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Review

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Drugs used in viral diseases – their mechanism of action, selected adverse effects and safety during pregnancy and lactation

Leki stosowane w chorobach wirusowych – ich mechanizm działania, działania niepożądane i bezpieczeństwo podczas stosowania w ciąży i laktacji

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Summary

Viruses cause many diseases in humans, from self-resolving diseases to acute fatal diseases. New antiviral drugs are registered and the efficacy and safety of other medicines are evaluated in clinical trials. Antiviral therapy significantly reduces the morbidity and mortality of patients, but may cause numerous adverse effects. The aim of this study is to discuss the mechanism, selected adverse effects of available antivirals and their safety during pregnancy and lactation. The authors refer to the classification of drugs used during pregnancy and recommendations for breastfeeding, which, for example, definitely prohibit the use of ribavirin. The authors also pay attention to the monitoring of selected diagnostic parameters to improve the treatment results. Clinicians should limit adverse effects through an individual, specific to the patient treatment regimen. Physicians should pay special attention to the use of antiviral drugs in pregnant and breast-feeding women. Clinical trials should be continued to increase knowledge about the adverse effects of antiviral medicines.

Keywords: **viral diseases • antiviral drugs • adverse effects • antivirals during pregnancy and lactation**

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INTRODUCTION

Viruses cause many diseases in humans, from self-resolving diseases to acute fatal diseases. Future antivirals are being developed due to the high risk of patient's mortality. In recent years, there have been drugs with new mechanisms of action that have been unused, and the effectiveness and safety of other drugs is being evaluated in clinical trials. Antiviral therapy significantly reduces the morbidity and mortality of patients, but is associated with complications in various body systems. Risk factors and the frequency of occurrence of selected adverse effects of pharmacological treatment are collected and documented. Identifying specific causes related to epidemiology, pathogenesis and the prevention of viral diseases is necessary for a clinician. Nevertheless, attention should be paid to selecting appropriate, individual treatment, especially during pregnancy and lactation, taking into account the adverse effects of the antiviral drugs used. The publication is a review and its aim is to discuss the available drugs that are used in the treatment of viral diseases, with the focus on their selected adverse effects. The safety of antiviral therapy during pregnancy and lactation deserve particular attention.

Table 1 presents the current range of antiviral substances divided into drug groups, taking into account their use in the therapy of individual viral diseases.

Interferons (IFNs) are a family of cytokines secreted by host cells in response to various pathogens, including viruses, bacteria and fungi. To protect our body from virus pathogen infestations, interferons activate the transcription of multiple Interferon-Stimulated Genes (ISGs) and thus promote a broad spectrum of antiviral responses. Hepatitis C Virus (HCV) is both a hepatotropic and a lymphotropic virus associated with several chronic infectious diseases. Among chronically infected patients, 20% to 35% suffer from cirrhosis and have a high risk of developing hepatocellular carcinoma. The extrahepatic manifestations of HCV infection include autoimmune diseases, hematologic diseases, and rheumatic diseases. Currently, the treatment of hepatitis C is based on a combination of interferon (IFN) or pegylated interferon (PEG-IFN α-2a or α-2b, peginterferon) and ribavirin (RBV) [47]. Three Nonstructural Protein 3-4A (NS3-4A) protease inhibitors are also used: telaprevir (TVR), boceprevir (BOC) and one RNA polymerase inhibitor dependent on NS5B RNA (RdRp) sofosbuvir (SOF). Interferons initiate a sequence of intracellular events, including the induction of specific enzymes. This process at least partly determines the different cell responses to interferon, including inhibition of virus replication in infected cells, inhibition of cell proliferation and immunomodulatory actions such as stimulation of macrophage phagocytic activity or stimulation of cytotoxic activity of lymphocytes against target cells. Each of these mechanisms consists in the therapeutic effect of interferon [45].

Type I interferons are associated with a unique heterodimeric receptor consisting of an interferon alpha 1/2 receptor (IFNAR1/IFNAR2). It leads to the activation of signal paths and the subsequent induction of a large number of ISGs. Proteins encoded by ISGs mediate the antiviral activity of interferons. IFNAR1 and IFNAR2 are associated with Janus activated kinases (JAKs) tyrosine kinase 2 (TYK2) and JAK1, respectively. Binding type I IFNs with their receptors leads to activation of JAKs, which in turn triggers tyrosine phosphorylation in the signal transducer and activator of transcription 2 (STAT2) and Signal transducer and activator of transcription (STAT1). STAT1/STAT2 migrates into the nucleus and associates with IFN regulatory factor 9 (IRF9), forming the STAT1–STAT2–IRF9 complex also known as Interferon-Stimulated Gene Factor 3 (ISGF3). This complex binds the IFN-stimulated response elements (ISREs) inside DNA to initiate the transcription of hundreds of different ISGs. These genes help both to remove virus from infected cells and to protect neighbouring, non-infected cells [45].

The genes induced by IFN I also include Protein Kinase R (PKR), which by means of phosphorylation of the eukaryotic initiation factor 2α (elF2α), inhibits the translation of virus proteins [45].

Interferons also have another important role to play. Type I IFNs can promote T cell proliferation, prevent T cell apoptosis, stimulate the activation of the Natural Killer Cell (NKC) and stimulate the maturation of Dendritic Cells (DCs). They can also regulate the synthesis of major histocompatibility complex (MHC) and major class I tissue compatibility systems, and promote the T-helper-1 phenotype over the T-helper-2 phenotype [45].

Some of the most common side effects include: gastrointestinal disorders, upper respiratory tract infections, coughing, dyspnoea, depression, mood changes, visual impairment, tachycardia, peripheral oedema, alopecia, muscle and joint pain, ear pain, fainting, dermatitis, impotence and fever [80].

