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ЛЕКАРСТВЕННАЯ СОВМЕСТИМОСТЬ В ЛЕЧЕНИИ ХРОНИЧЕСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

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Drug Compatibility in Treatment of Chronic Infectious Diseases

Резюме

В статье рассматриваются вопросы особенностей фармакотерапии у коморбидных пациентов с хроническими инфекционными заболеваниями и сопутствующей соматической патологией в условиях полипрагмазии, принципы метаболизма лекарственных препаратов, варианты нежелательных явлений и межлекарственного взаимодействия, возможностей эффективного комбинирования лекарственных средств. Цель: обосновать возможность и подчеркнуть актуальность дополнительного поиска и создания наиболее оптимальных комбинаций лекарственных средств в условиях длительной и массивной фармакотерапии, которые смогли бы, за счет выигрышного межлекарственного взаимодействия, оптимизации режима, способа введения препаратов и полиморбидности терапевтического эффекта, уменьшить фармакологическую нагрузку при сохранении эффективности лечения, повысить приверженность пациентов к лекарственной терапии.

Ключевые слова: *лекарственная совместимость, межлекарственное взаимодействие, фармакотерапия, полипрагмазия, хронические инфекционные болезни, ВИЧ-инфекция, антиретровирусная терапия, туберкулез, коморбидность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article considers the features of pharmacotherapy of patients with chronic infectious diseases and co-morbidities in conditions of polypharmacy, the principles of drug metabolism, variants of adverse effects and drug-drug interactions, the possibilities of effective drug combinations. The purpose is to substantiate the possibility and emphasize the relevance of the additional search of the creation of the most optimal combinations of drugs for long-term and massive pharmacotherapy, that could be due to a beneficial drug-drug interaction, optimization of the regimen, route of drug administration and multitarget of the therapeutic effect, reduce the pharmacological load while maintaining the effectiveness of the treatment, increase patient adherence to drug therapy.

Key words: *drug compatibility, drug-drug interactions, pharmacotherapy, polypharmacy, chronic infectious diseases, HIV infection, anti-retroviral therapy, tuberculosis, comorbidity*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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ADR — adverse drug reaction, AE — adverse event, ART — antiretroviral therapy, CHB — chronic hepatitis B, CHC — chronic hepatitis C, CHD — chronic hepatitis D, HIV — human immunodeficiency virus, MP — medicinal product, NADPH — reduced form of nicotinamide adenine dinucleotide phosphate, NAT — N-acetyltransferase, PT — pharmacogenetic testing, TI — therapeutic index

Introduction

Since the time of Hippocrates, medicine has followed this principle: treat the patient, not just the disease. This means that treatment always requires a personal approach and comprehensive strategy. In the case of chronic disease, pharmacotherapy ranks top alongside non-drug methods, regimen and surgical treatment. In very rare cases, a patient is going to take only one agent. Therapy usually includes 3 to 5–6 or more drug products that are well-established in clinical practice due to their effect on different pathogenetic mechanisms.

Using effective, tolerable and pharmacologically compatible drug products combinations is of particular importance.

Some cases require optimization of the drug administration route aimed either at providing a prolonged effect or better delivery to the epicenter of the pathological process. With regard to antimicrobial resistance, the development of fixed-dose drug combinations with maximum effectiveness and potentiating effect is of special importance. In such cases, effectiveness in relation to an infectious agent should be combined with a minimum effect on the macroorganism, if possible.

Adverse Drug Events

When a relationship is found between an adverse event (AE) and the intake of a medicinal product (MP), it is considered an adverse drug reaction (ADR), that is, a pathological reaction that develops when using conventional doses of medications. The reliability of the association of AEs with a particular drug is assessed by the sum of points calculated using the Naranjo Algorithm [1].

ADRs are classified by type, etiopathogenetic principle, the severity of the clinical course, clinical outcomes, incidence, reliability grade, and pattern of development (Table 1).

The development of prescription patterns for the management of tuberculosis, HIV, viral hepatitides and secondary infectious and non-infectious diseases that imply a high pharmacological load is extremely significant. A specific feature of chronic infectious disease is the duration of drug administration. With the average treatment period of 8–12 weeks, chronic hepatitis C (CHC) is a good example in that context. However, the average intensive phase of tuberculosis treatment is six months. Human immunodeficiency virus (HIV) infection should be managed for life; no elimination strategies have been invented. In most cases, chronic hepatitis B (CHB) should be managed for life as well. Recent studies of the bulevirtide agent used in chronic hepatitis D (CHD) treatment revealed that the suppression of the viral agent also requires a very long, possibly lifelong administration of the drug that causes tolerance issues [6].

