ORIGINAL STUDY ARTICLE
DOI: https://doi.org/10.36233/0507-4088-232

Efficacy of first-line ART regimens based on tenofovir in HIV-infected patients with pre-existing A62V mutation in reverse transcriptase

Ekaterina N. Ozhmegova✉, Anna I. Kuznetsova, Aleksey V. Lebedev, Anastasiia A. Antonova, Kristina V. Kim, Yana M. Munchak, Alexandr S. Tumanov, Elena V. Kazennova

National Research Center for Epidemiology and Microbiology named after the honorary academician N.F. Gamaleya of the Russian Ministry of Health, 123098, Moscow, Russia

Abstract

Introduction. The amino acid substitution A62V in reverse transcriptase was identified as a mutation correlated with virologic failure in patients on first-line therapy including tenofovir (TDF) and tenofovir alafenamide (TAF). A62V is a typically polymorphic mutation in HIV-1 sub-subtype A6, which is the most widespread virus variant in Russia.

Materials and methods. The European EuResist (EIDB) database was queried to form two equivalent groups of patients: group 1 – patients with A62V at baseline treated with TDF or TAF on the first-line therapy, group 2 – patients without A62V at baseline treated with TDF or TAF on the first-line therapy. Each group included 23 patients.

Results. There was no statistical difference between the two groups in virologic efficacy in 4, 12, and 24 weeks after the start of antiretroviral therapy (ART) and in the frequency of virologic failures.

Conclusion. This study has some limitations, and the exact role of A62V in the efficacy of the first-line ART based on tenofovir deserves further investigation.

Keywords: *HIV-1; A62V; reverse transcriptase; first-line ART regimen; TDF/TAF*

For citation: Ozhmegova E.N., Kuznetsova A.I., Lebedev A.V., Antonova A.A., Kim K.V., Munchak Ya.M., Tumanov A.S., Kazennova E.V. Efficacy of first-line ART regimens based on tenofovir in HIV-infected patients with pre-existing A62V mutation in reverse transcriptase. *Problems of Virology* (*Voprosy Virusologii*). 2024; 69(3): 231–240. DOI: https://doi.org/10.36233/0507-4088-232 EDN: https://elibrary.ru/lnmvih

Funding. The research was funded by the Russian Science Foundation, grant number 23–15-00027, https://rscf.ru/project/23-15-00027/, date of agreement 15 May 2023.

Acknowledgement. The authors thank Euresist Network for providing the data from the Euresist database.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
DOI: https://doi.org/10.36233/0507-4088-232

Эффективность схем АРТ первой линии на основе TDF у ВИЧ-инфицированных пациентов с предсуществующей мутацией A62V в обратной транскриптазе

Ожмегова Е.Н.✉, Кузнецова А.И., Лебедев А.В., Антонова А.А., Ким К.В., Мунчак Я.М., Туманов А.С., Казеннова Е.В.

ФГБУ «Национальный исследовательский центр эпидемиологии и микробиологии им. почетного академика Н.Ф. Гамалеи» Минздрава России, 123098, г. Москва, Россия

Резюме

Введение. A62V в обратной транскриптазе была идентифицирована как мутация, коррелирующая с вирусологической неудачей у пациентов, получавших терапию первой линии, включая тенофовир (TDF) или тенофовир алафенамид (TAF). A62V представляет собой типично полиморфную мутацию суб-субтипа A6 ВИЧ-1, который является наиболее распространенным вариантом вируса в России.

Материалы и методы. По результатам запроса к общеевропейской базе данных EuResist (EIDB) были сформированы две эквивалентные группы пациентов: 1-я группа – пациенты с A62V на исходном уровне, получавшие TDF или TAF в терапии первой линии; 2-я группа – пациенты без A62V на исходном уровне, получавшие TDF или TAF в терапии первой линии. В каждую группу входило по 23 пациента.

Результаты. Статистической разницы между двумя группами по вирусологической эффективности через 4, 12 и 24 нед после начала антиретровирусной терапии (АРТ) и по частоте вирусологических неудач не выявлено.
Заключение. Проведенное исследование имело некоторые ограничения, в связи с чем роль A62V в эффективности АРТ первой линии на основе TDF нуждается в уточнении и заслуживает дальнейшего изучения.

Ключевые слова: *ВИЧ-1; A62V; обратная транскриптаза; схема АРТ первого ряда; TDF/TAF*

Для цитирования: Ожмегова Е.Н., Кузнецова А.И., Лебедев А.В., Антонова А.А., Ким К.В., Мунчак Я.М., Туманов А.С., Казеннова Е.В. Эффективность схем АРТ первой линии на основе TDF у ВИЧ-инфицированных пациентов с предсуществующей мутацией A62V в обратной транскриптазе. *Вопросы вирусологии*. 2024; 69(3): 231–240. DOI: https://doi.org/10.36233/0507-4088-232 EDN: https://elibrary.ru/lnmvih

Финансирование. Исследование выполнено при финансовой поддержке Российского научного фонда, грант № 23–15-00027, https://rscf.ru/project/23-15-00027/, дата договора 15 мая 2023 г.
Благодарности. Авторы благодарят EuResist Network за предоставление данных из базы данных Euresist.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Introduction

The amino acid substitution A62V in reverse transcriptase is an accessory mutation associated with HIV-1 drug resistance [1, 2]. It is a part of the following multi-drug-resistant mutation complexes: the Q151M complex (A62V, V75I, F77L, F116Y and Q151M) and the T69SSS insertion complex (M41L, A62V, T69SSS, K70R and T215Y), which affect almost all nucleoside reverse transcriptase inhibitors (NRTI) drugs, including the widely used lamivudine (3TC), emtricitabine (FTC) and tenofovir (TDF) [3]. Furthermore, A62V often occurs in combination with the K65R mutation, which causes drug resistance to TDF, abacavir (ABC), stavudine (d4T), didanosine (ddI) and rarely to 3TC [4]. It was shown that A62V improved the fitness of drug-resistant viruses [3, 4]. A62V is a non-polymorphic mutation for all HIV-1 subtypes, with the exception of subtype A [3]. It is still unknown whether the pre-existing A62V mutation could influence the appearance of the main HIV-1 drug resistance mutations in first-line therapy patients. However, some authors identified A62V as one of the mutations correlated with virologic failure in patients on the first-line therapies including TDF, and highlighted the need to further study the possibility of the impact of A62V on drug resistance to TDF and tenofovir alafenamide (TAF) [5]. In countries where patients are mostly infected by non-A variants, A62V was rarely detected at baseline, prior to the initiation of the therapy [6, 7]. Furthermore, A62V in reverse transcriptase is typically a polymorphic mutation in sub-subtype A6, which is the most widespread HIV-1 variant in Russia [8, 9]. In the 2006–2022 period in Russia, A62V was detected in 39.9% of treatment-naïve patients [9].

