Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

Check for updates

Rev Invest Clin. 2024;76(6):274-85 ORIGINAL ARTICLE

Cardiovascular Risk Prediction Models in People Living with Human Immunodeficiency Virus under Antiretroviral Therapy in Northern Mexico

Arguiñe I. Urraza-Robledo[1], Francisco C. López-Márquez[2], Faviel F. González-Galarza[2], Domingo Pere-Pedrol[3], María E. Gutiérrez-Pérez[2], Ana P. Roiz-Bollain y Goytia[4], Pablo Ruiz-Flores[5], Fanny K. Segura-López[1], and Alberto A. Miranda-Pérez[2]*

[1]Unidad Médica de Alta Especialidad # 71, Instituto Mexicano del Seguro Social, Torreón, Coah., Mexico; [2]Department of Molecular Immunobiology, Centro de Investigación Biomédica, Torreón, Coah., Mexico; [3]Infectous Diseases Unit, Hospital de la Santa Creu y Sant Pau, Barcelona, Spain; [4]Department of Neonatology, Hospital Ignacio Morones Prieto San Luis Potosí, San Luis Potosí, Mexico; [5]Departament of Genetics, Centro de Investigación Biomédica, Torreón, Coah., Mexico

ABSTRACT

Background: The effective use of combination antiretroviral therapy (ART) has significantly improved the life expectancy of people living with the human immunodeficiency virus (HIV). However, complications have shifted from opportunistic infections to issues such as drug toxicity and resistance, as well as an increase in premature cardiovascular diseases (CVD). These conditions are attributed to chronic immune activation and persistent inflammation caused by HIV, along with lipid abnormalities and insulin resistance. **Objective:** The objective of the study was to predict cardiovascular risk at 5 and 10 years in people living with HIV with combination ART using three algorithmic models. **Methods:** This study included 186 HIV-seropositive patients under treatment. The variables analyzed included anthropometric measurements, family history of hypertension and CVDs, years of infection, years of treatment, and treatment scheme. We used three well-established algorithmic models for assessing cardiovascular risk: Framingham (10-year period), Data Collection on Adverse Events of Anti-HIV Drugs Study (D: A: D) reduced, and full (5-year period). **Results:** Approximately 65% of the study participants were undergoing a treatment regimen comprising two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a non-NRTIs. The mean body mass index analysis indicated that 28.5% of the participants were overweight and 17.7% obese. In addition, 53.8% of the patients exhibited hypertriglyceridemia, and 54.8% met the diagnostic criteria for metabolic syndrome. The D: A: D reduced and full models identified significant risk factors for individuals over 30 years of age, highlighting notable associations with cholesterol levels, triglyceride levels, and smoking status. In contrast, the Framingham model did not demonstrate significant risk associations. (REV INVEST CLIN. 2024;76(6):274-85)

Keywords: Human immunodeficiency virus. Cardiovascular risk. Overweight. Metabolic syndrome. Antiretroviral therapy.

***Corresponding author:**
Alberto A. Miranda-Pérez
E-mail: alberto.miranda@uadec.edu.mx

Received for publication: 26-08-2024
Approved for publication: 18-11-2024
DOI: 10.24875/RIC.24000176

INTRODUCTION

The effective implementation of combination antiretroviral therapy (cART) has significantly enhanced the life expectancy of people living with the human immunodeficiency virus (PLHIV)[1]. In recent years, there has been a shift in HIV-related health complications, changing from opportunistic infections related to immunodeficiency to other problems aasociated with the use of cART (e.g., drug toxicity or resistance to antiretrovirals)[2]. In addition, there is an increasing prevalence of comorbidities that are not directly associated with acquired immunodeficiency syndrome (AIDS)[2,3]. These morbidities, primarily those related to premature cardiovascular disease (CVD), are thought to be associated with a combination of the effects of an aging PLHIV along with long-term effects of HIV infection and ART[3]. One of the main factors behind the increased risk of CVDs in PLHIV patients is the chronic immune activation and persistent inflammation caused by the virus, even in those with suppressed viral loads[3]. This ongoing inflammation significantly contributes to atherosclerosis and endothelial damage. In addition, HIV patients often exhibit lipid abnormalities, such as elevated levels of low-density lipoproteins (LDL), cholesterol, and triglycerides and reduced levels of high-density lipoproteins (HDL), increasing a cardiovascular risk[2,4]. Moreover, insulin resistance is associated with a pro-inflammatory and pro-atherogenic state. The metabolic syndrome (MetS), characterized by the presence of at least three metabolic factors, i.e., abdominal obesity, dyslipidemia, hypertension, and/or hyperglycemia, significantly increases the likelihood of cardiovascular events in HIV patients. The risk of developing CVD in PLHIV is 1.5 times higher than in the HIV-negative population once traditional risk factors have been considered[5-11]. Despite the higher prevalence of cardiovascular risk factors in the HIV-positive population, additional independent risk factors for CVD have been identified. These include HIV-related immunological and virological parameters and disease characteristics that serve as predictors of cardiovascular events in the HIV-positive population. These predictors include low CD4+ count, high viral load, and the use of certain ARV drugs[12-14]. In addition to other factors, such as age, sex, and smoking[15], several conditions associated with aging and metabolic disorders have become more frequent in HIV-positive populations, including hypertension, type 2 diabetes (T2D), dyslipidemia, and obesity[16].

Predictive models are intended to improve the prediction of clinical events, individualized treatment, and correct decision-making[17]. A prediction model is a mathematical equation that quantifies risk based on data and the probability of an event occurring within a specified period. These models are utilized in clinical settings to evaluate overall risk, providing a comprehensive assessment that integrates individual risk factors[18-20]. Some models are capable of predicting multiple parameters simultaneously, including the 5- and 10-year risk of mortality, the risk of severe acute events such as reinfarction, and the likelihood of heart failure following myocardial infarction. The most commonly used CVD risk prediction models are GRACE, TIMI, atherosclerotic CVD (ASCVD), and the Framingham risk score22. In the general population, GRACE and TIMI are better scores to predict a cardiovascular event but are not specified for PLHIV[4]. Several risk prediction models developed for the general population are available to predict CVD risk, the most notable being the US-based pooled cohort equations, the Framingham risk functions, and the Europe-based systematic coronary risk evaluation. In validation studies in cohorts of PLHIV, these models generally underestimate CVD risk, especially in individuals who are younger, women, Black race or predicted to be at low/intermediate risk[20].

