DRUG MONITORING OF ANTIRETROVIRAL DRUGS IN CHILDREN WITH PERINATAL HIV INFECTION

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ABSTRACT

Therapeutic drug monitoring is the practice of measuring the concentration of a drug in patient's biological fluids to assess the effectiveness and safety of drug therapy. The results of determining the drug level in biological fluids can also indicate noncompliance of therapy regimen and low adherence to therapy.

The aim. *To compare the concentrations of some antiretroviral drugs (lopinavir, ritonavir, lamivudine, abacavir, zidovudine) in children living with HIV infection of different age groups.*

Methods. *We examined 184 children with perinatal HIV infection who underwent therapeutic drug monitoring of nucleoside reverse transcriptase inhibitors (lamivudine, abacavir, zidovudine) and protease inhibitors (lopinavir, ritonavir). Children were divided into four age groups. Group 1 included children 1–2 years old (n = 7); group 2 – children 3–5 years old (n = 14); group 3 – children 6–11 years old (n = 78); group 4 – children 12–17 years old (n = 85). The concentration of antiretroviral drugs in blood plasma was determined using high-performance liquid chromatography with mass selective detection.*

Results. *The lowest lopinavir concentration was found in children 12–17 years old (3782 [2117–5046] ng/ml), which was statistically significantly different from the similar values in children 6–11 years old (5614 [3521–7264] ng/ml; p = 0.011). For other antiretroviral drugs, no statistically significant differences in blood plasma concentrations were found in children of different age groups.*

Conclusion. *The lowest lopinavir concentrations are detected in children older than 11 years. For the other studied antiretroviral drugs, this pattern was not revealed.*

Key words: *antiretroviral therapy, HIV infection, therapeutic drug monitoring, children and adolescents, adherence*

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ЛЕКАРСТВЕННЫЙ МОНИТОРИНГ АНТИРЕТРОВИРУСНЫХ ПРЕПАРАТОВ У ДЕТЕЙ С ПЕРИНАТАЛЬНОЙ ВИЧ-ИНФЕКЦИЕЙ

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РЕЗЮМЕ

Терапевтический лекарственный мониторинг – практика измерения концентрации лекарственного препарата в биологических жидкостях пациента для оценки эффективности и безопасности лекарственной терапии.
Результаты определения уровня лекарственного препарата в биологических жидкостях также могут указывать на несоблюдение режима лечения и низкую приверженность к терапии.
Цель исследования. *Сравнить концентрации некоторых антиретровирусных препаратов (лопинавир, ритонавир, ламивудин, абакавир, зидовудин) у детей, живущих с ВИЧ-инфекцией, в разных возрастных группах.*
Методы. *Обследовано 184 ребёнка с перинатальной ВИЧ-инфекцией, которым проведён терапевтический лекарственный мониторинг нуклеозидных ингибиторов обратной транскриптазы (НИОТ) (ламивудин, абакавир, зидовудин) и ингибиторов протеазы (лопинавир, ритонавир). Дети разделены на 4 возрастные группы. В первую группу включены дети 1–2 лет (n = 7); во вторую – дети 3–5 лет (n = 14); в третью – дети 6–11 лет (n = 78); в четвёртую – дети 12–17 лет (n = 85). Концентрацию антиретровирусных препаратов в плазме крови определяли методом высокоэффективной жидкостной хроматографии с масс-селективной детекцией.*
Результаты. *Самая низкая концентрация лопинавира выявлена у детей 12–17 лет (3782 [2117–5046] нг/мл), которая статистически значимо отличалась от аналогичного показателя детей 6–11 лет (5614 [3521–7264] нг/ мл; p = 0.011). Для других антиретровирусных препаратов не выявлено статистически значимых различий концентраций в плазме крови у детей разных возрастных групп.*
Заключение. *Самые низкие концентрации лопинавира детектируются у детей старше 11 лет. Для других изучаемых антиретровирусных препаратов данной закономерности не выявлено.*

Ключевые слова: *антиретровирусная терапия, ВИЧ-инфекция, терапевтический лекарственный мониторинг, дети и подростки, приверженность*

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INTRODUCTION

According to estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS); in 2022 there were 1.5 million children under 15 years of age living with HIV worldwide [1]. The World Health Organization (WHO) has recommended combination antiretroviral therapy (ART), a combination of three drugs that leads to long-term suppression of the virus, which has made it possible to significantly reduce mortality and increase life expectancy in children with HIV infection [2].