The aim of this study was to compare the efficacy of the first-line ART regimens using tenofovir in two groups: 1) in the group of people living with HIV (PLWH) with A62V mutation in HIV-1 reverse transcriptase at baseline and 2) in the group of PLWH without A62V mutation in HIV-1 reverse transcriptase at baseline.

Materials and methods

Study design and participants

From EuResist Integrated DataBase (EIDB), one of the largest available databases of HIV genotypes and clinical response to ART, all available data were downloaded on March 21, 2023[1]. There was no demographic info from the patients; all the data were completely anonymous. Ethical approval was not required in this case.

The downloaded dataset encompassed nucleotide sequences and corresponding clinical information from 151,109 patients.

Then, the first group (A62V+), the group of PLWH with A62V mutation in HIV-1 reverse transcriptase at baseline, was formed according to the following criteria:

a) A62V mutation in HIV-1 reverse transcriptase at baseline, prior to the initiation of first-line therapy;

b) no other NRTI HIV drugs resistance mutations at baseline, prior to the initiation of first-line therapy;

c) no HIV-1 drug resistance mutations to the class of the main drug on the first-line therapy (non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) or integrase inhibitors (INSTIs)) at baseline, prior to the initiation of first-line therapy;

d) the first-line therapy based on NNRTI/PI/INSTI with two NRTIs as a backbone, one of which is TDF/TAF;

e) being on the first-line therapy for more than 4 weeks.

Twenty-three patients from EIDB met these criteria.

The number of patients in the 2nd group (A62V−), the group of PLWH without A62V mutation in HIV-1 reverse transcriptase at baseline, was equivalent to the A62V+ group: 23 patients. The A62V− group was formed based on random sampling and according to the following criteria:

a) no A62V mutation in HIV-1 reverse transcriptase at baseline, before starting treatment;

b) no NRTI HIV drug resistance mutations at baseline, prior to the initiation of first-line therapy;

c) no HIV-1 drug resistance mutations to the class of the main drug (NNRTI, PI, or INSTI) on the first-line therapy at baseline, prior to the initiation of first-line therapy;

d) the first-line therapy based on NNRTI or PI or INSTI with two NRTIs as a backbone, one of which is TDF/TAF;

e) being on the first-line therapy for more than 4 weeks.

Patients enrolled in the study were observed across different European centers, and none of the patients were from Russia.

[1]The Euresist Integrated Database (EIDB). Available at: https://euresist.org/eidb

For each patient, the following data were downloaded: the *pol* gene sequence for protease and reverse transcriptase before starting the first-line therapy and for integrase if the patient was on the first-line therapy based on INSTI; sequence date, HIV subtype, list of mutations (PR Major, PR Accessory, PR Other, NRTI, NNRTI, RT Other, INSTI), ART data (the composition of the first-line therapy, the data of the regimen start and stop) and the dynamic of viral load (VL).

The efficacy of the first-line ART was compared in two groups according to virologic response definitions in Russian and European guidelines (**Table 1**) [10, 11].

The virologic efficacy of ART in 4, 12, and 24 weeks was evaluated based on the definition outlined in the Russian guidelines. To determine the cases of virologic failure, the criteria from two guidelines were combined. VL < 50 was used as a cut-off or undetectable VL level.

The term «virologic blip» was understood as the point after the undetectable level of VL, an isolated detectable VL followed by a return to < 50 copies/mL.

Virologic failure was understood as the inability to achieve VL < 50 copies/ml or after undetectable VL confirmed detectable VL (> 50 copies/ml) in 24 weeks or more after ART starting. Initially, cases of virologic efficacy of the first-line ART in 4, 12, and 24 weeks after ART starting in two groups were identified.

The statistical analysis was conducted to compare the frequency of cases of virological efficacy in two groups at each time point.

Then, the cases of virologic failure were identified in each group. The statistical analysis was conducted to determine the difference in the frequency of virological failure in the two groups.

Statistical analysis and visualization

Statistical data analysis was performed using STATISTICA v6.0 (StatSoft Inc., USA). Presentation of quantitative data in the present study was carried out using the following descriptive statistics: sample size (N), median and interquartile interval (IQR; in the form of 25 and 75% percentiles). The statistical significance of differences between the observed parameters was assessed using Fisher's two-tailed exact test. The level of significance (p) adopted in this study was 0.05 (or 5.0%). Visualization was performed in GraphPad Prism v5.0 (GraphPad Software Inc., USA).

Results

Each group included 23 patients (**Table 2**).

Most patients took FTC + TDF + EFV: 30.4% (7/23) in the 1st group and 52.2% (12/23) in the 2nd. VL at baseline was higher in the 1st group (median 5.4 log10 RNA copies/ml) than in the 2nd group (4.6 log10 RNA copies/ml). In the 1st group, the most prevalent virus variant was sub-subtype A6 (87.0%), and in the 2nd group – subtype B (82.6%). On average, patients without A62V took longer therapy (168 weeks).

