CARDIOVASCULAR RISK MEASUREMENT TOOLS IN PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS: A SCOPING REVIEW

FERRAMENTAS MENSURADORAS DO RISCO CARDIOVASCULAR EM PESSOAS VIVENDO COM VÍRUS DA IMUNODEFICIÊNCIA HUMANA: UM SCOPING REVIEW

ABSTRACT

Objective: to map scientific evidence of cardiovascular risk measurement tools that are used in people living with human immunodeficiency virus. Method: scoping review, following the Joanna Briggs Institute guidelines, using two data portals to survey the studies. The protocol was reported according to recommendations of the PRISMA-ScR (PRISMA extension for Scoping Review) checklist and was registered in the Open Science Framework under DOI 10.17605/OSF.IO/Z3CMQ (https://osf.io/z3cmq/). Results: five tools for measuring cardiovascular risk were identified: Framingham Cardiovascular Risk Score (FRS), Prospective Cardiovascular Munster (PROCAM), Systemic Coronary Risk Evaluation (SCORE), Progetto CUORE, Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) risk equations (D:A:D). Among these tools, only the D:A:D score was built specifically for people living with the human immunodeficiency virus, while the others were designed for the general population. Conclusion: we highlight the relevance, for the Brazilian public health, of building specific instruments to measure cardiovascular risk in people living with the human immunodeficiency virus, adopting more robust statistical techniques.

Descriptors: Risk; Risk Assessment; Cardiovascular Diseases; HIV; Review.

RESUMO


Descritores: Risco; Medicação de Risco; Doenças Cardiovasculares; HIV; Revisão.
extensionforScopingReview), quedando registrado en el Open Science Framework bajo el DOI 10.17605/OSF.IO/Z3CMQ (https://osf.io/z3cmq/). **Resultados:** se identificaron cinco herramientas para medir el riesgo cardiovascular: Framingham Cardiovascular Risk Score (FRS), Prospective Cardiovascular Munster (PROCAM), Systemic Coronary Risk Evaluation (SCORE), Progetto CUORE. Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) risk equations (D:A:D). Entre estas herramientas, sólo la puntuación D:A:D se creó específicamente para las personas que viven con el virus de la inmunodeficiencia humana; las demás están dirigidas a la población general. **Conclusión:** destacamos la relevancia, para la salud pública brasileña, de la construcción de instrumentos específicos para la medición del riesgo cardiovascular en personas que viven con el virus de la inmunodeficiencia humana, adoptando técnicas estadísticas más robustas. **Descriptores:** Riesgo; Medición de Riesgo; Enfermedades Cardiovasculares; VIH; Revisión.

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**INTRODUCTION**

Worldwide, in the year 2020, 37.6 million people living with human immunodeficiency virus (HIV) were reported to be living with HIV, with a global decrease in new infections driven by substantial reductions in some regions, such as the Caribbean (29%), West and Central Africa (25%), Central Europe and North America (15%). In contrast, the epidemic continued to grow in Eastern Europe and Central Asia, with new HIV infections increasing by 72% between 2010 and 2019. There were also increases in the Middle East and North Africa (22%) and Latin America (21%).¹

In Brazil, 32,701 new cases were registered² and, since 2012, there has been a decrease in the acquired immunodeficiency syndrome (AIDS) detection rate, with a decrease of 18.7%. It is noteworthy that the treatment already reaches 81% of people diagnosed with HIV throughout the country.² Therefore, this reduction in the AIDS detection rate is justified, mainly, by the introduction of antiretroviral therapy (ART), which is a strategy used worldwide. Since its implementation, there has been a progressive decrease in mortality from opportunistic infections in this population, such as tuberculosis, pneumonia, Kaposi’s sarcoma, candidiasis, cytomegalovirus, among others, providing an increase in life expectancy.³⁻⁴

Despite the effectiveness of ART, there is evidence of its adverse effects, especially the increased risk of developing cardiovascular disease (CVD) in the HIV-positive population when compared with the general population⁵⁻⁶, and these diseases are currently presented in the literature as one of the leading causes of mortality in people living with HIV.³ The increased rates of CVD in the HIV population may be related to physiological factors of the virus itself, metabolic disorders associated with the use of ART and traditional risk factors such as obesity, heredity, sedentary lifestyle, alcohol use and high rates of smoking.⁷

Thus, regular screening and the targeting and treatment of conditions that predispose to CVD in this public should have high priority⁸⁻⁹, because the control of cardiovascular risk (CVR)
in this clientele is related to the early detection of cardiac dysfunction, a diagnosis that is facilitated with the use of measuring instruments. Thus, it is necessary to know methods of risk stratification for HIV-positive population because such tools may better identify HIV patients who are at high risk of CVD.