Early initiation and high adherence to antiretroviral therapy provide maximum suppression of HIV replication, reduce viral accumulation in cells, and help maintain immunological function that supports normal growth and development in children living with HIV [3–7]. Poor adherence and non-adherence to the ART regimen for just a few weeks can lead to loss of efficacy of the regimen and selection of strains resistant not only to the given drug combination, but also, possibly, to other antiretroviral drugs (ARVs) that the patient was not prescribed (cross-resistance) [8].

A highly informative method for assessing adherence is measuring the concentration of drugs and/or their metabolites in the blood, urine and other biological fluids, i.e. therapeutic drug monitoring (TDM). In people living with HIV infection, TDM is a laboratory method for monitoring the effectiveness and toxicity of ARVs, and involves the analysis of failures in the absence of viral resistance and non-compliance with the pharmacotherapy regimen. Moreover, the identification of suboptimal ARVs concentrations allows for timely correction of therapy, thereby avoiding the formation of drug-resistant strains of the virus [3].

Thus, TDM as a method for assessing adherence and evaluating the characteristics of ARV metabolism helps prevent the progression of HIV infection.

THE AIM OF THE STUDY

To compare the concentrations of antiretroviral drugs (lopinavir, ritonavir, lamivudine, abacavir, zidovudine) in children of different age groups living with HIV infection.

MATERIALS AND METHODS

The study included children and adolescents aged 1 to 18 years with perinatal HIV infection. A total of 184 patients registered at the Irkutsk Regional Center for the Prevention and Control of AIDS and Infectious Diseases (IOC AIDS) were examined from January 2019 to March 2022. A more detailed description of the study groups and data collection is published in our previous article [9].

According to the clinical guidelines for the treatment of HIV infection in children (2020), the drug dose was calculated taking into account the child's weight or body surface area using the Mosteller formula (mg/m^2). All children and adolescents were divided into four age groups depending on the preferred, according to the clinical guidelines "HIV infection in children" (2020), age-specific antiretroviral drug regimens [10]. In the first age group of children (≥ 1 year and < 3 years), the ART regimen included lopinavir (n = 5), ritonavir (n = 5), lamivudine (n = 7), abacavir (n = 5), zidovudine (n = 1). Children in the second age group (≥ 3 years and < 6 years) were prescribed lopinavir (n = 11), ritonavir (n = 11), lamivudine (n = 14), abacavir (n = 9), and zidovudine (n = 1). The ART regimen for children in the third age group (≥ 6 years and < 12 years) included lopinavir (n = 54), ritonavir (n = 54), lamivudine (n = 70), abacavir (n = 53), and zidovudine (n = 16). Children in the older age group (≥ 12 years) were prescribed ART regimens including lopinavir (n = 38), ritonavir (n = 38), lamivudine (n = 59), abacavir (n = 25), and zidovudine (n = 28). Information on ARVs and the duration of their use is presented in table 1.

The frequency of prescribing the studied ARVs did not differ in boys and girls. The viral load in children of different age groups taking the analyzed antiretroviral drugs also did not have statistically significant differences. A comparative analysis of the duration of ARVs intake revealed regular trends of increasing the duration of intake with increasing age of children. The shortest period of taking antiretroviral drugs (in months) was recorded in the youngest age group.

The study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from the parents or legal representatives of all participants under 15 years of age, as well as directly from adolescents aged 15 years and older. The study protocol was approved by the local Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (protocol No. 3 dated April 07, 2021).