The results of VL measurements in 4 ± 2, 12 ± 4, and 24 ± 4 weeks after ART initiation were analyzed. **Table 3** demonstrates the results of VL measurement in patients in both groups. VL values in 4 weeks after ART start were available for 36 patients (17 – 1st group, 19 – 2nd group). All patients from the 1st group and 18/19 patients from the 2nd group experienced a decrease in VL of more than 1 log10. Only one patient (6a) in the 2nd group exhibited a ΔLog10 decrease in VL of less than 1 log10 amounting to 0.9. There

Table 1. Virologic response definitions to ART in Russian and European guidelines
Таблица 1. Определение вирусологического ответа на АРТ в российских и европейских руководствах

Guidelines Руководство	Virologic efficacy Вирусологическая эффективность			Virologic blip Вирусологический всплеск	Virologic failure Вирусологический неуспех
	in 4 weeks через 4 нед	in 12 weeks через 12 нед	in 24 weeks через 24 нед		
Russian guidelines Российское руководство	VL decrease by ≥ 1 lg Снижение ВН на ≥ 1 lg	VL < 400 copies/mL ВН < 400 копий РНК/мл	VL < 50 copies/mL ВН < 50 копий РНК/мл	After undetectable VL (< 50 copies/mL) an isolated rising of VL to a level of less than 200 copies/ml После неопределяемой ВН (< 50 копий/мл) повышение ВН до уровня менее 200 копий РНК/мл	The inability to achieve VL < 50 copies/ml or after virologic suppression confirmed detectable VL > 50 copies/ml in 24 weeks or more after ART starting Невозможность достижения ВН < 50 копий РНК/мл, или после вирусологической супрессии подтвержденный обнаруживаемый уровень ВН > 50 копий РНК/мл через 24 нед или более после начала АРТ
European guidelines Европейское руководство	N/a Н.д.	N/a Н.д.	N/a Н.д.	After confirmed undetectable VL an isolated detectable VL level followed by a return to an undetectable level После подтверждения неопределяемой ВН обнаруживаемый уровень ВН с последующим возвращением к неопределяемому уровню	The inability to achieve or maintain VL < 200 copies/ml Невозможность достижения или поддержания ВН < 200 копий/мл

was no statistical difference between the two groups ($p = 0.95$).

In 12 weeks, the results of VL measurements were obtained for 33 patients (17 from the 1st group, 16 from the 2nd group). In the 1st group, 14/17 patients had VL less than 400 copies/ml, in the 2nd group – 15/16. There was no statistical difference between the two groups ($p = 0.6$).

In 24 weeks, the results of VL measurements were obtained for 36 patients (15 from the 1st group, 21 from the 2nd group). In the 1st group, 12/15 patients had VL less than 50 copies/ml, in the 2nd group – 18/21. There was no statistical difference between the two groups ($p = 0.7$)

The dynamics of VLs in patients in two groups for the entire follow-up periods are shown in **Figure**.

Based on the dynamics of VLs in the follow-up periods, the cases of virologic failures in the two groups were detected and analyzed.

Thus, in the A62V+ cohort, in 16 patients (1v, 3v, 4v, 6v, 7v, 8v, 10v, 11v, 13v, 14v, 15v, 16v, 19v, 20v, 21v, 22v), VL achieved an undetectable level (< 50 copies/ml). In three patients (5v, 9v, 12v), VL achieved an undetectable level followed by blips. In two patients (17v, 23v), VL achieved an undetectable level with the following confirmed VL rebound. In 2 patients (2v, 18v), VL did not achieve an undetectable level (< 50 copies/ml). Thus,

Table 2. Characteristics of the patients who participated in the study
Таблица 2. Характеристика пациентов, принявших участие в исследовании

ART first-line regimen Схема первого ряда АРТ	A62V+ (*n*=23)	A62V− (*n*=23)	*p*
3TC + TDF + DTG, *n* (%)	1 (4.3)	–	0.98
FTC + TAF + DRV, *n* (%)	1 (4.3)	–	0.98
3TC + TDF + EFV, N (%)	1 (4.3)	–	0.98
FTC + TDF + DRV/rtv, *n* (%)	1 (4.3)	2 (8.7)	0.97
FTC + TDF + RPV, *n* (%)	2 (8.7)	1 (4.3)	0.97
FTC + TDF + LPV/rtv, *n* (%)	2 (8.7)	1 (4.3)	0.97
FTC + TDF + FPV/rtv, N (%)	2 (8.7)	–	0.5
FTC + TDF + EFV, *n* (%)	7 (30.4)	12 (52.2)	0.48
FTC + TDF + DTG, *n* (%)	3 (13.0)	–	0.27
FTC + TAF + BIC, *n* (%)	1 (4.3)	–	0.98
FTC + TDF + ATV, *n* (%)	1 (4.3)	3 (13.0)	0.66
FTC + TAF + DRV + cob, *n* (%)	1 (4.3)	2 (8.7)	0.97
FTC + TDF + NVP, *n* (%)	–	1 (4.3)	0.97
FTC + TDF + RAL, *n* (%)	–	1 (4.3)	0.97
3TC + TDF + LPV/rtv, *n* (%)	–	1 (4.3)	0.97
Median [IQR] VL at baseline, log10 RNA copies/ml Медиана [IQR] ВН на исходном уровне, log10 копий РНК/мл	5.4 [2.9–6.3]	4.6 [1.7–5.6]	0.99
Median [IQR] duration of therapy, weeks Медиана [IQR] продолжительности терапии, нед	86.0 [46.0–152.0]	168.0 [128.0–176.0]	0.33
Subtype Субтип			
A6	20 (87.0)	1 (4.3)	0.001
B	–	19 (82.6)	0.003
G	2 (8.7)	–	0.5
CRF01_AE	1 (4.3)	–	0.98
CRF09_cpx	–	1 (4.3)	0.97
F	–	1 (4.3)	0.97
CRF02_AG	–	1 (4.3)	0.97

Note. TDF – tenofovir disoproxil fumarate; TAF – tenofovir alafenamide; FTC – emtricitabine; 3TC – lamivudine; DRV – darunavir; RPV – rilpivirine; LPV – lopinavir; FPV – fosamprenavir; EFV – efavirenz; DTG – dolutegravir; BIC – bictegravir; ATV – atazanavir; NVP – nevirapine; RAL – raltegravir; rtv – ritonavir; cob – cobicistat; IQR – interquartile range; VL – viral load.

Примечание. TDF – тенофовира дизопроксила фумарат; TAF – тенофовира алафенамид; FTC – эмтрицитабин; 3TC – ламивудин; DRV – дарунавир; RPV – рилпивирин; LPV – лопинавир; FPV – фосампренавир; EFV – эфавиренц; DTG – долутегравир; BIC – биктегравир; ATV – атазанавир; NVP – невирапин; RAL – ралтегравир; RTV – ритонавир; cob – кобицистат; IQR – межквартильный размах; ВН – вирусная нагрузка.

