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Variability of non-structural proteins of HIV-1 sub-subtype A6 (Retroviridae: *Orthoretrovirinae*: *Lentivirus*: *Human immunodeficiency virus-1,* sub-subtype A6) variants circulating in different regions of the Russian Federation

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Abstract

Introduction. HIV-1 non-structural proteins are promising targets for vaccine development and for creating approaches to personalized medicine. HIV-1 sub-subtype A6 has become the dominating form in Russia. However, the geographic, economic and demographic characteristics of the country can contribute to the formation of differences between A6 variants circulating in different regions.

The aim of the study is a comparative analysis of the consensus sequences of non-structural proteins in A6 variants circulating in the Amur Region, in Arkhangelsk, Irkutsk and Murmansk.

Materials and methods. 48 whole blood samples obtained from HIV-infected patients without experience of therapy observed at the AIDS Centers in Arkhangelsk, Irkutsk, Murmansk and Amur Region were analyzed. HIV-1 whole-genome nucleotide sequences were obtained and were subtyped. Consensus sequences of sub-subtype A6 variants non-structural proteins for each analyzed region were formed. Furthermore, reference sequences of sub-subtype A6 non-structural proteins were formed based on whole-genome sequences retrieved from the international Los Alamos database. Comparison of consensus sequences and references was performed using the MEGA v.10.2.2 and the PSIPRED programs.

Results. Vif, Vpr and Nef reference sequences have been obtained for HIV-1 sub-subtype A6. There was not difference in consensus sequences of Vpr in different regions. Characteristic features were found for consensus sequences of Tat, Rev, Vpu, Vif and Nef proteins in different regions.

Conclusion. A limitation of the study is a small sample size. Overall, the results demonstrate the existing diversity of non-structural proteins in sub-subtype A6 variants in different regions and indicate the relevance of studying the polymorphism of non-structural proteins of virus variants in different regions.

Keywords: *HIV-1; sub-subtype A6; non-structural proteins*

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
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Вариабельность неструктурных белков у вариантов ВИЧ-1 суб-субтипа A6 (Retroviridae: *Orthoretrovirinae*: *Lentivirus*: *Human immunodeficiency virus-1,* sub-subtype A6), циркулирующих в разных регионах Российской Федерации

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Резюме

Введение. Неструктурные белки ВИЧ-1 являются перспективными мишенями для разработки вакцин и для создания подходов персонализированной медицины. На протяжении многих лет на территории Российской Федерации доминирует суб-субтип A6 ВИЧ-1. Однако имеющиеся географические, экономические и демографические особенности страны могут способствовать формированию различий между вариантами вируса, циркулирующими в разных регионах России.

Цель работы: провести сравнительный анализ консенсусных последовательностей неструктурных белков ВИЧ-1 вариантов A6, циркулирующих в Амурской области, в гг. Архангельске, Иркутске и Мурманске.

Материалы и методы. Исследовали 48 образцов цельной крови, которые были получены от ВИЧ-инфицированных пациентов без опыта приема терапии, наблюдавшихся в центрах по профилактике и борьбе со СПИДом в гг. Архангельске, Иркутске, Мурманске и в Амурской области. Получали полногеномные нуклеотидные последовательности ВИЧ-1, субтипировали. Формировали консенсусные последовательности каждого неструктурного белка ВИЧ-1 для каждого анализируемого региона. Дополнительно формировали референсные последовательности неструктурных белков ВИЧ-1 суб-субтипа A6 на основе полногеномных последовательностей, загруженных из международной базы данных Los Alamos. Сравнение консенсусных и референсных последовательностей осуществляли с помощью программ MEGA v.10.2.2 и PSIPRED.

Результаты. Впервые представлены референсные последовательности белков Vif, Vpr и Nef ВИЧ-1 суб-субтипа A6. Для белка Vpr различий в консенсусных последовательностях вариантов вируса, циркулирующих в разных регионах РФ, не обнаружено. Для консенсусных последовательностей белков Tat, Rev, Vpu, Vif и Nef вариантов ВИЧ-1 из разных регионов РФ определены характерные особенности.

Заключение. Ограничением проведенного исследования является небольшая выборка образцов. В целом полученные результаты указывают на существующее разнообразие неструктурных белков ВИЧ-1 суб-субтипа A6 в разных регионах страны и обозначают актуальность исследования полиморфизма неструктурных белков вариантов вируса в разных регионах в будущем.

