

# Additional Cardiovascular Risk in Patients Living with HIV Associated with Antiretroviral Therapy

## Kardiovaskulární riziko jako nežádoucí účinek antiretrovirové léčby u pacientů s HIV

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### Abstract

HIV/AIDS is one of the biggest global health issues. To reduce the risk of long-term complication and prolong survival, HIV/AIDS infection requires continuous medical care with combined antiretroviral therapy (ART) and patient self-management education. Recent epidemiological data clearly demonstrated that the prevalence of CVDs among people living with HIV (PLWH) is increasing all over the world and is considered the most common cause of cardiovascular morbidity and mortality in these individuals. Despite therapeutic benefits mentioned in this review article, long term exposure to ART has been associated with metabolic complications such as lipodystrophy, insulin resistance, central adiposity, weight gain, pulmonary hypertension, dyslipidemia resulting in premature CVD manifestation.

**Key words:** antiretroviral drugs – cardiovascular risk – people living with HIV

### Abstrakt

HIV/AIDS je jedním z největších celosvětových zdravotních problémů. Ke snížení rizika dlouhodobých komplikací a prodloužení přežití vyžaduje infekce HIV/AIDS nepřetržitou lékařskou péči s kombinovanou antiretrovirovou léčbou a edukací pacientů v oblasti self-managementu. Nedávné epidemiologické údaje jasně prokázaly, že prevalence KVO u osob žijících s HIV celosvětově stoupá a u těchto osob je považována za nejčastější příčinu kardiovaskulární morbidity a mortality. Navzdory terapeutickým přínosům uvedeným v tomto přehledovém článku je dlouhodobá expozice antiretrovirové léčbě spojena s metabolickými komplikacemi, jako je lipodystrofie, inzulinová rezistence, centrální adipozita, přírůstek hmotnosti, plicní hypertenze a dyslipidemie vedoucí k předčasné manifestaci KVO.

**Klíčová slova:** antiretrovirové léky – kardiovaskulární riziko – pacienti s HIV

### Introduction

Human immunodeficiency virus (HIV) infection is a public health issue. In 2019, more than 38.0 million (31.6–44.6 million) people were living with HIV, and more than 1.7 million (1.2–2.2 million) people acquired HIV. Nearly 61% of the people newly infected with HIV live in sub-Saharan Africa. Between 2010 and 2019, the epidemic also continued to grow in eastern Europe and central Asia, with the number of people acquiring HIV rising by 72% in the Middle East and North Africa by (22%) and in Latin America by (21%).

The infection with the human immunodeficiency virus (HIV) is not only associated with a dysfunction of the immune

system but nearly every organ system can be involved. Opportunistic infections and weight loss were mostly responsible for significantly high morbidity and high mortality of PLWH. To reduce the risk of long-term complication, HIV/AIDS infection requires continuous medical care and patient self-management education. In 2019 the European AIDS Clinical Society (EACS), recommended antiretroviral therapy (ART) in all adults living with HIV, irrespective of CD4 counts. Immediate treatment is recommended when CD4 count is 350 cells/ $\mu$ L, age > 50 years, pregnancy, presence of severe or prolonged symptoms, and acute symptomatic infection [1–5]. Even though the success of combination

ART in the treatment has afforded marked gains in life expectancy for people with human immunodeficiency, the long term side effects may contribute to glucose and lipid metabolism disorders and premature cardiovascular disease (CVD) [1,6–8]. Mathematical models estimate an increase in the incidence of CVD in patients living with HIV (PLWH) by 50% between 2015 and 2030 [9,10]. However, CVD risk assessment remains challenging. Since the conventional stratification models such as Framingham Risk Score and 2018 ACC/AHA guidelines risk score have shown to underestimate the risk in PLWH, the European Society of Cardiology/European Atherosclerosis (ESC/EAS) 2021 guidelines (SCORE2, SCORE2-OP) seem to be more accurate. These guidelines acknowledge the increased risk of PLWH to develop lower extremity and coronary artery disease particularly for those with low CD<sub>4</sub><sup>+</sup> count (< 200 cells/mm<sup>3</sup>) [4]. However, the prevalence of CVD among PLWH is increasing all over the world and incidence of cardiovascular events is nearly 2- fold higher compared with uninfected counterparts [12,13]. Overall, there is a lack of comprehensive and contemporary studies assessing cardiovascular risk scores in PLWH with adequate follow-up recommendations [4,14]. Both HIV and antiretroviral therapy (ART) effect risk through multiple mechanisms [12,15,16]. The HIV-induced chronic inflammation together with the ART side effects cause endothelial injury, hypercoagulation, insulin resistance, dyslipidemia, abnormal fat distribution, obesity, and diabetes mellitus type 2 [12,17,19–21]. The low-grade inflammation accelerates atherogenesis namely by oxidative stress, endothelial injury and recruitment of circulating monocytes and lymphocytes. Atherosclerotic plaques in PLWH infection are more likely to be non-calcified and more prone to rupture. Before antiretroviral therapy is initiated, the dyslipidemia in PLWH is characterized by elevated triglycerides (TG) and apoprotein B (apoB) low levels of total cholesterol (TC), LDL cholesterol(LDL-C) and HDL cholesterol (HDL-C) [17–19]. After introduction of highly active antiretroviral therapy (HAART) concentrations of TC, LDL-C increase accompanied with further elevation of TG and apoB. Moreover, ART is associated with insulin resistance and its consequences (hyperglycemia-diabetes mellitus, dyslipidemia, and hypertension).

### Impact of Specific HIV Therapies on Cardiovascular Risks

The pathophysiology of the association between HIV and CVD, is important to recognise the magnitude of CVD risk in the HIV+/ART. The pathogenesis of atherosclerosis in HIV infection resembles that in noninfected individuals [4], however association between the immunological status and cardiovascular diseases have not yet been fully elucidated. First manifestation of CVD in PLWH differs worldwide. Potential reasons for this disparity include exposition to different infectious diseases, types of ART, disparities in cardiovascular preventive care, and poor compliance (e.g., smoking ces-

sation, dietary habits, physical activity, and general adherence to medication) [7]. The dramatic success of HAART has significantly improved overall survival and increased time of AIDS free living for patients infected with HIV but combination antiretroviral therapy (cART) also represents the leading cause of cardiovascular disease [4,20]. An increased cardiovascular (CV) event rate may not be apparent until after years of treatment depending on the ART regimen.

