125739 should be further evaluated for its effect on NVP plasma concentrations.

Cytochrome P450 proteins: effect of genetic polymorphisms on NNRTI metabolism (EFV).

***CYP2B6*: rs3745274.** The *CYP2B6* is a member of the cytochrome P450 superfamily and is involved in the PIs, the NNRTIs, and the INSTIs classes metabolism. Members of the CYP450 system interact with most metabolized drugs and are pharmacogenetically related to a growing number of those. EFV and NVP are principally metabolized by cytochrome P450 2B6 [29]. The gene that encodes *CYP2B6* is highly polymorphic. Variations in *CYP2B6* can predict pharmacokinetic characteristics of its substrates, for example, the 516G>T variant (rs3745274) results in lower enzymatic activity and has been linked to EFV and NVP toxicities [30]. Two SNPs, *CYP2B6* 516G>T and 983T>C, are the most studied and their clinical relevance has been reported, however, the latter is almost never observed in Caucasians, it is an ethnic-specific predisposing factor.

A study on the American population (n=95) reported better viral load suppression in female patients heterozygous or homozygous for minor T allele in rs3745274 [30]. However, an association of this allele with minor toxicities increases the risk for switching NNTRI-based treatment regimen for alternatives (Rotger et al, 2005; Gallien et al, 2017). Another study evaluated *CYP2B6* SNPs on 134 HIV-infected Thai adults treated with EFV concluded that *CYP2B6* 6*/6* haplotype (TT genotype) may have increased susceptibility to hepatotoxicity with EFV [31].

In 2019, CPIC® has published a Guideline for *CYP2B6* and EFV, which was mainly based on previous studies into 516G>T and 983T>C SNPs [32]. They have classified patients possessing certain alleles as NM: normal metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; RM: rapid metabolizer; UM: ultrarapid metabolizer. PMs carried TT alleles and were defined as being at greatest risk for higher dose-adjusted trough concentrations compared with NMs and IMs, and greater overall plasma EFV exposure, which puts these patients up to a 4.8-fold increased risk for adverse effects and treatment discontinuation. On the other hand, RM and UM profiles may impose a higher risk of developing drug resistance to EFV, but it is yet to be proven in the Caucasian population [29]. In other studies, the deficient *CYP2B6* 516G>T allele was also associated with higher EFV plasma drug levels and more frequent CNS-related symptoms in the Caucasian population. [11, 33] However, in the Thai population a different *CYP2B6* polymorphism, c.18492T>C, was associated with lower EFV concentrations, but particularly in patients with high body weight who are coinfected with tuberculosis and who carry *CYP2B6* haplotype 1*/1* [34, 35]. This might be a risk factor for successful virus suppression but needs to be confirmed in other populations.

While *CYP2B6* is a primary metabolic pathway for EFV, the cumulative influence of malfunctioning *CYP2B6* and accessory pathway elements *CYP2A6* (rs28399433 T>G) and *CYP3A4* (rs4646437 C>T) may seriously impair EFV plasma clearance. Polymorphisms in these genes were associated with a higher risk of EFV discontinuation [36–39]. However, evaluation of accessory metabolisers and their pharmacogenetics can be misleading and less informative without parallel analysis of the *CYP2B6* pathway [38]. These discoveries suggest that adverse events and EFV dose selection could be predicted by *CYP2B6* variant testing, however, it is likely to be more informative when *CYP2A6* and *CYP3A4* analysis is taken into account.

As was mentioned earlier, CPIC recommendations for *CYP2B6* genotyping to predict the course of drug metabolism in patients may aid optimal dose selection. Low EFV concentrations mitigate the risk of

high plasma levels in PM and IM, so this test could be clinically relevant for patient groups prescribed EFV in 600 mg dosage, and also for identification of high-risk-of-resistance genotypes for whom the initial dose should be lowered. It could help to minimise the risk for the poor metabolizers to suffer from adverse effects imposed by an increased EFV plasma exposure and from developing resistance.

