

# Characterization of cardiovascular risk factors and Framingham score in an HIV-1 population

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## Abstract

With the advent of high-potency antiretroviral treatment introduced in 1996, HIV infection ceased to be an acute and deadly disease to become chronic and controllable.

However, the early aging of this population, which according to some authors and cohorts, is 10 years less than in the "normal" population, has been studied.

Although the realities of these patients comorbidities are well known, the definition of time, when and how or with what to treat still seems to be a matter of debate.

The aim of this study is to evaluate the incidence and prevalence according to the state of the art for the non-HIV population of cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus) and apply the adjusted Framingham Risk Score by recording analytical and clinical factors in an HIV-1 population with more than 50 years of age, followed in the Infectious Diseases Service for more than 6 months.

**Keywords:** cardiovascular risk factors; HIV-1 population; Infectious Diseases

## Introduction

The introduction of Antiretroviral Therapy (ART) has led to a change in the paradigm of Human Immunodeficiency Virus (HIV) infection/Acquired Immunodeficiency Syndrome (AIDS). A condition viewed in the past as rapidly progressive and lethal is now seen as a chronic disease, with the different drugs allowing for an increase in survival rates and improvement in the quality of life. As expected, age related diseases are becoming a more frequent topic in HIV clinics [1].

Although mortality rates in an HIV population are 3 to 15 times superior to the general population, more than half are due to non-infectious complications, such as cardiovascular diseases, essential hypertension, diabetes and chronic kidney disease [1, 2]. These comorbidities are the result of a complex interaction between the virus, the host and ART. The virus is responsible for a state of chronic inflammation with endothelial hypercoagulation [2]. Several studies have showed that uncontrolled viral replication is an independent risk factor for lipid changes such as LDL and triglycerides increase, as well as lowering of HDL [3, 4]. Another mechanism that seems to be present, is the homeostasis of the fat tissue, with HIV promoting a state of lipodystrophy with redistribution of fat, with an increase in visceral deposition. There seems to be also an increase in endothelial inflammation with significant impact in the vulnerable atherosclerotic plaques, related to lymphocytes T CD4<sup>+</sup> nadir and the number of HIV copies/ mL in the blood [2, 3, and 5].

The host plays an essential role, not only due to genetic factors that increase the cardiovascular risk *per se*, but also for other comorbidities and therapeutics. Age, male gender and genetics, are non-modifiable features that influence cardiovascular risk. On the other spectrum, modifiable factors like life style, exercise, smoking, alcohol and other drugs also influence the risk of cardiovascular events and precocious death, with HIV population having a higher prevalence of the last factors mentioned [2, 3].

Last but not least, ART therapy has been associated with lipid changes not fully understood yet. Over the years, there have been several studies with controversial results, with the Swiss HIV Cohort showing a rapid increase in total cholesterol, LDL and HDL after the beginning of ART, contrasting with MACS cohort in which the levels decreased after ART [7, 9, and 10].

All the current guidelines recommend cardiovascular disease prevention, starting with the risk assessment and adjusting treatment to each patients individual profile and risk. Despite the several studies, it is still difficult to define the exact risk score values that should motivate an immediate pharmacological intervention [6, 9, and 12]. Therefore, risk categories were defined to help design an individual approach for each patient according to their specific probability of a cardiovascular event [9]. According to the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), physicians should do a systematic risk evaluation of family history of cardiovascular diseases,

smoking, essential hypertension, diabetes and lipid changes. If in healthy individuals this assessment should be made every 5 years after 40 years of age in men and 50 years of age in women, the presence of a condition like HIV should illicit an earlier assessment and intervention if necessary [12].

There are a number of cardiovascular risk scores that assess the probability of an event at 5 years, like the D.A.D. score or a 10year event like Framingham or PROCAM. In the several studies, it seems to be consensual that the D.A.D. score overestimates the 5year risk in HIV patients when compared to Framingham or PROCAM scores. On the opposite side, Framingham underestimates the percentage of low risk HIV patients [6, 9]. Based upon this, Giovanni Guaraldi proposed that Framingham risk score should be adjusted to this specific population, by adding 10 years to the real patient age in order to standardize the results and allow a more rigorous assessment [1, 13]. Patients are considered to be of low risk if they present with an adjusted Framingham score of less than 10%; moderate risk if the percentage stays between 10 and 20 and high risk when above 20%. By defining this, the physician can define an individual strategy towards controlling the risk factors and preventing cardiovascular events.

