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RISK ASSESSMENT OF FIRST-LINE TREATMENT FAILURE IN UNTREATED HIV PATIENTS IN NORTHWESTERN FEDERAL DISTRICT OF THE RUSSIAN FEDERATION

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Abstract. The HIV infection epidemic in Russia continues to evolve, and HIV infection cases have been registered in all territorial entities of the Russian Federation. 2021 Treatment coverage was 82.2% and 56.4% individuals under dispensary observation and living with diagnosed HIV infection. 79.9% receiving ART subjects were shown to achieve undetectable viral load. Highly active antiretroviral therapy (HAART) currently represents a combination of three (less frequently four) antiretroviral drugs targeting pathways involved in various stages of HIV replication *in vivo*. Treatment failure is a problem facing doctors and patients using HAART. The most common cause of therapeutic failure is the development of HIV drug resistance. The emergence of resistance is associated with processes involving mutation occurring in the viral genome influenced by evolutionary factors. Therefore, it is important clinically and programmatically to learn more about the rate of first-line treatment failure, the rate of switching to a second-line ART regimen, and to identify patients at risk to develop strategies for preventing development of further failure cases. The study was aimed at analyzing ineffectiveness of first-line ART therapy in patients in Northwestern Federal District of the Russian Federation. *Materials and methods.* Sequencing reactions were performed using the AmpliSens HIV Resist-Seq. Assembly of consensus sequences from fragments obtained during sequencing was carried out using Unipro UGENE software. Isolate genotyping was performed using the MEGA-X software with the Neighbor-joining algorithm. *Results.* The HIV *pol* genes in 239 patients with first-line ART failure and 100 naïve patients were sequenced; all sequences genotyped as HIV-1 subsubtype A6. According to analysis, 82% of patients had at least one significant mutation associated with drug resistance for the corresponding viral subtype. In total, we encountered 87 different drug resistance mutations. *Conclusion*. We have shown increased proportion of patients with first-line ART failure among all patients with treatment failure. The main cause for such changes is probably related to the prevalence of primary drug resistance, estimated here at 8%. Specific differences were found between drug resistance mutation profiles in patients without suppressed viral load and patients with virological breakthrough. The overall results of the study indicate a need to diagnose and characterize HIV drug resistance prior to initiation of therapy in order to avoid ineffective first-line antiretroviral treatment.

Key words: *HIV, recombinant forms of HIV, HIV drug resistance, laboratory diagnostics.*

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РИСК НЕЭФФЕКТИВНОСТИ ТЕРАПИИ ПЕРВОЙ ЛИНИИ У ПАЦИЕНТОВ С ВИЧ В СЕВЕРО-ЗАПАДНОМ ФЕДЕРАЛЬНОМ ОКРУГЕ РОССИИ

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Резюме. *Введение.* Эпидемия ВИЧ-инфекции в России продолжает развиваться, случаи ВИЧ-инфекции зарегистрированы во всех субъектах Российской Федерации. Охват лечением в 2021 г. составил 82,2% от числа находящихся на диспансерном наблюдении и 56,4% от всех лиц с ВИЧ-инфекцией. У 79,9% получавших АРТ, была достигнута неопределяемая вирусная нагрузка. Высокоактивная антиретровирусная терапия (ВААРТ) в настоящее время представляет собой комбинацию трех (реже четырех) антиретровирусных препаратов; эти пути-мишени участвуют в различных стадиях репликации ВИЧ в организме. Неэффективность лечения — проблема, с которой сталкиваются врачи и пациенты, применяющие ВААРТ. Наиболее распространенной причиной терапевтической неудачи является развитие лекарственной устойчивости ВИЧ. Возникновение резистентности связано с процессами, сопровождающимися мутациями, происходящими в вирусном геноме под влиянием эволюционных факторов. Таким образом, важно больше узнать о частоте неудач лечения первого ряда, частоте перехода на схему АРТ второго ряда, а также определить, какие пациенты подвержены риску, чтобы разработать стратегии предотвращения случаев неэффективности. Цель работы — проанализировать неэффективность терапии первой линии у больных в Северо-Западном федеральном округе России. *Материалы и методы.* Реакции секвенирования проводили с использованием AmpliSens HIV Resist-Seq. Сборку консенсусных последовательностей из фрагментов, полученных при секвенировании, проводили с помощью программного обеспечения Unipro UGENE. Генотипирование изолятов проводили с помощью программы MEGA-X с использованием алгоритма Neighbor-joining. *Результаты.* Были получены последовательности гена *pol* 239 пациентов с неэффективностью АРТ первой линии и 100 пациентов, ранее не получавших АРТ; все последовательности генотипированы как суб-субтип A6. Согласно анализу, у 82% пациентов была хотя бы одна значимая мутация, связанная с лекарственной устойчивостью для соответствующего подтипа вируса. Всего мы столкнулись с 87 различными мутациями лекарственной устойчивости. *Выводы.* Мы показали увеличение доли пациентов с неэффективностью АРТ первой линии среди всех пациентов с неэффективностью лечения. Основной причиной этих изменений, вероятно, является распространенность первичной лекарственной устойчивости, оцененная в этой статье в 8%. Определенные различия были обнаружены между профилями мутаций лекарственной устойчивости у пациентов без подавления вирусной нагрузки и у пациентов с вирусологическим прорывом. Общие результаты работы свидетельствуют о необходимости диагностики и характеристики лекарственной устойчивости ВИЧ до начала терапии во избежание неэффективности антиретровирусной терапии первой линии.