Ключевые слова: *ВИЧ-1; суб-субтип A6; неструктурные белки*

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Introduction

The genome of human immunodeficiency virus type 1 (HIV-1) (Retroviridae: *Orthoretrovirinae: Lentivirus: Human immunodeficiency virus-1*) encodes 6 non-structural proteins: Tat, Rev, Vpu, Vif, Vpr, Nef. The non-structural proteins create the necessary conditions for virus replication and protect the virus from the host immune system [1]. Earlier studies have shown that HIV-1 nonstructural proteins contain epitopes that can be used for vaccine development [2–4]. It was observed that immunization with Tat protein-based constructs promoted restoration of CD4-cell levels and reduction of viral reservoirs [5]. At present, the development of

new approaches to stimulate immune response based on non-structural proteins is ongoing [6–8]. In this regard, studying the variability of HIV-1 non-structural proteins is an important objective and provides a basis for such developments. Furthermore, amino acid substitutions have been identified in HIV-1 nonstructural proteins that are associated with both changes in the rate of HIV infection and the development of comorbid diseases in HIV-1-infected patients [1]. Thus, studying the diversity of HIV-1 nonstructural proteins may also become a platform for the development of personalized medicine approaches.

The molecular epidemiology of HIV-1 in Russia has its own characteristic features. Initially, the active spread of HIV infection in Russia was associated with the introduction of the sub-subtype A6 virus among injecting drug users (IDUs) in the 1990s and its subsequent rapid spread within this social group in all regions of the country [9]. A gradual decline in the proportion of IDUs in the HIV-infected population in the Russian Federation was then noted, with a simultaneous increase in the number of cases of transmission through heterosexual contacts [10]. Currently, sub-subtype A6 remains the dominant (82.9%) genetic variant of HIV-1 in Russia, but there is a constant increase in the genetic diversity of the virus [11, 12].

The epidemic process of HIV infection on the territory of the Russian Federation is of great interest and is caused by a number of peculiarities of the country: Russia is the 1st largest country in the world in terms of territory size, it is a multinational and multi-confessional country, which determines the difference in cultures and behavior, lifestyle and mobility patterns of the population. Furthermore, our country borders 18 states, has numerous transportation corridors, which contributes to high genetic diversity and rapid spread of HIV-1 due to migration processes [13, 14]. Thus, it was noted that the proportion and diversity of circulating non-A6 variants can differ significantly between different federal districts of the Russian Federation [12]. It is likely that the geographical location, peculiarities of socioeconomic development of the region and population composition can also influence the selection of circulating genetic variants of the virus within sub-subtype A6.

Taking into account the above, we hypothesized that nonstructural proteins may differ among HIV-1 variants of sub-subtype A6 circulating in different regions of the Russian Federation. To date, there have been no studies on the diversity of nonstructural proteins of HIV-1 sub-subtype A6 variants circulating in different regions of Russia.

The aim of this study was to comparatively analyze the consensus sequences of non-structural HIV-1 sub-subtype A6 proteins in virus variants circulating in different regions of Russia: Amur region, Arkhangelsk, Irkutsk and Murmansk.

Materials and methods

Clinical whole blood samples obtained from 48 ART-naïve (antiretroviral therapy), HIV-infected patients from the following regions of Russia: Amur region, Arkhangelsk, Irkutsk and Murmansk served as the material of the present study (**Table 1**). Blood was collected from patients once in 2012–2014 within the framework of the CHAIN project of the 7th Framework Program of the European Community «Single Network for Antiretroviral Drug Resistance Research» (https://cordis.europa.eu/project/id/223131). All obtained clinical material was used with the informed consent of the patients based on the permission of the Ethical Committee State Research Center of Virology and Biotechnology VECTOR on March 30, 2010.

Samples were analyzed by mass parallel sequencing using the AmpliSense HIV-Resist-NGS kit according to the manufacturer's instructions (Central Research Institute of Epidemiology of Rospotrebnadzor, Russia). Whole-genome sequencing of samples was performed using MiSeq technology and appropriate MiSeq reagent kits V2 (Illumina, USA) by analyzing 4 overlapping specific fragments (total length of the analyzed fragment 704-9563 by HXB2).

Genetic variants of the obtained whole-genome sequences were determined using the Comet program

Table 1. Characteristics of HIV-1 infected patients included in the study
Таблица 1. Характеристики ВИЧ-1-инфицированных пациентов, включенных в исследование

Region Регион	Number of patients Число пациентов	Date of sampling Год забора образца	Sex Пол		Age Возраст	Route of infection Путь инфицирования		Stage of HIV-infection* Стадия заболевания*			
			male муж.	female жен.		IDU ПИН	hetero гетеро	2	3	4	unknown неизвестно
Amur Region Амурская область	10	2012	8	2	30,8 (18–41)	4	6	–	4	5	1
Arkhangelsk Архангельск	12	2013	3	9	30,3 (18–42)	5	7	1	10	1	–
Murmansk Мурманск	13	2013–2014	6	7	33 (26–42)	10	3	–	5	8	–
Irkutsk Иркутск	13	2012	10	3	31,9 (23–49)	10	3	–	7	6	–

Note. *In according to clinical recommendation [15].