### Inflammatory biomarkers and procoagulant state in HIV patients

Chronic inflammation and atherosclerosis in HIV patients appear to be interconnected through several pathways [22,23]. Upon viral infection causing endothelial activation and dysfunction, the levels of pro-inflammatory cytokines (interleukin-1/IL-1, interleukin-6/IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), are elevated. The signal cascade leads to oxidative stress, and endothelial damage [1,22,24–26]. Atherosclerosis in HIV-infected patients present unique histological features of coronary artery disease, including a rapid progression of diffuse circumferential arterial lesions and endoluminal protrusions [27,28]. Circulating levels of immunokines and cytokines vary widely with different antiretroviral regimens and their concentrations are also essential in the early diagnosis of disease. In addition, reports of acute coronary thrombotic events in patients with HIV have been repeatedly documented. Schecter et al demonstrated that treatment of human arterial smooth muscle cells with HIV gp120 induces activity of the tissue factor (TF) [31].

### Antiretroviral Drugs

The key goals of antiretroviral therapy include prolonging survival, achieving and maintaining the suppression viremia in plasma. Although monotherapy of antiretroviral drugs showed a reduction in viral load, delayed disease progression and prolonged survival, the use of a single agent did not provide sustained viral suppression. The use of combination therapy consisting of a PI with 2-NRTI resulted in rapid reduction of HIV RNA. Using a combination of different agents targeting different steps within the HIV life cycle provides either synergistic or additive antiviral effect, thus enhancing the efficiency in which viral replication is suppressed [15,32]. The reduction of (HIV)-related deaths by introduction of (AR) has been challenged by increasing incidence of non-HIV related mortality that is mainly attributed to cardiovascular diseases [33,34]. Antiretroviral drugs act by interfering with vital viral replication processes and classified according to the step by step they inhibit in the viral life cycle [35]. There are currently six classes of antiretroviral drug: nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), integrase inhibitors, protease inhibitors, CCR5-inhibitors and fusion inhibitors [1,36,37]. HAART is typically a mixture of a minimum of three drugs and usually consists of two NRTIs with

either one integrase inhibitor (preferred), one non-nucleoside reverse transcriptase inhibitor or one protease inhibitor. In this article, 4 ART drug groups that are most commonly used in PLWH will be discussed.

### Reverse Transcription Inhibitors (RTI)

RTIs inhibit transcription of viral RNA into proviral DNA.

#### Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

NRTIs were the first class of drugs to be approved by the FDA and are administered as prodrugs, which require host cell entry and phosphorylation [38]. Most HAART regimens involve nucleoside analogues that inhibit the reverse transcriptase of the virus. Commercially available NRTIs include abacavir, emtricitabine, didanosine, lamivudine, stavudine, zidovudine and tenofovir. NRTI class has been historically associated with mitochondrial toxicity.

**Abacavir (ABC)** has been associated with vascular inflammation and atherosclerotic plaque progression and destabilization. A systematic review and meta-analysis of 17 studies found overall relative risks of 1.54 (95% CI 1.37–1.73) for acute myocardial infarction (MI) and 1.61 (95% CI 1.48–1.75) for all CVD from recent exposure to abacavir [39]. Some cohort data have reported an association between current or recent abacavir use and coronary heart disease (CHD) but not stroke [40,41]. There is some evidence that ABC causes endothelial nitric oxide synthase (eNOS) downregulation and superoxide anion production in human endothelial cells, both of which can lead to vascular dysfunction and leukocyte accumulation. In addition, ABC-treated patients exhibit elevated levels of the inflammatory markers C-reactive protein (CRP) and interleukin (IL-6) [42–44]. ABC has been in clinical use for the treatment of HIV since the late 1990s and it's unlikely to be involved in drug interactions via CYP3A4. Furthermore, ABC is associated with neither metabolic disorders (dyslipidemia, diabetes) nor lipodystrophy [45].

**Didanosine (DDI)** may have significant adverse effects in longer-term use. Judith et al. studied comparisons of body composition and metabolic changes among antiretroviral-naïve patients who were randomly assigned to NRTIs didanosine and stavudine (DDI + D4T) vs. abacavir and lamivudine (ABC + 3TC). For the mid-arm skinfold fat area, there was a significant decrease in regional fat for patients assigned to the DDI + D4T arm ( $P < 0.01$ ). The DDI + D4T therapy further showed an early and sustained increase of insulin resistance, LDL-cholesterol and triglycerides and decrease of HDL-cholesterol (83). It was also reported that the exposure to DDI was associated with increased relative rate of MI (RR = 1.53 (95% CI 1.10–2.13,  $P < 0.01$ ).

**Lamivudine (3TC)** (older NRTI) has no significant effect on plasma lipids as indicated by some studies (87). Crane et al. performed a longitudinal observation cohort study between 3TC and other NRTIs to assess changes in lipid levels among 2,267 individuals who started their first antiretroviral

regimen. Combination of tenofovir with lamivudine was associated with lower levels of total cholesterol (TC), (LDL-C) and TG, compared with other NRTI pairs in adjusted analyses.

**Tenofovir** (tenofovir alafenamide (TAF) is associated with greater increases in all fasting TC, LDL-C and TG compared with tenofovir disoproxil fumarate (TDF) [46]. In multiple studies [9,47] the tenofovir prodrug tenofovir disoproxil fumarate (TDF) has not been associated with increased risk of CVD [9]. In one randomized study of TAF vs. TDF the cardiovascular safety end points were monitored for 96 weeks, including fasting lipids, proportion eligible for statin therapy, cardiovascular adverse events and estimated 10-year (CVD) risk [9]. No significant differences between groups were noted, except for lower mean estimated 10-year CVD risk in TAF vs TDF (6.1% vs 6.2%,  $P = 0.04$ ) [46]. Both TAF and TDF are essential components of preferred initial HIV regimens because of their efficacy as well as improved tolerability in comparison to older agents. In another trial, up to 328 in treatment-naïve participants were randomized to tenofovir-emtricitabine (TDF/FTC) atazanavir-ritonavir ATV/r, darunavir – ritonavir (DRV/r) and raltegravir (RAL). After 4 weeks on therapy insulin resistance increased rapidly in the TDF/FTC group compared with the others [48].

#### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are allosteric inhibitors of HIV-1 reverse transcriptase and are used in combination regimens with ART agents that target two or more enzymes in the viral life cycle [49]. Combination of (NNRTI) with two (NRTIs) remain among the most commonly prescribed ART regimens worldwide [50]. Long term exposure to NNRTIs results in endothelial oxidative stress and activation of mononuclear cell recruitment into arterial intima [51]. Moreover NNRTIs are associated with increased concentrations of fasting (LDL-C) [49,52,53]. Substituting protease inhibitors (PIs) with NNRTIs for lipid level improvement is thus disputable. A preliminary report [54] from two cross sectional studies describe higher HDL- C levels in patients on NNRTIs compared with patients on PIs, but associated factors such as insulin resistance, physical activity, smoking or alcohol consumption were not taken into account [53,54].

**Efavirenz (EFV)** containing regimens can increase lipid levels (TC, LDL-C) [55,56] and its use was associated with hepatotoxic effects and alterations in body fat composition. Current practice guidelines recommend the use of EFV with two (NRTIs) EFV is commonly co-administered of EFV/3TC/ABC and it was revealed that the addition of EFV enhances production of reactive oxygen species (ROS) [57]. However, two large studies found no association of EFV therapy with myocardial infarction (MI) risk though other CV outcomes were not examined [41,58]. The cross-sectional study in children living with HIV in Addis Abeba, Ethiopia documented that current efavirenz EFV treatment was associated with increased arterial stiffness and intima-media thickness

in common carotid artery (cIMT) and impaired flow-mediated dilation (FMD) compared other NNRTI nevirapine (NVP) or no HAART [59].

**Rilpivirine** (RPV) when used as substitute for NVP was associated with improvement in both TC and LDL-C but may increase concentration of TG even more than NVP [60].

**Doravirine** (DOR) represents an attractive treatment option because of its favorable metabolic profile and neutral effect on body weight. Clinical trials documented in treatment-naïve adults that DOR based regimens have non inferior efficacy on plasma lipids compared with ritonavir-boosted darunavir (both PI) [61,62]. The most recent version of the European AIDS Clinical Society guidelines suggests 2NRTI + DOR as one of the recommended regimens for starting ART.

### Protease Inhibitors (PIs)

The mechanism of action of protease inhibitors (PIs) involves HIV aspartyl protease inhibition resulting in the creation of immature and non-infectious viral particles. Each of the currently available PIs has potent antiretroviral activity when given as a single agent. Among various classes of HAART regimens PIs represent the central component [63,64]. Although PIs have contributed to marked improvements in HIV-related disease progression and mortality, they are associated with metabolic abnormalities namely dyslipidemia, insulin resistance and central obesity [15,17,64]. Numerous studies demonstrated that patients taking PIs have higher blood levels of very-low-density lipoproteins (VLDLs) apo-protein B, TG, TC, LDL-C, insulin, and glucose which is accompanied by lipotrophy and/or trunk fat accumulation. The mechanisms underlying PI associated dyslipidemia have not been elucidated completely, but they appear to involve hepatic overproduction of VLDLs and to a lesser extent their impaired clearance [64,65]. PIs contribute to vascular diseases through series of overlapping pathways that affect the overall inflammatory status as well as the structural integrity of the arterial wall. In their *in vitro* study with cultivated THP-1 monocyte macrophages Dressman et al. demonstrated that PIs induced CD36 scavenger receptor expression thus increasing the intracellular accumulation of cholesteryl ester [66]. PIs have been associated with increased transforming growth factor 1 beta (TGF1 $\beta$ ) leading to myocardial fibrosis, impaired cardiac function left, ventricular hypertrophy and this therapy may thus worsen the outcomes esp. in PLWH with heart failure [67]. A significantly increased CVD risk was documented in two contemporary most frequently used PIs, darunavir (DRV) and atazanavir (ATV) representing a major concern in chronic therapy. The D:A:D group (Data Collection on Adverse Events of Anti-HIV Drugs) demonstrated that ritonavir (RTV) boosted darunavir (DRV) was associated with increased risk of cardiovascular disease (incidence rate ratio 1.59; 95% CI 1.33–1.91) whereas ritonavir (RTV) boosted atazanavir (ATV) was not (1.03; 95% CI 0.90–1.18 [68]. In addition, Chow et al. reported that RTV-boosted ATV treatment was associated with slower atherosclerosis

progression compared to RTV-boosted DRV and integrase inhibitor raltegravir (RAL) potentially due to the protective antioxidant effect of hyperbilirubinemia. Although hyperbilirubinemia may lead to increased rates of treatment discontinuation, it may contribute to a favourable cardiovascular (CV) profile of ATV [25]. The studies reporting the incidence of MI among HIV-infected patients showed that ATV (boosted and unboosted) was not associated with an increased risk of acute MI. In comparison with non-ATV-based regimens, ATV had beneficial effects on (cIMT) with no apparent impact on endothelial function [25,69].

### Integrase Inhibitors (INSTIs)

INSTIs block the strand transfer reaction catalysed by HIV-1 integrase and have been shown to potently inhibit infection with wild-type HIV-1. The first available INSTI was raltegravir (RAL), whereas bicitgravir (BIC) is currently in late-stage clinical trial [25]. INSTIs are often prescribed as a part of first-line treatment. Weight gain and obesity have been observed in all INSTIs, particularly in dolutegravir (DTG) [60,63,70], however, this ART class appears to have less impact on lipid profile. The Surveillance Cohort Long-Term Toxicity Antiretrovirals (SCOLTA) found that switching from a ritonavir-boosted PI-based therapy to INSTIs (elvitegravir EVG or dolutegravir DTG) even lowered TC [17,60,71]. The pathogenesis of weight gain with INSTIs in PLWH is still poorly understood [71]. Brazilian cohort study of 1,794 PLWH who initiated ART showed that clinical obesity was more likely to occur among those who used an INSTI vs. PI or NNRTI [18,70]. INSTI-based regimens have been associated with central and peripheral fat gain both in ART-naïve as well as ART-experienced patients [71,72]. However, data describing the effects of specific INSTIs on body composition are still limited. A small study reported some gains in trunk fat after 96 weeks of (RAL) compared with NNRTI efavirenz (EFV) [73]. Little data exist about direct effect of INSTIs on glucose metabolism. A small, single-arm, open-label study of 30 participants on RAL combined with NRTIs tenofovir/emtricitabine (TDF/FTC) reported no increase in insulin resistance over 104 weeks [48,74]. Another study comparing patients on PIs lopinavir/ritonavir plus RAL to lopinavir/ritonavir plus NRTIs showed no difference in insulin resistance between the arms over 48 weeks [75].