Conclusion. Routine application of diverse molecular testing methods for optimised prescription is not yet established, since the clear justification of the added benefit to standard laboratory testing, or even therapy switching, must be in place. Nevertheless, personalised medicine is a growing trend, and research into genetic polymorphisms aids to build a clearer picture of key factors that negatively affect treatment tolerability. It would be especially important to consider serious adverse effects that may be related to SNP possession in patients lacking any underlying conditions. Only highly interpretable and accurate tests with evident benefits may be successfully transferred from the discovery stage into the clinic. Continued generation of quantitative data that proves genetic associations with various side effects will eventually innovate ART allocation guidelines. Since pharmacogenetic effects may vary substantially between populations, testing ideally should be adapted for a specific population. It is also important to note that carefully defined sets of SNPs or scoring algorithms would be more informative instead of testing for one particular SNP.

In this review, the most recent information on SNPs in several genes coding for ART metabolising enzymes was analysed. These genetic markers may have a significant effect on ART outcomes in the Caucasian population. Efforts should be made to convert these findings into rapid qPCR-based methodologies for screening SNPs associated with toxicity from the extensively used drugs. PCR-based kits with consideration of population genetics and epidemiologic factors may become a feasible solution for rapid identification of patients who will benefit from dosing strategies assisted by pharmacogenetic data.

REFERENCES

1. Ryom L., Cotter A., De Miguel R., Béguelin C., Podlekareva D., Arribas J.R., Marzolini C., Mallon Pgm., Rauch A., Kirk O., Molina J.M., Guaraldi G., Winston A., Bhagani S., Cinque P., Kowalska J.D., Collins S., Battegay M., EACS Governing Board. 2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0 // *HIV Medicine*. 2020. Vol. 21, No. 10. P. 617–624. doi: 10.1111/hiv.12878.
2. Sousa-Pinto B., Pinto-Ramos J., Correia C., Gonçalves-Costa G., Gomes L., Gil-Mata S., Araújo L., Delgado L. Pharmacogenetics of abacavir hypersensitivity: A systematic review and meta-analysis of the association with HLA-B*57:01 // *Journal of Allergy and Clinical Immunology*. 2015. Vol. 136, No. 4. P. 1092–1094.e3. doi: 10.1016/j.jaci.2015.03.019.
3. Mounzer K., Hsu R., Fusco J.S., Brunet L., Henegar C.E., Vannappagari V., Stainsby C.M., Shaefer M.S., Ragone L., Fusco G.P. HLA-B*57:01 screening and hypersensitivity reaction to abacavir between 1999 and 2016 in the OPERA® observational database: a cohort study // *AIDS Research and Therapy*. 2019. Vol. 16, No. 1. doi: 10.1186/s12981-019-0217-3.
4. Sanchez-Giron F., Carnevale A. In Mexican Mestizos the HCP5 rs2395029 SNP may be a genetic marker for screening abacavir hypersensitivity // *Pharmacogenomics*. 2012. Vol. 13, No. 3. P. 251–252. doi: 10.2217/pgs.11.169
5. Zubiaur P., Saiz-Rodríguez M., Villapalos-García G., Navares-Gómez M., Koller D., Abad-Santos F. HCP5 rs2395029 is a rapid and inexpensive alternative to HLA-B*57 // *Pharmacogenetics and Genomics*. 2020. Publish Ahead of Print. doi: 10.1097/fpc.0000000000000421.
6. Chan J., Soraya G.V., Craig L., Uddin S.M., Todaro M., Huynh D.H., Abeyrathne C.D., Kostenko L., McCluskey J., Skafidas E., Kwan P. Rapid Detection of HLA-B*57:01-Expressing Cells Using a Label-Free Interdigitated Electrode Biosensor Platform for Prevention of Abacavir Hypersensitivity in HIV Treatment // *Sensors*. 2019. Vol. 19, No. 16. P. 3543. doi: 10.3390/s19163543.
7. Wallner J.J., Beck I.A., Panpradist N., Ruth P.S., Valenzuela-Ponce H., Soto-Nava M., Ávila-Ríos S., Lutz B.R., Frenkel L.M. Rapid, Near Point-of-Care Assay for HLA-B*57:01 Genotype Associated with Severe Hypersensitivity Reaction to Abacavir // *MedRxiv*. 2021. doi: 10.1101/2021.05.26.21257187.
8. Gammal R.S., Court M.H., Haidar C.E., Iwuchukwu O.F., Gaur A.H., Alvarellos M., Guillemette C., Lennox J.L., Whirl-Carrillo M., Brummel S.S., Ratain M.J., Klein T.E., Schackman B.R., Caudle K.E., Haas D.W. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing // *Clinical Pharmacology & Therapeutics*. 2015. Vol. 99, No. 4. P. 363–369. doi: 10.1002/cpt.269.
9. Du P., Wang A., Ma Y., Li X. Association between the UGT1A1*28 allele and hyperbilirubinemia in HIV-positive patients receiving atazanavir: a meta-analysis // *Bioscience Reports*. 2019. Vol. 39, No. 5. doi: 10.1042/bsr20182105.