Table 1. Classification of adverse drug reactions

Classification	Adverse drug reactions
According to the type [2]	Type A — predictable Type B — unpredictable Type C — with long-term use (dependence, withdrawal syndrome) Type D — delayed (carcinogenicity, teratogenicity, etc.)
According to the etiopathogenetic principle [3]	Toxic reactions Effects due to the pharmacological features of drugs True allergic reactions Pseudoallergic reaction Idiosyncrasy — genetically determined perverted pharmacological response to the first taking of drugs Psychogenic adverse reactions Iatrogenic adverse effects
According to the severity of the clinical course [4]	Light Moderate severity Severe (requiring withdrawal of drugs, additional treatment, and increased hospitalization time)
According to clinical outcomes [4]	Serious (resulting in the death of the patient, life-threatening conditions, the need for emergency hospitalization or the increase of the time of hospitalization. the development of genetic disorders, developmental defects, malignant and benign formations, decrease in vital activity for a period of 3 months or more, disability of the patient) Not serious
According to the frequency of occurrence [5]	Very frequent — occur in more than 10% of patients taking drugs Frequent — develop in 1-10% of patients Less frequent-develop in 0.1-1% of patients Rare — develop in 0.01-0.1% of cases Very rare — develop in less than 0,01% of cases
According to the accuracy (Naranjo scale) [1]	>9 — definite connection of the development of adverse reaction with drug intake 5-8 — probable connection 1-4 — possible connection

Perfect MP should have a wide therapeutic range; maximum efficiency preferably confirmed by the patient's self-assessment; minimal impact on the patient's lifestyle as well as a comfortable administration schedule; it also should not affect basic physiological functions (appetite, physical activity, circadian rhythms, sexual function, weight gain and loss, including abnormal one, i.e., lipodystrophy); such MP should be characterized by a good drug interaction profile, controlled metabolism, optimal elimination rate.

Metabolism of Medicinal Products

Metabolism, regardless of its mechanism, aims to facilitate the MP elimination process. The main goal of metabolism is the inactivation of the MP. However, several metabolites are pharmacologically active, in some cases — more active than the parent compound. In terms of stable pharmacokinetics, drug elimination is as important as absorption, release, and delivery.

Pro-drug is a drug that has little or no intrinsic pharmacological activity but has active metabolites that can provide more efficient delivery of the active ingredient.

MP metabolism can be performed by oxidation, reduction, hydrolysis, hydration, conjugation, or isomerization. Enzymes involved in metabolism are present in many tissues. However, they are mainly concentrated in the liver.

Metabolic reactions can be divided into two types, which can usually be combined in two consecutive phases. Phase I reactions are non-synthetic and involve the formation of new functional groups, or the modification of existing ones, or molecule cleavage (by oxidation, reduction, or hydrolysis). Phase II reactions are synthetic

and involve conjugation with endogenous substances (e.g. glucuronic acid, sulfate, glycine). Metabolites formed as a result of synthetic reactions have more ionized groups (polarity) and are excreted by kidneys (with urine) and the liver (with bile) more easily than metabolites formed during non-synthetic reactions. Some MPs undergo reactions of only one phase (I or II).

The most important enzymatic system of phase I metabolism is the microsomal oxidation system, which includes Cytochrome P-450, a family of microsomal isoenzymes that catalyze the oxidation of most MPs. The source of required electrons, in this case, is NADPH-cytochrome P450 reductase, a flavoprotein that transfers electrons from NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) to cytochrome P450.

Isoenzymes of the cytochrome P450 family are represented by 17 families; the most common isoforms are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4; they can be induced and inhibited by many agents and substances, as well as food components, which explains the mechanism of many drug interactions when one agent increases the toxicity or reduces the therapeutic effect of another [7, 8].

Conjugation makes most medications more soluble, facilitating their elimination by the kidneys. Glucuronidation is the most common way of conjugation and the only synthetic reaction that occurs in the system of liver microsomal enzymes. Hence, it changes with age. Glucuronides are secreted into bile and are also eliminated with urine.

Conjugation with glutamine or glycine leads to products that are easily eliminated with urine and are secreted into bile only in small amounts. Conjugation by acetylation or sulfonation is also possible. Sulfated esters are also polar and are easily eliminated with urine. The intensity of these processes is no longer dependent on age.

The higher the concentration of MP, the more intense its elimination. However, the process has a saturation limit in the form of certain renal or hepatic clearance, which can lead to toxic effects.

The metabolic rate of MP varies depending on genetic factors, comorbidities, age, and drug interactions. A decreased metabolic rate increases the toxicity of drugs, and fast metabolism decreases their effectiveness.