### Fusion Inhibitors

Fusion inhibitors (entry inhibitors) typically used in combination with two NRTIs represent new HIV-antiretroviral class developed in the recent years. Fusion inhibitors bind to viral gp41 and block conformational changes necessary to induce fusion of the viral particle with the host cell. Enfuvirtide (T20) is the first in this class to reach market approval [76–78]. Because of the very unique mechanism of action, T20 remains active against HIV-1 which is resistant to the other 3 classes of antiretroviral medications (NRTIs, NNRTIs, and PIs) and offers alternative options for patients

with multiple resistances to standard antiretroviral drugs, but also safer therapeutic profile. Mitochondrial interactions of these novel drugs have not been fully clarified, however enfuvirtide treatment was not associated with mitochondrial DNA depletion. The Taiwanese longitudinal study (TORO) investigated the effect of T20 on body composition and metabolic parameters over 48 weeks. There was a significant increase in mean body weight +0.99 kg (95% CI 0.54, 1.44) and no change in body weight in the control group. DEXA scans further revealed that patients on T20 had significant increase of truncular fat: +419,4 g (95% CI +71.3, +767.5). On week 48, changes from baseline in glycemia and lipid parameters did not significantly differ between the groups. Barroso et al randomized (T20) vs placebo or integrase inhibitor (RAL) vs placebo to test whether T20 and/or RAL have an early effect on metabolic, mitochondrial, renal, and hepatic toxicity parameters. Neither T20 nor RAL administration showed significant changes in metabolic markers of mitochondrial toxicity [79,84].

### Preventive Measures

Lifestyle modifications are always essential in cardiovascular risk reduction. PLWH should be offered individual consultations regarding dietary recommendations, alcohol consumption (< 10 g/day) and smoking cessation. Patients with hypercholesterolemia should limit saturated fatty acids (high fat meat products, high fat dairy products) and increase intake of fibres. Obese patients should limit their calory intake, avoid sweetened beverages and increase exercise. Mediterranean type of diet containing fish, vegetables and monosaturated fatty acids in olive oil is generally recommended. Regular physical activity represents another essential aspect of lifestyle optimization in PLWH [81,82]. According to Blashill et al. [83] increased physical activity

was associated with improvement of inflammatory and cardiometabolic parameters in these individuals. All identified cardiovascular risk factors in PLWH, namely hyperlipidemia, arterial hypertension, obesity, diabetes mellitus and smoking must be treated in complex with respect to latest preventive guidelines (SCORE2, SCORE2-OP) [11,80]. Regarding pharmacological intervention, most data documenting a direct effect on mortality reduction delivered the statin therapy. Meta-analysis of 7 prospective cohort studies including 35,078 PLWH showed that statin use was associated with a 33% reduction in all-cause mortality (pooled HR = 0.67, 95% CI 0.39–0.96) compared to placebo [31]. As shown in the BEIJRINCK study, adding PCSK9-inhibitor (evolocumab) to a maximum statin therapy was well tolerated and was associated with additional reduction of LDL-cholesterol by 56,9% (95% CI -61.6, -52.3) thus offering highly effective reduction of atherogenic lipid levels in PLWH. Cardiometabolic side effects attributed to specific ART class should always be considered when assessing cardiovascular risk at the beginning of the treatment and re-evaluated on follow-up visits. Presence of asymptomatic atherosclerosis (confirmed by e.g., ankle-brachial index (ABI) or ultrasound of carotid or femoral arteries) should be considered. Optimization of the ART regimen must be therefore done individually. For example, the switch from PIs to INSTIs can significantly lower concentrations of total and LDL-cholesterol on one hand but may lead to weight gain and insulin resistance on the other. Nevertheless, detailed guidelines regarding ART associated cardiovascular risk that would reflect latest knowledge of the new therapy regimens are still missing.

### Conclusion

Despite suppression of viremia and prolonging survival in PLWH achieved by ART regimens there has become and in-

Table | ART classes representatives and their side effects

ART class	representatives	side effects
NRTIs	didanosine	increased mitochondrial toxicity, endothelial cell death, lipodystrophy, insulin resistance, central adiposity;
	lamivudine	increased LDL-C and triglycerides and decrease of HDL-C
	tenofovir	endothelial oxidative stress and activation of mononuclear cell recruitment, increased concentrations of fasting TC and LDL-C
NNRTIs	rilpivirine	increased intima-media thickness and arterial stiffness
	efavirenz	
	doravirine	
protease inhibitors	ritonavir	dyslipidemia, insulin resistance, central obesity, lipoatrophy, trunk fat accumulation, hepatic VLDL overproduction, increased intracellular accumulation of cholesteryl ester
	darunavir	
	atazanavir	
integrase inhibitors	raltegravir	obesity
fusion inhibitors	enfuvirtide	mitochondrial DNA depletion and mitochondrial toxicity weight gain

DOR – doravirine EFV – efavirenz iIMT – increased Intima-Media Thickness NNRTIs – Non-Nucleoside Reverse Transcriptase Inhibitors RAL – raltegravir TC – Total

creased concern about higher CV risk in these individuals. Atherosclerosis acceleration in PLWH is partly attributed to the HIV-infection itself, however use of ART may substantially contribute to pathogenesis of atherosclerosis and high cardiovascular risk, namely by vascular inflammation, hyperlipidemia, weight gain and insulin resistance. CV risk should be assessed already at the initiation of the ART and on follow-up visits and all risk factors must be treated in complex. Moreover, optimization of the ART regimen should become essential part of cardiovascular prevention in PLWH.