Ключевые слова: *ВИЧ, рекомбинантные формы ВИЧ, лекарственная устойчивость ВИЧ, лабораторная диагностика.*

Introduction

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS), which is responsible for the deaths of over 38 million people [18, 33]. Because there is no cure for HIV, patients are subject to lifelong therapy, yet when the first HIV drugs were introduced, resistance evolved in nearly all treated individuals in the first 6 months of treatment, sometimes within weeks [13, 27]. This drug resistance (DR), often encoded by single mutations conferring strong resistance, led to rebounding viral populations and treatment failure [9, 14].

Highly active antiretroviral therapy (HAART), introduced in 1995, was expected to prevent the evolution of drug resistance and subsequent treatment failure [10]. However, while triple-drug combination therapies have saved many lives, HIV has continued to evolve drug resistance all the way up to the present [11, 15, 24, 35]. The high mutation rate of HIV is critical for its survival during drug therapies. The virus can obtain drug resistance mutations, and they are one of the major challenges for effective HAART. Some drug-resistant viruses are also capable of being transmitted, and consequently these strains can increase in prevalence as described below [2, 4, 17, 36]. Adhering to the ART regimen is crucial to achieve and maintain viral suppression as well as to prevent further HIV transmission and the progression of HIV infection [1, 3]. Furthermore, close adherence to ART (over 95% of the time) is required to achieve full viral load suppression. When patients fail to attain the required adherence level, they may experience a poorer prognosis, higher morbidity/mortality, or the development of resistance to ART [12, 21].

The HIV infection epidemic in Russia continues to evolve [32], and HIV infection cases have been registered in all territorial entities of the Russian Federation. The number of Russian regions with

a high prevalence of HIV infection (more than 0.5% of the population) reached 34 in 2018. In the first half of 2020, 38 126 individuals with antibodies to HIV-1 were newly identified in Russia. By the end of the first half of 2020, 1 094 050 Russians with laboratory-diagnosed HIV infection were known to be living in the country [6]. The number of patients receiving antiretroviral therapy was 660 821 in 2021. Treatment coverage in 2021 was 82.2% of the number of those under dispensary observation and 56.4% of the number of those living with a diagnosis of HIV infection. In 527 705 patients, 79.9% of those receiving ART, an undetectable viral load was achieved [7].

Therefore, surveillance of the HIV epidemic and HIV DR is strongly needed in the region since increased ART coverage and a subsequent increase in HIV DR to those drugs used can significantly worsen therapeutic effectiveness or make it impossible to achieve the goals of the 90–90–90 initiative [34]. With this intended rapid scaling up of detection and therapy, it is also important to sustain treatment success with undetectable viral loads in patients on first-line ART. Otherwise, failure on first-line regimens can lead to a complicated, less tolerable, and more expensive second-line ART regimen with fewer drug options if drug related toxicities develop.

Therefore, it is important clinically and programmatically to learn more about the rate of first-line treatment failure, the rate of switching to a second-line ART regimen, and to identify which patients are at risk in order to develop strategies to prevent development of further failure cases.

The aim of the work was to analyze ineffectiveness of first-line therapy in patients in Russia's Northwestern Federal District.