Примечание. *В соответствии с клиническими рекомендациями [15].

(https://comet.lih.lu). Pairwise and multiple alignment of nucleotide sequences was performed using the MEGA v.10.2.2. program (megasoftware.net), then the regions encoding the corresponding analyzed HIV-1 nonstructural proteins (Tat, Rev, Vpu, Vif, Vpr, Nef) were excised from the obtained alignments. Phylogenetic analysis was performed for all *tat*, *rev*, *vpu*, *vif*, *vpr*, *nef* gene sequences. Phylogenetic analysis was performed using the Maximum Likelihood (ML) method using the IQ-TREE program (http://www.iqtree.org). The source of reference sequences was the database of the Los Alamos Laboratory, USA (https://www.hiv.lanl.gov/). The nucleotide substitution model was determined in the jModelTest v.2.1.7 program based on the Akaike information criterion (AIC). The model with the lowest criterion value was considered the most appropriate model for further analysis. The validity of the inferred phylogenies was assessed using bootstrap test (bootstrap) and Shimodaira-Hasegawa approximate likelihood ratio test (SH-aLRT) with 1000 post-start iterations. Clusters with SH-aLRT support > 0.9 were considered to be reliably established. Visualization and graphical processing of the results of phylogenetic analysis were performed in the iTOL program (https://itol.embl.de).

In the next step of the study, the obtained nucleotide sequences were translated into amino acid sequences using an online translation tool available at https://www.bioinformatics.org/sms2/translate.html. Then, using the Simple Consensus Maker tool (https://www.hiv.lanl.gov/content/sequence/CONSENSUS/SimpCon.html), consensus sequences for each nonstructural protein (Tat, Rev,Vpu, Vif, Vpr, Nef) for each RF region were generated based on the obtained amino acid sequences.

For further comparative analysis of consensus sequences, reference sequences for each protein were additionally generated. For this purpose, all available whole-genome sequences of HIV-1 sub-subtype A6 (235 sequences as of 08/13/2024) were downloaded from the Los Alamos international database (Main Search Interface of HIV Sequence Database (lanl.gov)). The sequence sample contained no duplicates: only one sequence from a single patient. For each protein, amino acid and nucleotide sequences were simultaneously downloaded. Then, for each protein analyzed, the nucleotide and amino acid sequences were compared with each other in MEGA v.10.2.2. software (megasoftware.net). Sequences encoding an incomplete protein were removed from the analysis. Insertions were not considered in the generation of reference sequences. Reference sequences for each nonstructural protein (Tat, Rev,Vpu, Vif, Vpr, Nef) were generated using the Simple Consensus Maker tool (https://www.hiv.lanl.gov/content/sequence/CONSENSUS/SimpCon.html) based on amino acid sequences.

Further comparison of the obtained reference and consensus sequences was performed using the MEGA v.10.2.2 program. The positions of amino acids (a.a.) in the consensus sequences that contained amino acid substitutions relative to the reference sequences were determined.

Next, we compared the secondary structures of the consensus sequences obtained for each region with the reference sequences of the analyzed HIV-1 proteins using the PSIPRED program (http://bioinf.cs.ucl.ac.uk/psipred/).

Results

All nucleotide sequences (48) obtained in this study were deposited in the GenBank international genotype database under the following numbers (**Table 2**).

According to the results of preliminary subtyping, all nucleotide sequences analyzed belonged to HIV-1 sub-subtype A6. The phylogenetic analysis confirmed the results of preliminary subtyping (**Fig. 1**).

At the next stage of the study, consensus amino acid sequences of each HIV-1 nonstructural protein (Tat, Rev, Vpu, Vif, Vpr, Nef) were generated for each region: for the Amur region – based on 10 sequences, for Arkhangelsk – 12 sequences, for Murmansk – 13, for Irkutsk – 13. Insertions (amino acid insertions) were not taken into account in their formation. **Table 3** shows all insertions and deletions (point mutations associated with the absence of a.a. at a given position) that were detected during analysis.

Afterwards, reference protein sequences were generated based on the sequences retrieved from the Los Alamos international database. Tat, Rev, Vif, and Vpr protein reference sequences were generated based on 235 sequences and had the following lengths: 101 a.a., 123 a.a., 192 a.a., 96 a.a., respectively. The reference sequence of Vpu protein was generated based on 232 sequences and contained 81 a.a. The reference sequence of Nef protein was generated on the basis of 223 sequences and contained 207 a.a. (**Fig. 2**).