### Podpořeno COOP37

### Literature

- Antony I, Kannichamy V, Banerjee A et al. An Outlook on the Impact of HIV Infection and Highly Active Antiretroviral Therapy on the Cardiovascular System – A Review. *Cureus* 2020; 12(11): e11539. Dostupné z DOI: <<http://dx.doi.org/10.7759/cureus.11539>>.
- Eholié SP, Badje A, Kouame GM et al. Antiretroviral treatment regardless of CD4 count : the universal answer to a contextual question. *AIDS Res Ther* 2016; 13: 27. Dostupné z DOI: <<http://dx.doi.org/10.1186/s12981-016-0111-1>>.
- Perkins M V, Joseph SB, Dittmer DP et al. Cardiovascular Disease and Thrombosis in HIV Infection. *Arterioscler Thromb Vasc Biol* 2023; 43(2): 175–191. Dostupné z DOI: <<https://doi.org/10.1161/ATVBAHA.122.318232>>
- Fragkou PC, Moschopoulos CD, Dimopoulou D et al. Cardiovascular disease and risk assessment in people living with HIV: Current practices and novel perspectives. *Hellenic J Cardiol* 2023; 71: 42–54. Dostupné z DOI: <<https://doi.org/10.1016/j.hjc.2022.12.013>>.
- Lu WL, Lee YT, Sheu GT. Metabolic syndrome prevalence and cardiovascular risk assessment in hiv-positive men with and without antiretroviral therapy. *Medicina (Kaunas)* 2021; 57(6): 578. Dostupné z DOI: <<https://doi.org/10.3390/medicina57060578>>.
- Shitole SG, Lazar JM, Taub CC et al. Human Immunodeficiency Virus and Cardiac End-Organ Damage in Women : Findings From an Echocardiographic Study Across the United States. *Clin Infect Dis* 2023; 76(2): 210–219. Dostupné z DOI: <<https://doi.org/10.1093/cid/ciac795>>.
- Ozemek C, Erlanson KM, Jankowski CM et al. Physical activity and exercise to improve cardiovascular health for adults living with HIV. *Prog Cardiovasc Dis* 2020; 63(2):178–183. Dostupné z DOI: <<https://doi.org/10.1016/j.pcad.2020.01.005>>.
- Alonso A, Barnes AE, Guest JL et al. HIV Infection and Incidence of Cardiovascular Diseases : An Analysis of a Large Healthcare Database. *J Am Heart Assoc* 2019; 8(14): e012241. Dostupné z DOI: <<http://dx.doi.org/10.1161/JAHA.119.012241>>.
- Huhn GD, Shamblaw DJ, Baril J et al. Atherosclerotic Cardiovascular Disease Risk Profile of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate. *Open Forum Infect Dis* 2019; 7(1): ofz472. Dostupné z DOI: <<http://dx.doi.org/10.1093/ofid/ofz472>> .
- Mariana ADB, Busca DC, Mican R et al. Change in metabolic parameters after switching from triple regimens with tenofovir alafenamide to dolutegravir-based dual therapy . Bi-lipid study. *HIV Med* 2023; 24(5): 558–567. Dostupné z DOI: <<http://dx.doi.org/10.1111/hiv.13432>> .
- Eapc PC, Crawford C, Ireland N et al. [ESC National Cardiac Societies; ESC Scientific Document Group]. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42(34): 3227–3337. Dostupné z DOI: <<http://dx.doi.org/10.1093/eurheartj/ehab484>>. Erratum in *Corrigendum to: 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC)*. *Eur Heart J* 2022; 43(42): 4468. Dostupné z DOI: <<http://dx.doi.org/10.1093/eurheartj/ehac458>>.
- Pyarali F, Iordanov R, Ebner B et al. Cardiovascular disease and prevention among people living with HIV in South Florida. *Medicine (Baltimore)* 2021; 100(28): e26631. Dostupné z DOI: <<http://dx.doi.org/10.1097/MD.00000000000026631>>.
- Rossello X, Dorresteijn JAN, Janssen A et al. Risk prediction tools in cardiovascular disease prevention : A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology ( EAPC ) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Prev Cardiol* 2019; 26(14): 1534–1544- Dostupné z DOI: <<http://dx.doi.org/10.1177/2047487319846715>>.
- Cavassini M, Damas J, Beuret H et al. Cardiovascular risk assessment in people living with HIV compared to the general population. *Eur J Prev Cardiol* 2022; 29(4): 689–699. Dostupné z DOI: <<http://dx.doi.org/10.1093/eurjpc/zwab201>>.
- Pau AK, George JM. Antiretroviral Therapy : Current Drugs. *Infect Dis Clin North Am* 2015; 28(3): 371–402. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.idc.2014.06.001>>.
- Laurence J, Elhadad S, Ahamed J. HIV-associated cardiovascular disease: Importance of platelet activation and cardiac fibrosis in the setting of specific antiretroviral therapies. *Open Heart* 2018; 5(2):1–13. Dostupné z DOI: <<http://dx.doi.org/10.1136/openhrt-2018-000823>>.
- Maggi P, Di Biagio A, Rusconi S et al. Cardiovascular risk and dyslipidemia among persons living with HIV: A review. *BMC Infect Dis* 2017; 17(1): 551. Dostupné z DOI: <<http://dx.doi.org/10.1186/s12879-017-2626-z>>.
- Pao V, Lee GA, Grunfeld C. HIV therapy, metabolic syndrome, and cardiovascular risk. *Curr Atheroscler Rep* 2008; 10(1): 61–70. Dostupné z DOI: <<http://dx.doi.org/10.1007/s11883-008-0010-6>>.
- Wang HH, Garruti G, Liu M et al. Cholesterol and lipoprotein metabolism and atherosclerosis: Recent advances in reverse cholesterol transport. *Ann Hepatol* 2017;16(Suppl 1: 3–105): S27–S42. Dostupné z DOI: <<http://dx.doi.org/10.5604/01.3001.0010.5495>>.
- Ekun OA, Fasela EO, Oladele DA et al. Risks of cardio-vascular diseases among highly active antiretroviral therapy (Haart) treated hiv seropositive volunteers at a treatment centre in Lagos, Nigeria. *Pan Afr Med J* 2021; 38: 206. Dostupné z DOI: <<http://dx.doi.org/10.11604/pamj.2021.38.206.26791>>.
- Zanni M V, Faldyna B, Mccallum S et al. Sex Differences in Subclinical Atherosclerosis and Systemic Immune Activation / Inflammation Among People With Human Immunodeficiency Virus in the United States. *Clin Infect Dis* 2023; 76(2): 323–34. Dostupné z DOI: <<http://dx.doi.org/10.1093/cid/ciac767>>.
- Tousoulis D, Oikonomou E, Economou EK et al. Inflammatory cytokines in atherosclerosis : current therapeutic approaches. *Eur Heart J* 2016; 37(22): 1723–1732. Dostupné z DOI: <<http://dx.doi.org/10.1093/eurheartj/ehv759>>.
- HsuePY , David D Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nat Rev Cardiol* 2019; 16(12): 745–759. Dostupné z DOI: <<http://dx.doi.org/10.1038/s41569-019-0219-9>>.
- Spagnoli LG, Bonanno E, Sangiorgi G et al. Role of Inflammation in Atherosclerosis . *J Nucl Med* 2007; 48(11): 1800–1801. Dostupné z DOI: <<http://dx.doi.org/10.2967/jnumed.107.038661>>.
- Chow D, Shikuma C, Ritchings C et al. Atazanavir and Cardiovascular Risk Among Human Immunodeficiency Virus-Infected Patients : A Systematic Review. *Infect Dis Ther* 2016; 5(4): 473–489. Dostupné z DOI: <<http://dx.doi.org/10.1007/s40121-016-0132-z>>.
- Ohta H, Wada H, Niwa T et al. Disruption of tumor necrosis factor-alpha gene diminishes the development of atherosclerosis in ApoE-deficient mice. *Atherosclerosis* 2005; 180(1): 11–17. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.atherosclerosis.2004.11.016>>.
- Neto MG, Zwirter R, Brites C. A literature review on cardiovascular risk in human immunodeficiency virus-infected patients: Implications for clinical management. *Braz J Infect Dis* 2013; 17(6): 691–700. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.bjid.2013.05.004>>.
- Feinstein MJ, Hsue PY, Benjamin LA et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart Association. *Circulation* 2019; 140(2): e98–e124. Dostupné z DOI: <<https://doi.org/10.1161/CIR.0000000000000695>>.
- Kinlay S, Egado J. Inflammatory Biomarkers in Stable Atherosclerosis. *Am J Cardiol* 2006; 98(11A): 2P–8P. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.amjcard.2006.09.014>>.