However, there is only one model that specifically predicts cardiovascular risk to 5 years in PLHIV under treatment, the Data Collection on Adverse Events of Anti-HIV Drugs Study (D: A: D). This model includes age, gender, systolic blood pressure (BP), smoking status, family history of CVD, diabetes, total cholesterol, HDL CD4+ lymphocyte count, cumulative exposure to protease (PI)- and nucleoside reverse transcriptase-inhibitors (NRTIs), and current use of abacavir[2].

At present, there is limited information about the estimation of cardiovascular risk in PLHIV in Mexico and Latin America. Therefore, the objective of this study was to evaluate the 5- and 10-year cardiovascular risk in this popularion under treatment, using the Framingham, D:A:D reduced, and D:A:D full algorithmic models. These models were chosen for their robustness and validation in diverse populations, providing a comprehensive assessment of cardiovascular risk. In addition, this study aimed to identify factors that contribute to increased cardiovascular risk, such

as MetS, lipid profile alterations, and other metabolic issues, which are particularly relevant in a context with a high prevalence of overweight and obesity. This comprehensive evaluation is essential for guiding effective interventions tailored to the cardiovascular health of PLHIV.

METHODS

The present investigation was a cross-sectional and comparative study. Participants were recruited from the Outpatient Centers for the Prevention and Care of AIDS and Sexually Transmitted Infections in Torreon, Coahuila, Mexico, and the Hospital Comprehensive Care Services in Gomez Palacio, Durango, Mexico.

This study was approved by the Bioethics Committee of the Faculty of Medicine of the Autonomous University of Coahuila, in Torreon, Mexico (ref C.B/08-10-17). This research also adhered to the criteria of the Declaration of Helsinki established for medical research involving human subjects.

Participants

The sample size was calculated based on the prevalence of hypertension in the Laguna region. A total of 186 HIV-positive subjects over 18 years of age who were under ART treatment were included in the study. In addition, a questionnaire was applied to all participants to describe sociodemographic and clinical data, and history of HIV infection. The inclusion criteria were women and men with established diagnosis of HIV infection, who were receiving ART, and signed a letter of informed consent.

Anthropometric measurements

Bodyweight was measured with an electronic scale (Beurer, Gmbh Soflinger, Str. 218 Germany), whereas height was measured using a stadiometer. The body mass index (BMI) was defined according to World Health Organization (WHO) criteria (kg/m^2): (i) low weight (< 18.5 kg/m^2), (ii) normal weight (18.5-24.9 kg/m^2), (iii) overweight (25-29.9 kg/m^2), and obesity (≥ 30 kg/m^2)[24]. The abdominal circumference was measured with a tape, considering as reference values for centripetal obesity a circumference in men > 90 cm and in women > 80 cm.

Metabolic syndrome

Participants were classified according to the presence/absence of components that comprise the MetS based on two scales: (i) The first was according to the WHO criteria, i.e., presence of type 2 diabetes (T2D), insulin resistance, and the presence of at least 2 of the following factors, BMI ≥ 30 kg/m^2, triglycerides ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men and < 50 mg/dL in women, blood pressure (BP) ≥ 140/90 mmHg, or fasting glucose ≥ 110 mg/dL; (ii) for the second scale, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) was considered under the following criteria: insulin resistance (IR) and 3 of the following factors, triglycerides ≥ 150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, abdominal obesity ≥ 102 cm in men and ≥ 88 cm in women, BP ≥ 130/85 mmHg, or fasting glucose ≥ 100 mg/dL[21].

Biochemical measurements

Blood samples were collected after an 8 h fasting period. The samples were subsequently centrifuged at 3000 RPM for 10 min to obtain blood serum. Glucose (mg/dL), total cholesterol (mg/dL), HDL (mg/dL), LDL (mg/dL), very LDL (VLDL) (mg/dL), triglycerides (mg/dL), and atherogenic index (AI) were determined. All measurements were analyzed by colorimetry on a Vitros® 250 automated dry chemical analyzer according to the manufacturer's specifications.

Evaluation of the homeostatic model of insulin resistance (HOMA-IR)

Insulin levels were determined using the chemiluminescence method in the serum sample; the reference values considered for the hormone were 2–15 µIU/mL. Later, the HOMA index was calculated to obtain the IR value using the following formula: HOMA-IR = [fasting serum glucose (mmol/L) × fasting insulin (µIU/mL)] / 22.5[22].

Cardiovascular risk assessment for cases

The cardiovascular risk of each participant was calculated using three logarithmic models: D: A: D (5-year risk) full and reduced, and Framingham (10-year risk).

Table 1. Anthropometric, biochemical and clinical variables of individuals classified by gender