Because of the low levels in milk and poor oral absorption by the infant, it is unlikely that interferon use by a nursing mother presents any serious risk to the breastfed infant. Mothers with hepatitis B are encouraged to

Table 1. Drugs used in various viral diseases

Interferon alfa		
	Hepatitis B Virus, Hepatitis C Virus, Herpes Simplex Virus, Epstein-Barr Virus, Human Papilloma Virus	[47, 54, 135, 136]
Antimetabolites (polymerase inhibitors)		
analogue of adenosine		
adefovir	Hepatitis B Virus	
analogues of guanosine		
ganciclovir	Cytomegalovirus, Herpes Simplex Virus, Epstein-Barr Virus, Hepatitis B Virus, Varicella Zoster Virus	[18, 33, 66, 90, 111, 124, 136]
valganciclovir	Cytomegalovirus, Herpes Simplex Virus, Epstein-Barr Virus, Varicella Zoster Virus	[68, 111, 127]
acyclovir	Varicella Zoster Virus, Herpes Simplex Virus	[90, 131]
valacyclovir	Varicella Zoster Virus, Herpes Simplex Virus, Cytomegalovirus	[58, 131]
famciclovir	Herpes Simplex Virus, Varicella Zoster Virus, Epstein-Barr Virus, Hepatitis B Virus	[9, 66, 131]
penciclovir	Herpes Simplex Virus	[118]
analog of cytosine		
cidofovir	Cytomegalovirus, Herpes Simplex Virus	[18, 114]
lamivudine	Hepatitis B Virus	[92]
analogues of thymidine		
trifluridine	Herpes Simplex Virus	[90]
brivudine	Herpes Simplex Virus, Varicella Zoster Virus	[123]
Inhibitor of the terminase complex		
letermovir	Cytomegalovirus	[11]
Another antimetabolities		
ribavirin	Hepatitis C Virus, Respiratory Syncytial Virus, Arenaviruses, Adenoviruses, Flaviviruses	[62, 73, 78, 91, 99]
foscarnet	Hepatitis B Virus, Cytomegalovirus, Herpes Simplex Virus	[18, 26, 130]
imiquimod	Human Papilloma Virus	[88]
Nonstructural 5A (NS5A) protein inhibitors		
daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir	Hepatitis C Virus	[35, 46, 61, 82, 126]
NS5B polymerase inhibitors		
sofosbuvir, dasabuvir	Hepatitis C Virus	[35, 61, 82, 107]
Inhibitors of the HBV polymerase		
entecavir, tenofovir	Hepatitis B Virus	[66, 92, 128]
NS3 protease inhibitors		
paritaprevir, asunaprevir, grazoprevir	Hepatitis C Virus	[38, 55, 57]
Neuraminidase inhibitors		
oseltamivir, zanamivir	Influenza viruses A and B	[53, 93]

Interferon alfa		
peramivir	Influenza viruses A and B	[69]
Inhibitors of the M2 proton channel		
rimantadine	Influenza Virus A	[5]
Nucleoside reverse-transcriptase inhibitors (NRTIs)		
zidovudine, didanosine, stavudine	Human Immunodeficiency Virus	[27]
lamivudine	Human Immunodeficiency Virus,	[66]
abacavir	Human Immunodeficiency Virus	[27]
emtricitabine	Human Immunodeficiency Virus, Hepatitis B Virus	[27, 64]
Nucleotide reverse-transcriptase inhibitors (NtRTIs)		
tenofovir	Human Immunodeficiency Virus, Hepatitis B Virus	[66, 92]
adefovir	Hepatitis B Virus	[66, 135]
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)		
nevirapine, efavirenz, etravirine, rilpivirine	Human Immunodeficiency Virus	[27]
HIV protease inhibitors		
saquinavir, ritonavir, indinavir, nelfinavir, lopinavir, tipranavir, fosamprenavir, atazanavir, darunavir	Human Immunodeficiency Virus	[27]
Entry inhibitors: fusion inhibitors and CCR5 antagonists		
enfuvirtide, maraviroc	Human Immunodeficiency Virus	[28]
Integrase strand transfer inhibitors (INSTIs)		
raltegravir, elvitegravir, dolutegravir	Human Immunodeficiency Virus	[102]

breastfeed after their infants receive these preventative measures [7]. Hepatitis C is not transmitted through breastmilk and breastmilk has been shown to inactivate hepatitis C virus (HCV). However, the Centers for Disease Control recommends that mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding [19, 81, 125]. The levels of interferon beta-1a in breastmilk are minuscule. In addition, because interferon is poorly absorbed orally, it is not likely to reach the infant's bloodstream. A small number of nursing mothers receiving interferon beta-1a while partially breastfeeding their infants and one woman exclusively breastfed her infant while taking interferon beta-1b and reported no adverse effects [49].

A 26-year-old woman was diagnosed with acute hepatitis C in the 16th week of pregnancy. She received a total dose of 72 million units of interferon alfa-2b during a 2 1/2 month period. Although the therapy was discontinued due to adverse effects, a complete biochemical and virologic response was obtained. Premature labor occurred and healthy, but growth-restricted, twin infants were born transvaginally. At 18 months of age, they had normal development, with a negative hepatitis C serology [77].

Clinicians assess the side effects of antiviral drugs mainly during the treatment period, ignoring side effects in the future. Bukhari et al. conducted a retrospective study on infertility in 40 men treated for HCV in 2008–2015. The possible effects of interferon on fertility hormones and semen parameters were evaluated. Fertility hormones such as Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and testosterone were measured. Of the forty HCV patients who received interferon, only 14 (35%) have children and 26 (65%) could not conceive. After treating HCV in HCV-positive patients there was a significant change in the level of FSH and LH. In particular, testosterone levels decreased. Treatment of HCV also significantly reduced the number of sperm and their motility [58].

The type-III subset of the IFN family was co-discovered by two independent research groups in 2003. It includes three members: IFN-λ1, -λ2 and -λ3, also known as IL-29, IL-28A and IL-28B, respectively. Like type-I IFNs (IFN-α/β), the type-III IFNs induce antiviral activity in cells that express IFN-λ receptors. IFN-α (type-I IFN) and IFN-λ (type-III IFN) signal through distinct receptor complexes, but activate the same intracellular signaling pathway. IFN-λ binds to a distinct receptor complex composed of the IFN-λ receptor chain (IFN-λR1) and IL-10R2 chains [29].