30. Kearns A, Burdo TH, Qin X. Editorial Commentary: Clinical management of cardiovascular disease in HIV-infected patients. *Trends Cardiovasc Med* 2017; 27(8): 564–566. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.tcm.2017.07.007>>.
31. Uthman OA, Ndaka C, Watson SI et al. Statin use and all-cause mortality in people living with HIV: a systematic review and meta-analysis. *BMC Infect Dis* 2018; 18(1): 258. Dostupné z DOI: <<https://doi.org/10.1186/s12879-018-3162-1>>.
32. Louie M, Markowitz M. Goals and milestones during treatment of HIV-1 infection with antiretroviral therapy: A pathogenesis-based perspective. *Antiviral Res* 2002; 55(1): 15–25. Dostupné z DOI: <[http://dx.doi.org/10.1016/s0166-3542\(02\)00022-0](http://dx.doi.org/10.1016/s0166-3542(02)00022-0)>.
33. Zaaqoq AM, Khasawneh FA, Smalligan RD. Cardiovascular Complications of HIV-Associated Immune Dysfunction. *Cardiol Res Pract* 2015; 2015: 302638. Dostupné z DOI: <<http://dx.doi.org/10.1155/2015/302638>>.
34. Chow DC, Saiki KMW, Siriwardhana C et al. Increased transmigration of intermediate monocytes associated with atherosclerotic burden in people with HIV on antiretroviral therapy. *AIDS* 2023; 37(7): 1177–1179. Dostupné z DOI: <<http://dx.doi.org/10.1097/QAD.0000000000003534>>.
35. Aquaro S, Borrajo A, Pellegrino M et al. Mechanisms underlying of antiretroviral drugs in different cellular reservoirs with a focus on macrophages. *Virulence* 2020;11(1):400–413. Dostupné z DOI: <<http://dx.doi.org/10.1080/21505594.2020.1760443>>.
36. Alvarez A, Rios-Navarro C, Blanch-Ruiz MA et al. Abacavir induces platelet-endothelium interactions by interfering with purinergic signalling: A step from inflammation to thrombosis. *Antiviral Res* 2017; 141: 179–185. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.antiviral.2017.03.001>>.
37. Glaser V, Powderly W. Metabolic complications associated with HIV infection and antiretroviral therapy. *AIDS Patient Care STDS*. 2004; 18(8): 431–435. Dostupné z DOI: <<https://doi.org/10.1089/1087291041703638>>.
38. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harb Perspect Med* 2012; 2(4): a007161. Dostupné z DOI: <<http://dx.doi.org/10.1101/cshperspect.a007161>>.
39. Dorjee K, Choden T, Baxi SM et al. Risk of cardiovascular disease associated with exposure to abacavir among individuals with HIV: A systematic review and meta-analyses of results from 17 epidemiologic studies. *Int J Antimicrob Agents* 2018; 52(5): 541–553. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.ijantimicag.2018.07.010>>.
40. Moyle GJ, Orkin C, Fisher M et al. RESEARCH ARTICLE A Randomized Comparative Trial of Continued Abacavir / Lamivudine plus Efavirenz or Replacement with Efavirenz / Emtricitabine / Tenofovir DF in Hypercholesterolemic HIV-1 Infected Individuals. *PLoS One* 2015; 10(2): e0116297. Dostupné z DOI: <<http://dx.doi.org/10.1371/journal.pone.0116297>>.
41. Worm SW, Sabin C, Weber R et al. Risk of Myocardial Infarction in Patients with HIV Infection Exposed to Specific Individual Antiretroviral Drugs from the 3 Major Drug Classes: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. *J Infect Dis* 2010; 201(3): 318–330. Dostupné z DOI: <<http://dx.doi.org/10.1093/infdis/jin318>>.
42. Pablo C De, Orden S, Apostolova N et al. Abacavir and didanosine induce the interaction between human leukocytes and endothelial cells through Mac-1 upregulation. *AIDS* 2010; 24(9): 1259–1266. Dostupné z DOI: <<http://dx.doi.org/10.1097/QAD.0b013e318259875b>>.
43. De Luca A, de Gaetano Donati K, Cozzi-Lepri A et al. Exposure to Abacavir and Biomarkers of Cardiovascular Disease in HIV-1 - Infected Patients on Suppressive Antiretroviral Therapy: A Longitudinal Study. *J Acquir Immune Defic Syndr* 2012; 60(3): e98–101. Dostupné z DOI: <<http://dx.doi.org/10.1097/QAI.0b013e318259875b>>.
44. Neuhaus J, Jacobs DR, Baker J V et al. Markers of Inflammation, Coagulation, and Renal Function Are Elevated in Adults with HIV Infection. *J Infect Dis* 2010; 201(12): 1788–1795. Dostupné z DOI: <<http://dx.doi.org/10.1086/652749>>.
45. Keiser PH, Sension MG, Dejesus E et al. Substituting abacavir for hyperlipidemia-associated protease inhibitors in HAART regimens improves fasting lipid profiles, maintains virologic suppression, and simplifies treatment. *BMC Infect Dis* 2005; 5:2. Dostupné z DOI: <<http://dx.doi.org/10.1186/1471-2334-5-2>>.