10. Kanestri V., Mironov K., Kravchenko A., Pokrovskaya A., Dribnohodova O., Dunayeva E., Tsiganova G., Harbutly M., Goliusova M., Konnov V., Kozirina N., Shahgildyan V., Kuimova U., Popova A., Efremova O., Konnov D. Clinical significance of the UGT1A1*28 allele detection in HIV-infected patients // *Journal of the International AIDS Society*. 2014. No. 17 (4 Suppl. 3): 19579. doi: 10.7448/ias.17.4.19579.
11. Poblete D., Bernal F., Llull G., Archiles S., Vasquez P., Chanqueo L., Soto N., Lavanderos M.A., Quiñones L.A., Varela N.M. Pharmacogenetic Associations Between Atazanavir/UGT1A1*28 and Efavirenz/rs3745274 (CYP2B6) Account for Specific Adverse Reactions in Chilean Patients Undergoing Antiretroviral Therapy // *Frontiers in Pharmacology*. 2021. No. 12:660965. doi: 10.3389/fphar.2021.660965.
12. Johnson D.H., Venuto C., Ritchie M.D., Morse G.D., Daar E.S., McLaren P.J., Haas D.W. Genomewide association study of atazanavir pharmacokinetics and hyperbilirubinemia in AIDS Clinical Trials Group protocol A5202 // *Pharmacogenetics and Genomics*. 2014. Vol. 24, No. 4. P. 195–203. doi: 10.1097/fpc.0000000000000034.
13. Alam C., Whyte-Allman S.K., Omeragic A., Bendayan R. Role and modulation of drug transporters in HIV-1 therapy // *Advanced Drug Delivery Reviews*. 2016. No. 103. P. 121–143. doi: 10.1016/j.addr.2016.05.001.
14. Rodríguez-Nóvoa S., Labarga P., Soriano V., Egan D., Albalater M., Morello J., Cuenca L., González-Pardo G., Khoo S., Back D., Owen A. Predictors of Kidney Tubular Dysfunction in HIV-Infected Patients Treated with Tenofovir: A Pharmacogenetic Study // *Clinical Infectious Diseases*. 2009. Vol. 48, No. 11. P. e108-e116. doi: 10.1086/598507.
15. Manosuthi W., Sukasem C., Thongyen S., Nilkamhang S., Sungkanuparph S. ABCC2*1C and plasma tenofovir concentration are correlated to decreased glomerular filtration rate in patients receiving a tenofovir-containing antiretroviral regimen // *Journal of Antimicrobial Chemotherapy*. 2014. Vol. 69, No. 8. P. 2195–2201. doi: 10.1093/jac/dku129.
16. Danjuma M.I., Egan D., Abubeker I.Y., Post F., Khoo S. Polymorphisms of tenofovir disoproxil fumarate transporters and risk of kidney tubular dysfunction in HIV-positive patients: genetics of tenofovir transporters // *International Journal of STD & AIDS*. 2018. Vol. 29, No. 14. P. 1384–1389. doi: 10.1177/0956462418786562.
17. García-Blanco D., Gravier-Hernández R., Rabeiro-Martínez C.L., Gil Del Valle L., Pérez-Ávila J. Pharmacogenetic markers: A path toward individualized HIV therapy // *MEDICC Review*. 2019. No. 21(2–3). doi: 10.37757/mr2019.v21.n2-3.11.
18. Cheli S., Baldelli S., De Silvestri A., Fusi M., Minisci D., Gervasoni C., Cattaneo D., Clementi E., Meraviglia P., Montrasio C. ABCC4 single-nucleotide polymorphisms as markers of tenofovir disoproxil fumarate-induced kidney impairment // *The Pharmacogenomics Journal*. 2021. doi: 10.1038/s41397-021-00235-7.
