VPLYV ANTIRETROVÍRUSOVEJ LIEČBY NA ROZVOJ KARDIOVASKULÁRNYCH KOMORBIDÍT U HIV POZITÍVNYCH PACIENTOV

The Impact of Antiretroviral Therapy on the Development of Cardiovascular Comorbidities in HIV-Positive Patients

Ondrej ZAHORNACKY[1,2], Alena ROVNAKOVA[1,2], Pavol JARCUSKA[1,2], Stefan PORUBCIN[1,2]

[1]The Department of Infectious Diseases and Travel Medicine, Louis Pasteur University Hospital, Kosice, head prof. MUDr. P. Jarčuška, PhD.
[2] Faculty of Medicine, Pavol Jozef Safarik University in Kosice, head prof. MUDr. D. Pella, PhD.

Abstrakt
Kombinovaná antiretrovírusová terapia (cART) výrazne celkovo zlepšila prognózu HIV pozitívnych pacientov, no jej dlhodobé užívanie môže prispieť spolu s ostatnými rizikovými faktormi k rozvoju rôznych kardiovaskulárnych komorbidít. Tento článok skúma hlavné mechanizmy, ktorými HIV infekcia a antiretrovírusová liečba ovplyvňujú výskyt kardiovaskulárnych ochorení, vrátane chronického zápalu, metabolických zmien a liekových interakcií. Predstavujeme tri kazuistiky pacientov liečených cART, u ktorých došlo k rozvoju kardiovaskulárnych komplikácií v dôsledku interakcií alebo vedľajších účinkov liečby. Naše skúsenosti zdôrazňujú potrebu pravidelného monitorovania kardiovaskulárneho zdravia, personalizovaného prístupu k výberu cART režimov a interdisciplinárnej starostlivosti. Záverom apelujeme na význam znižovania stigmy spätej s HIV, ktorá môže brániť včasnému prístupu k zdravotnej starostlivosti (lit. 12). *Text v PDF www.lekarsky.herba.sk.*
KĽÚČOVÉ SLOVÁ: HIV, antiretrovírusová liečba, kardiovaskulárne ochorenia, komorbidity, liekové interakcie.
Lek Obz 2025, 74 (3): 120-122

Abstract
Combination antiretroviral therapy (cART) has significantly improved the overall prognosis of HIV-positive patients. However, its long-term use, along with other risk factors, can contribute to the development of various cardiovascular comorbidities. This article explores the main mechanisms by which HIV infection and antiretroviral therapy influence the occurrence of cardiovascular diseases, including chronic inflammation, metabolic changes, and drug interactions. We present three case reports of patients treated with cART who developed cardiovascular complications due to treatment interactions or side effects. Our findings highlight the need for regular cardiovascular health monitoring, a personalized approach to selecting cART regimens, and interdisciplinary care. Finally, we emphasize the importance of reducing HIV-related stigma, which can hinder timely access to healthcare (Ref. 12). *Text v PDF www.lekarsky.herba.sk.*
KEY WORDS: HIV, antiretroviral therapy, cardiovascular diseases, comorbidities, drug interactions.
Lek Obz 2025, 74 (3): 120-122

Introduction

Since the discovery of the human immunodeficiency virus (HIV), this disease has undergone a remarkable transformation, particularly in treatment advancements. HIV infection remains a significant public health issue, with an estimated global prevalence of 38.4 million people living with HIV (PLWH) as of 2022. More than two-thirds of PLWH live in the African region (25.6 million) (1).

Advances in HIV management, particularly the widespread use of cART, characterized by its high efficacy, tolerability, and substantial resistance barrier, have significantly reduced the morbidity and mortality associated with HIV. Consequently, individuals with HIV now live much longer than in the past. The aging of HIV-positive individuals is naturally associated (as in the HIV-negative population) with the development of additional comorbidities, such as cardiovascular diseases (CVD), chronic kidney and liver diseases, and metabolic disorders (e.g., diabetes mellitus). Moreover, chronic and long-term cART use contributes to the development of these comorbidities due to its adverse effects and drug interactions (2).