Variable	All patients (n = 186)	Male (n = 145)	Female (n = 41)	p
	Mean (± s.d.)	Mean (± s.d.)	Mean (± s.d.)	
Age	39.14 (± 10.89)	38.92 (± 0.914)	39.93 (± 1.671)	0.608
Weight	71.97 (± 14.44)	72.91 (± 13.9)	68.67 (± 15.95)	0.100
Height	1.67 (± 0.89)	1.71 (± 0.065)	1.56 (± 0.064)	< 0.0001
BMI (kg/m^2)	25.44 (± 5.3)	24.88 (± 4.43)	28.04 (± 5.96)	0.027
Waist circumference (cm)	79.74 (± 31.89)	89.69 (± 12.65)	93.03 (± 15.97)	0.297
Blood pressure (mmHg)	112/73 (± 9.96)	111/75 (± 1.05)	110/70 (± 2.16)	0.499
Glucose (mg/dL)	91.38 (± 30.57)	90.82 (± 29.62)	93.37 (± 33.85)	0.578
Insulin (U-100)	10.88 (± 7.42)	10.62 (± 7.56)	11.84 (± 6.94)	0.176
Insulin resistance	2.64 (± 2.32)	2.57 (± 2.39)	2.86 (± 2.05)	0.158
Cholesterol (mmg/dL)	174.8 (± 38.44)	173.6 (± 39.22)	178.9 (± 35.72)	0.421
Triglycerides (mmg/dL)	225.5 (± 202.11)	225.5 (± 211.3)	192.9(± 165.5)	0.367
HDL (mmg/dL)	46.23 (± 13.44)	44.88 (± 12.67)	51.00(± 15.08)	0.012
LDL (mmg/dL)	90.79 (± 31.1)	90.21 (± 32.91)	92.87 (± 23.85)	0.470
VLDL (mmg/dL)	37.78 (± 22.48)	38.57 (± 22.82)	34.99 (± 21.30)	0.402
Viral load (copies)	11118.22 (± 63217.11)	10529 (± 6257)	13121(± 6710)	0.996
CD4+ cel/mm^3	447.84 (± 276.78)	437.0 (± 278.8)	486.3 (± 270.4)	0.238

BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; s.d.: standard deviation; p < 0.05 after t-test comparison are shown in bold.

The three models estimate the risk of CVD by combining information on age, sex, systolic BP, total cholesterol, HDL, diabetes, and smoking. While the equation of D: A: D includes the use of ART[23,24], Framingham's and atheroschlerotic cardiovascular disease (ASCVD) equations estimate the risk including antihypertensive therapy but not ART[28,29]. In addition, for the D: A: D model, we used two versions: D: A: D reduced model (including age, gender, systolic BP, smoking, family history of CVD, diabetes, total cholesterol, HDL, CD4 cell count) and D: A: D full model (including age, gender, systolic BP, smoking, family history of CVD, diabetes, total cholesterol, HDL, CD4 cell count, cumulative exposure to protease and reverse transcriptase nucleoside-inhibitors, and current use of abacavir). Finally, the risk for participants according to D: A: D was considered as low (< 1%), moderate (1–5%), high (5–10%), and very high (> 10%); the risk according to Framingham was low (< 10%), moderate (10–20%), high (21-30%), and very high (> 30%)[27], and for ASCV was < 5% low risk; 5–7.5% borderline risk; 7.5–20% intermediate risk, and ≥ 20% high risk.

Statistical analysis

Sociodemographic and clinical quantitative variables were analyzed using parametric measurements (i.e., means and standard deviations). Kolmogorov–Smirnov was used to test for normality. In addition, Student's t test was used to compare two groups' quantitative variables, whereas analysis of variance test was to compare three groups. Statistical significance was considered when p < 0.05. Data were analyzed using the statistical software package Statistical Package for the Social Sciences v25.0 (IBM Corp, Chicago IL, USA).

RESULTS

Sociodemographic and clinical characteristics

The present study included 186 PLHIV/AIDS under ART treatment. The sociodemographic and clinical data are shown in table 1. At the time of the study,

all HIV+ subjects were receiving ART had a mean of 7.18 (± 6.15) years of treatment, and 9.73 (± 6.46) years with the infection. The mean count of CD4+ at the beginning of the treatment was 520.17 (± 438.62 cell/mm^3) and viral load was 4.04 $^{log\ 10}$ copies/ml (± 0.4.08 $^{log\ 10}$ copies/mL). Regarding ART treatment, ~65% of the participants were under a treatment scheme of two NRTI plus a NNRTI (Table S1).

Physical and biological profile of the participants

Considering the traditional risk factors for the development of CVD, 70 out of the 186 participants (37.6%) were smokers and 94 individuals (50.5%) were former smokers. The mean of BMI was 25.44 ± 5.3 kg/m^2. Approximately, 4.3% of the participants were classified as underweight, 49.5% had normal weight, 28.5% were overweight, and 17.7% were obese. One hundred patients (53.8%) had hypertriglyceridemia, 44 (23.7%) hypercholesterolemia, 72 (38.7%) presented HDL levels < 40 mg/dL, and 69 (37.7%) had insulin resistance. According to metabolic parameters, 51.3% of the population had a history of hypertension, whereas 5.4% had T2D; subjects had insulin resistance and 102 (54.8%) met the criteria of MetS.

In addition, a bivariate analysis was conducted to assess the population's overall status. HDL levels were significantly associated (p = 0.04, OR = 1.27). Cholesterol levels were also significantly associated with age > 40 years (p = 0.02, OR = 3.11) and smoking (p = 0.048, OR = 1.18), whereas triglycerides and the AI were both significantly associated with the presence of MetS (p < 0.001, OR = 6.56 and p < 0.001, OR = 5.64, respectively). These findings are detailed in table 2.

Risk factors based on the three algorithmic models

To evaluate the predictive capacity of each model concerning traditional risk factors, adjusted ORs, and p-values were calculated to ascertain the statistical significance of predictor variables and potential interactions within the study population. It was observed that the Framingham model did not reveal significant risks. In contrast, both the D: A: D reduced and D: A: D full models showed significant risks of OR = 2.90 and OR = 3.90, respectively, among individuals over 30 years old. Following adjustment for age and sex, these risks increased substantially to OR = 23.4 and OR = 34.8, respectively, with a p < 0.0001. In addition, cholesterol exhibited an OR of 1.32 for D: A: D reduced and 1.33 for D: A: D full, whereas triglycerides showed ORs of 2.44 for D: A: D reduced and 1.84 for D: A: D full, all with significant p-values. Current smoking status indicated an OR of 1.42 for D: A: D reduced and 1.44 for D: A: D full, maintaining risks of 1.38 and 1.22, respectively, after adjustment for age and sex, with a p = 0.001. In the D: A: D full model, the variable of more than 10 years of antiretroviral treatment also showed an OR of 2.06 with a p = 0.033 (Table 3).

Another critical factor in evaluating cardiovascular risk was the treatment regimens, with 65% of patients receiving a combination of two NRTIs and two protease inhibitors. The D: A: D full model demonstrated a higher or increasing risk compared to the Framingham model. This suggests that the Framingham model may underestimate cardiovascular risk in HIV patients undergoing treatment, whereas the D: A: D model offers a more accurate and tailored risk assessment for this population.