Quantitation of antiretroviral drugs in plasma

Blood sampling for determination of concentration of antiretroviral drugs in blood plasma was performed once during the next scheduled appointment. Patients and their legal representatives were not informed in advance about the upcoming blood sampling. To determine the concentration of ARVs, a method of multiplex concentration assessment using high-performance liquid chromatography with mass-selective detection was developed. The analytical standards of ritonavir, lopinavir, abacavir, lamivudine and zidovudine prepared in accordance with the American Formulary (United States Pharmacopeia) and the European Pharmacopoeia were used as compounds for identification of substances. All organic solvents were of MS-grade/extra pure. Water for preparation of eluent was prepared using the Arium Mini Plus water purification system (Sartorious AG,

TABLE 1

CHARACTERISTICS OF PATIENTS AT THE TIME OF DETERMINING THE CONCENTRATION OF ANTIRETROVIRAL DRUGS IN BLOOD PLASMA

Characteristics	Lopinavir	Ritonavir	Lamivudine	Abacavir	Zidovudine
Total (n = 184)	108	108	150	92	82
	incl. girls, n (%)				
≥ 1 year and < 3 years (n = 7)	3 (60 %)	3 (60 %)	4 (57 %)	3 (60 %)	0
≥ 3 years and < 6 years (n = 14)	7 (64 %)	7 (64 %)	9 (64 %)	4 (44 %)	1 (100 %)
≥ 6 years and < 12 years (n = 78)	25 (46 %)	25 (46 %)	35 (50 %)	24 (45 %)	8 (50 %)
≥ 12 years (n = 85)	18 (47 %)	18 (47 %)	33 (56 %)	13 (52 %)	18 (64 %)
Total girls, n (%)	53 (49.1 %)	53 (49.1 %)	81 (54 %)	44 (47.8 %)	27 (32.9 %)
p	0.7095	0.7095	0.7617	0.8849	0.3940
	Duration of therapy (months), Me [Q1–Q3]				
≥ 1 year and < 3 years (n = 7)	10 [6–11]	10 [6–11]	10 [7.5–13.5]	10 [6–11]	16
≥ 3 years and < 6 years (n = 14)	34 [21–52]	34 [21–52]	42.5 [26.2–53.8]	53 [47–57]	34
≥ 6 years and < 12 years (n = 78)	68.5 [48–92]	68.5 [48–92]	68 [48.2–86.8]	66 [48–83]	69 [47.5–104]
≥ 12 years (n = 85)	65 [31–116]	65 [31–116]	36 [12–92]	47 [11–94]	40.5 [26.2–110]
p	0.00027*	0.00027*	0.04771*	0.00766*	0.3171
	Viral load ($\log_{10}$ copies/ml), Me [Q1–Q3]				
≥ 1 year and < 3 years (n = 7)	0 [0–0]	0 [0–0]	0 [0–1.3]	0 [0–0]	2.6
≥ 3 years and < 6 years (n = 14)	0 [0–2.15]	0 [0–2.15]	0.95 [0–2.75]	0 [0–2,3]	5.6
≥ 6 years and < 12 years (n = 78)	0 [0–1.2]	0 [0–1.2]	0 [0–0]	0 [0–0]	0 [0–2.03]
≥ 12 years (n = 85)	0 [0–2.3]	0 [0–2.3]	0 [0–2.5]	0 [0–2,3]	0 [0–2.4]
p	0.5718	0.5718	0.0895	0.5207	0.1668

Note. The χ^2 test was used to compare groups by gender; for other parameters, the Kruskal – Wallis test was used; * – $p < 0.05$.