HIV Infection and Cardiovascular Diseases (CVD)

The median age of PLWH receiving cART continues to rise. It is estimated that up to 78% of PLWH will be diagnosed with some form of CVD. In general, PLWH have more than a two-fold increased risk of developing

CVD, with the pathogenesis of these comorbidities being nearly identical to that of HIV-negative individuals (3).

Atherosclerosis, a fundamental risk factor for CVD development, is generally exacerbated by physiological aging and traditional CVD risk factors, such as arterial hypertension, hyperlipidemia, diabetes, metabolic syndrome, smoking, and a positive family history (4).

HIV infection can both trigger and accelerate atherosclerosis and endothelial dysfunction through several mechanisms:

- **Pro-inflammatory effects of HIV proteins:** These lead to chronic immune system activation, resulting in persistent low-grade inflammation. This accelerates the formation of atherosclerotic plaques, damages vascular endothelium, disrupts coagulation, and alters cholesterol metabolism. Acute myocardial infarction is the most common manifestation of CVD in PLWH, with a 1.5- to 2-fold higher risk compared to the general population (5).
- **CD4+ T-lymphocyte depletion:** This is often linked to undiagnosed or late-diagnosed HIV infection, leading to opportunistic infections that further promote inflammation and accelerate atherosclerosis. Opportunistic infections may also directly damage the heart through infectious endocarditis or cardiomyopathy(6).
- **Virological suppression and inflammation:** Evidence shows that even patients with full virological suppression—whether on cART or not (elite controllers)—face an increased risk of CVD compared to the HIV-negative population. This phenomenon is attributed to ongoing HIV-induced inflammation and chronic immune activation (7).
- **Increased gut permeability:** This allows microbial products to pass through the disrupted intestinal lining, triggering chronic immune activation and inflammation (8).

The use of cART has greatly improved the life expectancy of PLWH. Despite its undeniable benefits, lifelong use of these drugs poses certain risks associated with prolonged drug exposure. Clinical practice encounters include cardiometabolic toxicity, which induces new cardiovascular risk factors—such as dyslipidemia, insulin resistance, and weight gain or exacerbates pre-existing ones. Furthermore, older drugs, particularly first-generation protease inhibitors and abacavir, have been associated with adverse effects such as altered glucose and lipid metabolism, mitochondrial toxicity leading to cardiomyopathy, and impaired left ventricular function (9).

In the clinical practice of HIV specialists, various forms of CVD in PLWH are frequently encountered, exacerbated by a wide range of risk factors. Below, we present some of the most noteworthy experiences from our clinical practice.

Case 1

A 45-year-old patient followed up at an HIV center for 3 years. The infection was diagnosed in stage B2 (CDC classification). Currently treated with a dual combination of antiretroviral drugs – rilpivirine and dolutegravir. The patient adheres to treatment without complications or side effects, as evidenced by the last CD4+ T lymphocyte count of $0.45x10^9$/L (normal range) and an undetectable viral load (VL) in serum. The patient suddenly collapsed at home, experiencing palpitations but no loss of consciousness. Emergency medical services transported him to a regional internal medicine emergency department. An electrocardiogram (ECG) revealed atrial fibrillation with rapid ventricular conduction, irregular heart rhythm, a rate of 130–150 beats per minute, and blood pressure of 90/50 mmHg. In the initial medical history, the patient did not disclose his HIV-positive status or cART use.

He refused hospitalization and was treated in an outpatient setting with intravenous amiodarone, achieving conversion to sinus rhythm. Continued amiodarone treatment in tablet form was recommended.