The obtained consensus sequences of nonstructural proteins were compared with reference sequences. **Table 4** shows the positions in which the consensus sequences of HIV-1 nonstructural proteins of individual regions of Russia differed from the reference sequences.

The consensus sequences of protein of virus variants circulating in the analyzed regions did not contain substitutions relative to the reference sequences. Therefore, comparative analysis of the secondary structure of the Vpr protein was not performed in the further study.

The results of predicting the secondary structures of the reference sequences of the analyzed HIV-1 proteins are presented in **Table 5**.

Similarly, the secondary structures of consensus sequences of non-structural protein sequences of HIV-1 sub-subtype A6 variants circulating in the analyzed regions of Russia were predicted.

When comparing the predicted secondary structures of consensus sequences with reference sequences, the following differences were found:

– a shift of the helix location from position 86–95 to position 85-94 was detected for the Tat protein variant, characteristic of HIV-1 sub-subtype A6 in the Amur region, containing P68L and R99P substitutions;

– a shift of the strand location from position 38–41 to position 39–41 was detected for the Vif protein variant, characteristic of HIV-1 sub-subtype A6 in the Amur region. At the same time, a shift in strand location from position 38–41 to position 38–39 was observed for Vif

Table 2. GenBank accession numbers for the HIV-1 nucleotide sequences used in the work
Таблица 2. Регистрационные номера GenBank использованных в работе нуклеотидных последовательностей ВИЧ-1

Region of the Russian Federation Регион РФ	GenBank accession numbers for sequences Номера последовательностей GenBank
Amur region Амурская область	MH330347, MH330348, MH330349, MH330350, MH330351, MH330352, MH330353, MH330354, MH330355, MH330356
Arkhangelsk Архангельск	MG902950, MG902951, MH330337, MH330338, MH330339, MH330340, MH330341, MH330342, MH330343, MH330344, MH330345, MH330346
Murmansk Мурманск	MH330370, PP816220, MH330371, MH330372, MH330373, MH330374, MH330375, MH330376, MH330377, MH330378, MH330379, MH330380, MH330381
Irkutsk Иркутск	MH330357, MH330358, MH330359, PP816221, MH330361, PP816222, MH330363, MH330364, MH330365, PP816223, MH330367, PP816224, PP816225

Table 3. Insertions and deletions of amino acids (a.a.) in the analyzed sequences*
Таблица 3. Инсерции и делеции аминокислот в анализируемых последовательностях*

HIV-1 protein Белок ВИЧ-1	Amur region Амурская область		Arkhangelsk Архангельск		Murmansk Мурманск		Irkutsk Иркутск	
	insertion (sequence ID) инсерция (N посл-ти)	deletion (sequence ID) делеция (N посл-ти)	insertion (sequence ID) инсерция (N посл-ти)	deletion (sequence ID) делеция (N посл-ти)	insertion (sequence ID) инсерция (N пос-ти)	deletion (sequence ID) делеция (N посл-ти)	insertion (sequence ID) инсерция (N пос-ти)	deletion (sequence ID) делеция (N посл-ти)
Tat	–	–	–	–	79–80insE (MH330380)	–	54–55insS (MH330364)	–
Rev	–	del97–119 (MH330355, (MH330353)	–	del93–99 (MH330341), del94–115 (MH330339)	33–34insR (MH330380)	–	8–9insA (MH330364)	del91–97 (MH330358)
Vpu	–	–	–	–	–	del77 (PP816220)	7–8insTIV (PP816225)	del5 (PP816223)
Vif	–	–	–	–	–	–	–	del109–115 (PP816224)
Vpr	–	–	–	del85–86 (MH330345)	84–85insI/M (MH330371)	–	–	del85–86 (PP816225)
Nef	25–26insPA (MH330352, MH330354), 25–26ins PAASGVE (MH330355), 63–64insEE (MH330355)	del8–11 (MH330351), del8–11 (MH330355)	25–26insPA (MH330342, MH330343)	Del8–9 (MG902950)	25–26insPA (MH330371), 25–26insP (MH330370), 25–26in-sPAAGG[G/V] (MH330378), 25–26ins PXARRAPE (MH330380), 63–64insE (PP816220, MH330380)	–	25–26insPAP (PP816221), 25–26insPA (PP816225), 25–26insPAA (MH330363), 63–64insE (MH330358)	del8–11 (PP816221, MH330361), del10 (PP816223)

Note. *The locations of insertions and deletions are shown according to the consensus sequence of the corresponding HIV-1 protein.