Germany). The chemical reagents used in the work met the standard requirements for bioanalytical studies. To prepare control and calibration solutions, a precisely dosed amount of a solution of a mixture of analytical standards was placed into a "blank" biological material (pooled K2EDTA human blood plasma containing no analyzed drugs). During the preparation of model mixtures, the original biomaterial was diluted by no more than 5 % of its volume so that the resulting mixture reflected the composition of real human blood as accurately as possible. Chromatographic separation was performed on a Shimadzu Nexera X2 system (Japan) with two high-pressure pumps and gradient creation on the high-pressure side. Analyte detection was carried out using a LCMS-8060 triple-quadrupole tandem mass spectrometer (Shimadzu, Japan) in the positive ionization mode with a hybrid dual ionization source (DUIS) and the use of multiple reaction monitoring (MRM).

Statistical analysis

Statistical analysis was performed using R studio, a free and open-source software development environment for the R programming language, designed for statistical data processing and graphics.

The χ^2 criterion is used to evaluate qualitative variables. The Kruskal – Wallis criterion was used to evaluate differences in quantitative variables. The difference was considered statistically significant at $p < 0.05$. When statistically significant differences were detected between groups, a posteriori pairwise comparison was additionally performed using the Mann – Whitney criterion. The difference was considered statistically significant with the Bonferroni correction ($p < 0.0125$).

RESULTS

A comparative analysis of the concentrations of the studied antiretroviral drugs in different age groups is presented in figure 1.

When comparing the concentration of lamivudine in children of different age groups taking this drug as part of a combination ARV regimen, no statistically significant differences were found ($p > 0.05$). Thus, the median and interquartile range (Me [Q1–Q3]) of the lamivudine concentration were 198 [186–444] ng/ml in the first age group, 276 [142–1664] ng/ml in the second, 400 [162–1708] ng/ml in the third, and 494 [134–1279] ng/ml in the fourth. No statistically significant differences were found when comparing the concentration of another nucleoside reverse transcriptase inhibitor, abacavir: 16 [0–31], 1018 [58–1914], 128 [42.1–688], and 70.4 [6–402] ng/ml in the first, second, third, and fourth age groups, respectively. A similar trend was found for zidovudine in blood plasma. The first and second age groups for zidovudine included one patient each, so it is impossible to calculate the median and interquartile range for them. For the third group, the zidovudine concentration was 10.5 [0–80.5] ng/ml, for the fourth – 33.1 [3–115] ng/ml.

A different pattern was demonstrated for protease inhibitor ARVs: the lowest median lopinavir concentration was observed in the fourth age group (in children over 11 years old) and amounted to 3782 [2117–5046] ng/ml, which is statistically significantly lower than the same indicator in the third age group (≥ 6 years and < 12 years) – 5614 [3521–7264] ng/ml ($p = 0.011$). The median lopinavir concentration in the first group was 4872 [4765–5809] ng/ml, which is lower than in the second group – 8024 [6339–9370] ng/ml, although the difference did not reach statistical significance ($p > 0.05$).

The lowest concentrations of ritonavir, as well as lopinavir, were found in children of the fourth age group – 212 [119–489] ng/ml, then in ascending order: in the second group – 451 [223–797] ng/ml, in the first group – 326 [311–510] ng/ml, in the third group – 290 [151–745] ng/ml ($p > 0.05$).

Next, we analyzed the frequency of occurrence of undetectable concentrations of the studied ARVs in children; the prescription regimen included the drugs