Table 3. Results of viral load (VL) measurement
Таблица 3. Результаты измерения вирусной нагрузки (ВН)

Patient No. Номер пациента	VL at baseline, RNA copies/ml ВН на исходном уровне, копий РНК/мл	Follow-up period, months Срок наблюдения, мес	Follow-up period, weeks Срок наблюдения, нед	Number of VL measurements during the observation period Число измерений ВН за период наблюдения	VL in 4 weeks, RNA copies/ml ВН через 4 нед, копий РНК/мл	VL decrease in 4 weeks (Δ Lg) ВН через 4 нед (ΔLog_{10})	VL in 12 weeks, RNA copies/ml ВН через 12 нед, копий РНК/мл	VL in 24 weeks, RNA copies/ml ВН через 24 нед, копий РНК/мл
				A62V+				
1v	4683	4	16	2	–	–	40	–
2v	7852	6	24	2	–	–	–	69 200
3v	726	5	20	2	–	–	–	40
4v	6520	23	92	5	40	2.2	40	–
5v	5817	45	180	12	–	–	5817	99
6v	6660	80	320	19	0	> 1 lg	0	130
7v	77 006	94	376	31	587	2.1	40	40
8v	157 783	2	8	2	–	–	40	–
9v	64 201	63	252	19	528	2.1	275	40
10v	32 200	7	28	4	315	2.0	10	10
11v	92 000	28	112	9	830	2.0	33	15
12v	49 437	130	520	37	597	1.9	–	40
13v	7286	15	60	5	1	3.8	130 120	–
14v	16 200	5	20	3	0	> 1 lg	0	–
15v	42 400	3	12	3	459	1.9	34	–
16v	12 454	2	8	2	–	–	50	–
17v	41 225	30	120	29	330	2.1	–	40
18v	211 000	27	108	7	469	2.6	6 150 000	–
19v	209 136	6	24	3	25	3.9	–	20
20v	2 080 000	58	232	15	233	3.9	38	40
21v	160 000	43	172	14	478	2.5	0	0
22v	1 740 000	61	244	11	2180	2.9	–	0
23v	155 707	45	180	20	1579	1.9	219	40
				A62V−				
1a	78 000	28	112	5	–	–	–	25
2a	69 000	51	204	10	390	2.2	50	25
3a	134 896	22	88	7	1413	2.0	813	129
4a	61 000	30	120	15	50	3.1	50	25
5a	67 000	40	160	14	990	1.8	50	50
6a	34 000	32	128	7	3900	0.9	50	50
7a	230 000	35	140	16	57	3.6	50	50
8a	910 000	23	92	4	3700	2.4	–	150
9a	398 107	20	80	6	2754	2.1	282	63
10a	360 000	49	196	10	850	2.6	–	25
11a	490 000	56	224	14	850	2.7	50	50
12a	425 187	7	28	2	1191	2.5	–	40
13a	3000	31	124	6	50	1.8	50	25
14a	9900	15	60	5	140	1.9	50	50
15a	50	77	308	13	–	–	–	–
16a	3000	50	200	11	50	1.8	50	50
17a	6600	29	116	9	50	2.1	50	50
18a	490	53	212	11	–	–	50	50
19a	14 000	17	68	4	–	–	50	50
20a	14 000	60	240	15	50	1.6	50	50
21a	26 915	3	12	4	631	1.6	65	–
22a	4100	33	132	8	50	1.9	–	25
23a	17 000	45	180	9	56	2.5	–	25