Expression of IFN-λ receptors is largely restricted to cells of epithelial origin such as keratinocytes, bronchial epithelial cells and hepatocytes, which suggesting that recombinant IFN-λ induce the hematopoietic and neuro-

logic adverse reactions less. IFN-λ-induced antiviral activity has been demonstrated against many different viruses, including the encephalomyocarditis virus (EMCV), vesicular stomatitis virus (VSV) and influenza virus. IFN-λ has also been shown to inhibit replication of hepatitis B virus (HBV) in a differentiated murine hepatocyte cell line and to inhibit replication of both subgenomic and full-length HCV replicons in the human hepatoma cell line [29].

Only chronic HCV infection benefits from interferon-lambda (IFN-λ) therapy. IFN-λ treatment induced more-rapid viral suppression compared with IFN-α during the first 12 weeks. However, at week 24, the rates of viral suppression are almost identical for IFN-λ and IFN-α. The difference between IFN-λ and IFN-α treatment has been evident in the incidence of side effects, because IFN-λ induces limited side effects. Furthermore numerous studies have clearly demonstrated the involvement of IFN-α in the pathogenesis of autoimmune diseases in contrasts to the findings associated with IFN-λ. A low incidence of autoimmune thyroid disease has been recently described in chronic HCV patients treated with IFN-λ, which contrasts with IFN-α [60].

The mechanism of action of ribavirin (RBV), which is used to treat viral hepatitis, is unclear. Soota et al. suggest that one of the possible mechanisms through which ribavirin acts synergistically with IFN in HCV therapy is passive haemolysis. It deliveres the heme to hepatocytes and Kupffer-Browicz cells. The heme is then metabolized and detoxified by heme oxygenase 1 (HMOX1) to carbon monoxide (CO), biliverdin and free iron. The heme metabolites obtained have anti-inflammatory and antioxidant properties. HMOX1 plays an important antioxidant, anti-inflammatory and cytoprotective role, especially in Kupffer cells and hepatocytes. HMOX1 has been found to have antiviral activity in hepatitis C infected cell lines. Moreover, it has been shown to enhance the response to IFN-α by restoring interferon-stimulated genes (ISGs) [99].

In one of their studies, Sinclair et al. assessed the effect of ribavirin on the fetus. Exposure to RBV was classified as direct exposure to RBV during pregnancy or 6 months before conception, or indirectly to women exposed to sexual contact, 6 months before or during pregnancy, with a man who had been taking or receiving RBV during the previous 6 months. Women were observed until delivery and for one year during the development of infants. There were 272 pregnant women with 180 living newborns in the register: among 85 directly exposed women there were seven cases of congenital malformations [7/85 (8.2%)] and four cases of congenital malformations among 95 indirectly exposed women [4/95 (4.2%)]. Out of 11 infants, nine had structural anomalies and two had chromosomal anomalies [97]. It is not known whether ribavirin penetrates into breast milk [87].

Human respiratory syncytial virus types A and B of the species human respiratory syncytial virus are found within the genus Orthopneumovirus, family Pneumoviridae, order Mononegavirales. Structurally, human respiratory syncytial virus is an enveloped, spherical virus with a diameter of approximately 150 nm. Respiratory syncytial virus (RSV) infection is a significant cause of hospitalization of children in North America and one of the leading causes of death in infants younger than 1 year of age worldwide, second only to malaria. Despite its global impact on human health, there are relatively few therapeutic options available to prevent or treat RSV infection. There are currently only two antivirals for RSV available, palivizumab for prevention and ribavirin for treatment. Numerous blinded trials of RSV-infected patients have demonstrated faster RSV clearance, decreased viral shedding, and shorter hospitalization stays with the use of ribavirin to treat RSV infection. Palivizumab is a humanized monoclonal antibody that is directed to RSV fusion protein expressed on the surface of the RSV virion [93]. Palivizumab is not indicated for use in adults. There are no data on fertility, pregnancy and breastfeeding [104].

Table 2 presents adverse reactions related to biochemical parameters caused by antiviral drugs, occurring at a frequency equal to or greater than 1:100.

DNA and RNA polymerase inhibitors are a group of drugs used in the treatment of many viral diseases. They inhibit the replication of virus genetic material. This group includes ganciclovir. Ganciclovir is a potent inhibitor of viruses of the herpes family, including cytomegalovirus (CMV), which are pathogenic for humans and animals. Ganciclovir's main mechanism of action against CMV is the inhibition of viral DNA replication by ganciclovir 5'-triphosphate (ganciclovir-TP), by selective and strong inhibition of viral DNA polymerase [28]. Puliyanda et al. described the use of ganciclovir to treat CMV infection in a fetus at 22 weeks' gestation. The mother had received a renal transplant before pregnancy and had been treated for CMV infection subsequent to a blood transfusion. Although the mother had no signs or symptoms of infection, an amniocentesis at 21 weeks' gestation suggested fetal CMV infection. Oral administration of ganciclovir at a dose of 3g/day was started in the 22nd week of pregnancy. At 25 weeks, a repeat amniocentesis revealed that the CMV-DNA level had decreased to within the negative range. The minimum inhibitory concentration for CMV was 3μM, whereas the amniotic fluid concentration of ganciclovir was 14.5 μM. A cesarean section at 36 weeks delivered a healthy female infant with no signs or symptoms of CMV infection. At 3 years of age, the child had no signs of neurological, opthalmological, or developmental abnormalities [67]. Animal data indicate that ganciclovir is secreted into the milk of nursing rats. Therefore, breastfeeding must be discontinued during treatment with ganciclovir. Some of the most common side effects of ganciclovir use include: gastrointestinal disorders, septicaemia, inflammation of the connective tissue, infection of the urinary tract, anorexia, depression, anxiety, entanglement, paraesthesia, seizures, taste distur-

Table 2. Adverse reactions related to biochemical parameters caused by antiviral drugs, occurring at a frequency equal to or greater than 1:100 [3, 6, 8, 14, 17, 20, 22, 24, 30, 31, 32, 34, 36, 37, 38, 41, 43, 48, 50, 51, 65, 76, 84, 87, 89, 95, 100, 103, 104, 105, 108, 109, 110, 115, 117, 119, 120, 122, 132, 133]