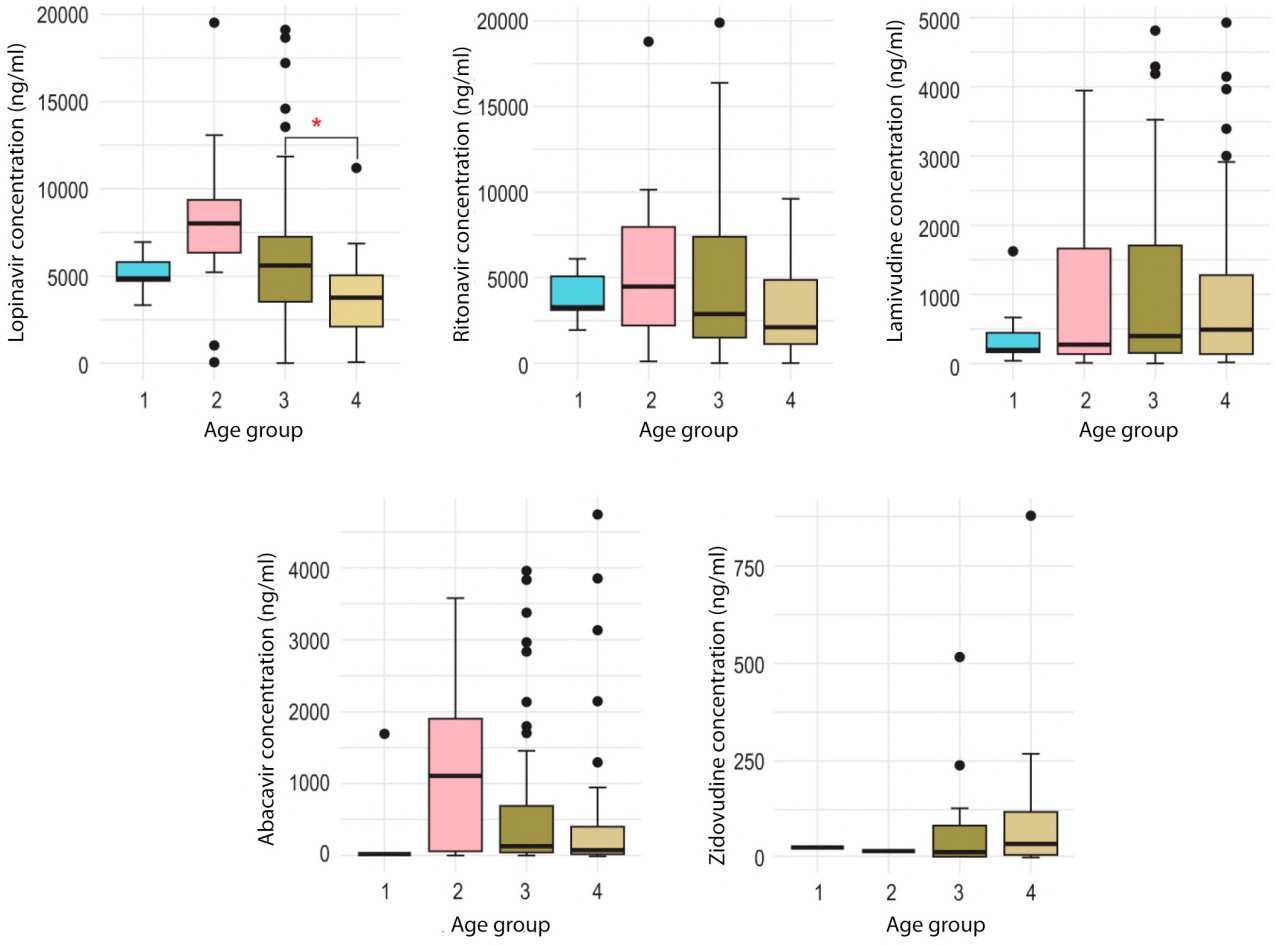

FIG. 1.
*Comparison of antiretroviral drug concentrations in different age groups using pairwise method by the Mann – Whitney test; statistical significance with Bonferroni correction: * – p < 0.0125*

lopinavir, ritonavir, lamivudine, abacavir, and zidovudine. The results are presented in table 2.

Of the ARVs analyzed, only 4.7 % of children had undetectable plasma lamivudine concentrations, which may indicate greater adherence to this drug. The highest frequency of children with undetectable concentrations was found for zidovudine, which may indicate that children living with HIV infection may have low adherence to zidovudine.

In age groups 1 and 2, no children were found with undetectable concentrations of nucleoside reverse transcriptase inhibitors (lamivudine, zidovudine) and protease inhibitors (lopinavir with ritonavir booster). Undetectable concentrations of abacavir were found in children in all analyzed age groups and with a higher frequency in children of older age groups.