Примечание. *Расположение инсерций и делеций указано относительно консенсусной последовательности неструктурного белка ВИЧ-1 соответствующего региона.

protein variants of HIV-1 sub-subtype A6, circulating in Arkhangelsk, Murmansk, and Irkutsk. Furthermore, a shift of the strand from position 93–97 to position 94–97 was detected for the Vif protein, characteristic of the virus variants in Murmansk, and a lack of strand structure at position 128–129 was found for the Vif protein characteristic of the virus variants in Arkhangelsk;

– a displacement of the helix element from position 13–21 to 14–21 was detected for the Nef protein variants, characteristic of HIV-1 sub-subtype A6 in Arkhangelsk, Murmansk and Irkutsk. Furthermore, a shift of the helix element from position 57–66 to 56–66 was detected for the Nef protein variant of the virus characteristic of Arkhangelsk.

Discussion

Currently, studies of the HIV-1 *pol* gene are regularly conducted in Russia both in virus variants circulating in individual regions [17–19] and in the whole country [11, 12, 20]. This is explained by the fact that inhibitors of

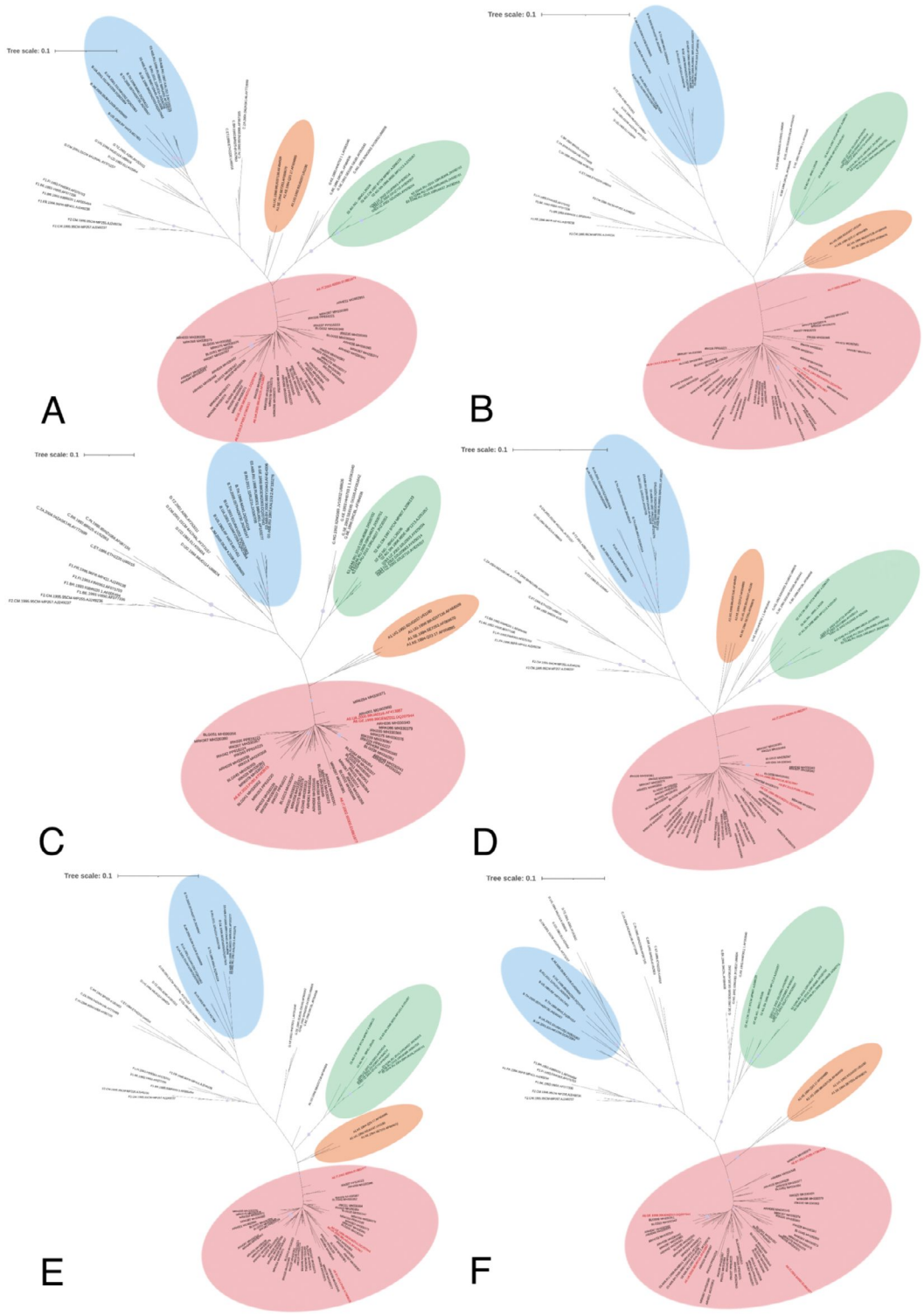

Fig. 1. Phylogenetic analysis of the obtained sequences: *tat* (A), *rev* (B), *vpu* (C), *vif* (D), *vpr* (E), *nef* (F).