Interferon alfa	**Hypothyroidism, hypothyroidism**
Antimetabolites (polymerase inhibitors)	
ganciclovir	Increased activity of alkaline phosphatase (ALP) in blood, abnormal liver function, increased aspartate transaminase (AspAT) activity, kidney function disorders, decreased creatinine clearance, increased creatinine concentration in blood
valganciclovir	Disorders of liver function, increased activity of ALP, increased activity of AspAT, reduction of creatinine clearance, impairment of kidney function, increased concentration of creatinine in blood
famciclovir	Abnormal liver function tests
cidofovir	Proteinuria, increased concentration of creatinine in blood
Another antimetabolities	
ribavirin	Hypothyroidism, hypothyroidism, virilism
NS5B polymerase inhibitors	
sofosbuvir	Increased concentration of bilirubin in blood
Inhibitor of the HBV polymerase	
entecavir	Increased activity of aminotransferases
NS3 protease inhibitors	
asunaprevir	Increase in ALT
Neuraminidase inhibitors (NAIs)	
peramivir	Increased activity of lactate dehydrogenase in blood
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
zidovudine	Excessive concentration of lactic acid, increased activity of liver enzymes, increased concentration of bilirubin in blood
stavudine	Lipoatrophy, lipodystrophy, asymptomatic hyperlactatemia
emtricitabine	Hypertriglyceridaemia, hyperglycaemia, increased amylase activity including increased pancreatic amylase activity, increased serum lipase activity, increased activity of AspAT and/or increased acitivity of alanine transaminase (ALT), hyperbilirubinemia, increased activity of creatine kinase (CK)
lamivudine	Increased activity of ALT, increased activity of CK
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
tenofovir	Hypophosphatemia, increased activity of transaminases
adefovir	Hypophosphatemia, increased concentration of creatinine in blood
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
nevirapine	Increased activity of ALT, AspAT, γ-glutamyltransferase (GGT), hypertransaminasemia
efavirenz	Hypertriglyceridaemia, increased activity of AspAT, ALT and GGT
etravirine	Diabetes, hyperglycaemia, hypercholesterolemia, hypertriglyceridaemia, hyperlipidemia
rilpivirine	Increased total cholesterol, increased LDL cholesterol, increased triglyceride concentration, increased pancreatic amylase activity, increased aminotransferases activity, increased concentration of bilirubin in blood
HIV protease inhibitors	
darunavir	Diabetes, hypertriglyceridaemia, hypercholesterolemia, hyperlipidemia, increased blood amylase activity, increased activity of ALT
atazanavir	Jaundice
ritonavir	Hypercholesterolemia, hypertriglyceridaemia, gout, hepatitis (including increased activity of AspAT, ALT GGTP), increased concentration of bilirubin in blood (including jaundice), pancreatitis, increased activity of CK, increased concentration of creatinine in blood, increased amylase activity, decreased free and total thyroxine concentration

Interferon alfa	Hypothyroidism, hypothyroidism
saquinavir	Increase in blood cholesterol concentration, increase in blood triglycerides, diabetes, increase activity of ALT, AspAT, increase in low-density lipoprotein concentration, increased concentration of bilirubin in blood, increase in amylase activity, increased concentration of creatinine in blood
indinavir	Isolated asymptomatic hyperbilirubinemia, increased activity ofALT and AspAT
fosamprenavir	Increase in blood cholesterol concentration, increase in blood triglycerides concentration, increase activity of ALT and AspAT, increase in lipase activity
tipranavir	Hypertriglyceridaemia, hyperlipidemia
Entry inhibitors: fusion inhibitors and CCR5 antagonists	
maraviroc	Increased activity of ALT and AspAT
enfuvirtide	Increased concentration of triglycerides in blood, diabetes
Integrase strand transfer inhibitors (INSTIs)	
raltegravir	Increased activity of ALT and AspAT, increase in blood triglycerides concentration, increase in lipase activity, increased activity of pancreatic amylase
dolutegravir	Increased acitivity of ALT and (or) AspAT, increased activity of creatine phosphokinase (CPK)

bances, insomnia, macular edema, retinal detachment, eye pain, ear pain, dyspnoea, cough, dermatitis, joint and muscle pains, fever and fatigue [22].

Cytomegalovirus (CMV) is a major cause of morbidity and mortality in immunocompromised patients. CMV infection remains a common complication after allogeneic hematopoietic-cell transplantation. Available antivirals are subject to adverse effects and risk of the development of CMV resistance. Letermovir is a novel antiviral in the late stages of drug development for the treatment and prevention of CMV. Letermovir is an antiviral drug that inhibits the CMV–terminase complex. Only five adverse events were considered as possibly being related to letermovir including gastroenteritis, nasopharyngitis, dyspnea, dyspepsia, and increased creatinine [11]. It is not known whether letermovir is excreted in human milk. Available data from animal studies indicate that letermovir penetrates into milk [83].

The imidazoquinoline, imiquimod, is a low molecular weight, synthetic immune response modifier that is used for the treatment of external genital and perianal warts. This therapy has shown good efficacy and safety in the treatment of external genital and perianal warts caused by human papillomavirus (HPV) infection. The antiviral mechanism of action of this compound is unlike any other approved antiviral therapy in that it induces the production of antiviral cytokines and cytokines that enhance cellular immunity believed to be necessary for the control or elimination of HPV infection. Imiquimod does not exert its antiviral effects directly on virus-infected cells. Preclinical data demonstrate in vitro and in vivo that imiquimod directly induces antiviral and immunomodulating cytokines from monocytes, macrophages and dendritic cells. These immunomodulating cytokines have been shown to potentiate type 1 helper T (Th1) cells immunity [88]. It is not recommended for pregnant women. Moreover, it is not known whether topically applied imiquimod is excreted in breast milk [40].

Foscarnet is a pyrophosphate analogue with activity against herpes viruses, human immunodeficiency virus (HIV), and other RNA and DNA viruses. Foscarnet interferes with the exchange of pyrophosphate from deoxynucleoside triphosphate during viral replication by binding to a site on the herpesvirus DNA polymerase or HIV reverse transcriptase [21].

A case describing the use of a foscarnet during human pregnancy has been located. A 21-year-old woman at 18 weeks' gestation was treated with an 8-day course of foscarnet for severe, genital acyclovir-resistant Herpes simplex virus type 2 (HSV type 2). The patient, who also had a 3-year history of HIV, was being treated with saquinavir, lamivudine and zidovudine. After being discharged from hospital, repeat cultures yielded HSV type 2 sensitive to acyclovir. The woman was treated with oral doses of acyclovir until the end of pregnancy. The woman gave birth to a healthy, HIV-negative child who was developing normally at 1 year of age [4].