**OBJECTIVE**

The objective of this study was to map scientific evidence of CVR measuring tools used in people living with HIV

**METHOD**

This is a scoping review, developed according to the method of the Joanna Briggs Institute (JBI). The protocol was reported according to the recommendations of the PRISMA-ScR (PRISMA extension for Scoping Review) checklist and registered in the Open Science Framework under DOI 10.17605/OSF.IO/Z3CMQ.

The study was conducted from the following phases: definition and alignment of objectives and question; development and alignment of inclusion criteria, with objectives and question; description of the planned approach for evidence search, selection, data extraction and presentation of evidence; search for evidence; evidence selection; evidence extraction; evidence analysis; presentation of results; summary of evidence in relation to the review objective, drawing conclusions and noting any implications of the results.

The Population, Concept, and Context (PCC) strategy was used to define the question, with "Q" being people living with HIV; "C" (concept), cardiovascular risk measurement tools; and "C" (context), health area. Thus, the following guiding question was defined: What are the tools (scores/instruments) for measuring cardiovascular risk used in people living with HIV and how are they characterized?

The studies selected for inclusion were full-text studies, available in full, with instrument or score measuring the CVR used in people living with HIV, in which was present the reference of its creation or validation for consultation of the original tool. The type of article, date of publication, language or language was not limited, but documents related to protocols and manuals were not included in the search. Studies were searched from June to July 2021.

In the search strategies, the following Health Science Descriptors (DeCS) were applied: (Risk) OR ("Risk measurement") AND ("Cardiovascular Diseases") AND (HIV); and Medical Subject Headings (MeSH): ((("Risk" [Mesh]) OR "Risk Assessment" [Mesh]) AND "Cardiovascular Diseases" [Mesh]) AND "HIV" [Mesh]. The first step was a search in the Virtual Health Library (VHL). The second step was carried out in the National Library of Medicine (PubMed). In the third step, the reference list of all included studies was checked, and thus additional studies were searched.

The search was conducted through independent reading and by peers, to maintain methodological rigor, with discussions among the authors to make decisions about the inclusion of some studies. This step was performed by four of the five authors. Finally, the authors analyzed titles, abstracts, and descriptors of the studies found. The selected studies that met the eligibility criteria were read in full and the data were entered into an instrument created by the authors in Excel, version 2016 of the Microsoft Office suite pack.
To export the articles to the database, we used information contained in the studies, such as title; measurement instrument used and its variables; year of publication; and continent where the study was conducted. The exportation to the database was done by three of the five authors, after the analysis of all the evidences.

RESULTS

Initially, 534 articles were identified in the data portals for selection of studies and three were included from the search in the reference list, totaling 537 studies. After reading the title, abstract, keywords, and checking for duplicates, 412 were excluded, leaving 125 studies. Then, after reading each study in full, 113 studies were excluded because the analyzed studies did not present the reference of the creation or validation of the evidenced instrument, making it impossible to consult the original tool. Meanwhile, 12 studies were included in this review, of which nine were identified by searching the data portals and the others were added in the third stage of the search, from the analysis of the list of references (Figure 1).

Figure 1. Diagram of the inclusion and exclusion process of the studies. Fortaleza, Ceará, Brazil, 2021. Source: PRISMA Flow Diagram for the scoping review process\textsuperscript{11,13}.

The studies were published in the years 2004 to 2017, predominantly developed in the continents of Europe and North America (Chart 1). Five tools were identified for measuring the CVR, used in people living with HIV, but only one was built in a way directed to the public with HIV, considering the characteristics and specificities of this population. Chart 2 shows the measurement tools found in the studies and describes the variables used for CVR prediction. It is noteworthy that none of the tools found underwent analysis of their psychometric properties.
<table>
<thead>
<tr>
<th>Title</th>
<th>Type of Study</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Identifying HIV patients with an unfavorable cardiovascular risk profile in the clinical practice: Results from the SIMONE study”</td>
<td>Multicenter cross-sectional study</td>
<td>2008</td>
</tr>
<tr>
<td>“The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study”</td>
<td>Prospective observational study</td>
<td>2006</td>
</tr>
<tr>
<td>“Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects”</td>
<td>Cross-sectional study</td>
<td>2004</td>
</tr>
<tr>
<td>“Comparison Between the Framingham and Prospective Cardiovascular of Münster Scores for Risk Assessment of Coronary Heart Disease in Human Immunodeficiency Virus–Positive Patients in Pernambuco, Brazil”</td>
<td>Cross-sectional study</td>
<td>2010</td>
</tr>
<tr>
<td>“Global Cardiovascular Risk in Patients with HIV Infection: Concordance and Differences in Estimates According to Three Risk Equations (Framingham, SCORE, and PROCAM)”</td>
<td>Cross-sectional study</td>
<td>2007</td>
</tr>
<tr>
<td>“Suboptimal primary and secondary cardiovascular disease prevention in HIV-positive individuals on antiretroviral therapy”</td>
<td>Cross-sectional cohort analysis</td>
<td>2017</td>
</tr>
</tbody>
</table>
“Cardiovascular risk score change in HIV-1-infected patients switched to an atazanavir-based combination antiretroviral regimen”