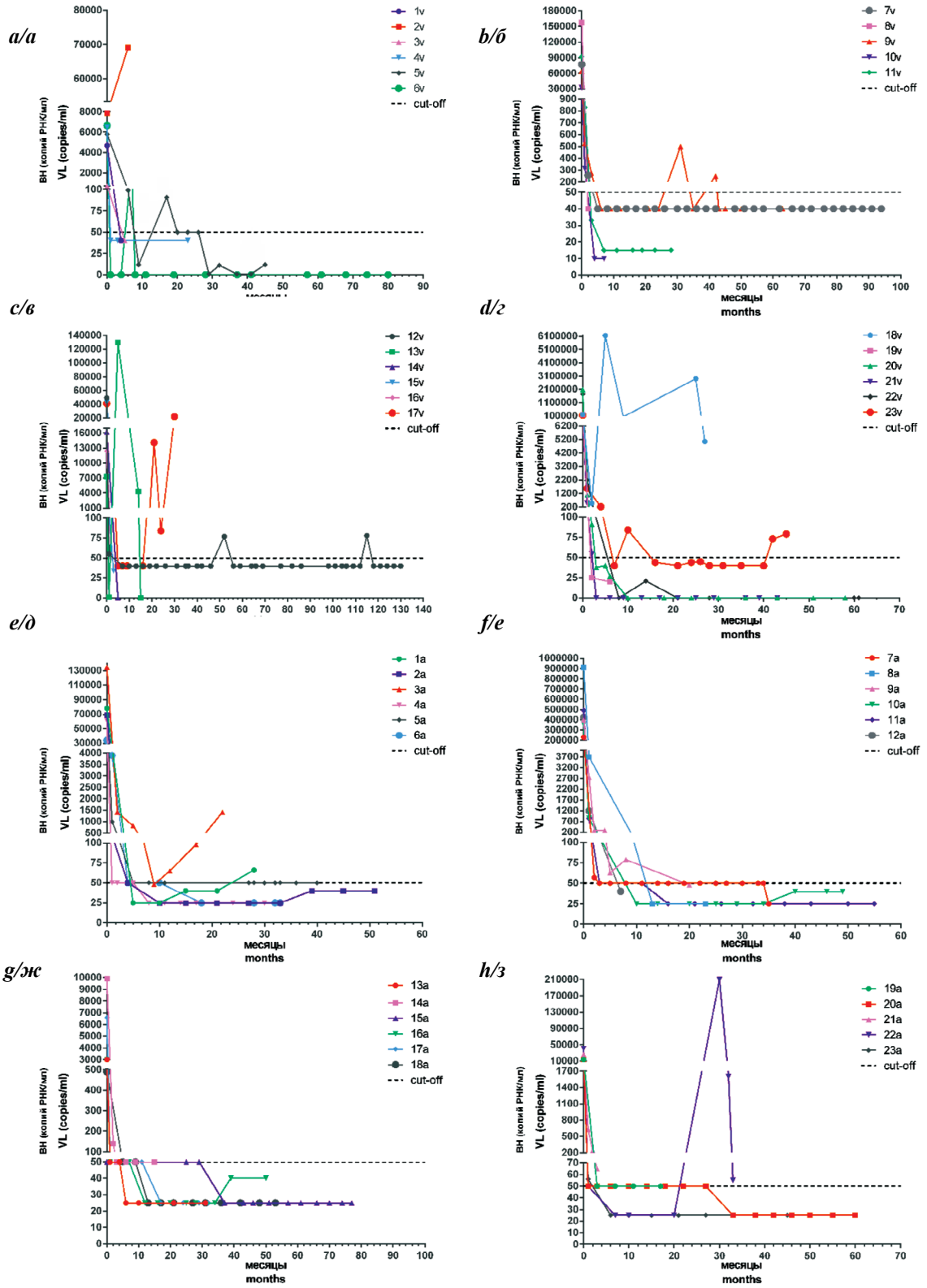

Figure. The dynamics of VLs during the follow-up period.

The VL level below 50 copies/ml was defined as a cut-off. *a–d* (A62V+ group): *a* – patients 1v, 2v, 3v, 4v, 5v, 6v; *b* – patients 7v, 8v, 9v, 10v, 11v; *c* – patients 12v, 13v, 14v, 15v, 16v, 17v; *d* – patients 18v, 19v, 20v, 21v, 22v, 23v; *e–h* (A62V− group): *e* – patients 1a, 2a, 3a, 4a, 5a, 6a; *f* – patients 7a, 8a, 9a, 10a, 11a; *g* – patients 12a, 13a, 14a, 15a, 16a, 17a; *h* – patients 18a, 19a, 20a, 21a, 22a, 23a.

Рисунок. Динамика ВН в период наблюдения.

Уровень ВН ниже 50 копий/мл определялся как пороговый. *а–г* (группа A62V+): *а* – пациенты 1v, 2v, 3v, 4v, 5v, 6v; *б* – пациенты 7v, 8v, 9v, 10v, 11v; *в* – пациенты 12v, 13v, 14v, 15v, 16v, 17v; *г* – пациенты 18v, 19v, 20v, 21v, 22v, 23v; *д–з* (группа A62V−): *д* – пациенты 1a, 2a, 3a, 4a, 5a, 6a; *е* – пациенты 7a, 8a, 9a, 10a, 11a; *ж* – пациенты 12a, 13a, 14a, 15a, 16a, 17a; *з* – пациенты 18a, 19a, 20a, 21a, 22a, 23a.

in the A62V+ cohort, virologic failure was detected in 4 (2v, 17v, 18v, 23v) out of 23 patients.

In the A62V− cohort, in 19 patients (2a, 4a, 5a, 6a, 7a, 8a, 9a, 10a, 11a, 12a, 13a, 14a, 15a, 16a, 17a, 18a, 19a, 20a, 23a), VL achieved an undetectable level (< 50 copies/ml). In one patient (1a), VL achieved an undetectable level with the following unconfirmed blip. In one patient (21a), VL did not achieve an undetectable level (< 50 copies/ml). At the same time, in 12 weeks, VL decreased to 65 copies/ml, which corresponds to virologic efficacy, and there were no results of VL measurement in the subsequent observation period. This result has not been interpreted as a virologic failure. In two patients (3a, 22a), VL dropped to a lower cut-off level with the following confirmed VL rebound. Thus, in the A62V− cohort, virologic failure was detected in 2 (3a, 22a) out of 23 patients.

Multivariate logistic regression analysis in both groups did not reveal an association between virologic failure and variables such as the composition of ART, HIV-1 subtype and duration of ART.

There was no statistical difference in cases of virologic failure in the two groups (p = 0.66; Fisher's two-tailed test).

Discussion

HIV-1 variants prevalent in Russia are different from virus variants circulating in Europe, Asia and North America [12]. Notably, the most widespread HIV-1 variant in Russia is sub-subtype A6 detected in 78.6% of cases [9]. Sub-subtype A6 has certain typical polymorphic mutations, which are associated with drug resistance: E138A and A62V in reverse transcriptase, L74I in integrase [8, 9, 13]. Earlier, we studied the influence of the pre-existing E138A mutation in reverse transcriptase on the efficacy of first-line ART regimens [14]. This study focuses on A62V in reverse transcriptase.

In earlier studies in Russia, A62V in reverse transcriptase in sub-subtype A6 was detected in 63% of cases in naïve patients and in 78% of cases among patients with antiretroviral experience [15, 16]. Although there is a current trend indicating a decrease in the frequency of A62V occurrence, its prevalence remains relatively high. Thus, in a surveillance study in Russia based on clinical samples collected from pretreatment HIV-infected patients in 2017–2019, A62V was detected in 37.1% of cases [17].

A recent study in Russia found a potential association between A62V and the virological breakthrough [18], which correlates with the findings of a previous study [5]. This is the first study where the efficacy of the first-line therapy including TDF/TAF was compared in two groups: PLWH with and without pre-existing A62V in reverse transcriptase at baseline.

In Russia, HIV genotyping before ART initiation is optional and, as a rule, is not routinely conducted [10]. Therefore, to form two groups of patients, we referred to the EIDB.

The results showed that there were no statistical differences between the two groups in virologic efficiency in 4, 12, and 24 weeks after ART initiation and in the frequency of virologic failures. However, virologic failure was observed in 4 patients in the A62V+ group and in 2 – in the A62V− group.

The main limitation of this project was the absence of virus sequencing data at the end of the first-line therapy in patients with virologic failure. Therefore, there was no possibility to assess whether the virologic failure was associated with the appearance of the main HIV drug resistance mutations associated with A62V or if it was attributable to other HIV drug resistance mutations or inadequate patient adherence. Therefore, among 4 patients with virologic failure in the A62V+ group: one patient (2v) took 3TC + TDF + EFV and three (17v, 18v, 23v) were on ART based on PI: FTC + TAF + DRV + cob, FTC + TDF + FPV/rtv and FTC + TDF + LPV/rtv, respectively. Two patients with virologic failure in the A62V− group (3a, 22a) took FTC + TDF + EFV. Therefore, efavirenz causes neuropsychiatric side effects in approximately 50% of patients [19], which can impact treatment adherence. The most common toxicities of PIs are effects on the gastrointestinal tract, in particular, diarrhea; moreover, the preferred regimen of PIs is twice a day, which could pose potential challenges for patients [20].