DISCUSSION

Mexico has been characterized by having a high prevalence of obesity in the HIV-seronegative population, in which ~75% of the population has been classified as overweight/obese based on BMI criteria[25]. A study conducted by Kang et al., in China, showed that the male population presented a higher prevalence of overweight compared to the female population. In our study, approximately, 4.3% of the participants were underweight, 49.5% had normal weight, 28.5% were overweight, and 17.7% had obesity[26]. In 2015, Shen et al. showed that the prevalence of traditional risk factors for the development of CVD in PLHIV was 36.4% and 3.5% for hypertriglyceridemia and hypercholesterolemia, respectively. They also observed that the prevalence of low HDL-C combined with high TG was 46.6%[25]. At the time of this study, all HIV+ subjects were receiving ART with a mean of 7.18 (± 6.15) years, and had been infected for 9.73 (± 6.46) years. The mean count of CD4+ at the beginning of the treatment was 520.17 (± 438.62 cell/mm^3).

Table 2. Association of lipid profile and risk factors in people with HIV/AIDS undergoing cART

Variable	Cholesterol (> 200 mg/dL) OR (IC 95%)	p	HDL (< 40 mg/dL) OR (IC 95%)	p	LDL (> 130 mg/dL) OR (IC 95%)	p	Triglycerides (> 150 mg/dL) OR (IC 95%)	p	Atherogenic index (> 4.5) OR (IC 95%)	p
Male	1.05 (0.86-1.27)	0.588	1.27 (0.94-1.72)	0.04	0.85 (0.71-1.02)	0.201	0.91 (0.78-1.07)	0.280	0.87 (0.75-1.02)	0.162
Female	0.84 (0.46-1.54)		0.52 (0.29-0.94)		2.21 (0.58-8.46)		1.34 (0.78-2.31)		1.78 (0.75-4.23)	
Age (> 40 years)	0.96 (0.47-1.94)	0.901	1.25 (0.57-2.78)	0.579	0.19 (0.13-1.38)	0.055	0.80 (0.556-1.147)	0.192	1.26 (1.12-1.41)	0.051
Smoking	1.18 (1.01-1.37)	0.048	1.08 (0.97-1.22)	0.174	0.98 (0.40-2.34)	0.940	1.15 (0.833-1.503)	0.307	1.01 (0.58-1.83)	0.977
BMI (≥ 25.00 kg/m^2)	1.74 (0.83-3.45)	0.107	0.35 (0.14-0.88)	0.02	2.15 (0.80-5.75)	0.118	2.60 (1.43-4.73)	0.001	1.48 (0.72-3.09)	0.287
Metabolic syndrome	1.11 (0.56-2.20)	0.763	0.61 (0.27-1.39)	0.24	0.44 (0.17-1.18)	0.096	6.56 (3.450-12.45)	<0.001	5.64 (2.23-14.40)	<0.001
Blood pressure (> 140 mmHg)	0.24 (0.18-0.39)	0.074	0.86 (0.81-0.96)	0.869	0.90 (0.85-0-95)	0.736	0.54 (0.456-0.618)	0.354	0.79 (0.73-0.87)	0.606
CD4+ (< 350 cel/mm^3)	0.80 (0.45-1.33)	0.359	1.09 (0.54-2.20)	0.808	0.80 (0.33-1.92)	0.610	1.07 (0.81-1.40)	0.634	0.97 (0.54-1.76)	0.931
Viral load ¡ (> 50 copies)	0.63 (0.23-1.67)	0.344	0.91 (0.37-2.26)	0.840	0.46 (0.10-2.09)	0.304	0.87 (0.65-1.15)	0.344	0.66 (0.34-1.29)	0.240
cART	0.87 (0.42-1.81)	0.708	0.80 (0.42-1.53)	0.503	1.21 (0.43-3.31)	0.708	1.36 (0.72-2.57)	0.344	1.40 (0.65-3.03)	0.319

BMI: body mass index; cART: highly active antiretroviral therapy; p < 0.05 after bivariate analysis are shown in bold.

Regarding ART treatment, ~65% of the participants were under a treatment scheme of two NIs plus a NNRTIs. Notably, the proportion of current smokers and former smokers in the sample was high (88.1%), as smoking is a well-established risk factor for CVDs. In addition, the average BMI may suggest that a large part of the participants is overweight/obese, conditions that also increase the risk of CVDs. Previous studies have also mentioned that chronic inflammation and persistent immune activation are characteristics of HIV that are linked to a higher risk of CVD[3].