19. Nishijima T., Hayashida T., Kurosawa T., Tanaka N., Oka S., Gatanaga H. Drug transporter genetic variants are not associated with tdf-related renal dysfunction in patients with HIV-1 infection: a pharmacogenetic study // *PLoS One*. 2015. Vol. 10, No. 11. P. e0141931. doi: 10.1371/journal.pone.0141931.
20. Rungtivasuwan K., Avihingsanon A., Thammajaruk N., Mitruk S., Burger D.M., Ruxrungtham K., Punyawudho B., Pengsuparp T. Influence of ABCC2 and ABCC4 Polymorphisms on Tenofovir Plasma Concentrations in Thai HIV-Infected Patients // *Antimicrobial Agents and Chemotherapy*. 2015. Vol. 59, No. 6. P. 3240–3245. doi: 10.1128/aac.04930-14.
21. Likanonsakul S., Suntisuklappon B., Nitiyanontakij R., Prasithsirikul W., Nakayama E.E., Shioda T., Sangsajja C. A Single-Nucleotide Polymorphism in ABCC4 Is Associated with Tenofovir-Related Beta2-Microglobulinuria in Thai Patients with HIV-1 Infection // *PLoS One*. 2016. Vol. 11, No. 1. P. e0147724. doi: 10.1371/journal.pone.0147724.
22. Rungtivasuwan K., Avihingsanon A., Thammajaruk N., Mitruk S., Burger D.M., Ruxrungtham K., Sukasem C., Punyawudho B. Pharmacogenetics-based population pharmacokinetic analysis of tenofovir in Thai HIV-infected patients // *Pharmacogenomics*. 2017. Vol. 18, No. 16. P. 1481–1490. doi: 10.2217/pgs-2017-0128.
23. Kiser J.J., Aquilante C.L., Anderson P.L., King T.M., Carten M.L., Fletcher C.V. Clinical and Genetic Determinants of Intracellular Tenofovir Diphosphate Concentrations in HIV-Infected Patients // *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2008. Vol. 47, No. 3. P. 298–303. doi: 10.1097/qai.0b013e31815e7478.
24. Salvaggio S.E., Giacomelli A., Falvella F.S., Oreni M.L., Meraviglia P., Atzori C., Clementi E.G.I., Galli M., Rusconi S. Clinical and genetic factors associated with kidney tubular dysfunction in a real-life single centre cohort of HIV-positive patients // *BMC Infectious Diseases*. 2017. Vol. 17, No. 1. doi: 10.1186/s12879–017–2497–3.
25. Liptrott N.J., Pushpakom S., Wyen C., Fätkenheuer G., Hoffmann C., Mauss S., Knechten H., Brockmeyer N.H., Hopper-Borge E., Siccardi M., Back D.J., Khoo S.H., Pirmohamed M., Owen A. Association of ABCC10 polymorphisms with nevirapine plasma concentrations in the German Competence Network for HIV/AIDS // *Pharmacogenetics and Genomics*. 2012. Vol. 22, No. 1. P. 10–19. doi: 10.1097/fpc.0b013e32834dd82e
26. Pushpakom S.P., Liptrott N.J., Rodríguez-Nóvoa S., Labarga P., Soriano V., Albalater M., Hopper-Borge E., Bonora S., Di Perri G., Back D.J., Khoo S., Pirmohamed M., Owen A. Genetic Variants of ABCC10, a Novel Tenofovir Transporter, Are Associated With Kidney Tubular Dysfunction // *The Journal of Infectious Diseases*. 2011. Vol. 204, No. 1. P. 145–153. doi: 10.1093/infdis/jir215.
27. Giacomet V., Cattaneo D., Viganò A., Nannini P., Manfredini V., Ramponi G., Clementi E., Zuccotti G.V. Tenofovir-induced Renal Tubular Dysfunction in Vertically HIV-infected Patients Associated With Polymorphisms in ABCC2, ABCC4 and ABCC10 Genes // *The Pediatric Infectious Disease Journal*. 2013. Vol. 32, No. 10. P. e403–e405. doi: 10.1097/inf.0b013e31829e6c9c.