Another limitation of this study is that the patients in two groups were infected by different types of HIV-1: in the A62V+ group – in 87.0% (20/23) cases by sub-subtype A6, and in the A62V− group – in 82.6% (19/23) cases by subtype B. Currently, there are contradictory data about the influence of the HIV-1 subtype on pathogenesis and on the development of drug resistance. The results of certain research confirmed the hypothesis that different HIV-1 variants may have distinct clinical characteristics [21].

Furthermore, due to this being a retrospective study, VL measurement and patient follow-up were not scheduled sequentially, and only a limited number of patients could be observed at all checkpoints.

Conclusion

This is the first pilot study aimed at evaluating the efficacy of first-line ART regimens based on tenofovir in HIV-infected patients with pre-existing A62V mutation in reverse transcriptase, and the results of this study will contribute to the understanding of virologic failure risk in the presence of A62V in reverse transcriptase.

In conclusion, this study demonstrated that A62V in reverse transcriptase at baseline was not likely to reduce the efficacy of first-line regimens containing TDF or TAF. However, the role of this mutation deserves further investigation.

REFERENCES

1. Stanford University HIV Drug Resistance Database. Available at: http://hivdb.stanford.edu
2. Wensing A.M., Calvez V., Ceccherini-Silberstein F., Charpentier C., Günthard H.F., Paredes R., et al. 2022 update of the drug resistance mutations in HIV-1. *Top. Antivir. Med.* 2022; 30(4): 559–74.
3. Maldonado J.O., Mansky L.M. The HIV-1 reverse transcriptase A62V mutation influences replication fidelity and viral fitness in the context of multi-drug-resistant mutations. *Viruses*. 2018; 10(7): 376. DOI: https://doi.org/10.3390/v10070376

4. Svarovskaia E.S., Feng J.Y., Margot N.A., Myrick F., Goodman D., Ly J.K., et al. The A62V and S68G mutations in HIV-1 reverse transcriptase partially restore the replication defect associated with the K65R mutation. *J. Acquir. Immune Defic. Syndr.* 2008; 48(4): 428–36. DOI: https://doi.org/10.1097/QAI.0b013e31817bbe93
5. Rhee S.Y., Varghese V., Holmes S.P., Van Zyl G.U., Steegen K., Boyd M.A., et al. Mutational correlates of virological failure in individuals receiving a WHO-recommended Tenofovir-containing first-line regimen: an international collaboration. *EBioMedicine*. 2017; 18: 225–35. DOI: https://doi.org/10.1016/j.ebiom.2017.03.024
6. Wagner T., Zuckerman N.S., Halperin T., Chemtob D., Levy I., Elbirt D., et al. Epidemiology and transmitted HIV-1 drug resistance among treatment-naive individuals in Israel, 2010–2018. *Viruses*. 2021; 14(1): 71. DOI: https://doi.org/10.3390/v14010071
7. Zhukova A., Dunn D., Gascuel O. Modeling drug resistance emergence and transmission in HIV-1 in the UK. *Viruses*. 2023; 15(6): 1244. DOI: https://doi.org/10.3390/v15061244
8. Kazennova E.V., Lapovok I.A., Laga V.Y., Vasilyev A.V., Bobkova M.R. Natural polymorphisms of HIV-1 IDU-A variant pol gene. *VICh-infektsiya i immunosupressii*. 2012; 4(4): 44–51. EDN: https://elibrary.ru/pjowuj (in Russian)
9. Kirichenko A.A., Kireev D.E., Shlykova A.V., Lopatukhin A.E., Lapovok I.A., Saleeva D.V., et al. HIV-1 drug resistance in patients with virological inefficiency on ART in Russia in 2013–2021. *Epidemiologiya i infektsionnye bolezni. Aktual'nye voprosy.* 2021; 11(3): 53–62. DOI: https://doi.org/10.18565/epidem.2021.11.3.53-62 EDN: https://elibrary.ru/uqiuni (in Russian)
10. Ministry of Health of the Russian Federation. Clinical Guidelines «HIV Infection in Adults»; 2020. Available at: http://rushiv.ru/wp-content/uploads/2022/11/KR79.pdf (in Russian)
11. Clinicalinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf
12. Bbosa N., Kaleebu P., Ssemwanga D. HIV subtype diversity worldwide. *Curr. Opin. HIV AIDS.* 2019; 14(3): 153–60. DOI: https://doi.org/10.1097/coh.0000000000000534
13. Kirichenko A., Lapovok I., Baryshev P., van de Vijver D., van Kampen J.J.A., Boucher C.A.B., et al. Genetic features of HIV-1 integrase sub-subtype A6 predominant in Russia and predicted susceptibility to INSTIs. *Viruses*. 2020; 12(8): 838. DOI: https://doi.org/10.3390/v12080838
14. Kuznetsova A., Lebedev A., Gromov K., Kazennova E., Zazzi M., Incardona F., et al. Pre-existing singleton E138A mutations in the reverse transcriptase gene do not affect the efficacy of first-line ART regimens using rilpivirine in human immunodeficiency virus-infected patients. *Clin. Case Rep.* 2022; 10(2): e05373. DOI: https://doi.org/10.1002/ccr3.5373
15. Sukhanova A.L., Rudinskii N.I., Bogoslovskaya E.V., Kruglova A.I., Bashkirova L.Yu., Tsyganova G.M., et al. Polymorphism of the genome region coding for protease and reverse transcriptase in HIV type 1 subtype a variants prevailing in CIS countries. *Molekulyarnaya biologiya.* 2005; 39(6): 934–41. DOI: https://doi.org/10.1007/s11008-005-0115-8 EDN: https://elibrary.ru/ljarmp
16. Kolomeets A.N., Varghese V., Lemey P., Bobkova M.R., Shafer R.W. A uniquely prevalent nonnucleoside reverse transcriptase inhibitor resistance mutation in Russian subtype A HIV-1 viruses. *Aids*. 2014; 28(17): F1–8. DOI: https://doi.org/10.1097/qad.0000000000000485
17. Kirichenko A., Kireev D., Lopatukhin A., Murzakova A., Lapovok I., Saleeva D., et al. Prevalence of HIV-1 drug resistance in Eastern European and Central Asian countries. *PLoS One*. 2022; 17(1): e0257731. DOI: https://doi.org/10.1371/journal.pone.0257731
18. Shchemelev A.N., Ostankova Yu.V., Valutite D.E., Serikova E.N., Zueva E.B., Semenov A.V., et al. Risk assessment of first-line treatment failure in untreated HIV patients in Northwestern federal district of the Russian Federation. *Infektsiya i immunitet.* 2023; 13(2): 302–8. DOI: https://doi.org/10.15789/2220-7619-RAO-2122 EDN: https://elibrary.ru/ciclmu (in Russian)
19. Costa B., Vale N. Efavirenz: history, development and future. *Biomolecules*. 2022; 13(1): 88. DOI: https://doi.org/10.3390/biom13010088
20. Lv Z., Chu Y., Wang Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. *HIV AIDS (Auckl.).* 2015; 7: 95–104. DOI: https://doi.org/10.2147/hiv.S79956
21. Salvaña E.M.T., Dungca N.T., Arevalo G., Li K., Francisco C., Penalosa C., et al. HIV-1 subtype shift in the Philippines is associated with high transmitted drug resistance, high viral loads, and fast immunologic decline. *Int. J. Infect. Dis.* 2022; 122: 936–43. DOI: https://doi.org/10.1016/j.ijid.2022.06.048