Clusters of the most typical HIV-1 genetic variants for the territory of the Russian Federation are marked in color on the phylogenetic trees: pink – HIV-1 sub-subtype A6, blue – subtype B, light green – circulating recombinant forms CRF02_AG and CRF63_02A6; a cluster formed by the reference sequences of HIV-1 sub-subtype A1 is also marked. Within the HIV-1 sub-subtype A6 cluster, the reference sequences are shown in red, the studied sequences are shown in black; all other clusters of HIV-1 of other genetic variants (A1, C, D, F1, F2, G) include exclusively reference sequences (HIV Databases (lanl.gov).

Рис. 1. Филогенетический анализ полученных последовательностей: *tat* (A), *rev* (B), *vpu* (C), *vif* (D), *vpr* (E), *nef* (F).

Цветом на филогенетических деревьях отмечены кластеры наиболее характерных для территории РФ генетических вариантов ВИЧ-1: розовым цветом – ВИЧ-1 суб-субтипа А6, голубым – субтипа В, салатовым – циркулирующих рекомбинантных форм CRF02_AG и CRF63_02A6; также отмечен кластер, образованный референсными последовательностями ВИЧ-1 суб-субтипа А1. Внутри кластера ВИЧ-1 суб-субтипа А6 референсные последовательности обозначены красным цветом, исследуемые последовательности – черным цветом; все остальные кластеры ВИЧ-1 других генетических вариантов (A1, C, D, F1, F2, G) включают исключительно референсные последовательности (HIV Databases (lanl.gov).