At the next stage, a comparative analysis of the concentration of five antiretroviral drugs in children of different sexes was carried out, and the results are presented in table 3.

Thus, when comparing ARVs concentrations between samples of boys and girls, we did not find any statistically significant differences.

DISCUSSION

To date, of the possible objective methods for laboratory assessment of patient adherence to antiretroviral therapy, the most widely used are viral load assessment and monitoring of CD3 and CD4 counts [10]. However, according to M.V. Akulova (2016), unsatisfactory viral load and immune status indicators may indicate both patient non-adherence and an incorrectly selected treatment regimen and the presence of viral resistance to certain ARVs. Measuring the concentration level of drugs is more objective, since it confirms the fact of taking the drug, but not its regularity. Moreover, according to the author, the method is technically complex and has a high cost [11].

TABLE 2

NUMBER OF CHILDREN WHO HAD UNDETECTABLE CONCENTRATIONS OF ANTI-RETROVIRAL DRUGS, *n* (%)

Groups	Lopinavir (*n* = 108)	Ritonavir (*n* = 108)	Lamivudine (*n* = 150)	Abacavir (*n* = 92)	Zidovudine (*n* = 46)
≥ 1 year and < 3 years	0	0	0	2 (2.17 %)	0
≥ 3 years and < 6 years	0	0	0	1 (1.08 %)	0
≥ 6 years and < 12 years	5 (4.63 %)	6 (5.55 %)	4 (2.67 %)	6 (6.52 %)	6 (7.3 %)
≥ 12 years	6 (5.55 %)	6 (5.55 %)	3 (2 %)	5 (6.43 %)	7 (8.54 %)
Total	11 (10.19 %)	12 (11.11 %)	7 (4.67 %)	14 (15.22 %)	13 (28.26 %)
p	0.704	0.558	0.748	0.313	0.658

Note. The χ^2 test was used to compare groups; differences are statistically significant at $p < 0.05$.

TABLE 3

COMPARATIVE ANALYSIS OF THE ANTIRETROVIRAL DRUGS CONCENTRATIONS IN CHILDREN OF DIFFERENT SEXES (NG/ML)

Sex	Lopinavir Me [Q1–Q3], *n*	*p*	Ritonavir Me [Q1–Q3], *n*	*p*	Lamivudine Me [Q1–Q3], *n*	*p*	Abacavir Me [Q1–Q3], *n*	*p*	Zidovudine Me [Q1–Q3], *n*	*p*
Male	4957 [2167–6804] *n* = 64	0.3443	228 [88–525] *n* = 65	0.7769	387 [114–1327] *n* = 71	0.7976	208 [19.5–1764] *n* = 51	0.3544	26,1 [3–158] *n* = 20	0.324
Female	4765 [454–7025] *n* = 71		283 [20.5–625] *n* = 71		398 [112–1622] *n* = 89		99,6 [32.2–674] *n* = 46		60,1 [8.5–376] *n* = 35	

Note. The Kruskal – Wallis test was used for comparison; differences are statistically significant at $p < 0.05$.

However, previous studies highlight the utility of therapeutic drug monitoring in assessing adherence, determining dosage, and predicting ARVs efficacy in children living with HIV [12–16]. A 2002 review of 17 clinical trials examining factors that contribute to ART success or failure in children showed higher rates of virologic efficacy (60–90 %) in patients who had adherence assessed using TDM [17]. Other studies have questioned the value of routine use of therapeutic drug monitoring of ART in children and adolescents living with HIV. Other studies have questioned the value of routine use of therapeutic drug monitoring of ARVs in children and adolescents living with HIV. A.E. Engelbrecht et al. retrospectively reviewed indications for antiretroviral TDM requests at Tygerberg Children's Hospital (Cape Town, South Africa) from January 2012 to June 2017 and found that the majority of TDM requests were in children with suspected lopinavir non-adherence (83 % – 53 of 64 children), therapy inconsistency, and lopinavir-rifampicin drug interactions. Plasma lopinavir concentrations, although expected to be low for these indications, were highly variable and were detected in the main therapeutic range (> 1000 ng/ml) [18].