Foscarnet has low bioavailability after oral administration, therefore it must be administered intravenously. Adalsteinsson et al. presented the case of a 29-year-old man with acute myeloid leukemia who was treated in CMV prophylaxis. Three weeks after switching to a foscarnet due to neutropenia, two painful, symmetric ulcers appeared on the lower side of the penis glans. The cultures of viruses and bacteria were negative. Two weeks after the infusion was stopped, the ulcers disappeared without any additional treatment. It is important that doctors are not only able to diagnose the potential complications of foscarnet correctly, but above all that they know how to prevent this. In addition to genital

ulcerations, nephrotoxicity, electrolyte disturbances, nausea and convulsions are often reported as severe side effects. Other side effects include arrhythmias or epileptic seizures, which may be the result of a temporary reduction in serum calcium ion concentration [1].

The non-structural 5A (NS5A) HCV enigmatic protein has various functions in the HCV replication cycle: it binds the HCV RNA, interacts with the host cellular proteins, it is necessary in virion production, and it is postulated that it can play a role in the phenomenon of interferon resistance. NS5A protein inhibitors are a key element of effective treatment regimens, but the genetic heterogeneity of HCV reduces the efficacy of these drugs and mutations lead to resistance. The names of medicines belonging to this group end with "asvir". These include: ledipasvir (LDV), daclatasvir (DCV) and ombitasvir (OBV), elbasvir (EBV) and velpatasvir (VEL) [24, 46, 61, 82, 126]. Some of the most common side effects of daclatasvir include insomnia, dizziness, migraine, nausea, diarrhea, joint and muscle pains and fatigue [110].

There are no data on the use of daclatasvir in pregnant women. Animal studies on daclatasvir have shown its embryotoxic and teratogenic effects. The risk to people is not known. In one study, daclatasvir was excreted in the milk of lactating animals at concentrations 1.7- to 2 times higher than maternal plasma concentrations [78, 101].

The non-structural 5B (NS5B) HCV protein is the RNA-dependent RNA polymerase responsible for the complete copy of the RNA viral genome and is the target of choice for the development of anti-HCV drugs. The names of nucleoside and non-nucleoside NS5B polymerase inhibitors end with "buvir". One of them is sofosbuvir, which is a nucleotide analogue. SOF is converted intracellularly into the active metabolite of sofosbuvir – triphosphate. NS5B protein is viral phosphoprotein, and its inhibition prevents replication of viral RNA HCV in all HCV genotypes [61, 79, 82].

The most common side effects of sofosbuvir include: nasopharyngitis, insomnia, depression, headaches, shortness of breath, coughing, constipation, nausea, alopecia, itching, joint and muscle pains, fever, fatigue and irritability [100].

Little is known regarding the use of sofosbuvir in pregnant women. The outcomes of fewer than 300 pregnancies are mentioned in the product characteristics reports of the European Medical Agency, but no data about those outcomes are available in the Pubmed database. In studies conducted on animals (rats and rabbits), sofosbuvir metabolites crossed the placenta and entered the milk of lactating animals. However, this process did not appear to significantly affect the viability or the development of embryos or fetuses. The FDA classified sofosbuvir in Pregnancy Category B when used alone or with ledipasvir, and in Pregnancy Category X when used in combination with Ribavirin [101].

Hepatitis B virus (HBV) polymerase and human immunodeficiency virus (HIV) reverse transcriptase are structurally related. However, the HBV enzyme has a protein priming activity absent in the HIV enzyme. Approved nucleoside/nucleotide inhibitors of the HBV polymerase include lamivudine, adefovir, entecavir and tenofovir. Although most of them target DNA elongation, guanosine and adenosine analogs (e.g. entecavir and tenofovir, respectively) also impair protein priming [70].

Entecavir is a guanosine analogue and it inhibits HBV polymerase. It is phosphorylated to the active form of triphosphate (TP). By competing with the natural substrate deoxyganosine triphosphate, entecavir-TP inhibits three viral polymerase activities: DNA replication, reverse transcription of negative DNA strand and synthesis of positive DNA strand [63].

There were 10 cases of exposure to entecavir (9 in the first trimester and 1 in the second trimester) in combination with other antiretroviral drugs. There were no congenital malformations [12]. It is not known whether the entecavir penetrates into human milk. Danger to children cannot be excluded. Breastfeeding should be discontinued during entecavir treatment [8].

The most common side effects caused by entecavir are headache, fatigue, dizziness and nausea. Song JH et al. presented a case of peripheral neuropathy, which probably occurred after treatment with entecavir in a patient with hepatitis B. The possibility of this side effect should be carefully considered when the patient is taking a high dose of entecavir for an extended period of time or when the patient has risk factors for neuropathy development at the time of initiation of entecavir treatment [98].

The NS3/4A hepatitis C virus (HCV) protease is an important target for antiviral therapy. Several NS3/4A protease inhibitors are currently used to treat chronic hepatitis C, and others are under clinical development. The names of non-structural protein 3/4A inhibitors end with "previr". Inhibition of protease activity may block RNA replication. Telaprevir and boceprevir are two first-generation oral HCV NS3/4A protease inhibitors. The role of the NS3/4A HCV protein is to form HCV proteins after the translation process. Additionally, NS3/4A protease causes the Interferon-β Promotor Stimulator-1 (IPS-1) to split. This causes IFN type 1 activation. Inhibiting the NS3/4A protease not only disrupts the life cycle of the virus, but also restores the congenital immune response. Paritaprevir (PRV) and asunaprevir (ASV) also inhibit HCV NS3/4A. It is not known whether asunaprevir is excreted in human milk [6, 55, 57].

Influenza is a major health problem worldwide. Both seasonal influenza and pandemics have a significant impact on the health and economy of countries. Influenza virus is a single-stranded RNA (ssRNA) virus belonging to the Orthomyxoviridae family. There are 3 major types of influenza virus: types A, B and C, of which types A and B are responsible for most of the infections globally observed in humans [86].