Materials and methods

The study was approved by the Ethics Committee of the Saint Petersburg Pasteur Institute. It included analysis of HIV samples obtained from: 239 patients with first-line ART failure who contacted the Northwestern Federal District AIDS Center for diagnostic clarification of drug resistance status in the period 2014–2018; and from 100 patients without any history of ART.

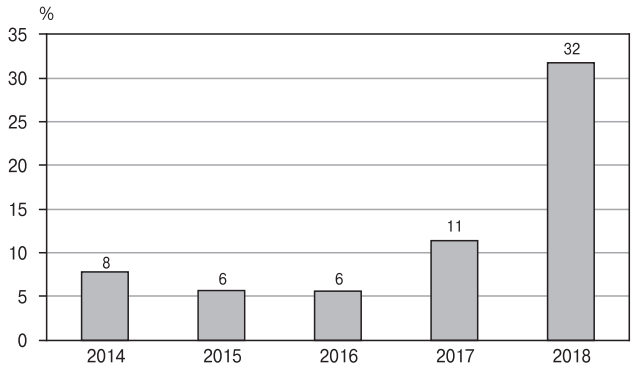

Figure 1. 2014–2018 proportion of patients with first-line ART failure

Quantitative analysis of HIV RNA was carried out with the AmpliSens® HIV-Monitor-FRT commercial kit (Central Research Institute of Epidemiology, Russia), with a sensitivity threshold of 500 copies/ml. Samples with a detectable viral load (VL) were analyzed using RT-PCR and Sanger sequencing. For reverse transcription and amplification of HIV RNA, the RT-PCR-kit-Pro/Rev and PCR-kit-Pro/Rev commercial kits (Central Research Institute of Epidemiology, Russia) were used. Sequencing reactions were performed using the AmpliSens® HIVResist-Seq kit (Central Research Institute of Epidemiology, Russia) according to manufacturer instructions, as described earlier [26]. Sequencing was carried out using Applied Biosystems 3500 genetic analyzers according to instructions.

Assembly of consensus sequences from fragments obtained during sequencing was carried out using Unipro UGENE software [8, 22, 25]. The consensus sequence included a 1302 nt region of the polymerase *(pol)* gene encoding protease (PR) and a part of reverse transcriptase (RT/OT) in the 2253–3554 nt region; coordinates are given for HIV HXB2 in the GenBank database (K03455.1). The resulting sequences were analyzed for the presence of drug resistance mutations using the Stanford database [31]. Sample genotyping was performed using the REGA HIV-1 Subtyping Tool 3.0 [23].

The statistical significance of differences was determined using the chi-square test (χ^2). The level of significance (p) adopted in this work was 0.05 (or 5.0%). Confidence intervals were determined by the method of Klopper–Pearson.

Results

Study patients contacted the Northwestern Federal District AIDS Center for diagnostic clarification of drug resistance status over the 2014–2018 period. The proportion of patients with first-line ART failure (among all patients with ART failure) was not the same across years (Fig. 1).

The HIV pol genes of 239 patients with first-line ART failure were sequenced; all sequences genotyped as HIV-1 subsubtype A6. According to analysis, 82% (82% NRTI, 72% NNRTI) of patients had at least one significant mutation associated with drug resistance for the corresponding viral subtype. In total, we encountered 87 different drug resistance mutations (49 NRTI, 38 NNRTI). The most common mutations in patients are presented in Table 1.

The HIV *pol* genes of 100 patients with no history of ART were sequenced; all sequences genotyped as HIV-1 subsubtype A6. Viral genomes from 8 subjects (8%, 95% CI 3.52–15.16%) were found to harbor resistance-conferring mutations to NRTIs. Four

of these were found to harbor mutations associated with zidovudine resistance. All significant drug resistance mutations encountered were found in single cases: K70E; K70R; D67N; L74; and M184V (in combination with NNRTI-related resistance mutations V106M and G190S). An isolated amino acid substitution, D67N, was found in one sample; it is associated with resistance to zidovudine only in combination with other resistance-conferring mutations (i.e., M41L, K70R, and T215Y). A62V (n = 4) was identified by itself (3 samples) and once in combination with an NNRTI resistance mutation, V179D (1 sample).

Discussion

We draw attention here to the fact of an increase in the number of patients experiencing ineffectiveness with 1st line ART. Federal AIDS Center reports also point to the insufficient effectiveness of ART. In only 80% of those receiving ART was an undetectable viral load achieved [7]. This trend is likely associated with an increase in the prevalence of primary HIV drug resistance in Russia, which is 5–7% according to various estimates [16].