Approximately one week later, the patient developed diarrhea, vomiting, fatigue, and malaise at home. He was re-evaluated in the internal medicine outpatient clinic, where blood tests showed elevated liver enzymes (AST 5 μkat/L, ALT 7 μkat/L). The patient agreed to hospitalization, disclosed his HIV status, and admitted to using cART. Amiodarone was immediately discontinued and replaced with a beta-blocker (metoprolol). Symptomatic treatment was initiated, leading to gradual improvement in clinical and laboratory findings.

Diagnostic Conclusion – Drug interaction between amiodarone and dolutegravir/rilpivirine leading to hepatotoxicity.

Mechanism of Interaction – Amiodarone-induced inhibition of cytochrome CYP3A4, the enzyme responsible for metabolizing dolutegravir and rilpivirine. Elevated serum levels of dolutegravir and rilpivirine resulted in hepatotoxicity (10).

Management – Potentially severe drug interactions between amiodarone and dolutegravir/rilpivirine necessitate careful risk-benefit evaluation of amiodarone treatment for atrial fibrillation.

Case 2

A 50-year-old patient followed up at an HIV center for 10 years. He has been on cART (bictegravir, emtricitabine, and tenofovir alafenamide) for the past 2 years without complications. The most recent CD4+ T lymphocyte count was $0.50x10^9$/L, with an undetectable VL.

During an occupational health check-up, asymptomatic ventricular extrasystoles were detected on the ECG. A 7-day Holter monitor recorded 14,000 ventricular extrasystoles daily. Beta-blocker therapy (bisoprolol) was initiated but was ineffective. A cardiologist recommended changing the treatment to verapamil and propafenone.

After starting the new therapy, the patient experienced dizziness, weakness, and fatigue, followed by syncope at home. An ECG revealed a prolonged QTc interval (540 ms).

Diagnostic Conclusion – Pharmacological interaction – bictegravir is minimally associated with QTc interval prolongation. However, calcium channel blockers can prolong the QTc interval under certain circumstances. A synergistic effect between verapamil and bictegravir likely resulted in a more severe QTc interval prolongation (11).

Management – After consultation with a cardiologist, verapamil was discontinued, and monotherapy with propafenone was maintained. Ablation was planned for the patient.

The cART regimen with bictegravir was continued unchanged. Following verapamil discontinuation, the QTc interval normalized (440 ms), symptoms resolved, and the patient reported significant improvement.

Case 3

A 55-year-old patient followed up at an HIV center in Italy for over 15 years and, in the past 3 months, in Slovakia. He had been on cART (abacavir, dolutegravir, and emtricitabine) for approximately 5 years.

At home, the patient developed sudden retrosternal chest pain characteristic of angina pectoris. He was transported and hospitalized at a cardiology center with suspected acute myocardial infarction (STEMI). Coronary angiography confirmed two-vessel coronary artery disease. Abacavir was immediately discontinued.

Diagnostic Conclusion – Acute myocardial infarction of combined etiology, with a contributory role of abacavir-induced cardiotoxicity.

Mechanism – Abacavir inhibits mitochondrial DNA polymerase – and increases platelet activity, promoting aggregation, endothelial damage, and dysfunction, ultimately leading to thrombosis (12).

Management – Cardiotoxicity is a rare but potentially serious adverse effect of abacavir. Its use should be carefully evaluated in patients at risk for CVD.

Conclusion

The introduction of combination antiretroviral therapy has significantly improved the prognosis and survival of PLWH. The number of HIV-positive patients in Slovakia is gradually increasing, with a rising average age in this cohort. This naturally brings new health challenges associated with aging and comorbidities, particularly in cardiovascular health.

Our clinical experience highlights the significant risks associated with both the natural aging process of HIV-positive patients and the side effects and interactions of cART. Managing PLWH with comorbid CVD requires a comprehensive, interdisciplinary approach, emphasizing caution with potential drug interactions and regular monitoring of cardiovascular functions. Our findings also underscore the need for routine CVD screening in HIV-positive patients on cART, particularly those with additional risk factors (e.g., smoking, dyslipidemia). Finally, beyond clinical considerations, addressing the stigma associated with HIV is crucial to ensuring patients seek and receive appropriate care.*

*__Declaration of Human Rights:__ The authors declare that all procedures used were in compliance with the ethical standards of the relevant ethics committee for clinical work with humans, and the work was conducted in accordance with the Declaration of Helsinki.