Influenza virions have three surface proteins, the hemagglutinin (HA), neuraminidase (NA), and the Matrix-2 (M2) protein. There are two major classes of antivirals for the treatment and prevention of influenza: the M2 protein inhibitors and the NA inhibitors (NAIs). M2 protein inhibitor: rimantadine and amantadine act only on influenza A viruses, whereas influenza A and B viruses are susceptible to NA inhibitors: oseltamivir and zanamivir [69].

HA binds to the terminal sial acids at the cellular receptors, after which the virus is endocytised. After replication, the NA catalyses the cut-off of the sialic acid residues from the glycoproteins and glycolipids of the external part of the host cell membrane and from the newly formed viral particles. Any disturbance to this process during the use of neuraminidase inhibitors results in the binding of haemagglutinin to sialic acid, which leads to the formation of cellular-virus aggregates. In such cases, the release of progeny virions from the surface of the membrane is hindered [53, 62].

The most common side effects caused by oseltamivir are: bronchitis, herpes, upper respiratory infections, headache, insomnia, coughing, sore throat, nausea, vomiting, conjunctivitis, and otitis media [105].

In a report from 2009, Tanaka et al. summarized the safety of neuraminidase inhibitors in pregnant and breastfeeding women. The data, which came from two Japanese teratogen information services, involved 90 pregnant women exposed during the 1st trimester to therapeutic doses of oseltamivir (75 mg twice a day for up to 5 days). The outcomes of the pregnancies were three spontaneous abortions, one elective abortion, four preterm births, seven infants with low birth weight, and one major malformation (ventricular septa-defect) [106].

Data on breastfed children receiving oseltamivir and the secretion of oseltamivir into breast milk are very limited. Limited data indicate that oseltamivir and the active metabolite were detected in breast milk, but their concentrations were so low that the dose in a breastfed infant would be sub-therapeutic. Taking into account the above information oseltamivir may be considered if there are significant potential benefits for the breastfeeding mother [105].

The M2 protein – ion channel protein is an integral membrane protein that forms tetramers in the lipid envelope of the virus. It has a trans-membrane domain and a cytoplasmic amphipatic helix. The amino acids His37 and Trp41, located in the domain building the ion channel, are important elements for the transport of protons. Trp41 has a Ph close to neutral and creates a gate that closes the channel. This channel opens at a low pH due to TM information changes. Lowering the pH results in His37 protonation, which increases the flow of protons through the ion channel. Then, the interior of the virion becomes acidic. This allows the release of RNA into the cytoplasm and initiation of replication. Therapy using M2 protein inhibitors stops this process [71]. The most common side effects caused by rimantadine are: insomnia, nervousness, dizziness, headaches, fatigue, nausea, vomiting, anorexia, abdominal pain, dry mouth, and weakness. The drug should not be used during pregnancy, nor should the drug be used during breastfeeding [5].

Table 3 shows adverse reactions of the blood and lymphatic system caused by antiviral drugs, occurring at a frequency equal to or greater than 1:100.

The first cases of AIDS were reported in the United States 37 years ago. Since then, >77 million people have been infected worldwide, resulting in over 35 million deaths. Currently, there are 36.9 million people living with HIV. Every year, 1.8 million new infections and nearly 1 million AIDS-related deaths occur [94].

Infections with the human immunodeficiency virus (HIV) are typically treated with drug combinations consisting of at least three different antiretroviral drugs. Highly active antiretroviral therapy (HAART) includes: HIV protease inhibitors (PIs), non-nucleoside and nucleoside reverse transcriptase inhibitors (NNRTIs and NRTIs), integrase strand transfer inhibitors (INSTIs) and entry inhibitors: fusion inhibitors (FIs) and CCR5 antagonists. Currently, the following combinations are preferred for use: two NRTIs and one NNRTI or two NRTIs and one PI. The choice of a treatment regimen for a given individual is based on: expected side effects, convenience, comorbidities, interactions with concomitant medications and genotypic drug resistance testing [113].

Efavirenz (EFV), etravirine (ETR), nevirapine (NVP) and rilpivirine (RPV) are medicinal substances which are included in the NNRTI group. All of these are registered by the Food and Drug Administration (FDA), and all except for delavirdine (DLV) have been approved by the European Medicines Agency (EMA). NNRTIs drugs prevent HIV-1 replication by noncompetitively inhibiting reverse transcriptase (RT) [113]. The mechanism is based on binding the inhibitor at the allosteric side, followed by the three-dimensional shape of the active site necessary for transcription of the viral RNA changes and inhibits the action of the enzyme [75]. This group is not active against HIV-1 strains in group O, HIV-2 or animal retroviruses [113].

Women using this group of drugs during pregnancy should continue with the exception of efavirenz, but it is advisable to use zidovudine during childbirth to prevent infection of the newborn [12]. In developed countries breastfeeding by HIV carriers woman is not recommended, whereas in developing countries breastfeeding occurs despite the risk, as there is no access to inexpensive mother's milk substitutes [71].

The next group of drugs used in HIV infections is NRTI. This group includes: abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir (TFV) and zidovudine (AZT). All

Table 3. Adverse reactions of the blood and lymphatic system caused by antiviral drugs, occurring at a frequency equal to or greater than 1:100 [3, 6, 8, 14, 17, 20, 22, 24, 30, 31, 32, 34, 36, 37, 38, 41, 43, 48, 50, 51, 65, 76, 84, 87, 89, 95, 100, 103, 104, 105, 108, 109, 110, 115, 117, 119, 120, 122, 132, 133]