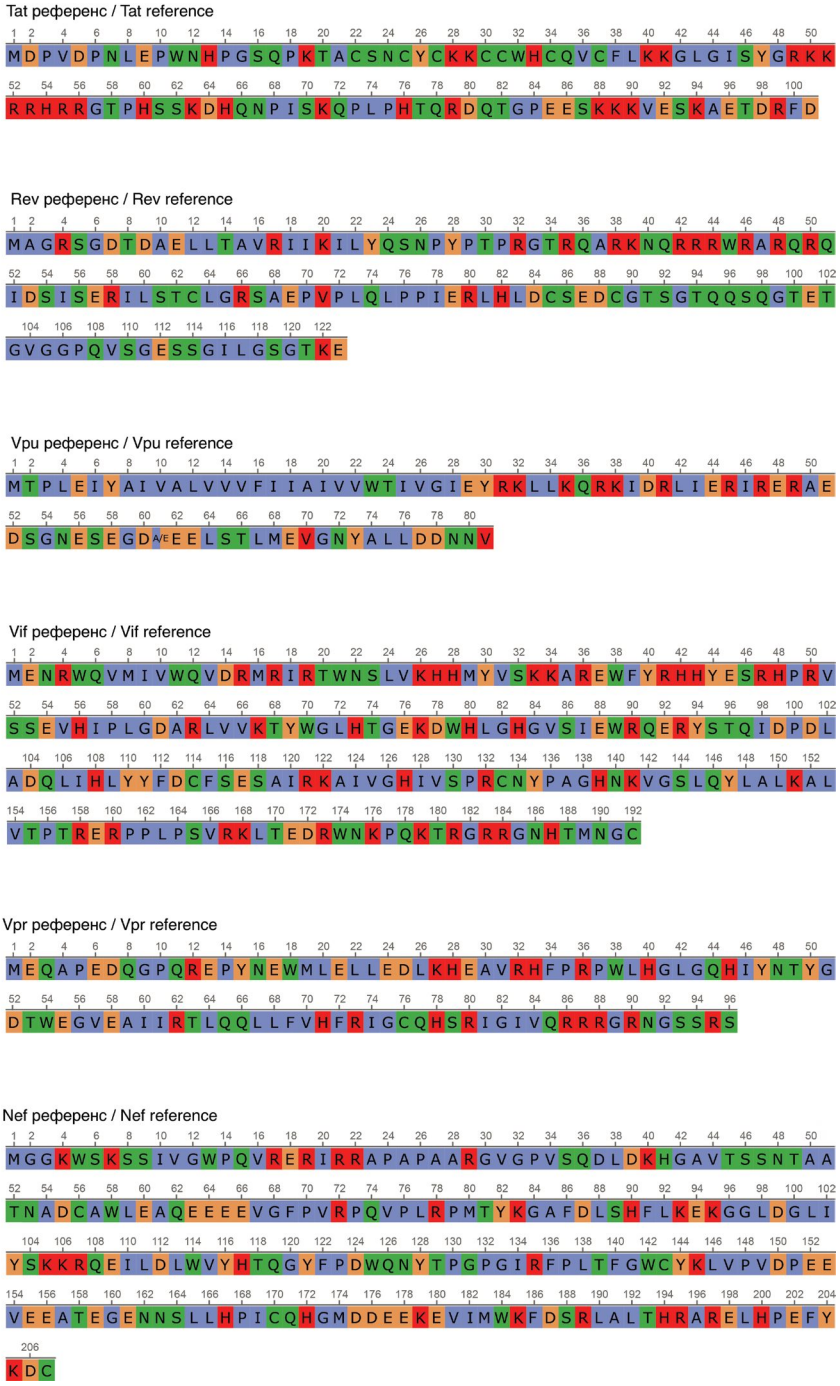

Fig. 2. Reference sequences of the proteins Tat, Rev, Vpu, Vif, Vpr, Nef.

Non-polar amino acids: G (glycine), A (alanine), V (valine), L (leucine), I (isoleucine), P (proline), M (methionine) and F (phenylalanine), – are marked in blue; Polar uncharged, neutral, amino acids: S (serine), T (threonine), C (cysteine), N (asparagine), Q (glutamine) and W (tryptophan) – green; polar acidic, negatively charged, amino acids: D (aspartic acid) and E (glutamic acid), Y (tyrosine) – orange; polar basic, positively charged amino acids: K (lysine), R (arginine) and H (histidine) [16].

Рис. 2. Референсные последовательности белков Tat, Rev, Vpu, Vif, Vpr, Nef.

Неполярные аминокислоты: G (глицин), A (аланин), V (валин), L (лейцин), I (изолейцин), P (пролин), M (метионин) и F (фенилаланин) – отмечены синим цветом; полярные незаряженные, нейтральные, аминокислоты: S (серин), T (треонин), C (цистеин), N (аспарагин), Q (глутамин) и W (триптофан) – зеленым; gполярные кислые, отрицательно заряженные, аминокислоты: D (аспарагиновая кислота) и E (глутаминовая кислота), Y (тирозин) – оранжевым; полярные основные, положительно заряженные, аминокислоты: K (лизин), R (аргинин) и H (гистидин) – красным [16].

viral enzymes, integrase, protease, and reverse transcriptase, which are encoded by the *pol* gene [1, 15], are mainly used to treat HIV infection. Accordingly, most antiretroviral drug resistance mutations occur in the *pol* gene, and the study of this region of the genome is regulated by regulatory documents in clinical practice. Nonstructural protein genes are outside the analyzed region of the genome, and the variability of nonstructural proteins of virus variants circulating in different regions of the country remains unstudied. In a recent study, we showed that some regions of the Tat protein in HIV-1 sub-subtype A6 variants circulating in the Moscow region are less conserved than in the general population of HIV-1 sub-subtype A6 variants [21].

This study was based on the assumption that there is variability in non-structural proteins of HIV-1 sub-subtype A6 variants circulating in different regions of our country. We analyzed the sequences of non-structural proteins of HIV-1 sub-subtype A6 variants obtained by analyzing clinical whole blood samples of naive patients, i.e., those who had not previously received ART, between 2012 and 2014. Patients were under observation at AIDS centers in the Amur region, Arkhangelsk, Murmansk and Irkutsk (Table 1).

When generating consensus sequences for each HIV-1 non-structural protein, sequences containing deletions/insertions were noted (Table 3), with only one sequence

Table 4. Amino acid substitutions in the consensus sequences of non-structural proteins of virus variants circulating in the Amur Region, Arkhangelsk, Murmansk, and Irkutsk, relative to the reference sequences*

Таблица 4. Аминокислотные замены в консенсусных последовательностях неструктурных белков вариантов вирусов, циркулирующих в Амурской области, гг. Архангельске, Мурманске, Иркутске, относительно референсных последовательностей*