The effect of age on the functional activity of the liver is inconclusive. Drug substances metabolized by the microsomal enzyme system, characterized by decreasing effectiveness with age, reach higher concentrations in elderly patients and have a long half-life. In newborns, the liver microsomal enzyme system is not yet developed, so the metabolism of many MPs also becomes difficult. The process of glucuronide formation is slower in newborns, which can cause serious adverse effects, for example, in the case of chloramphenicol use [9].

MP metabolism can have significant individual differences associated with the polymorphism of genes that encode enzyme systems — and this fact should also be considered when choosing a therapy. Point mutations, i.e., single nucleotide polymorphisms, are very diverse. They can affect the aspects of pharmacokinetics, pharmacodynamics, interfere with the structure of genes responsible for encoding enzymes in both biotransformation phase I (cytochrome P450 isoenzymes, butyrylcholinesterase, paraoxonase) and phase II (N-acetyl transferase, thiopurine methyltransferase epoxide hydrolase).

For example, several MPs, like other exogenous substances, are metabolized with the help of isoenzymes arylamine-N-acetyltransferases: NAT1 and NAT2. The activity of each of them is genetically programmed and determines the rate of acetylation of a particular substance; depending on this rate, fast and slow acetylators are released. Acetylator status can greatly affect the pharmacokinetics of drugs.

The effect of genotype on the development of AEs when using the anti-tuberculosis drug isoniazid is well known. Even when using average therapeutic daily doses, individuals with slow acetylation phenotype have numerous adverse reactions in the form of peripheral neuritis [10], while fast acetylators, on the other hand, have a low response to isoniazid therapy. Most of the results demonstrated that individuals with slow acetylation phenotype are more prone to hepatotoxicity when taking this agent [11].

Pharmacogenetic Testing

Pharmacogenetic testing (PT) helps to identify specific genetic features of individual drug efficacy and, ideally, should precede any pharmacological exposure. The range of studied genes is constantly expanding. There is a great need for algorithms and clinical guidelines on this issue [12].

PT is especially important when one requires a therapy with oral anticoagulants (warfarin, acenocoumarol, phenylin) or prolonged use of antipsychotics, voriconazole, abacavir, hormonal contraceptives, azathioprine, irinotecan; and for the study of hepato- and

neurotoxicity of anti-tuberculosis agents (isoniazid, pyrazinamide, rifampicin) [13]. The ineffectiveness of clopidogrel can become critical in the management of acute myocardial ischemia, and using anticoagulants in almost 30% of cases causes bleeding. PT revealed that sensitivity to warfarin and clopidogrel in a fairly large percentage of cases significantly differs from the general population: in particular, in the study cohort, 22% of patients were resistant to clopidogrel and 21% were highly sensitive to warfarin. A personalized approach to warfarin dosing using a special PT-based algorithm reduces the frequency of bleeding by 4.5 times [14]. PT in relation to clopidogrel is of particular importance in terms of the management of the post-COVID syndrome.

Monitoring drug concentration in blood and studying concentration in other biological substrates can help obtain important information as part of set tasks. Work in this area is vital [15–17]. Studying drug concentration in blood by liquid chromatography and mass spectrometry is an integral part of assessing the individual tolerance of MP.

Along with PT, high-potential areas of personalized medicine include pharmaco-transcriptomic tests and sequencing (determination of the primary nucleotide sequence) of an infectious agent [18].

Doses of Medicinal Products

The classical therapeutic school allows for varying doses of medicinal products depending on the severity of the clinical presentation, the localization of the process (for example, local infection, sepsis, meningitis); the dosage of MP can vary depending on the function of the kidneys or liver.

In case of mass therapeutic interventions (treatment program for the management of HIV and the elimination of hepatitis C), fixed-dose combinations (FCD) are crucial. Fixed-dose combinations are also effective for non-infectious diseases: combined pain relievers, agents for managing hypertension, diabetes mellitus, bronchial asthma, which reduce the number of tablets by 2–3 times.

The demand for such drugs is due to the decreased frequency of administration, decreased total effective dosages and increased compliance. Using combined drugs also demonstrates greater clinical efficacy than separate administration of agents, which is confirmed by clinical trials [19].

Dose, frequency of administration, and therapeutic index (TI) are determined based on the dose-response relationship. TI is the ratio of the maximum dose of a drug with no toxicity to the dose that produces the required effect. It allows assessing the effectiveness and safety of a drug. If a combination of drugs has a potentiating effect, the drug can be used in lower dosing, which increases the TI.

Agents for managing infectious diseases (HIV, viral hepatitides, other infectious diseases) are not used in subtherapeutic concentrations. This is due to the potential variability of pathogens, namely, the development of drug resistance mutations. In these conditions, a decrease in MP concentration below a certain level is dangerous.