A similar prevalence of primary drug resistance was obtained in this study. Moreover, the most common DR mutations in naive patients are multiple drug resistance to drugs of the NRTI and NNRTI classes, which are most often the main first-line ART. The pattern of DR mutations among patients with first-line ART failure is consistent with the most common resistance mutations described in the literature [19, 29].

However, there is significant heterogeneity in the occurrence of some mutations within the study group. Conventionally, the group can be divided into two subgroups: the first — patients who did not achieve viral load suppression (n = 124); and the second — patients in whom the viral load was suppressed, after which there was a virological breakthrough, i.e., a growth in viral load (n = 115). Comparison of these subgroups revealed a difference in the occurrence of some significant drug resistance mutations (Fig. 2). For individual mutations, differences in occurrence reached statistical significance ($p < 0.05$) (Table 2).

The most characteristic mutations for patients in the first group (inadequate suppression) were K65R, Y181C, and Y115F. In the second group (inadequate suppression with breakthrough), they were M184V, D67N, K103N, and T215Y. Accordingly, for patients who experienced a virological breakthrough after long-term use of one ART regimen, thymidine analogue resistance mutations (TAM) were more common, as well as the K103N NNRTI resistance mutation. For patients who initially failed therapy, mutations to non-thymidine nucleoside analogues and NNRTI resistance mutation Y181C were seen.

Table 1. Prevalence and description of drug resistance mutations in the studied HIV-1 samples using the Stanford HIVdb Program (https://hivdb.stanford.edu/hivdb/by-mutations)

Mutation	Percentage (95% confidence interval)	Description
M184V	53% (46.59–59.34%)	M184V/I causes high-level resistance to 3TC and FTC, and low-level resistance to ddI and ABC.
G190S	37% (30.98–43.33%)	G190S is a nonpolymorphic mutation causing high-level resistance to NVP and EFV (> 50-fold reduced susceptibility).
K101E	24% (18.82–29.81%)	K101E is a nonpolymorphic mutation causing intermediate resistance to NVP (~5-fold reduced susceptibility) and low-level resistance (~2-fold reduced susceptibility) to EFV, ETR and RPV.
K65R	23% (17.91–28.74%)	K65R causes intermediate/high-level resistance to TDF, ddI, ABC and d4T (2 to 3-fold reduced susceptibility) and low to intermediate-level resistance to 3TC and FTC (5 to 7-fold reduced susceptibility). K65R increases susceptibility to AZT.
A62V	15% (10.79–20.07%)	A62V is an accessory mutation that often occurs in combination with the multinucleoside resistance mutations K65R or Q151M. Alone it does not reduce NRTI susceptibility. A62V is widespread in subtype A viruses in former Soviet Union countries but is otherwise nonpolymorphic.
Y181C	14% (9.92–18.96%)	Y181C is a nonpolymorphic mutation selected in patients receiving NVP, ETR and RPV. Although Y181C itself reduces EFV susceptibility by as few as 2-fold, it is associated with a reduced response to EFV-containing regimen because viruses with this mutation often harbor additional minority variant NNRTI resistance mutations.
K103N	11% (7.38–15.59%)	K103N is a nonpolymorphic mutation causing high-level resistance to NVP and EFV
E138A	11% (7.38–15.59%)	E138A is a common polymorphic accessory mutation weakly selected in patients receiving ETR and RPV.
L74V	9% (5.73–13.29%)	L74V/I cause high-level resistance to ddI and intermediate-level resistance to ABC. L74V increases susceptibility to AZT and TDF, but this increase is of uncertain clinical significance.