It is known that lipid abnormalities prevail in HIV-seropositive people with ART and may contribute to an increased risk of CVD[27]. The prevalence of dyslipidemia in this population, with more than half of the patients presenting hypertriglyceridemia and almost 40% with low HDL levels, underscores the need for intensive lipid management[28]. There are also studies that have reported the association of ARV drugs with toxicological effects and the induction of oxidative stress through the generation of oxidative radicals that decrease the levels of antioxidant complexes. They have also associated it with mitochondrial toxicity and the development of dyslipidemia, which may explain the high risk of cardiovascular complications in PLHIV[29]. Sex hormones modulate lipid profiles: estrogens, which are present at higher levels in women, elevate HDL levels, whereas androgens, which are more prevalent in men, can reduce HDL levels[3]. In this study, HDL levels in the HIV-positive male population were lower compared to the female population. In two Latin American populations (Brazil and Colombia), low HDL levels (< 40 mg/dL) were reported in HIV-positive men[28,39]. The cholesterol ester transfer protein (CETP), which transfers cholesterol esters from HDL-C to proteins containing apolipoprotein B[30,31], is elevated in HIV infection. This increased CETP activity is inversely correlated with serum HDL levels[32], which may explain why these low HDL-C levels are present in PWHIV[33]. These factors, combined with the presence of hypertension in more than a third of the patients, shade a picture of high cardiovascular risk in individuals with HIV. The CVD is a comorbidity of HIV infection which has also been linked to ART exposure in the HIV-seropositive population[24]. It is known that comorbidity increases with HIV severity. The greater prevalence of comorbidities among PLHIV may be attributed to antiretroviral toxicity (e.g., diabetes, vascular disease, and liver disease) or caused by the HIV infection itself (e.g. vascular, pulmonary, and renal diseases)[34,35]. The use of ART has been associated with obesity. NNRTIss, PI, and integrase inhibitors (IIs) are among the most associated, as they are lipophilic and susceptible to diffusion in adipose tissue, which concentrates antiviral activity and is related to plasma antiviral concentrations[36,37]. The MetS is a clustering of cardiometabolic risk factors, including abdominal obesity, atherogenic dyslipidemia, hypertension, and hyperglycemia, all of which are strongly interrelated with insulin resistance[38]; therefore, there is an increased risk of CVDs and potential development of CVD. In the present study, we observed elevated levels of insulin resistance and hypertriglyceridemia in the general population, with no significant differences between genders (Table 1). In 2020, Melo et al. point out that PLHIV under treatment have a higher BMI and waist circumference, which are factors that increase the risk of CVD, also increasing insulin levels and the presence of insulin resistance[39]. Globally, it is estimated that the prevalence of MetS in the HIV-seropositive population is 29.6% (according to the ATPIII criteria), which is similar to that of study of Dzudzor[40]. In a study conducted by Sears et al., in 2019, the prevalence of MetS was 34% in an HIV-seropositive population from the Southern United States[41]. This percentage was also higher than in a population from Bologna, Italy, where the prevalence of MetS was 20.9%[37]. In the present study, 58% of cases presented metabolic syndrome (according to the WHO criteria) and 46.2% were overweight/obese status. In contrast, an HIV-seropositive population from Peru presented a prevalence of 52.70% for overweight and obesity[42]. However, another study conducted in India showed alarming percentages of 91% for both conditions in HIV-seropositive subjects[43], which is even higher than our study population.

MetS is an independent predictive factor of CVD in PLHIV; however, there is also a strong association between the increasing number of MetS components and the risk of CVD, emphasizing the importance of identification and management of all CVD factors in HIV-seropositive population under cART treatment[44]. There are other populations with a high prevalence of MetS, as observed in a study conducted in several populations from Latin America (Venezuela, Brazil, Colombia, Peru, and Ecuador), where PLHIV/AIDS showed a high prevalence of MetS[45]. According to the literature, the presence of MetS is positively

Table 3. Cardiovascular risk assessment according to the Framingham and D:A:D algorithmic models

Variable	Low risk (%)				Moderate risk (%)				High risk (%)				Very-high risk (%)			
	Framing-ham	D: A: D reduce d	D: A: D Full	p	Framing-ham	D: A: D reduced	D: A: D full	p	Framing-ham	D: A: D reduce d	D: A: D full	p	Framing-ham	D: A: D reduced	D: A: D full	p
Male (individuals)	1.37 (108)	0.48 (54)	0.48 (50)	0.002	13.40 (4)	2.35 (69)	2.49 (68)	0.007	NC (0)	6.96 (17)	6.95 (14)	0.99	31 (1)	12.76 (5)	18.45 (12)	0.02
Female (individuals)	1.31 (29)	0.47 (22)	0.42 (19)	0.06	NC (0)	2.64 (19)	2.12 (21)	0.934	NC (0)	NC (0)	5.34 (1)	–	31 (3)	NC (0)	NC (0)	–
Smoking (individuals)	2.10 (46)	0.58 (19)	0.57 (15)	0.02	12.67 (3)	2.90 (36)	2.50 (37)	0.0001	NC (0)	7.13 (10)	6.91 (7)	0.733	31 (1)	12.76 (5)	17.21 (9)	0.008
Non-smoking (individuals)	1.65 (62)	0.41 (37)	0.47 (32)	0.003	12.67 (3)	2.56 (44)	2.47 (47)	0.0001	NC (0)	7.11 (10)	7.43 (7)	0.99	31 (1)	13.24 (3)	18.33 (8)	0.126
< 40 years (individuals)	0.89 (41)	0.36 (62)	0.53 (59)	0.02	NC (0)	1.84 (26)	2.34 (28)	0.312	NC (0)	7.95 (1)	5.34 (1)	–	NC 0	NC 0	25 (1)	–
> 40 years (individuals)	1.38 (88)	0.66 (14)	0.62 (10)	0.96	13.40 (3)	2.59 (63)	2.67 (61)	<0.0001	NC (0)	6.90 (16)	6.95 (13)	0.90	31.00 (2)	12.80 (4)	17.86 (11)	<0.001
Diabetes (individuals)	0.88 (5)	NC (0)	NC (0)	–	11.20 (1)	2.33 (4)	3.06 (5)	0.421	NC (0)	5.73 (3)	6.66 (2)	0.540	31 (1)	NC (0)	NC (0)	–
Total CVR	Framing-ham	2.6%		DAD (R)	2.30%		DAD (F)	3.11%								

CVR: total cardiovascular risk; p < 0.05 after analysis of variance test are shown in bold.

Table 4. Multivariate analysis of risk factors according to the Framingham and D: A: D algorithmic models