Concentration of MP in various media is also of interest. For example, the penetration of antiretroviral therapy (ART) components into different matrices is always analyzed based on the changes in clinical manifestations of HIV; its possible effect on virus reservoirs in various tissues is being studied. Clinical polymorphism and the precedence of affecting certain targets (lymph nodes, central nervous system, internal organs) should also be investigated, including in relation to possible drug exposure. For example, the severity of HIV-associated lymphadenopathy and its response to antiviral treatment is believed to be associated with variability in the penetration of ART components into lymph node tissues, which impacts the overall effectiveness of treatment.

Genetic differences in the pharmacokinetics of drug metabolism may influence the dosage of the drug. For example, isoniazid doses are selected depending on the acetylation level [20].

Due to the age-related features of pharmacokinetics, doses of several agents should also be changed [21].

Microbial translocation with the development of systemic inflammation [22], bacterial overgrowth syndrome, enteropathy, impaired microbiota that leads to inflammatory changes in the intestinal wall [23], and specific intestinal damage by MAC infection can lead to a significantly decreased concentration of drugs in the blood due to impaired diffusion processes and active transport in the intestines [24–26]. At the same time, medicinal products themselves can affect intestinal microbiota, altering drug absorption and closing the vicious circle [27].

In phthisiatric practice, the transition from intensive treatment to a continuation phase has been used for a long time. However, in the management of HIV, treatment phases represent a new direction. The transition from triple regimens to dual regimens, especially with tenofovir withdrawal, ensures complete safety while

maintaining effectiveness (G. D. Kaminsky et al., 2020). However, co-infection of hepatitis B virus does not allow using treatment regimens without tenofovir.

Drug-Drug Interactions

The range of drug interactions is very wide; it is determined by both pharmacokinetic and pharmacodynamic mechanisms that can lead to synergy, or can be neutral, or, on the contrary, lead to mutual suppression. Possible development of additional side effects of varying severity, up to fatal ones, cannot be excluded. When analyzing an agent before its release into clinical practice, maximum attention is paid to drug incompatibility.

There are many examples of successful combinations that have proven to be effective within the established treatment regimens. These include ART, anti-tuberculosis therapy (ATT), combined antihypertensive therapy, combinations of agents in anesthesiology; all these have undeniably proven their advantage over monotherapy.

Possible positive aspects of the combination of drugs with multidirectional effects stay in the background. There is virtually no information in literature sources that is confirmed by clinical trials of the mutual efficacy of ART and ATT drugs, pharmacotherapy of opportunistic infections, and somatic comorbidities. Evaluation of drug combinations always implies just the assessment of incompatibility; in this regard, public databases such as the Liverpool sites are used. www.hiv-druginteractions.org [28], www.hep-druginteractions.org [29]. Compatibility and potentiation stay in the background. This cohort of patients is exposed to one of the most extensive and prolonged pharmacological interventions; the list of medications sometimes includes ten items or more, and their combination is usually not evaluated from a positive perspective.

Winning combinations are possible. One agent can have several practical targets. For example, nucleotide and nucleoside analogs (tenofovir) affect the replication of both HIV and hepatitis B viruses. Dapagliflozin, which is used to manage diabetes mellitus, has been shown to be effective in reducing mortality in cases of heart failure with reduced ejection fraction in the absence of diabetes [30] due to its diuretic and hypotensive effect.

All pharmacokinetic and pharmacodynamic factors that can be analyzed should be considered and compared: drug metabolism pathways, association with groups with the specific features of drug metabolism, specificity of transport, permeability to substrates and distribution, way and rate of elimination, also considering comorbidities that change the elimination rate, the mechanism of the action itself.

Today, HIV and hepatitides are often managed by internists. Considering the universal availability of treatment and required global coverage, an internist will become the primary physician in this area in the future.

When treating patients with HIV, attention is paid to comorbidities that reduce the life expectancy of this cohort due to dyslipidemia, insulin resistance, disorders of bone tissue metabolism induced by the virus and medications, as well as immune complex kidney disease, thrombocytopenia, and encephalopathy of mixed complex origin.

Due to active measures to detect and manage HIV, the life expectancy of individuals with HIV is progressively increasing, and with high compliance, it approaches the life expectancy in the general population. As a result, the average age in this cohort is increasing, and the proportion of elderly patients receiving ART is growing. Therefore, the prevalence of chronic comorbidities and metabolic disorders is increasing, and drug therapy issues in gerontological practice are becoming relevant, complicating the choice of a treatment regimen [31, 32]. Special features of pharmacokinetics (absorption, distribution, metabolism, elimination) in elderly and senile patients increase the frequency of adverse drug reactions by 2–3 times and raise the need for more careful monitoring of treatment tolerance.