46. Wassner C, Bradley N, Lee Y. A Review and Clinical Understanding of Tenofovir: Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide. *J Int Assoc Provid AIDS Care* 2020; 19:2325958220919231. Dostupné z DOI: <<http://dx.doi.org/10.1177/2325958220919231>>.
47. Santos JR, Saumoy M, Curran A et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis* 2015; 61(3): 403–408. Dostupné z DOI: <<http://dx.doi.org/10.1093/cid/civ296>>.
48. Dirajlal-Fargo S, Moser C, Brown TT et al. Changes in Insulin Resistance After Initiation of Raltegravir or Protease Inhibitors With Tenofovir Emtricitabine: AIDS Clinical Trials Group A5260s. *Open Forum Infect Dis* 2016; 3(3): ofw174. Dostupné z DOI: <<http://dx.doi.org/10.1093/ofid/ofw174>>.
49. Vanangamudi M, Kurup S, Namasivayam V. ScienceDirect Non-nucleoside reverse transcriptase inhibitors (NNRTIs): a brief overview of clinically approved drugs and combination regimens. *Curr Opin Pharmacol* 2020; 54:179–187. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.coph.2020.10.009>>.
50. Hagins D, Orkin C, Daar ES et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. *HIV Med* 2018; 19(10): 724–733. Dostupné z DOI: <<http://dx.doi.org/10.1111/hiv.12664>>.
51. Kline ER, Bassit L, Hernandez-santiago BI et al. *Cardiovasc Toxicol* 2009; 9(1): 1–12. Dostupné z DOI: <<http://dx.doi.org/10.1007/s12012-008-9029-8>>.
52. Kiage JN, Heimbürger DC, Nyirenda CK et al. Cardiometabolic risk factors among HIV patients on antiretroviral therapy. *Lipids Health Dis* 2013; 12:50. Dostupné z DOI: <<http://dx.doi.org/10.1186/1476-511X-12-50>>.
53. Bergersen BM, Tonstad S. Low prevalence of high-density lipoprotein cholesterol level  $< 1 \text{ mmol/L}$  in non-nucleoside reverse transcriptase inhibitor recipients. *Int J STD AIDS* 2005; 16(5): 365–369. Dostupné z DOI: <<http://dx.doi.org/10.1258/0954642053888808>>.
54. Bavinger C, Bendavid E, Niehaus K et al. Risk of Cardiovascular Disease from Antiretroviral Therapy for HIV: A Systematic Review. *PLoS One* 2013; 8(3): e59551. Dostupné z DOI: <<http://dx.doi.org/10.1371/journal.pone.0059551>>.
55. Rosenblatt L, Farr AM, Johnston SS et al. Risk of Cardiovascular Events Among Patients Initiating Efavirenz-Containing Versus Efavirenz-Free Antiretroviral Regimens. *Open Forum Infect Dis* 2016; 3(2): ofw061. Dostupné z DOI: <<http://dx.doi.org/10.1093/ofid/ofw061>>.
56. Hill A, Sawyer W, Gazzard B. Effects of first-line use of nucleoside analogues, efavirenz, and ritonavir-boosted protease inhibitors on lipid levels. *HIV Clin Trials* 2009; 10(1): 1–12. Dostupné z DOI: <<http://dx.doi.org/10.1310/hct1001-001>>.
57. Apostolova N, Ballesteros D, Monleo D et al. Inhibition of Mitochondrial Function by Efavirenz Increases Lipid Content in Hepatic Cells. *Hepatology* 2010; 52(1): 115–125. Dostupné z DOI: <<http://dx.doi.org/10.1002/hep.23647>>.
58. Lang S, Krause MM, Kote L. Impact of Individual Antiretroviral Drugs on the Risk of Myocardial Infarction in Human Immunodeficiency Virus-Infected Patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort C04. *Arch Intern Med* 2010; 170(14): 1228–38. Dostupné z DOI: <<http://dx.doi.org/10.1001/archinternmed.2010.197>>.
59. Gleason R, Caulk A, Seifu D et al. Efavirenz and ritonavir-boosted lopinavir use exhibited elevated markers of atherosclerosis across age groups in people living with HIV in Ethiopia. *J Biomech* 2016; 49(13): 2584–2592. Dostupné z DOI: <<http://dx.doi.org/10.1016/j.jbiomech.2016.05.018>>.
60. Ahmed M, Ahmed M, Mital D. Management of hypercholesterolemia in individuals living with HIV/AIDS. *Cholesterol* 2022; 999–1020. Dostupné z DOI: <<http://dx.doi.org/10.1016/B978-0-323-85857-1.00006-7>>.
61. Orkin C, Elion R, Thompson M et al. Changes in weight and BMI with first-line doravirine-based therapy. *AIDS* 2021; 35(1): 91–99. Dostupné z DOI: <<http://dx.doi.org/10.1097/QAD.0000000000002725>>.
62. Iannone V, Farinacci D, Angelillo AD et al. Cardiovascular Disease Risk in a Cohort of Virologically Suppressed People Living with HIV Switching to Doravirine: Preliminary Data from the Real Life: *AIDS Res Hum Retroviruses* 2022; 38(11): 878–880. Dostupné z DOI: <<http://dx.doi.org/10.1089/AID.2022.0050>>.
63. Lewis W. Atherosclerosis in AIDS: Potential pathogenetic roles of antiretroviral therapy and HIV. *J Mol Cell Cardiol* 2000; 32(12): 2115–2129. Dostupné z DOI: <<http://dx.doi.org/10.1006/jmcc.2000.1271>>.
64. Cunha J, Morganti L, Maselli F et al. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old