Interferon alfa	**leukopenia, thrombocytopenia, anemia**
Antimetabolites (polymerase inhibitors)	
ganciclovir	neutropenia, anemia, thrombocytopenia, leukopenia, pancytopenia
valganciclovir	neutropenia, anemia, thrombocytopenia, leukopenia, pancytopenia
cidofovir	neutropenia
Another antimetabolities	
ribavirin	anemia, neutropenia, thrombocytopenia, lymphadenopathy, lymphopenia
NS5B polymerase inhibitors	
sofosbuvir	decrease in haemoglobin concentration, anemia
NS3 protease inhibitors	
asunaprevir	anemia, thrombocytopenia
Neuraminidase inhibitors (NAIs)	
peramivir	decrease in neutrophils count
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
zidovudine	anemia, neutropenia and leukopenia
emtricitabine	neutropenia
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
nevirapine	granulocytopenia
etravirine	anemia, thrombocytopenia
rilpivirine	decrease in leukocyte count, decrease in haemoglobin concentration, decrease in platelet count
HIV protease inhibitors	
ritonavir	decrease in white blood cells count, decrease in haemoglobin concentration, decrease in neutrophils count, increase in eosinophils count, thrombocytopenia
saquinavir	decrease in platelet count, anaemia, decrease in haemoglobin concentration, decrease in lymphocyte count, decrease in leukocyte count
indinavir	increase in mean corpuscular volume (MCV), decrease in neutrophils count
Entry inhibitors; CCR5 inhibitor	
maraviroc	anemia
enfuvirtide	lymphadenopathy
Integrase strand transfer inhibitors (INSTIs)	
raltegravir	atypical lymphocytes

medical substances from this group work in a similar way to AZT. The substance administered to the patient must undergo three phosphorylation reactions, and after these processes one of NRTI acts as an alternative substrate/competitive inhibitor with respect to the natural substrates (deoxythymidine triphosphate Dttp, deoxycytidine triphosphate Dctp, deoxyadenosine triphosphate Datp, deoxyguanosine triphosphate Dgtp) in the RT reaction [27].

Oral use of zidovudine in the perinatal period is well tolerated. It provides a 38% reduction in early, vertical HIV-1 infection despite breastfeeding [23]. HIV-positive women are advised not to breastfeed to avoid mother-to-child transmission of HIV [16].

Tenofovir (TFV) and adefovir (ADV) belong to nucleotide reverse transcriptase inhibitors (NtRTIs) [116].

HIV-1 protease is a 99 amino acid aspartyl protease which functions as a homodimer with only one active site [13]. HIV-1 protease cleaves the viral encoded Gag/Pol polyproteins to generate the structural proteins required for virion formation and enzymes required for viral replication [59]. PIs inhibit HIV-1 protease and prevent the cleavage of the precursor polyprotein, which is required for the formation of the mature viral proteins needed for the infectivity of the progeny virions. PIs include: atazanavir (ATV), darunavir (DRV), fosamprenavir (F-APV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), tipranavir (TPV) [27].

A retrospective review was carried out in six centres in the United States and Puerto Rico to assess the effect of the use of protease inhibitors during pregnancy on maternal and neonatal safety. 89 women took part in the study. In neonates, no other adverse effects were observed except those previously noticed in diseased mothers. The most common side effect was anaemia (12%). Protease inhibitors seemed to be generally safe for mothers and infants [74].

Enfuvirtide is a fusion inhibitor, which interferes with penetration of HIV-1 in the cells. Enfuvirtide exhibits potent and selective inhibition of membrane of viral and cells [56]. Enfuvirtide blocks HIV GP41 fusion to the extracellular membrane of host cells [28]. Marawiroc is a CCR5 antagonist. Before fusion of the HIV viral envelope and host cell membrane can occur, an HIV glycoprotein complex consisting of glycoproteins gp41 and gp120 must bind with the CD4 receptor on the membrane of the host cell. This binding causes conformational changes in gp120 that expose coreceptor binding sites. These sites bind to coreceptor CCR5 or CXCR4 on the membrane of the host cell, an event that initiates steps that culminate in the fusion of the HIV envelope with the host cell membrane and entry of viral contents into the host cell. Maraviroc binds to and changes the shape of coreceptor CCR5 so that it is not recognized by the gp120 coreceptor binding sites [129].

Jeantils V et al. studied seven cases in France that suggest the enfuvirtide is safe. All infants were without abnormalities [52].

The last group comprises INSTIs. After the reverse transcription is complete, integrase (IN) assembles on the viral DNA forming the preintegration complex (PIC). IN processes the viral DNA ends creating a free 3' OH, which is the nucleophile for the strand transfer reaction in which IN covalently links the viral DNA with the host DNA. INSTIs block the process of integration by binding free 3' OH. HIV-1 DNA is subject to metabolism by several cellular processes which can degrade the DNA or recombine and repair the viral ends forming circles. By means of these cellular processes the metabolism of the viral DNA results in an irreversible block to the HIV-1 infection process [42]. Raltegravir, elvitegravir and dolutegravir present the group described above [102].

One of the largest studies conducted by Karolinska University Hospital did not indicate that dolutegravir had teratogenic effects [10]. No published information is available on the use of raltegravir, elvitegravir, or dolutegravir during breastfeeding.

Apo3G, an intrinsic human protein capable of restricting HIV-1, is a promising candidate for future anti-HIV therapeutics. Apo3G is a powerful DNA-mutating enzyme thath blocks the replication of HIV-1 virus in the abscence of its viral infectivity factor (vif) protein [96]. The innate immune system is a key line of defense against human immunodeficiency virus type 1 (HIV-1), reducing viral replication and protecting neighboring cells from infection. Key in this battle between host and virus are cytosolic host cell proteins with antiretroviral activities, termed restriction factors. The apolipoprotein B (apo B) messenger RNA (mRNA)-editing, catalytic polypeptide-like 3 (APOBEC3) family of proteins are known to be potent restriction factors and to counteract infection by HIV-1. While the seven APOBEC3 proteins have varying levels of potency, in in vitro tissue culture APOBEC3G (A3G) exhibits the highest activity against HIV-1 that lacks the vif gene. APOBEC3G can counteract HIV infection in at least two ways: by inducing lethal mutations on the viral cDNA; and by blocking steps in reverse transcription and viral integration into the host genome. As a protein, APOBEC3G has the advantage that it can be genetically encoded, while small molecules cannot [44].

It should be noted that some drugs have been withdrawn by the FDA from the treatment antiviral scheme, mainly due to severe adverse effects. Boceprevir, telaprevir, fomivirsen, telbivudine, zalcitabine, amprenavir, vidarabine, idoxuridine and simeprevir are no longer used in therapy [112].

Table 4 shows the Food and Drug Administration (FDA) classification of medicines used during pregnancy and recommendations for breastfeeding. It is worth noting SMV combined therapy with RBV and peginterferon alpha, because such a therapeutic scheme is classified in category X.