Careful attention is focused on gerontological problems, the significance and prevalence of metabolic disorders in the HIV-infected cohort, namely dyslipidemia, lipodystrophy, impaired mineral metabolism, insulin resistance [31–33].

The peculiarities of liver pathomorphology of a polyetiological nature in comorbid patients have high requirements for the choice of medications [34, 35]. Despite that timely and rational ART has demonstrated its hepatological safety and even some antifibrotic effect in cases of concomitant viral hepatitis [36], such a comorbid background significantly increases the incidence of toxic and drug hepatitides in the treatment of tuberculosis, especially generalized drug-resistant forms.

The number of medicinal products that should be taken constantly, together with AEs, leads to depression in patients and adversely affect their compliance. The fact that the patient is already taking many MPs further reduces his/her willingness to take concomitant glucose-lowering, antihypertensive, hypurcemic, lipid-lowering therapy.

Table 2. *Drug interactions between anti–TB and antiretroviral drugs*

	ATV/r	DRV/r	LPV/r	SQV	RTV	DOR	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	ABC	FTC и 3TC	F/TAF	TDF	ZDV
Рифампицин Rifampicin	–⇓72%	–⇓57%	–⇓75%	–⇓	–	–⇓82%	**Н**⇓26%	–⇓	–⇓58%	–⇓80%	**С**⇓q	**С**⇓54%[r]	–⇓	–⇓	**С**⇓40%	+↔	+↔	С⇓p	+⇓12%	**С**⇓47%
Рифапентин Rifapentine	–⇓	–⇓	С⇓	С⇓	С	–⇓	Н⇓	–⇓	С⇓	–⇓	**С**⇓q	**С**⇓s	–⇓	–⇓	С⇓	+↔	+↔	С⇓p	+↔	+↔
Рифабутин Rifabutin	С↑	С↑⇑50%	С↑	С⇓	С	**С**⇓50%[l]	С↓38%	**С**⇓37%	Н↑17%	**С**⇓42%[m]	Сn	+↔	С↑⇓	С↑⇓	+⇑19%	+↔	+↔	С⇓p	+↔	+↔
Изониазид Isoniazid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Пиразинамид Pyrazinamid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Этамбутол Ethambutol	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Стрептомицин Streptomycin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Амикацин Amikacin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Канамицин Kanamycin	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	С↔[a]	+↔	+↔	+↔	+↔	С↔[a]	+↔
Капреомицин	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	Н↑[c]	Н↑⇑[b]	С↑⇑[a,d]	+↔	+↔	Н↑⇑[e]	Н↑⇑[b]	С↑⇑[a]	+↔
Офлоксацин Ofloxacin	С♥	+	С♥	–♥	+	+	+	+	+	Н♥	+	+	+	+	+	+	+	+	+	+
Левофлоксацин Levofloxacin	С♥	+	С♥	–♥	+	+	+	+	+	С♥	+	+	+	+	+	+	+	+	+	+
Моксифлоксацин Moxifloxacin	С↓♥	С↓	С↓♥	–♥	С	+↔	С↓	С↓	+↔	С↔♥	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Бедаквилин Bedaquilin	С↑♥	С↑	С↑62%♥	–♥	С	+↔	С↓18%	С↓	+↑3%	Н↔♥	+↔	+↔	С↑	С↑	+↔	+↔	+↔	+↔	+↔	+↔
Циклосерин Cycloserine	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
Этионамид Etionamid	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔	+↔
ПАСК PAS	+↔	+↔	+↔	+	+	+↔	+↔	+↔	+↔	+↔	+↔	Н↑	Н↑⇑[i]	Н↑⇑[j]	+↔	Н⇓	Н↑⇑[k]	Н↑⇑[i]	Н↑⇑	+↔
Линезолид Linezolid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Меропенем Meropenem	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

	ATV/r	DRV/r	LPV/r	SQV	RTV	DOR	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	ABC	FTC и 3TC	F/TAF	TDF	ZDV
Имипенем + циластатин Imipinem + cylastatin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Амоксициллин + клавулановая кислота Amoxicillin + clavulanic acid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Условные обозначения:

The power and significance of drug–drug interactions:

+ No clinically significant interactions are expected

– The combination of drugs is not recommended

H Potential low-intensity interaction: the combination of drugs is possible, monitoring is necessary, but dose correction is probably not required.