Variable	OR (IC95%) unadjusted						OR (IC95%) adjusted by age and sex					
	Framingham (> 10%)	p	D: A: D reduced (> 1%)	p	D: A: D full (> 1%)	p	Framingham (> 10%)	p	D: A: D reduced (> 1%)	p	D: A: D full (> 1%)	p
Male	1.25 (0.726-2.15)	0.303	1.44 (1.01-2.05)	0.059	0.759 (0.510-1.26)	0.192	0.689 (0.121-3.92)	0.675	2.47 (0.69-6.08)	0.06	5.28 (1.34-20.8)	0.017
Female	0.581 (0.225-1.05)	–	0.738 (0.519-1.05)	–	1.20 (0.877-1.64)	–	–	–	–	–	–	–
Age (> 30 years)	1.05 (1.01-1.09)	0.601	2.90 (2.17-3.89)	<0.0001	3.91 (2.79-5.49)	<0.0001	82734463.245	0.999	23.47 (7.93-69.4)	<0.0001	34.8 (8.0-151.1)	<0.0001
Cholesterol (> 200 mg/dL)	1.32 (0.331-5.29)	0.692	1.32 (1.04-1.67)	0.033	1.33 (1.07-1.64)	0.020	0.688 (0.125-3.56)	0.637	0.620 (0.221-1.73)	0.620	0.62 (0.162-2.44)	0.503
Triglycerides (> 150 mg/dL)	NI	–	2.44 (1.34-4.44)	0.003	1.84 (1.01-3.36)	0.044	1.88 (0.316-11.27)	0.468	2.04 (0.905-4.61)	0.08	1.89 (0.61-5.83)	0.267
HDL (< 40 mg/dL)	2.13 (0.39-11.37)	0.367	0.594 (0.262-1.34)	0.209	0.718 (0.315-1.63)	0.430	0.853 (0.08-9.06)	0.468	0.555 (0.173-1.77)	0.322	0.409 (0.08-1.99)	0.269
Blood pressure (> 140/80 mmHg)	0.938 (0.891-0.981)	0.789	0.614 (0.545-0.639)	0.429	0.657 (0.588-0.733)	0.470	0.000	1.00	282770118.532	1.00	244108192.591	1.00
Current smoker	0.583 (0.140-2.43)	0.456	1.42 (1.12-1.80)	0.004	1.44 (1.15-1.79)	0.002	0.387 (0.07-2.08)	0.269	1.38 (1.15-2.06)	0.006	1.22 (1.08-1.78)	0.001
Former smoker	NI	–	1.13 (0.632-2.03)	0.674	1.24 (0.686-2.25)	0.472	NI	–	1.08 (0.462-2.53)	0.856	0.992 (0.120-1.42)	0.991
Diabetes	NI	–	1.80 (0.534-5.95)	0.331	2.34 (0.629-8.69)	0.193	NI	–	1.60 (0.343-7.52)	0.548	6.08 (0.5511-6.70)	0.141
Blood pressure background	NI	–	NI	-	0.657 (0.588-0.733)	0.470	NI	–	NI	-	0.491 (0.117-2.07)	0.333
CD4+ (< 350 cel/mm^3)	NI	–	0.838 (0.459-1.53)	0.564	0.878 (0.476-1.61)	0.675	NI	–	0.824 (0.362-1.87)	0.645	1.72 (0.544-5.44)	0.356
Years with cART (> 10)	NI	–	NI	–	2.06 (1.05-4.04)	0.033	NI	–	NI	–	0.968 (0.274-3.42)	0.960
Total cART	NI	–	NI	–	1.82 (0.960-3.48)	0.065	NI	–	NI	–	1.73 (0.526-5.69)	0.366
2NRTI + 1NNRTI	NI	–	NI	–	1.47 (0.946-2.27)	–	NI	–	NI	–	–	–
2INTR + 2IP	NI	–	NI	–	0.870 (0.650-1.00)	–	NI	–	NI	–	–	–

HDL: high-density lipoprotein; cART: highly active antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; IP: protease inhibitor; NC: variables not calculated due to a small number of individuals in the stratum; NI: variables not included in the model; p < 0.05 after multivariate analysis are shown in bold.

correlated with AI, being known as a good predictor for the presence of a cardiovascular event. Thus, the AI may be an important factor that affects the risk of CVD among PLHIV with HIV[46]. Regarding cardiovascular risk prediction, in 2019, Van Zoest et al. evaluated four algorithmic models for cardiac risk prediction in the ATHENA cohort find that the population living with HIV older than 40 years, in which lipid levels were increased compared to those < 40 years old in PLHIV[47]. Consistent with findings from other studies, our research also determined that individuals over the age of 40 were associated with elevated cholesterol levels and a high AI. The estimation of cardiovascular risk, as calculated by the Framingham score, was developed for the general population; however, its applicability to individuals living with HIV has not been well established[39]. For that reason, no significant differences were observed using the Framingham algorithm. The multivariate analyses performed in table 4 showed significant differences, particularly in the age groups over 30 years old, but specifically in the D: A: D reduced and D: A: D full algorithms. The D: A: D reduced and D: A: D full algorithms successfully identified groups at very high risk, where male sex, smoking, and age over 30 stood out as major risk factors. Once we adjusted for age and sex, the OR levels increased significantly to 23.4 and 34.8, respectively, with a $p < 0.0001$. These results underscore that of those groups that exhibited the highest risk among the studied patients. Therefore, this finding highlights the effective capability of the D: A: D reduced and D: A: D full algorithms in discerning patients with significantly elevated risks as shown in table 4. ASCVD prevention and treatment represent a major clinical challenge in PLHIV, who are now facing age-associated conditions under highly efficient cART. The performance of cardiovascular risk scores developed for the general population in PLHIV is debated, and it remains unclear which score is appropriate in clinical practice[23,48].

The assessment of cardiovascular risk in HIV patients on treatment reveals that the D: A: D full model provides a more accurate and higher risk estimation compared to the Framingham model, which tends to underestimate this risk. This is particularly relevant given that 65% of the patients are receiving specific treatment regimens, highlighting the need for using tailored assessment tools for this population. Within this research it can be observed that the most specific and sensitive model for the prediction of cardiovascular risk and possible development of pathologies is the D: A: D full model, in comparison with D: A: D reduced, ASCVD, Framingham, which could be established as a specific tool in the population living with HIV for the prediction of cardiac risk. This is consistent with the findings of van Zoest et al[47]. In this study involving PLHIV on cART, factors contributing to the increased risk and early onset of CVD were identified. In addition, the D: A: D and Framingham algorithmic models for estimating cardiovascular risk indicated a low-to-moderate risk, which may be attributed to the relatively young age of the population. Consistent with the findings of So-Armah et al.[49], the D: A: D model demonstrated greater specificity and sensitivity for estimating cardiovascular risk within a low-to-medium range among individuals living with HIV on ART.