28. Dickinson L., Gurjar R., Stöhr W., Bonora S., Owen A., D'Avolio A., Cursley A., Molina J.-M., Fäetkenheuer G., Vandekerckhove L., Di Perri G., Pozniak A., Richert L., Raffi F., Boffito M., NEAT001/ANRS143 Study Group. Population pharmacokinetics and pharmacogenetics of ritonavir-boosted darunavir in the presence of raltegravir or tenofovir disoproxil fumarate/emtricitabine in HIV-infected adults and the relationship with virological response: a sub-study of the NEAT001/ANRS143 randomized trial // *Journal of Antimicrobial Chemotherapy*. 2019. Vol. 75, No. 3. P. 628–639. doi: 10.1093/jac/dkz479.
29. Maseng M.J., Tawe L., Thami P.K., Seatla K.K., Moyo S., Martinelli A., Kasvosve I., Novitsky V., Essex M., Russo G., Gaseitsiwe S., Paganotti G.M. Association of CYP2B6 Genetic Variation with Efavirenz and Nevirapine Drug Resistance in HIV-1 Patients from Botswana // *Pharmacogenomics and Personalized Medicine*. 2021. No. 14. P. 335–347. doi: 10.2147/pgpm.s289471.
30. Frasco M.A., Mack W.J., Van Den Berg D., Aouizerat B.E., Anastos K., Cohen M., De Hovitz J., Golub E.T., Greenblatt R.M., Liu C., Conti D.V., Pearce C.L. Underlying genetic structure impacts the association between CYP2B6 polymorphisms and response to efavirenz and nevirapine // *AIDS*. 2012. Vol. 26, No. 16. P. 2097–2106. doi: 10.1097/qad.0b013e3283593602.
31. Manosuthi W., Sukasem C., Lueangniyomkul A., Mankatitham W., Thongyen S., Nilkamhang S., Manosuthi S., Sungkanuparph S. CYP2B6 haplotype and biological factors responsible for hepatotoxicity in HIV-infected patients receiving efavirenz-based antiretroviral therapy // *International Journal of Antimicrobial Agents*. 2014. Vol. 43, No. 3. P. 292–296. doi: 10.1016/j.ijantimicag.2013.10.022.
32. Desta Z., Gammal R. S., Gong L., Whirl-Carrillo M., Gaur A. H., Sukasem C., Hockings J., Myers A., Swart M., Tyndale R. F., Masimirembwa C., Iwuchukwu O. F., Chirwa S., Lennox J., Gaedigk A., Klein T. E., Haas D. W. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy // *Clinical Pharmacology & Therapeutics*. 2019. Vol. 106, No. 4. P. 726–733. doi: 10.1002/cpt.1477.
33. Gallien S., Journot V., Loriot M.-A., Sauvageon H., Morlat P., Reynes J., Reliquet V., Chêne G., Molina J.-M., ANRS 099 ALIZE trial study group. Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms: a substudy of the ANRS ALIZE trial // *HIV Medicine*. 2017. Vol. 18, No. 8. P. 537–545. doi: 10.1111/hiv.12488.
34. Manosuthi W., Sukasem C., Thongyen S., Nilkamhang S., Manosuthi S., Sungkanuparph S. CYP2B618492T C Polymorphism Compromises Efavirenz Concentration in Coinfected HIV and Tuberculosis Patients Carrying CYP2B6 Haplotype *1/*1 // *Antimicrobial Agents and Chemotherapy*. 2014. Vol. 58, No. 4. P. 2268–2273. doi: 10.1128/aac.02384-13.