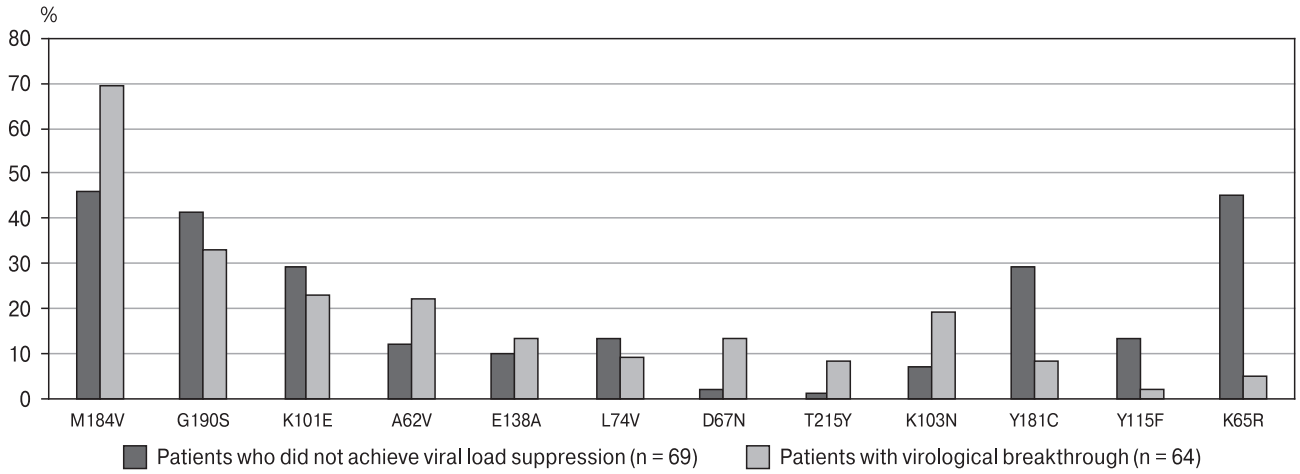

Figure 2. Heterogeneity in distribution of drug resistance mutations in patients with first-line ART failure

It is interesting that M184V (the most common mutation both in the study group and in patients with HIV DR generally) was significantly more common among patients who have experienced a virological breakthrough. Apparently, mutations causing DR were obtained mainly before initiation of treatment in the first group. In such cases (before treatment), probably only those mutations that are least associated with impaired replication remain in the viral genome. In the absence of selective drug pressure, mutations which negatively affect replication have no competitive advantage and likely self-eliminate in the viral population. With ART, however, their ability to confer resistance and permit replication at all likely outweighs their detriment to replication.

However, this assumption casts doubt on the fact that TAM and the M184V mutation were also detected among naive patients in this study. In this light, additional studies are required to establish the causes of differences in the mutation profiles in the studied subgroups. It is worth noting differences in the occurrence of the A62V mutation in the different study groups. Among naive patients, the occurrence of this mutation was 4%, yet among patients with ART failure, it reached 15%. At the same time, in ART failure subgroups 1 and 2, the prevalence of this mutation was also different: 12% and 22%, respectively. This difference does not reach statistical significance (χ^2 (Yates) = 3.319, p = 0.069), but it closely approaches it.

HIV-1 reverse transcriptase (RT), the enzyme responsible for converting the single-stranded viral RNA genome into its double-stranded DNA counterpart, can acquire an A62V amino acid substitution. This is known to be associated with multidrug resistance, but is not a resistance-conferring mutation by itself [28, 30]. It is known that the A62V mutation alone can significantly increase viral mutation frequency [5, 20], while negatively impacting replicative capacity and viral fitness in the absence or presence of AZT. The fact that differences in A62V occurrence did not reach significance may be due to insufficient sample sizes. Nevertheless, the current trend may suggest that presence of this mutation is associated with an increased risk of virological breakthrough in patients and subsequent higher mortality rates.

Table 2. Mutations with significant differed prevalence between patients achieving no viral load suppression and virological breakthrough

Mutation	Patients achieving no viral load suppression	Patients with virological breakthrough	χ^2 (Yates)	p-value
K65R	45%	5%	47.494	< 0.001
M184V	46%	69%	11.658	< 0.001
Y181C	29%	8%	16.196	< 0.001
Y115F	13%	2%	9.135	< 0.001
D67N	2%	13%	8.306	0.004
K103N	7%	19%	6.636	0.012
T215Y	1%	8%	5.687	0.018

Conclusion

We have shown an increase in the proportion of patients with first-line ART failure among all patients with treatment failure. The main reason for these changes is probably the prevalence of primary drug resistance, estimated in this paper at 8%. Specific differences were found between drug resistance mutation profiles in patients without viral load suppression and patients with virological breakthrough. A possible connection between the A62V mutation and the likelihood of a virological breakthrough was found. The overall results of the work indicate the need to diagnose and characterize HIV drug resistance before initiation of therapy in order to avoid ineffective first-line antiretroviral treatment.

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