HIV-1 protein Белок ВИЧ-1	Amur region Амурская область	Arkhangelsk Архангельск	Murmansk Мурманск	Irkutsk Иркутск
Tat	P68L**, R99P**/R	–	–	P68L
Rev	K39R	K39R, **A68E**, V109I	K39R, V109I	–
Vpu	**F16S**/A	**F16**F/**S**/A	L33V	**Y73L**
Vif	F39V	**E37G**, R50K, **E92**E/**K**, V125V/L	**E37G**, R50K, **E92R**, I98I/V, H127Q	**E37G**, R50K/R
Vpr	–	–	–	–
Nef	I10I/L, K179R	**R29T**,**Y82F**, **E152**E/**S,** K179R	**R29T**, **I134**I/**E**, **Y144**Y/**F**, E152D, K179R, **T193**T/**K**	**R29P/T**, G84A, **F136Y**, K179R, **T193K**

Note. *R99P/R indicates that the consensus sequence contained amino acids P and R with equal probability at the position. Substitutions associated with changes in the properties of amino acids, charged/uncharged or polar/non-polar, are highlighted in bold.

Примечание. *R99P/R обозначает, что в консенсусной последовательности с равной вероятностью в позиции встречались аминокислоты P и R. Жирным шрифтом выделены замены, ассоциированные с изменениями свойств аминокислот: заряженная/незаряженная, полярная/неполярная.

Table 5. Predicted arrangement of helical and strand elements in secondary structures of reference sequences of HIV-1 nonstructural proteins

Таблица 5. Спрогнозированное расположение элементов спиралей и цепей во вторичных структурах референсных последовательностей неструктурных белков ВИЧ-1

Secondary structure type Тип вторичной структуры	Tat (a.a. position / позиция АК)	Rev (a.a. position / позиция АК)	Vpu (a.a. position / позиция АК)	Vif (a.a. position / позиция АК)	Nef (a.a. position / позиция АК /)
Helix Спираль	32–33, 36–39, 86–95	9–24, 35–61	3–52, 61–70	15–31, 78–80, 100–110, 117–124, 145–153	13–21, 38–40,50–51, 57–66, 82–94, 106–110, 151–156, 168–171, 188–192, 196–199, 201–204
Strand Цепь	–	–	–	4–13, 38–41, 50–59, 63–69, 85–91, 93–97, 128–129	102–104, 111–118, 142–148, 181–186

(PP816224) containing a deletion (del109–115) in the Vif protein, and the greatest number of deletions/insertions analyzed sequences contained in the Nef protein (Table 3). This result can be explained by the fact that the main function of the Vif protein is to counteract the cellular protein APOBEG3G, whereas the Nef protein has multiple activities and contacts more host cell proteins, which, accordingly, implies a more flexible structure [1].

Reference sequences of HIV-1 sub-subtype A6 non-structural proteins were generated from 235 whole-genome sequences downloaded from the Los Alamos International Database.

The generated Tat protein reference sequence contained histidine (H) at position 54 and 60, glycine (G) at position 57, and the ^{78}QRD^{80} motif characteristic of HIV-1 sub-subtype A6 [21, 22].

The generated Rev protein reference sequence contained glutamine (Q) at position 41 and, after position 95, a QSQGTET motif characteristic of HIV-1 sub-subtype A6 [23].

The generated Vpu protein reference sequence relative to the previously published Vpu sub-subtype A6 sequence contained tyrosine (Y) instead of leucine (L) at position 73 [24].

The reference sequences of Vif, Vpr, and Nef proteins of HIV-1 sub-subtype A6 were generated and presented for the first time.

Despite the variability characteristic of Vpr protein in the COOH-terminal region reported earlier, the consensus sequences of Vpr protein from different regions of the Russian Federation did not contain substitutions relative to the reference sequence [25].

The consensus sequences of Tat, Rev, Vpu, Vif, and Nef proteins differed from the reference sequences and differed among themselves by the presence of characteristic amino acid substitutions. Some of the identified amino acid substitutions were associated with changes in the chemical properties of the amino acids, and changes in the secondary structure of the protein relative to the reference sequences were detected for Tat, Vif, and Nef proteins.

The results obtained indicate the existence of differences in non-structural proteins in HIV-1 sub-subtype A6 variants, circulating in different regions of the Russian Federation, which can be explained by the founder effect.

This study has a limitation due to the small sample of analyzed sequences. To confirm the results obtained, it is necessary to conduct further studies of the polymorphism of non-structural proteins of HIV-1 sub-subtype A6

variants, circulating in different regions of the country.

Conclusion

A comparative analysis of consensus sequences of non-structural proteins of HIV-1 sub-subtype A6 variants circulating in different regions of the Russian Federation was performed for the first time. The reference sequences of Vif, Vpr, and Nef proteins of HIV-1 sub-subtype A6 were obtained and presented for the first time. The Vpr protein was determined to be the most conserved. In summary, the results obtained indicate the presence of peculiarities in non-structural proteins of HIV-1 sub-subtype A6 variants in different regions of Russia.

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