**Methods**

We conducted a retrospective transversal observational study, by which we characterized a population with HIV-1, with more than 50 years of age in 2019, followed in the Infectious Diseases Service at Hospital Pedro Hispano for more than 6 months. We evaluated their demography, their cardiovascular risk factors, including age and gender, as well as smoking, essential hypertension, diabetes and lipid changes. We also recorded characteristics of their HIV, such as number of years with the disease, treatment, number of lymphocytes T CD4+ and T CD8+ cells and viral load of the virus at each appointment. We later proceeded to analyse their Framingham score and adjusted Framingham score.

The statistical treatment of the data was conducted through Excel and IBM SPSS®, version 20. The study was conducted according to the recommendations of the Declaration of Helsinki of the World Medical Association.

**Results**

In table 1 we present the sociodemographic characteristics of our 160 appointments, where 75% were man, with a mean age of 60 years old. Patients were infected with HIV between 2 and 31 years, with a mean number of years of infection of 13 and the main form of transmission being sexual in 87.5% of the cases.

Regarding the infection *per se*, the mean viral load of patients was 97 [0-14366] copies/μL, with most patients having zero copies (89%, n=143). The mean number of TCD4+ cells was 663 [148-1430] and TCD8+ cells was 887 [271-3356]. A total of 47 patients (29%) were defined to have AIDS.

Total	160
Male gender	120 (75%)
Mean age (years)	60
Number of years with HIV (mean)	13,125
Transmission form	
. Sexual	140 (87.5%)
. Intravenous drug use	20 (12.5%)
Characteristics of HIV infection	
. Viral load (mean, copies/μ)	97,81
. Lymphocytes T CD4+ (mean, cells/μ)	663,8
. Lymphocytes T CD8+ (mean, cells/μ)	887,16
AIDS	47 (29%)

**Table 1.** Sociodemographic characteristics

When looking for deeper characterization of HIV infection, we found that most patients – 50.6% (n=81) were in CDCs stage A1 at the time of the appointment, followed by 15.6% in stage A2 or C1 (n=25) and 13.1% (n=21) in stage C2 – see table 2.

A1	81	50,6%
A2	25	15,6%
A3	0	0,0%
B1	5	3,1%
B2	2	1,3%
B3	0	0,0%
C1	25	15,6%
C2	21	13,1%
C3	1	0,6%
Total	160	100,0%

**Table 2.** CDC Stage of HIV infection

A total of 47 patients had an AIDS defining disease through the course of their condition, in which *Pneumocistis jirovecii* was the most common (n=12), followed by pulmonary tuberculosis (n=10) and non-Hodgkin Lymphoma (n=6). The mean number of years between diagnosis of HIV and opportunistic disease was 10 years.

When looking at the therapy used, the most used drugs belonged to the class of integrase Inhibitors (INIs) used in 97 patients (60.6%) immediately followed by Nucleoside analogue reverse-transcriptase inhibitors (NRTIs) used in 96 patients (60%) – Table 3.

	n	%
<b>NRTIs</b>		
TDF/FTC	30	19
ABC/3TC	63	39
AZT/3TC	3	2
<b>Total</b>	<b>96</b>	<b>60</b>
<b>NNRTIs</b>		
ETR	31	19
EFV	27	17
NVP	11	7
RLP	2	1
<b>Total</b>	<b>71</b>	<b>44.3</b>
<b>b/PI</b>		
DVR/r	19	12
LPV/r	5	3
<b>Total</b>	<b>24</b>	<b>15</b>
<b>INIs</b>		
RAL	81	51
DTG	16	10
<b>Total</b>	<b>97</b>	<b>60.6</b>
<b>CCR5</b>		
MVC	3	2
<b>COMBINATION THERAPY</b>		
TDF/FTC/EFV	6	4
TDF/FTC/RLP	6	4
TAF/FTC/EVG/C	4	3
TAF/FTC/RLP	2	1
<b>Total</b>	<b>18</b>	<b>11.2</b>

**Table 3.** ART in this HIV population

Concerning the cardiovascular risk factors and events, 36% (n=58) of our patients were smokers; 43% (n=69) had essential hypertension; 16% (n=26) had diabetes and the biggest percentage was towards dyslipidaemia, with 86% of patients (n=138) having this disturbance.

When looking at the events, 9 patients had myocardial infarctions and there were a total of 4 ischemic strokes (3 in one patient alone).

For further characterization, we found that the mean total cholesterol of our population was 179 [101-287] mg/dL, the mean LDL was 108 [42-195] mg/dL the mean HDL was 49 [24-106] mg/dL and the mean triglycerides was 119 [41-993] mg/dL. Finally, we looked at Framingham risk score and the adjusted score like Guaraldi suggested. We found that most patients, 66% (n=106) had a high risk of 10year mortality and events in the adjusted Framingham risk score compared to 48% (n 77) in the non-adjusted risk score – Table 4. A total of 10 patients switched from low risk to moderate risk and 29 patients switched from moderate risk to high mortality risk, when changing from the general score to the adjusted one.