35. Sukasem C., Manosuthi W., Koomdee N., Santon S., Jantararoungtong T., Prommas S., Chamnanphol M., Puangpetch A., Sungkanuparph S. Low level of efavirenz in HIV-1-infected Thai adults is associated with the CYP2B6 polymorphism // *Infection*. 2013. Vol. 42, No. 3. P. 469–474. doi: 10.1007/s15010-013-0560-6.
36. Cummins N.W., Neuhaus J., Chu H., Neaton J., Wyen C., Rockstroh J. K., Skiest D. J., Boyd M. A., Khoo S., Rotger M., Telenti A., Weinshilboum R., Badley A. D., INSIGHT Study Group. Investigation of Efavirenz Discontinuation in Multi-ethnic Populations of HIV-positive Individuals by Genetic Analysis // *EBioMedicine*. 2015. Vol. 2, No. 7. P. 706–712. doi: 10.1016/j.ebiom.2015.05.012.
37. Lubomirov R, Colombo S, di Iulio J., Ledergerber B., Martinez R., Cavassini M., Hirschel B., Bernasconi E., Elzi L., Vernazza P., Furrer H., Günthard H. F., Telenti A., Swiss HIV Cohort Study. Association of Pharmacogenetic Markers with Premature Discontinuation of First-line Anti-HIV Therapy: An Observational Cohort Study // *The Journal of Infectious Diseases*. 2011. Vol. 203, No. 2. P. 246–257. doi: 10.1093/infdis/jiq043.
38. Phillips E., Pavlos R. Individualization of antiretroviral therapy // *Pharmacogenomics and Personalized Medicine*. 2012. No. 5. P. 1–17. doi: 10.2147/pgpm.s15303.
39. Arab-Alameddine M., Di Iulio J., Buclin T., Rotger M., Lubomirov R., Cavassini M., Fayet A., Décosterd L.A., Eap C. B., Biollaz J., Telenti A., Csajka C., Swiss HIV Cohort Study. Pharmacogenetics-Based Population Pharmacokinetic Analysis of Efavirenz in HIV-1-Infected Individuals // *Clinical Pharmacology & Therapeutics*. 2009. Vol. 85, No. 5. P. 485–494. doi: 10.1038/clpt.2008.271.
40. Elliot E. R., Neary M., Else L., Khoo S., Moyle G., Carr D. F., Wang X., Mcclure M., Boffito M., Owen A. Genetic influence of ABCG2, UGT1A1 and NR1I2 on dolutegravir plasma pharmacokinetics // *Journal of Antimicrobial Chemotherapy*. 2020. Vol. 75, No. 5. P. 1259–1266. doi: 10.1093/jac/dkz558.
41. Wyen C., Hendra H., Siccardi M., Platten M., Jaeger H., Harrer T., Esser S., Bogner J.R., Brockmeyer N.H., Bieniek B., Rockstroh J., Hoffmann C., Stoehr A., Michalik C., Dlugay V., Jetter A., Knechten H., Klinker H., Skaletz-Rorowski A., Fätkenheuer G., Egan D., Back D. J, Owen A., German Competence Network for HIV/AIDS Coordinators. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens // *Journal of Antimicrobial Chemotherapy*. 2011. Vol. 66, No. 9. P. 2092–2098. doi: 10.1093/jac/dkr272.
42. Ayuso P., Neary M., Chiong J., Owen A. Meta-analysis of the effect of CYP2B6, CYP2A6, UGT2B7 and CAR polymorphisms on efavirenz plasma concentrations // *Journal of Antimicrobial Chemotherapy*. 2019. Vol. 74, No. 11. P. 3281–3290. doi: 10.1093/jac/dkz329.
43. Cusato J., Calcagno A., Marinaro L., Avataneo V., D Avolio A., Di Perri G., Bonora S. Pharmacogenetic determinants of kidney-associated urinary and serum abnormalities in antiretroviral-treated HIV-positive patients // *The Pharmacogenomics Journal*. 2019. Vol. 20, No. 2. P. 202–212. doi: 10.1038/s41397-019-0109-x.