__Informed Consent:__ The authors of the publication declare that informed consent was obtained from patients.

__Conflict of Interest:__ The authors declare that they have no conflicts of interest.

References

1. DE LA MORA L, MALLOLAS J, AMBROSIONI J. Epidemiology, treatment and prognosis of HIV infection in 2024: A practical review. Med Clin (Barc) 2024, 162 (11): 535 – 541. DOI: 10.1016/j.medcli.2023.12.007.
2. AVAGIMYAN A, POGOSOVA N, KAKTURSKIY L, al. HIV-Related Atherosclerosis: State-of-the-Art-Review. Curr Probl Cardiol 2023, 48 (9): 101783. DOI: 10.1016/j.cpcardiol.2023.101783.
3. KUATE A, DEFO M.D., CHALATI C, LABOS LK, et al. Association of HIV infection and antiretroviral therapy with arterial stiffness: a systematic review and meta-analysis. Hypertens (Dallas 1979), 2021, 78 (2): 320 – 322. DOI: 10.1161/hypertensionaha.121.17093
4. GRAND M, BIA D, DIAZ A. Cardiovascular Risk Assessment in People Living With HIV: A Systematic Review and Meta-Analysis of Real-Life Data. Curr HIV Res 2020, 18 (1): 5 – 18.
5. KRIKKE M, VAN LELYVELD SFL, TESSELAAR K, et al. The Role of T Cells in the Development of Cardiovascular Disease in HIV-Infected Patients. Atherosclerosis 2014, 237: 92–98.
6. MÁRQUEZ M, ROMERO-CORES P, MONTES-OCA M, et al. Immune Activation Response in Chronic HIV-Infected Patients: Influence of Hepatitis C Virus Coinfection. PLoS ONE 2015, 10: e0119568.
7. SIEDNER MJ. START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection. Open Forum Infect Dis 2016, 3 (1): ofw032, 10.1093/ofid/ofw032.
8. YOUNAS M, PSOMAS C, REYNES C, et al. Microbial Translocation Is Linked to a Specific Immune Activation Profile in HIV-1-Infected Adults With Suppressed Viremia. Front Immunol 2019, 10: 2185. 10.3389/fimmu.2019.02185
9. HATLEBERG C, RYOM L, SABIN C. Cardiovascular risks associated with protease inhibitors for the treatment of HIV Expet Opin Drug Saf 2021, 20 (11): 1351 – 1366. DOI: 10.1080/14740338.2021.1935863
10. HAKKOLA J, HUKKANEN J, TURPEINEN M, PELKONEN O. Inhibition and induction of CYP enzymes in humans: an update. Arch Toxicol 2020, 94 (11): 3671 – 3722. DOI: 10.1007/s00204-020-02936-7.
11. LIU Y, YUMEI X, SHULIN W, et al. Effect of verapamil in the treatment of type 2 long QT syndrome is not a dose-dependent pattern: a study from bedside to bench, and back, *European Heart Journal Supplements 2016,* 18 (Suppl_A): A37–A46, https: //doi.org/10.1093/eurheartj/suw006
12. BARBARINO JM, KROETZ DL, ALTMAN RB, KLEIN TE. PharmGKB summary: abacavir pathway. Pharmacogenet Genomics 2014, 24 (5): 276 – 282. DOI: 10.1097/FPC.0000000000000040.

Do redakcie došlo 4. 12. 2024.

Address for correspondence:
Stefan Porubcin, MD, PhD.
The Department of Infectious Diseases and Travel Medicine
Louis Pasteur University Hospital
Rastislavova 43
040 11 Kosice
E-mail: *stefan.porubcin@gmail.com*