CONCLUCIONS

The adverse effects that occur during antiviral therapy remain a significant problem in patients with viral diseases, which affect their quality of life. Individual treatment is crucial for therapy and determining effective methods for monitoring adverse reactions. Based on scientific data, physicians should prevent their occurrence. Monitoring specific diagnostic parameters is important to improve the results of treatment. When using IFN alpha, blood morphology should be ordered and cardiac function should be monitored. The use of polymerase inhibitors may be associated with the appearance of respiratory inflammations and eye inflammations. To identify the etiology of the infection, swabs must be taken for microbiological examination and a biochem-

ical study must be commissioned with the determination of C-reactive protein (CRP) and procalcitonin. When the patient has symptoms of anaemia, blood morphology should be ordered immediately. It is worth noting the complications related to the thyroid gland, which are due to the inclusion of ribavirin in therapy. The concentration of TSH, fT4 should be monitored in the patient and in case of abnormal values, the thyroid function should be immediately investigated by ultrasonography. In patients with suspected cardiac dysfunction, clinicians may have ECG and UKG examined, and in the event of symptoms of cardiovascular failure, appropriate drugs may be necessary. When using some nucleotide analogues and pyrophosphate analogues, kidney function should be monitored. It is advisable to have a general urinalysis or 24-hour urine collection. Therapy with NS5B polymerase inhibitors requires control of blood cell parameters. Protease inhibitors used to treat HCV infections cause many adverse effects. These may include: hypothyroidism, problems with the visual and hearing organs requiring the ophthalmologic or laryngologic intervention, as well as skin or cardiovascular diseases. Boceprevir can cause erectile dysfunction in men, which may require pharmacological intervention to improve the quality of life. Neuraminidase inhibitors used in therapy or prophylaxis of influenza have fewer adverse effects than M2 protein inhibitors. Most frequently these cause nausea and vomiting. It is worth evaluating the patient's nutritional status by performing anthropometric tests, e.g. BMI. The assessment of albumin concentrations may also be crucial. Treatment with M2 protein inhibitors, special attention should be paid to the assessment of the patient's mental condition. The use of drugs in HIV therapy is associated with a wide spectrum of adverse effects. When using HAART therapy, the following should be monitored: blood count, lipid profile, fasting blood glucose level or random (casual) blood glucose level with the symptoms of diabetes and also moreover parameters such as: bilirubin, ALAT, ASPAT, GGTP and uric acid. When taking NNRTI into account, the acid-base balance of the patient should be assessed by examining the pH of blood, the concentration of inorganic phosphorus, bicarbonates, and the value of the anion gap should be determined.

The long-term benefits of antiviral therapy are associated with adverse reactions in various body systems. The clinicians should limit them by an individual, patient-specific treatment scheme. Physicians should pay special attention to the use of antiviral drugs in pregnant and breast-feeding women. Clinical trials should be continued to increase knowledge about the adverse effects of antivirals.

Table 4. Effect of antivirals in pregnancy and Food and Drug Administration Pregnancy Categories [2, 3, 6, 8, 12, 14, 17, 20, 22, 24, 30, 31, 32, 34, 36, 37, 38, 39, 41, 43, 48, 50, 51, 65, 76, 84, 87, 88, 89, 95, 100, 103, 104, 105, 108, 109, 110, 115, 117, 119, 120, 121, 122, 132, 133].

Names of substance	FDA pregnancy categories	Breastfeeding recommendation
Interferon alfa	C	Limited Human Data – Probably Compatible
Ganciclovir	C	No Human Data – Potential Toxicity
Valganciclovir	C	Contraindicated
Aciclovir	B	Compatible
Valacyclovir	B	Compatible
Famciclovir	B	No Human Data – Potential Toxicity
Penciclovir	B	No Human Data – Probably Compatible
Cidofovir	C	Contraindicated
Brivudine	NA	No Human Data – Potential Toxicity
Trifluridine	C	No Human Data – Potential Toxicity
Ribavirin	X	No Human Data – Potential Toxicity
Letermovir	NA	No Human Data – Potential Toxicity
Imiquimod	C	No Human Data – Potential Toxicity
Foscarnet	C	No Human Data – Potential Toxicity
Daclatasvir	NA	No Human Data – Potential Toxicity
Ledipasvir	NA	No Human Data – Potential Toxicity
Ombitasvir	B	No Human Data – Potential Toxicity
Elbasvir	NA	No Human Data
Velpatasvir	NA	No Human Data
Sofosbuvir	B	No Human Data – Potential Toxicity

Names of substance	FDA pregnancy categories	Breastfeeding recommendation
Dasabuvir	B	No Human Data – Potential Toxicity
Entecavir	C	Contraindicated
Asunaprevir	NA	No Human Data – Potential Toxicity
Paritaprevir	B	No Human Data – Potential Toxicity
Grazoprevir	B	No Human Data
Oseltamivir	C	Compatible
Zanamivir	C	No Human Data – Probably Compatible
Peramivir	NA	No Human Data – Potential Toxicity
Amantadine	C	Contraindicated
Rimantadine	C	No Human Data – Potential Toxicity
Zidovudine	C	Contraindicated
Didanosine	B	Contraindicated
Stauvudine	C	Contraindicated
Lamivudine	C	Contraindicated
Abacavir	C	Contraindicated
Adefovir	C	Contraindicated
Tenofovir	B	Contraindicated
Emtricitabine	B	Contraindicated
Nevirapine	C	Contraindicated
Efavirenz	C	Contraindicated
Etravirine	B	Contraindicated
Rilipivirine	B	Contraindicated
Saquinavir	B	Contraindicated
Ritonavir	B	Contraindicated
Indinavir	C	Contraindicated
Nelfinavir	B	Contraindicated
Lopinavir	C	Contraindicated
Tipranavir	C	Contraindicated
Fosamprenavir	C	Contraindicated
Atazanavir	B	Contraindicated
Darunavir	B	Contraindicated
Enfuvirtide	B	Contraindicated
Maraviroc	B	Contraindicated
Raltegravir	C	Contraindicated
Elvitegravir	B	Contraindicated
Dolutegravir	B	No Human Data – Potential Toxicity

Meaning of symbols: NA: Not available, B category – No risk in other studies: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

C category – Risk not ruled out: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

X category – Contraindicated in pregnancy: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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