C Potential interaction: the combination of drugs is possible; however, the dose correction or constant monitoring of efficiency and safety is necessary

Comments:

↑ The enhancing of the effect of anti–TB drugs is possible

↓ The weakening of the effect of anti–TB drugs is possible

↔ No significant influence on the drug effect is expected

⇑ The increase of the ART effect is possible

⇓ The weakening of the effect of ART is possible

♥ The increase of the cardiotoxicity (one or both drugs may cause prolongation of the QT and/or PR interval). The ECG monitoring is recommended, according to the combination of the drug with ATV or LPV

% The figures shown in the table express the increase or decrease in AUC observed in studies of drug–drug interactions.

a Drug combinations should be avoided due to the increased risk of nephrotoxicity. If co–prescription of drugs is unavoidable, careful monitoring of kidney function is necessary.

b Co–prescription of drugs may increase the concentration of capreomycin and emtricitabine. The intensity of monitoring of kidney function is determined by the clinical situation.

c The risk of nephrotoxicity of aminoglycosides depends on the dose and duration of administration. The intensity of monitoring of kidney function and the need for dos correction of antiretroviral drugs is determined by the clinical situation.

d Co–prescription may increase concentrations of capreomycin, emtricitabine, and tenofovir. The intensity of monitoring of kidney function is determined by the clinical situation.

e Co-prescription may increase concentrations of capreomycin, emtricitabine or lamivudine. The intensity of monitoring of kidney function is determined by the clinical situation.

i Co–prescription may increase the concentration of PAS and emtricitabine in the blood.

j Co–prescription may increase concentrations of PAS, emtricitabine and tenofovir in the blood.

k Co–prescription may increase concentration of PAS and emtricitabine or lamivudine in the blood.

l In the instructions for DOR, it is recommended to increase the dose of this drug to 100 mg 2 times a day when it is assigned together with rifabutin. DOR 100 mg twice a day should be continued for at least 2 weeks after discontinuation of rifabutin due to ongoing induction of cytochrome P450.

m The dose of rilpivirin should be increased to 50 mg 1 time a day when using the drug in combination with rifabutin. After discontinuation of rifabutin, the dose of rilpivirine should be reduced to 25 mg, but not earlier than 2 weeks later (due to the ongoing induction of cytochrome P450).

n Without protease inhibitors in the treatment regimen, there is no need to correct the dose of MVC. In combination with protease inhibitors (except TPV/ r, FPV/r), it is necessary to prescribe MVC at a dose of 150 mg 2 times a day.

p Co–prescription may decrease the effect of tenofovir alafenamide; no significant influence on emtricitabine effect is expected.

q It is necessary to prescribe MVC at a dose of 600 mg 2 times a day.

r Patients who have not previously taken integrase inhibitors should be prescribed dolutegravir at a dose of 50 mg 2 times a day. In cases of proven or suspected by clinical data resistance to integrase inhibitors, an alternative to the use of rifampicin should be sought, if possible.

s Taking into account the results of studying the interaction of dolutegravir with rifabutin and rifampicin, it is necessary to consider the possibility of increasing the dose of dolutegravir to 50 mg 2 times a day when it is prescribed with rifapentine.

Infectious and phthisiatric patients that are interested in their health are compliant and disciplined with regard to the adherence to their treatment regimen: such patients give special attention to compliance, and most of them understand its significance for the prognosis.

The issue of a patient's self-assessment of drug effectiveness is very relevant; it motivates the patient to undergo treatment and increases compliance. A combination of infectious disease, tuberculosis and chronic somatic diseases raises the issue of minimizing drug exposure. The number of dosage forms taken, in addition to their effectiveness, cost, and frequency of administration, is one of the most important factors of compliance that makes the development of combined agents very promising and desirable.

A rational combination of MPs should be confirmed clinically.

Such combinations can be made considering various criteria available for assessment: pharmacokinetic factors — positive effect on the bioavailability of components, mutual change in metabolism or elimination that allows reducing the dosage of components; pharmacodynamic benefits — mutual potentiation due to the effect on different links of the pathological process, therapeutic value for the treatment of comorbidities, mutual offsetting of side effects with an increase in TI of components and, finally, optimization of the administration regimen.

When choosing treatment regimens, infectious disease experts are usually guided by the summary tables of drug interactions. Careful consideration of the interaction mechanism can help to find different options. So, using the example of the interaction of ART and antituberculosis agents, combinations were found, where the concentration of a particular drug increases or decreases, or additional side effects arise in the form of increased cardio- or nephrotoxicity (Table 2). This should be considered when choosing a therapy.

When treating patients with HIV complicated by secondary diseases, tuberculosis, hepatitides, a wide range of somatotropic pharmacological agents should be added to etiotropic therapy (Table 3).

