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/μL, 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_4 + count (< 200 cells/mm^3) [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 cessation, 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-α (TNF-α), 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 (NNRTs), 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-naive 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 then 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) apoprotein B, TG, TC, LDL-C, insulin, and glucose which is accompanied by lipoatrophy 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 (TGF1ß) 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 signicantly 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 atanazavir (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 unbooted) 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 NSTI was raltegravir (RAL), whereas bictegravir (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-naive 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 optimalization 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. Optimalization 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 regiments 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, optimalization of the ART regimen should become essential part of cardiovascular prevention in PLWH.

Podpořeno COOP37

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