ЛИТЕРАТУРА

1. Stanford University HIV Drug Resistance Database. Available at: http://hivdb.stanford.edu
2. Wensing A.M., Calvez V., Ceccherini-Silberstein F., Charpentier C., Günthard H.F., Paredes R., et al. 2022 update of the drug resistance mutations in HIV-1. *Top. Antivir. Med.* 2022; 30(4): 559–74.
3. Maldonado J.O., Mansky L.M. The HIV-1 reverse transcriptase A62V mutation influences replication fidelity and viral fitness in the context of multi-drug-resistant mutations. *Viruses*. 2018; 10(7): 376. DOI: https://doi.org/10.3390/v10070376
4. Svarovskaia E.S., Feng J.Y., Margot N.A., Myrick F., Goodman D., Ly J.K., et al. The A62V and S68G mutations in HIV-1 reverse transcriptase partially restore the replication defect associated with the K65R mutation. *J. Acquir. Immune Defic. Syndr.* 2008; 48(4): 428–36. DOI: https://doi.org/10.1097/QAI.0b013e31817bbe93
5. Rhee S.Y., Varghese V., Holmes S.P., Van Zyl G.U., Steegen K., Boyd M.A., et al. Mutational correlates of virological failure in individuals receiving a WHO-recommended Tenofovir-containing first-line regimen: an international collaboration. *EBioMedicine*. 2017; 18: 225–35. DOI: https://doi.org/10.1016/j.ebiom.2017.03.024
6. Wagner T., Zuckerman N.S., Halperin T., Chemtob D., Levy I., Elbirt D., et al. Epidemiology and transmitted HIV-1 drug resistance among treatment-naive individuals in Israel, 2010–2018. *Viruses*. 2021; 14(1): 71. DOI: https://doi.org/10.3390/v14010071
7. Zhukova A., Dunn D., Gascuel O. Modeling drug resistance emergence and transmission in HIV-1 in the UK. *Viruses*. 2023; 15(6): 1244. DOI: https://doi.org/10.3390/v15061244
8. Казеннова Е.В., Лаповок И.А., Лага В.Ю., Васильев А.В., Бобкова М.Р. Естественные полиморфизмы гена pol варианта ВИЧ-1 IDU-A. *ВИЧ-инфекция и иммуносупрессии.* 2012; 4(4): 44–51. EDN: https://elibrary.ru/pjowuj
9. Кириченко А.А., Киреев Д.Е., Шлыкова А.В., Лопатухин А.Э., Лаповок И.А., Салеева Д.В. и др. Лекарственная устойчивость ВИЧ-1 у пациентов с вирусологической неэффективностью АРТ в России (2013–2021 гг.). *Эпидемиология и инфекционные болезни. Актуальные вопросы.* 2021; 11(3): 53–62. DOI: https://doi.org/10.18565/epidem.2021.11.3.53-62 EDN: https://elibrary.ru/uqiuni
10. Минздрав России. Клинические рекомендации «ВИЧ-инфекция у взрослых»; 2020. Available at: http://rushiv.ru/wp-content/uploads/2022/11/KR79.pdf
11. Clinicalinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf
12. Bbosa N., Kaleebu P., Ssemwanga D. HIV subtype diversity worldwide. *Curr. Opin. HIV AIDS.* 2019; 14(3): 153–60. DOI: https://doi.org/10.1097/coh.0000000000000534