Let us analyze a case. The patient is taking a first-line scheme for the management of HIV: efavirenz, tenofovir, and lamivudine. He is also receiving a fixed combination of amlodipine, indapamide and perindopril for the management of hypertension (essential arterial hypertension). The patient started complaining of fatigue, low mood, insomnia that prevented him from driving the car he had just purchased. In order to prevent possible undesirable effects of efavirenz on the central nervous system and as a "reward therapy" after taking three tablets for many years, the patient is prescribed FDC elvitegravir / cobicistat / emtricitabine / tenofovir / alafenamide. According to the physician, such a regimen will eliminate the long-term osteorenal toxicity of tenofovir (replaced with tenofovir alafenamide) and enhance the effectiveness of suppressing the virus: viral replication inhibition index of emtricitabine is higher than that of lamivudine. Is the physician doing the right thing? No. Because amlodipine is metabolized by CYP3A4, prescribing a drug with a cobicistat booster will increase amlodipine concentration twofold. Indapamide is metabolized by cytochrome P450, and the cobicistat booster also potentially increases indapamide concentration. This can result in critical hypotension and deterioration of the patient's condition. In this case, one should either consider an alternative agent for managing HIV or adjust hypertension therapy to achieve total pharmacological compatibility. It is also possible to change both drug schemes.

The use of these drugs is determined by the need to manage the main diseases and their complications, the need to correct AEs of etiotropic treatment regimens, and the required symptomatic treatment. The presence and aggravation of somatic comorbidities require the involvement of specialists in various areas: therapist, cardiologist, gastroenterologist, pulmonologist, neurologist, ophthalmologist, urologist; they should also know the peculiarities of interaction of special agents with basic therapy.

Here is an example of the interaction of antihypertensive and antiretroviral agents (Table 4). It should be noted that only four ART agents have no drug interactions with antihypertensive drugs. Other combinations require careful attention due to the mutual effect on the concentration level. Two antihypertensive drugs — lercanidipine and aliskiren — require special attention, up to the avoidance of these combinations, due to a very significant increase in their concentrations. The rest should be monitored by the clinician during dosage selection in relation to the severity of clinical effect and AE. Antiretroviral drugs can affect the concentration of antihypertensive drugs in both directions. However, the most commonly used antihypertensive drugs have less effect — in some cases, they only increase the concentration of antiretroviral drugs.

Table 3. The most commonly used drugs in the treatment of patients with chronic infectious diseases

ATC-Classification System of Drugs	Subgroup	Examples of drugs
Digestive tract and metabolism	Proton pump inhibitors	Omeprazole, rabeprazole
	Antiemetics	Ondansetron
	Motility stimulants	Metoclopramide, trimebutine
	Gastroprotectors	Bismuth preparations
	Hepatoprotectors	Ademetionine, UDCH, phospholipids, milk thistle preparations
	Enzymes	Pancreatin
	Laxatives	Lactulose, sodium picosulfate
	Carminative	Simethicone
	Antispasmodics	Drotaverine, mebeverin
Hematopoiesis and blood	Stimulants of hematopoiesis	Iron preparations, erythropoietin
	Hemostatic drugs	Eltrombopag
The cardiovascular system	ACE inhibitor, Angiotensin II receptor blockers	Enalapril, perindopril, losartan, amlodipine
	Calcium channel blockers	Amlodipin
	Beta-blockers	Bisoprolol, metoprolol
	Hypolipidemic drug/	Atorvastatin, fenofibrate
	Diuretics	Furosemide, torasemide, indapamid
Hormones for systemic use	Systemic corticosteroids	Dexamethasone, prednisone
Antimicrobials for systemic use	Penicillins	Amoxicillin/clavulanate
	Macrolides	Clarithromycin, Azithromycin
	Aminoglycosides	Amikacin
	Cephalosprorins	Ceftriaxone
	Fluoroquinolones	Levofloxacin, Moxifloxacin
	Sulfonamides	Sulfamethoxazole + Trimethoprim
	Antimycotics	Fluconazole, voriconazole
Antineoplastic and immunomodulating agents	Antineoplastic antibiotics	Doxorubicin
	Colony-stimulating factors	Filgrastim
Musculoskeletal system	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Diclofenac, Ibuprofen, Ketoprofen
	Antigout Agents	Allopurinol, febuxostat
Nervous system	Analgesics	Tramadol, paracetamol, acetylsalicylic acid
	Anticonvulsants	Carbamazepine, gabapentin
	Benzodiazepines	Bromodihydrochlorophenylbenzodiazepine
	Antidepressant	Amitriptilline, escitalopram, sertraline
Respiratory system	Mucolytics	Ambroxol, acetylcysteine
	Antitussives	Butamirat
	Antihistamines	Chloropyramine, cetirizine, Loratadine / Desloratadine