	Framingham risk score		Adjusted framingham risk score	
	n	%	n	%
<b>Low risk</b>	31	19	21	13
<b>Moderate risk</b>	52	33	33	21
<b>High risk</b>	77	48	106	66

**Table 4.** Framingham and adjusted Framingham Risk Score

## Discussion

We conducted this analysis in order to characterize a specific HIV population with over 50 years of age that will undoubtedly increase over the next years due to better diagnosis, better care and bigger variety of ART available [14]. Most of our patients were male and contracted the disease through risk sexual contacts, which is in accordance to the Portuguese report regarding HIV/ AIDS infection in 2019 that shows 14.2 male cases per 10<sup>5</sup> people *versus* only 5.1 female cases per 10<sup>5</sup> people and more than 80% being transmission through sexual contact [15].

Another highlight of our cohort, is the fact that most of our patients are probably very well adherent to ART. One can speculate about this fact since mean viral load didn't reach 100 [0-14366] copies/μL and mean TCD4<sup>+</sup> was above 500 [148-1430] cells/μL. Alongside, the fact that most of our patients are in the A1 clinical stage which corresponds to having over 500 T CD4<sup>+</sup> cells/μL and no opportunistic infection.

When looking at AIDS defining conditions, of our 47 patients, the most common one was *Pneumocystis jirovecii* infection, followed by Pulmonary Tuberculosis. According to the 2019 Portuguese report on HIV/ AIDS infection, *Pneumocystis jirovecii* was still the most common opportunistic condition representing 34.5% of all AIDS defining diseases in Portugal in 2018 [15]. On the other hand, Pulmonary Tuberculosis was less frequent in the report, represented in 11.9% of people with AIDS, coming only after Oesophageal Candidiasis and Cytomegalovirus infection [15].

As expected, the most frequently used class of ART were INIs and NRTIs. These are first-line therapeutics in naïve patients, with Raltegravir being the most frequently used medication [16].

When looking at the cardiovascular risk factors, dyslipidaemia was the most frequent risk factor in agreement several series in the literature. For example, the HOPS study group reports a prevalence of 81% in HIV positive men and 67% among HIV women [17], while ours reports a prevalence of 86% among total population. The second most prevalent risk factor was essential hypertension, present in almost half the patients included. This is also in accordance to several cohorts, with the same HOPS sample mentioning between 54.4 and 57.4% of the HIV population having essential hypertension [17]. Last but not least, diabetes was present in 16% with the MACS cohort mentioning a similar prevalence of 14% (2, 18).

By analysing the Framingham risk score, we realize that most of our patients had a high risk of myocardial infarction or death at 10 years, meaning a risk above 20%. This was the case in both the Framingham and the adjusted Framingham risk score, with the later one including 29 more patients than the first one. As we know, the accuracy of these risk scores for predicting cardiovascular events in HIV-infected patients is not well established [6]. In the Nery *et al* cohort, only 5.7% of the patients were classified as having high risk, but with a different, younger, population [6]. On the other hand, by applying the adjusted score, the authors also found an increase in the number of patients classified as having intermediate or high score, as expected [6, 9]. According to Pris *et al*, Framingham risk score underestimated the cardiovascular event risk in their HIV population, defending that a high proportion of patients classified as having low risk, had already subclinical atherosclerosis [9]. Although a high proportion of our patients had a high risk score, it would be interesting to evaluate if the patients with a low or moderate risk score, already had atherosclerotic changes.

## Conclusion

Due to notable extension of life expectancy in HIV-infected patients, cardiovascular complications are becoming more frequent as this population ages. This indicates the necessity of routine screening, appropriate monitoring and management of the broad spectrum of risk factors contributing to cardiovascular complications. Although the several risk scores help stratify the risk of these events, these equations were not developed to assess cardiovascular risk in HIV-infected patients, and their accuracy in this population is still uncertain. A different tool, validated and appropriate for an HIV population is needed, instead of an adjustment of the existing ones.

## Conflicts of interest

**Sara Moreira Pinto** declares no conflicts of interest.

**Clara Batista** declares no conflicts of interest

**R. Correia de Abreu** declares to have received honorary fees from Gilead Sciences, Janssen, ViiV / GlaxoSmithKline and Merck Sharp & Dohme and research funding from Merck Sharp & Dohme.

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