Although there are several studies worldwide where predictive models for cardiovascular risk are evaluated, in the Mexican population there are no findings that determine the cardiac risk in PLHIV. In addition, this study found factors that increase the risk of presenting a cardiac event such as dyslipidemias and MetS, and it is also the first study that considers the D: A: D model that takes into account variables such as CD4+, viral load, years of exposure to ART, and types of inhibitors.

In conclusion, comparison of cardiovascular risk predictive models indicates that the Framingham model, which is designed for the general population, does not adequately capture the risk in individuals with HIV. Conversely, the D: A: D reduced and full models provide more precise and relevant estimations for this cohort. This finding underscores the critical importance of employing specific assessment tools for individuals with HIV on ART. Such tools enable more effective and personalized cardiovascular health management within this population. By accurately identifying high-risk individuals, healthcare providers can implement targeted interventions, potentially reducing morbidity and mortality associated with CVD in PLHIV. Future research should aim to refine these models and explore their applicability across diverse populations to further enhance their predictive power and clinical utility. In addition, healthcare policies should support the integration of these specialized tools into routine clinical practice to optimize care for this vulnerable group.

ACKNOWLEDGMENTS

This study was supported by the Department of Immunobiology at the Center for Biomedical Research, Autonomous University of Coahuila (Coah.), and Consejo Nacional de Humanidades, Ciencias y Tecnologías (CONACyT, Mexico).

SUPPLEMENTARY MATERIAL

Supplementary data are available at DOI: 10.24875/RIC.24000176. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

REFERENCES

1. Ray M, Logan R, Sterne JA, Hernández-Díaz S, Robins JM, Sabin C, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. AIDS (London, England). 2010;24(1):123-37.
2. Friis-Møller N, Ryom L, Smith C, Weber R, Reiss P, Dabis F, et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Eur J Prev Cardiol. 2016;23(2):214-23.
3. McManus H, O'Connor CC, Boyd M, Broom J, Russell D, Watson K, et al. Long-term survival in HIV positive patients with up to 15 Years of antiretroviral therapy. PloS one. 2012;7(11):e48839.
4. Yanqiao L, Shen L, Yutong M, Linghong S, Ben H. Comparison of GRACE and TIMI risk scores in the prediction of in-hospital and long-term outcomes among East Asian non-ST-elevation myocardial infarction patients. BMC cardiovascular disorders. 2022/01/09 ed2022. p. 4.
5. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, 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. The Journal of infectious diseases. 2010;201(3):318-30.
6. Law MG, Friis-Møller N, El-Sadr WM, Weber R, Reiss P, D'Arminio Monforte A, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV medicine. 2006; 7(4):218-30.
7. Freiberg MS, Chang C-CH, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. 2013;173(8):614-22.
8. Silverberg MJ, Leyden WA, Xu L, Horberg MA, Chao CR, Towner WJ, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. Journal of acquired immune deficiency syndromes (1999). 2014; 65(2): 160-6.
9. Marcus JL, Leyden WA, Chao CR, Chow FC, Horberg MA, Hurley LB, et al. HIV infection and incidence of ischemic stroke. AIDS (London, England). 2014;28(13):1911-9.
10. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of Clinical Endocrinology & Metabolism. 2007; 92(7):2506-12.
11. García-Peña AA, De-Vries E, Aldana-Bitar J, Cáceres E, Botero J, Vásquez-Jiménez J, et al. Cardiovascular Risk Prediction Models in People Living with HIV in Colombia. Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion. 2022;74(1):23-30.
12. Adela R, Banerjee SKJJodr. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: a translational prospective. 2015;2015.
13. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med. 2013;173(8):614-22.
14. Triant VA. Cardiovascular disease and HIV infection. Current HIV/AIDS reports. 2013;10(3):199-206.
15. Bergersen BM. Cardiovascular risk in patients with HIV Infection: impact of antiretroviral therapy. Drugs. 2006;66(15):1971-87.
16. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study. Clinical Infectious Diseases. 2011; 53(11):1130-9.
17. Ramspek CL, Jager KJ, Dekker FW, Zoccali C, van Diepen M. External validation of prognostic models: what, why, how, when and where? Clinical kidney journal. 2021;14(1):49-58.
18. D'Agostino Sr RB, Pencina MJ, Massaro JM, Coady SJGh. Cardiovascular disease risk assessment: insights from Framingham. 2013;8(1):11-23.
19. Grant SW, Collins GS, Nashef SAJEJoC-TS. Statistical Primer: developing and validating a risk prediction model. 2018; 54(2): 203-8.
20. Achhra AC, Lyass A, Borowsky L, Bogorodskaya M, Plutzky J, Massaro JM, et al. Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations. Current HIV/AIDS reports. 2021;18(4):271-9.
21. Cabrera-Rode E, Stusser B, Cálix W, Orlandi N, Rodríguez J, Cubas-Dueñas I, et al. Concordancia diagnóstica entre siete definiciones de síndrome metabólico en adultos con sobrepeso y obesidad. Revista Peruana de Medicina Experimental y Salud Publica. 2017;34:19-27.
22. Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R, et al. Homeostasis Model Assessment Is a Reliable Indicator of Insulin Resistance During Follow-up of Patients With Type 2 Diabetes. Diabetes Care. 2001;24(2):362-5.
23. Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2010;17(5):491-501.
24. Noumegni SR, Ama VJM, Assah FK, Bigna JJ, Nansseu JR, Kameni JAM, et al. Assessment of the agreement between the Framingham and DAD risk equations for estimating cardiovascular risk in adult Africans living with HIV infection: a cross-sectional study. Tropical diseases, travel medicine and vaccines. 2017;3:12.
25. Shen Y, Wang J, Wang Z, Qi T, Song W, Tang Y, et al. Prevalence of Dyslipidemia Among Antiretroviral-Naive HIV-Infected Individuals in China. Medicine (Baltimore). 2015;94(48):e2201-e.
26. Chen K, Shen Z, Gu W, Lyu Z, Qi X, Mu Y, et al. Prevalence of obesity and associated complications in China: A cross-sectional, real-world study in 15.8 million adults. Diabetes, obesity & metabolism. 2023;25(11):3390-9.
27. Madelain V, Le MP, Champenois K, Charpentier C, Landman R, Joly V, et al. Impact of obesity on antiretroviral pharmacokinetics and immuno-virological response in HIV-infected patients: a case–control study. Journal of Antimicrobial Chemotherapy. 2017;72(4):1137-46.
28. Noumegni SR, Nansseu JR, Bigna JJ, Ama Moor VJ, Kembe Assah F, Dehayem MY, et al. Atherogenic index of plasma and 10-year risk of cardiovascular disease in adult Africans living with HIV infection: A cross-sectional study from Yaoundé, Cameroon. JRSM cardiovascular disease. 2017;6:2048004017740478.
29. Gutiérrez-Pérez ME, Urraza-Robledo AI, Miranda-Pérez AA, Molina-Flores CA, Ruíz-Flores P, Delgadillo-Guzmán D, et al. Role of β-Klotho and Malondialdehyde in Metabolic Disorders, HIV Infection, and Antiretroviral Therapy. DNA and cell biology. 2022;41(7):691-8.
30. Feeney ER, Mallon PW. HIV and HAART-Associated Dyslipidemia. The open cardiovascular medicine journal. 2011;5:49-63.
31. Daminelli EN, Spada C, Treitinger A, Oliveira TV, Latrilha Mda C, Maranhão RC. Alterations in lipid transfer to high-density lipoprotein (HDL) and activity of paraoxonase-1 in HIV+ patients. Revista do Instituto de Medicina Tropical de Sao Paulo. 2008; 50(4):223-7.