Note: *ATC — classification of drugs — anatomical-therapeutic-chemical classification of drugs

Table 4. *Interactions between ARVT and hypotensive therapy*

АРТ/ ARVT	АГП/ AHD	иАПФ/ ACE inhibitors	БРА/ Angiotensin II receptor blockers					БКК/ Calcium channel blockers					Диуретики/ Diuretics						β-блокаторы/ β-blockers				Агонисты I_1- рецепторов/ I_1 receptor agonists		Другие/ Other		
		Каптоприл Рамиприл Эналаприл Периндоприл	Лозартан	Ирбесартан	Телмисартан	Валсартан	Азилсартан	Нифедипин	Амлодипин	Дилтиазем	Лерканидипин	Верапамил	Фуросемид	Торасемид	Индапамид	Гидрохлортиазид	Хлорталидон	Спиронолактон	Атенолол	Бисопролол	Метопролол	Небиволол	Моксонидин	Рилменидин	Доксазозин	Сакубитрил	Алискирен
НИОТ NRTI	3TC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↑E	-	-	-	-	-	-	-	-
	ABC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	TDF	-	-	-	-	-	-	-	-	-	-	E	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	TAF	-	-	-	-	-	-	-	-	-	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	FTC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ННИОТ NNRTI	NVP	-	-	-	-	-	-	↓	↓	↓	↓	↓	-	-	-	↓	-	-	-	-	-	-	-	-	↓	-	-
	EFV	-	↑	↑	-	-	-	↓	↓	↓	↓	↓	-	↑	↓	↓	-	-	-	-	-	-	-	-	↓	-	-
	ETV	-	↑	↑	-	-	-	↓	↓	↓E	↓	↓	-	↑	-	↓	-	-	-	-	-	-	-	-	↓	-	↑
	RPV	-	-	-	-	-	-	↓	↓	E	↓	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	DOR	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ИП PI	ATV	-	↓	↓	-	↑	-	↑	↑	↑		↑	-	↓	↑	↑	-	-	↑	↑	↑	-	-	-	↑	↑	□
	LPV/r	-	↓	↓	-	↑	-	↑	↑	↑	□	↑	-	-	↑	↑	-	-	↑	↑	↑	↑	-	-	↑	↑	□
	DRV/r	-	↓	↓	-	↑	-	↑	↑	↑	□	↑	-	↓	-	↑	-	-	↑	-	↑	-	-	-	↑	↑	-
	FPV	-	-	-	-	↑	-	↑	↑	↑	↑	↑	-	-	-	↑	-	-	-	-	↑	-	-	-	↑	↑	-
	RTV		-	-	-	-	-	-	-	-	□	-	-	-	-	-	-	-	-	-							□
ИИ II	RAL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	DTG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↑	-	-	-	-	-	-	-	-
	EVG/c	-	↓	↓	-	-	-	↑	↑	↑	□	↑	-	↓	↑	↑	-	-	↑	↑	↑	↑	-	-	↑	-	□
	BIC	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	↑	-	-	-	-	-	-	-	-
ИРП PRI	MVC	-	-	-	-	-	-	-	-	E	-	E	-	-	-	-	-	-	-	-	-	-	-	-	-	E	-

Symbols:

↑	Increased concentration of AHD (antihypertensive drug)
□	Significant increase in concentration AHD, incompatibility
↓	Increase in concentration AHD
E	Increase in concentration ARVT
↑E, ↓E	Simultaneous concentration change AHD and ARVT
АГП (AHD)	Antihypertensive drug
НИОТ(NRTI)	Nucleoside reverse transcriptase inhibitors
ННИОТ (NNRTI)	Non-nucleoside reverse transcriptase inhibitors
ИРП (PRI)	Penetration receptor inhibitors
NVP	Nevirapine
EFV	Efavirenz
ETV	Etravirine
RPV	Rilpivirine
ИП (PI)	Protease inhibitors
ATV	Atazanavir
LPV/r	Lopinavir / ritonavir
RTV	Ritonavir
SQV-inv	Saquinavir
FPV	Fosamprenavir
DRV	Darunavir
II	Integrase inhibitors
RAL	Raltegravir
DTG	Dolutegravir
EVG/c	Elvitegravir/cobicistat
BIC	Bictegravir
MVC	Maraviroc
ENF	Enfuvirtide

Clinicians have accumulated valuable empirical evidence in the combined use of drugs, which could lead to widespread implementation when objectified using informative research tools, clinical and observational studies.

Therefore, the analysis of drug combinations from the perspective of their favorable effects is a promising area in medicine and an important object of research interest; available tools can help provide an objective presentation that will comply with the concept of evidence-based medicine.

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