44. Olagunju A., Schipani A., Siccardi M., Egan D., Khoo S., Back D., Owen A. CYP3A4*22 (c.522–191 C>T; rs35599367) is associated with lopinavir pharmacokinetics in HIV-positive adults // *Pharmacogenetics and Genomics*. 2014. Vol. 24, No. 9. P. 459–463. doi: 10.1097/fpc.0000000000000073.
45. Borghetti A., Calcagno A., Lombardi F., Cusato J., Belmonti S., D'Avolio A., Ciccarelli N., La Monica S., Colafigli M., Delle Donne V., De Marco R., Tamburrini E., Visconti E., Di Perri G., De Luca A., Bonora S., Di Giambenedetto S. SLC22A2 variants and dolutegravir levels correlate with psychiatric symptoms in persons with HIV // *Journal of Antimicrobial Chemotherapy*. 2018. Vol. 74, No. 4. P. 1035–1043. doi: 10.1093/jac/dky508.

Received by the Editor/Поступила в редакцию: *22.09.2022*.

Authorship: Contribution to the concept and plan of the study — *A. Ya. Bazhenova*. Contribution to data collection — *K. O. Mironov, A. Ya. Bazhenova*. Contribution to data analysis and conclusions — *A. V. Kravchenko, A. Ya. Bazhenova*. Contribution to the preparation of the manuscript — *A. Ya. Bazhenova, K. O. Mironov, V. G. Akimkin*.

Авторство: Вклад в концепцию и план исследования — *А. Я. Баженова*. Вклад в сбор данных — *К. О. Миронов, А. Я. Баженова*. Вклад в анализ данных и выводы — *А. В. Кравченко, А. Я. Баженова*. Вклад в подготовку рукописи — *А. Я. Баженова, К. О. Миронов, В. Г. Акимкин*.

Authors' information:

Alexandra Ya. Bazhenova — Laboratory assistant of laboratory of molecular methods for genetic polymorphisms investigation, Central Research Institute of Epidemiology, Russian Federal Service for Supervision of Consumer Rights Protection and Human Well-Being; e-mail: bazhenovaaleksandra@gmail.com; ORCID 0000–0002–7086–2779;

Konstantin O. Mironov — Dr. Sci. (Med.), Head of laboratory of molecular methods for genetic polymorphisms investigation, Central Research Institute of Epidemiology, Russian Federal Service for Supervision of Consumer Rights Protection and Human Well-Being; e-mail: mironov@pcr.ru; ORCID 0000–0001–8207–9215;

Alexey V. Kravchenko — MD, Professor, Leader Researcher, Central Research Institute of Epidemiology, Russian Federal Service for Supervision of Consumer Rights Protection and Human Well-Being; e-mail: alexey-kravtchenko@yandex.ru; ORCID 0000–0001–7857–3763;

Vasily G. Akimkin — Dr. Sci. (Med.), Professor, RAS Full Member, Director, Central Research Institute of Epidemiology, Russian Federal Service for Supervision of Consumer Rights Protection and Human Well-Being; e-mail: akimkin@pcr.ms; ORCID 0000–0003–4228–9044.

Сведения об авторах:

Баженова Александра Ярославна — лаборант-исследователь лаборатории молекулярных методов изучения генетических полиморфизмов федерального бюджетного учреждения науки «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека; 111123, Москва, Новогиреевская ул., д. 3а; e-mail: bazhenovaaleksandra@gmail.com; ORCID 0000–0002–7086–2779;

Миронов Константин Олегович — доктор медицинских наук, заведующий лаборатории молекулярных методов изучения генетических полиморфизмов «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека; 111123, Москва, Новогиреевская ул., д. 3а; e-mail: mironov@pcr.ru; ORCID 0000–0001–8207–9215;

Кравченко Алексей Викторович — доктор медицинских наук, профессор, ведущий научный сотрудник федерального бюджетного учреждения науки «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека; 111123, Москва, Новогиреевская ул., д. 3а; e-mail: alexey-kravtchenko@yandex.ru; ORCID 0000–0001–7857–3763;

Акимкин Василий Геннадьевич — доктор медицинских наук, профессор, академик РАН, директор федерального бюджетного учреждения науки «Центральный научно-исследовательский институт эпидемиологии» Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека; 111123, Москва, Новогиреевская ул., д. 3а; e-mail: akimkin@pcr.ms; ORCID 0000–0003–4228–9044.