Lopinavir 1000 ng/ml has been shown to provide adequate lopinavir exposure in ART-naive patients, and this level is used as a target for TDM in both adults and children [19]. Lopinavir/ritonavir (LPV/r) is licensed for use in children aged 14 days. Due to cardiac and metabolic toxicity, and the risk of adrenal insufficiency, LPV/r should not be used in children aged < 14 days. Lopinavir can be administered as a liquid or tablet formulation (for children weighing > 15 kg). LPV/r doses of 230/57.5 mg/m^2 and 300/75 mg/m^2 are consistent with US Food and Drug Administration (FDA) guidelines [20] and have shown adequate efficacy and acceptable toxicity in randomized trials [21]. However, concerns have been raised about the established lopinavir exposure levels achieved with the 230/57.5 mg/m^2 dose due to the risk of viral resistance, particularly in children < 2 years of age who have increased lopinavir clearance. Because of these concerns, the 300/75 mg/m^2 LPV/r dose is recommended for treatment-experienced children of all ages, and the 230/57.5 mg/m^2 dose may be used in treatment-naive children > 1 year of age. Furthermore, N. Rakhmanina et al. concluded that the current LPV/r dosing strategy for the ART-experienced appears adequate for treatment of children infected with wild-type virus but is unlikely to be sufficient for viruses with lopinavir resistance. Therefore, the authors conclude that in such cases, patients would benefit from TDM and viral resistance testing [22]. In a modeling study, J. Yang et al. from the School of Pharmacy and Pharmaceutical Sciences at the University of California observed the effects of tablet formulations and aging on the effects of lopinavir. A sharp decrease in clearance with the onset was noted in the first 2 years of life, and an increase in bioavailability was observed when children were switched from the liquid to the tablet form, indicating the need to reassess the current dose of lopinavir [23].

We conducted TDM in children and adolescents living with HIV infection. Statistically significant differences in lopinavir concentrations were shown between children from age groups 3 and 4: the lowest lopinavir concentration was detected in children over 11 years old and amounted to 3782 [2117–5046] ng/ml versus 5614 [3521–7264] ng/ml in the third group ($p = 0.011$).

We did not detect any differences in nucleoside reverse transcriptase inhibitors (lamivudine, abacavir, zidovudine) concentrations in the different age groups analyzed. Intracellular concentrations of some nucleoside reverse transcriptase inhibitors are known to correlate with markers of therapeutic efficacy, such as viral load reduction and CD4 increase [24]. Measuring intracellular concentrations of the active compound is expensive and labor-intensive, and therefore these concentrations are not usually targeted for TDM except for research purposes. Unfortunately, the dose or plasma concentration of the parent compound correlates poorly with the intracellular concentration of the active form of the drug in the target cell [25].

It is known that adherence to ART in children and adolescents depends largely on a number of factors, including age, gender of the child, disclosure of information about HIV status, attitude to treatment, complexity of treatment regimens, mental health (of the child and caregiver), family status (e.g., orphan status), timely visits to the clinic, as well as residence in a rural or urban area [7].

CONCLUSION

Increasing adherence to ART is a relevant and global task that allows reducing the further spread of HIV infection. One of the methods for assessing adherence to ART is therapeutic drug monitoring, and its use in the presented study made it possible to identify some factors influencing adherence to therapy in children living with HIV infection. Such factors include the patient's age and antiretroviral drug. Thus, it was shown that the highest frequency of undetectable concentrations was found for zidovudine, and the lowest – for lamivudine. Adolescents have statistically significantly lower concentrations of lopinavir than children of other age groups. We believe that the comprehensive use of adherence assessment, including therapeutic drug monitoring, will support efforts to develop simplified safe and effective dosages of ARVs in the pediatric population.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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