32. Marín-Palma D, Castro GA, Cardona-Arias JA, Urcuqui-Inchima S, Hernandez JCJFii. Lower high-density lipoproteins levels during human immunodeficiency virus type 1 infection are associated with increased inflammatory markers and disease progression. 2018;9:1350.
33. Nou E, Lo J, Grinspoon SK. Inflammation, immune activation, and cardiovascular disease in HIV. AIDS (London, England). 2016; 30(10):1495-509.
34. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. American heart journal. 1991;121(1 Pt 2):293-8.
35. Nsagha DS, Assob JCN, Njunda AL, Tanue EA, Kibu OD, Ayima CW, et al. Risk factors of cardiovascular diseases in HIV/AIDS patients on HAART. The open AIDS journal. 2015;9:51.
36. Goulet JL, Fultz SL, Rimland D, Butt A, Gibert C, Rodriguez-Barradas M, et al. Do patterns of comorbidity vary by HIV status, age, and HIV severity? Clinical Infectious Diseases. 2007; 45(12):1593-601.
37. Lorenc A, Ananthavarathan P, Lorigan J, Banarsee R, Jowata M, Brook G. The prevalence of comorbidities among people living with HIV in Brent: a diverse London Borough. London journal of primary care. 2014;6(4):84-90.
38. SeyedAlinaghi S, Afsahi AM, Moradi A, Parmoon Z, Habibi P, Mirzapour P, et al. Current ART, determinants for virologic failure and implications for HIV drug resistance: an umbrella review. AIDS research and therapy. 2023;20(1):74.
39. Melo ES, Antonini M, Costa CRB, Sorensen W, Gir E, Reis RK. Evaluation of cardiovascular risk factors in people living with HIV in São Paulo, Brazil. The Journal of Infection in Developing Countries. 2020;14(01):89-96.
40. Dzudzor B, Essel S, Musah L, Agyekum JA, Yeboah K. Metabolic Syndrome and Combination Antiretroviral Therapy in HIV Patients in Periurban Hospital in Ghana: A Case-Control Study. AIDS research and treatment. 2023;2023:1566001.
41. Sears S, Buendia JR, Odem S, Qobadi M, Wortley P, Mgbere O, et al. Metabolic Syndrome Among People Living with HIV Receiving Medical Care in Southern United States: Prevalence and Risk Factors. AIDS and Behavior. 2019:1-10.
42. Calza L, Colangeli V, Magistrelli E, Rossi N, Rosselli Del Turco E, Bussini L, et al. Prevalence of metabolic syndrome in HIV-infected patients naive to antiretroviral therapy or receiving a first-line treatment. HIV Clinical Trials. 2017;18(3):110-7.
43. Nguyen KA, Peer N, Mills EJ, Kengne AP. A meta-analysis of the metabolic syndrome prevalence in the global HIV-infected population. PloS one. 2016;11(3):e0150970.
44. Hidalgo JA, Florez A, Agurto C, Pinedo Y, Ayarza R, Rodriguez L, et al. Metabolic and Cardiovascular Comorbidities Among Clinically Stable HIV Patients on Long-Term ARV Therapy in Five Ambulatory Clinics in Lima-Callao, Peru. Open AIDS J. 2018;12:126-35.
45. Worm SW, Sabin CA, Reiss P, El-Sadr W, Monforte A, Pradier C, et al. Presence of the metabolic syndrome is not a better predictor of cardiovascular disease than the sum of its components in HIV-infected individuals: data collection on adverse events of anti-HIV drugs (D:A:D) study. Diabetes Care. 2009;32(3):474-80.
46. Theengh DP, Yadav P, Jain AK, Nandy P. Assessment of metabolic syndrome in HIV-infected individuals. Indian journal of sexually transmitted diseases and AIDS. 2017;38(2):152-6.
47. van Zoest RA, Law M, Sabin CA, Vaartjes I, van der Valk M, Arends JE, et al. Predictive Performance of Cardiovascular Disease Risk Prediction Algorithms in People Living With HIV. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2019;81(5):562-71.
48. Silva AG, Paulo RV, Silva-Vergara ML. Subclinical Carotid Atherosclerosis and Reduced DAD Score for Cardiovascular Risk Stratification in HIV-Positive Patients. Arquivos Brasileiros de Cardiologia. 2020;114(1):68-75.
49. So-Armah K, Benjamin LA, Bloomfield GS, Feinstein MJ, Hsue P, Njuguna B, et al. HIV and cardiovascular disease. 2020; 7(4):e279-e93.