13. Kirichenko A., Lapovok I., Baryshev P., van de Vijver D., van Kampen J.J.A., Boucher C.A.B., et al. Genetic features of HIV-1 integrase sub-subtype A6 predominant in Russia and predicted susceptibility to INSTIs. *Viruses*. 2020; 12(8): 838. DOI: https://doi.org/10.3390/v12080838
14. Kuznetsova A., Lebedev A., Gromov K., Kazennova E., Zazzi M., Incardona F., et al. Pre-existing singleton E138A mutations in the reverse transcriptase gene do not affect the efficacy of first-line ART regimens using rilpivirine in human immunodeficiency virus-infected patients. *Clin. Case Rep.* 2022; 10(2): e05373. DOI: https://doi.org/10.1002/ccr3.5373
15. Суханова А.Л., Рудинский Н.И., Богословская Е.В., Круглова А.И., Башкирова Л.Ю., Цыганова Г.М. и др. Полиморфизм области генома, кодирующей протеазу и обратную транскриптазу, вариантов ВИЧ-1 подтипа А, распространенных на территории СНГ. *Молекулярная биология*. 2005; 39(6): 1063–71. EDN: https://elibrary.ru/hsjkol
16. Kolomeets A.N., Varghese V., Lemey P., Bobkova M.R., Shafer R.W. A uniquely prevalent nonnucleoside reverse transcriptase inhibitor resistance mutation in Russian subtype A HIV-1 viruses. *Aids*. 2014; 28(17): F1–8. DOI: https://doi.org/10.1097/qad.0000000000000485
17. Kirichenko A., Kireev D., Lopatukhin A., Murzakova A., Lapovok I., Saleeva D., et al. Prevalence of HIV-1 drug resistance in Eastern European and Central Asian countries. *PLoS One.* 2022; 17(1): e0257731. DOI: https://doi.org/10.1371/journal.pone.0257731
18. Щемелев А.Н., Останкова Ю.В., Валутите Д.Э., Серикова Е.Н., Зуева Е.Б., Семенов А.В. и др. Риск неэффективности терапии первой линии у пациентов с ВИЧ в Северо-Западном федеральном округе России. *Инфекция и иммунитет*. 2023; 13(2): 302–8. DOI: https://doi.org/10.15789/2220-7619-RAO-2122 EDN: https://elibrary.ru/ciclmu
19. Costa B., Vale N. Efavirenz: history, development and future. *Biomolecules*. 2022; 13(1): 88. DOI: https://doi.org/10.3390/biom13010088
20. Lv Z., Chu Y., Wang Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. *HIV AIDS (Auckl.)*. 2015; 7: 95–104. DOI: https://doi.org/10.2147/hiv.S79956
21. Salvaña E.M.T., Dungca N.T., Arevalo G., Li K., Francisco C., Penalosa C., et al. HIV-1 subtype shift in the Philippines is associated with high transmitted drug resistance, high viral loads, and fast immunologic decline. *Int. J. Infect. Dis*. 2022; 122: 936–43. DOI: https://doi.org/10.1016/j.ijid.2022.06.048

Information about the authors:

Ekaterina N. Ozhmegova✉ **–** PhD, researcher at the laboratory of leukemia viruses of the department of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: ozhmegova.eka@gmail.com; https://orcid.org/0000-0002-3110-0843

Anna I. Kuznetsova – PhD, Head of the Laboratory of Leukemia Viruses of the Department of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: a-myznikova@list.ru; https://orcid.org/0000-0002-3110-0843

Alexey V. Lebedev – PhD, researcher at the Laboratory of Leukemia Viruses of the Department of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: lebedevalesha236@gmail.com; https://orcid.org/0000-0001-6787-9345

Anastasia A. Antonova – PhD, researcher at the Laboratory of Leukemia Viruses of the Department of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: anastaseika95@mail.ru; https://orcid.org/0000-0002-9180-9846

Kristina V. Kim – junior researcher at the laboratory of leukemia viruses, division of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: kimsya99@gmail.com; https://orcid.org/0000-0002-4150-2280

Yana M. Munchak – junior researcher at the laboratory of leukemia viruses, division of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: yanka.zabavnaya@mail.ru; https://orcid.org/0000-0002-4792-8928

Alexander S. Tumanov – researcher at the laboratory of leukemia viruses of the department of the Institute of Virology named after. DI. Ivanovsky, National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: desep@mail.ru; https://orcid.org/0000-0002-6221-5678

Elena V. Kazennova – doctor of science, leading researcher at the Laboratory of Leukemia Viruses of the Department of the Institute of Virology named after. DI. Ivanovsky National Research Center for Epidemiology and Microbiology named after Honorary Academician N.F. Gamaleya, Moscow, Russia. E-mail: kazennova@rambler.ru; https://orcid.org/0000-0002-7912-4270

Contribution: Ozhmegova E.N. – the study concept and design, analysis and interpretation of the data, preparing of the text; Kuznetsova A.I. – the study concept and design, analysis and interpretation of the data, preparing of the text; Lebedev A.V. – interpretation of the data; Antonova A.A. – interpretation of the data; Kim K.V. – interpretation of the data; Munchak Y.M. – interpretation of the data; Tumanov A.S. – interpretation of the data; Kazennova E.V. – final approval of the article for publication.

Received 21 February 2024
Accepted 15 April 2024
Published 30 June 2024

Информация об авторах:

Ожмегова Екатерина Никитична✉ **–** канд. биол. наук, научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: ozhmegova.eka@gmail.com; https://orcid.org/0000-0002-3110-0843

Кузнецова Анна Игоревна – канд. биол. наук, заведующая лабораторией вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: a-myznikova@list.ru; https://orcid.org/0000-0002-3110-0843

Лебедев Алексей Владимирович – канд. биол. наук, научный сотрудник лаборатории вирусов лейкозов подразделения Институт вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: lebedevalesha236@gmail.com; https://orcid.org/0000-0001-6787-9345

Антонова Анастасия Александровна – канд. биол. наук, научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: anastaseika95@mail.ru; https://orcid.org/0000-0002-9180-9846

Ким Кристина Вячеславовна – младший научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: kimsya99@gmail.com; https://orcid.org/0000-0002-4150-2280

Мунчак Яна Михайловна – младший научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: yanka.zabavnaya@mail.ru; https://orcid.org/0000-0002-4792-8928

Туманов Александр Сергеевич – научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: desep@mail.ru; https://orcid.org/0000-0002-6221-5678

Казеннова Елена Валерьевна – д-р биол. наук, ведущий научный сотрудник лаборатории вирусов лейкозов Института вирусологии им. Д.И. Ивановского ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России, Москва, Россия. E-mail: kazennova@rambler.ru; https://orcid.org/0000-0002-7912-4270

Участие авторов: Ожмегова Е.Н. – концепция и дизайн исследования, анализ и интерпретация данных, подготовка текста; Кузнецова А.И. – концепция и дизайн исследования, анализ и интерпретация данных, подготовка текста; Лебедев А.В. – интерпретация данных; Антонова А.А. – интерпретация данных; Ким К.В. – интерпретация данных; Мунчак Ю.М. – интерпретация данных; Туманов А.С. – интерпретация данных; Казеннова Е.В. – окончательное одобрение статьи к публикации.

Поступила 21.02.2024
Принята в печать 15.04.2024
Опубликована 30.06.2024