- and new drugs. *World J Virol* 2015; 4(2): 56–77. Dostupné z DOI: <<http://dx.doi.org/10.5501/wjv.v4.i2.56>>.
65. Stein JH. Dyslipidemia in the Era of HIV Protease Inhibitors. *Prog Cardiovasc Dis* 2003; 45(4): 293–304. Dostupné z DOI: <<http://dx.doi.org/10.1053/pcad.20034>>.
66. Dressman J, Kincer J, Matveev S V et al. HIV protease inhibitors promote atherosclerotic lesion formation independent of dyslipidemia by increasing CD36-dependent cholesterol ester accumulation in macrophages. *J Clin Invest* 2003; 111(3): 389–397. Dostupné z DOI: <<http://dx.doi.org/10.1172/JCI16261>>.
67. Werbel WA, Durand CM. Solid Organ Transplantation in HIV-Infected Recipients: History, Progress, and Frontiers. *Curr HIV/AIDS Rep* 2019; 16(3): 191–203. Dostupné z DOI: <<http://dx.doi.org/10.1007/s11904-019-00440-x>>.
68. Ryoum L, Mocroft A, Kirk O et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: The D:A:D Study. *J Infect Dis* 2013; 207(9): 1359–1369. Dostupné z DOI: <<http://dx.doi.org/10.1093/infdis/jit043>>.
69. Chow DC, Saiki KM, Siriwardhana C et al. Increased transmigration of intermediate monocytes associated with atherosclerotic burden in people with HIV on antiretroviral therapy. *AIDS* 2023; 37(7): 1177–1179. Dostupné z DOI: <<http://dx.doi.org/10.1097/QAD.0000000000003534>>.
70. Eckard AR, Mccomsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis* 2020; 33(1): 10–19. Dostupné z DOI: <<http://dx.doi.org/10.1097/QCO.0000000000000616>>.
71. Gorwood J, Bourgeois C, Pourcher V et al. The Integrase Inhibitors Dolutegravir and Raltegravir Exert Proadipogenic and Profibrotic Effects and Induce Insulin Resistance in Human/Simian Adipose Tissue and Human Adipocytes. *Clin Infect Dis* 2020; 71(10): e549–e560. Dostupné z DOI: <<http://dx.doi.org/10.1093/cid/ciaa259>>.
72. Koethe JR, Jenkins CA, Lau B et al. Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. *AIDS Res Hum Retroviruses* 2016; 32(1): 50–58. Dostupné z DOI: <<http://dx.doi.org/10.1089/aid.2015.0147>>.
73. Mccomsey GA, Moser C, Currier J et al. Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors : ACTG A5260s. *Clin Infect Dis* 2016; 62: 853–862. Dostupné z DOI: <<http://dx.doi.org/10.1093/cid/ciw017>>.
74. Young L, Wohl DA, Hyslop WB et al. Effects of raltegravir combined with tenofovir/emtricitabine on body shape, bone density, and lipids in African-Americans initiating HIV therapy. *HIV Clin Trials* 2018; 16(5): 163–169. Dostupné z DOI: <<http://dx.doi.org/10.1179/1945577115Y.0000000002>>.
75. Martin A, Moore CL, Mallon PWG et al. HIV lipodystrophy in participants randomised to lopinavir/ritonavir (LPV/r) +2–3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) or LPV/r + raltegravir as second-line antiretroviral therapy. *PLoS One* 2013; 8(10): e77138. Dostupné z DOI: <<http://dx.doi.org/10.1371/journal.pone.0077138>>.
76. Greenberg ML, Cammack N. Resistance to enfuvirtide , the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; 54(2): 333–340. Dostupné z DOI: <<http://dx.doi.org/10.1093/jac/dkh330>>.
77. Barroso S, Garrabou G. The effects of HIV and the antiretrovirals on the mitochondria. In: *Mitochondrial Intoxication*. Academic Press 2023: 351–378. ISBN 978-0-323-88462-4. Dostupné z DOI: <<https://doi.org/10.1016/B978-0-323-88462-4.00031-6>>.
78. Fung HB, Guo Y. Enfuvirtide : A Fusion Inhibitor for the Treatment of HIV Infection. *Clin Ther* 2004; 26(3): 352–378. Dostupné z DOI: <[http://dx.doi.org/10.1016/s0149-2918\(04\)90032-x](http://dx.doi.org/10.1016/s0149-2918(04)90032-x)>.
79. Gonza À, Arnaiz JA, Manriquez M et al. Metabolic , mitochondrial , renal and hepatic safety of enfuvirtide and raltegravir antiretroviral administration : Randomized crossover clinical trial in healthy volunteers. *PLoS One* 2019; 14(5): e0216712. Dostupné z DOI: <<http://dx.doi.org/10.1371/journal.pone.0216712>>.
80. [SCORE2 working group and ESC Cardiovascular risk collaboration]. SCORE2 risk prediction algorithms : new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021; 42(25): 2439–2454. Dostupné z DOI: <<https://doi.org/10.1093/eurheartj/ehab309>>.
81. Sanusi A, Elseiy H, Golder S et al. Cardiovascular health promotion: A systematic review involving effectiveness of faith-based institutions in facilitating maintenance of normal blood pressure. *PLOS Glob Public Health* 2023; 3(1): e0001496. Dostupné z DOI: <<http://dx.doi.org/10.1371/journal.pgph.0001496>>.
82. Fitch KV. Contemporary Lifestyle Modification Interventions to Improve Metabolic Comorbidities in HIV. *Curr HIV/AIDS Rep* 2019; 16(6): 482–491. Dostupné z DOI: <<http://dx.doi.org/10.1007/s11904-019-00467-0>>.
83. Grasso C, Mathews WC. Physical activity and health outcomes among HIV-infected men who have Sex with Men : A Longitudinal Mediation Analysis. *Ann Behav Med* 2014; 46(2): 149–56. Dostupné z DOI: <<http://dx.doi.org/10.1007/s12160-013-9489-3>>.
84. Cooper DA, Cordery DV, Reiss P et al. The effects of enfuvirtide therapy on body composition and metabolic parameters over 48 weeks in the TORO body imaging substudy. *HIV Med* 2011; 12(1): 31–39. Dostupné z DOI: <<http://dx.doi.org/10.1111/j.1468-1293.2010.00845.x>>.