Cohort study 2008

“Cardiovascular risk assessment in persons with HIV infection in the developing world: comparing three risk equations in a cohort of HIV-infected Thais”

Cross-sectional analysis 2011

“Lipid-lowering effect and changes in estimated cardiovascular risk after switching to a tenofovir-containing regimen for the treatment of HIV-infected patients”

Observational study 2016

“Plasma plasminogen activator inhibitor-1 predicts myocardial infarction in HIV-1-infected individuals”

Case-control study 2014

Chart 2. Characterization of cardiovascular risk measurement tools in people living with HIV. Fortaleza, Ceará, Brazil, 2021.

<table>
<thead>
<tr>
<th>Tool</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Cardiovascular Risk Score (FRS)</td>
<td>Gender, Age, Smoking, Diabetes, Blood Pressure, LDL-Cholesterol, HDL-Cholesterol</td>
</tr>
<tr>
<td>Prospective Cardiovascular Munster (PROCAM)</td>
<td>Family history, Gender, Age, Smoking, Diabetes, Blood Pressure, LDL-Cholesterol, HDL-Cholesterol</td>
</tr>
<tr>
<td>Systemic Coronary Risk Evaluation (SCORE)</td>
<td>Age, Gender, Smoking, Blood pressure, Total cholesterol ratio, High-density lipoprotein cholesterol (TC / HDL)</td>
</tr>
<tr>
<td>Progetto CUORE</td>
<td>Age, Smoking, HDL, Systolic blood pressure, Total cholesterol, Diabetes, Drug treatment for hypertension, Family History</td>
</tr>
<tr>
<td>Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) risk equations (D:A:D)</td>
<td>Gender, Age, Smoking, Family history, Systolic blood pressure, CD4 cell count, Total cholesterol</td>
</tr>
</tbody>
</table>
DISCUSSION

The mapping of the studies performed in this review allowed us to identify five tools to measure the CVR used in people living with HIV, of which it is valid to discuss initially the Framingham Cardiovascular Risk Score (FRS), since it is one of the best-known and most widely used CVR measurement scores worldwide. The FRS aims to analyze the probability of occurrence, in a 10-year period of coronary events in patients who do not present symptoms of any CVD. The statistical technique applied in the development of the tool was Cox proportional hazards regression.26-28

To measure cardiovascular risk, the FRS uses the variables presented in chart 2. The score described in each variable considers the sex of the individual, because there is a differentiation in the scoring table, with specific values according to gender.26 Based on the percentage, acquired through the score result, it is possible to perform the risk stratification, divided into low, medium, and high risk. The stratification of the result makes it possible to define the best intervention, with the purpose of preventing cardiovascular events.5

Among the advantages of the FRS, evidenced in literature, is its ease of application in the population and the possibility of performing an appropriate clinical management, according to the degree of risk presented.29-30 However, it was found that the instrument has limitations in the accuracy of risk factors in some populations, namely: Asians, Europeans and people living with HIV, because its score was developed for the general population, without considering the context and the specificities of each population.25-29

The Prospective Cardiovascular Munster Study (PROCAM) was initiated in 1979 in Munster, Europe, by Gerd Assmann and colleagues, and in 2002, the same researchers developed the PROCAM score.31-33 This score was constructed with the aim of determining the prevalence of risk factors, improving the prediction of CVD and, consequently, assisting in the early detection of these diseases in the German population.32 The statistical technique used was also the Cox proportional hazards model, applying a total of eight variables (Chart 2).33

Unlike the tools already presented, the Systemic Coronary Risk Evaluation (SCORE) is applied to estimate the 10-year chances of fatal cardiovascular events, not considering non-fatal events.34 It was developed in Europe, using the Weibull model, and includes six variables (Chart 2).35 A significant factor of the SCORE is that its use allows estimating the risk of fatal CVD in the population, but it becomes limited by not considering non-fatal cardiac events.34

Another measurement score evidenced was the Progetto CUORE, developed in Italy, by means of the Cox proportional hazards model.36 It was created with the objective of evaluating the risks for the development of cardiovascular diseases in 10 years for men and women, using eight variables (Chart 2).36-37 The CUORE score presents an accuracy of the CVR, because it considers a greater number of variables/risk factors, besides considering fatal and non-fatal cardiovascular events.38
The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group was identified as a multicenter study involving 11 cohorts of HIV-positive patients treated in 212 clinics in the United States, Europe, Argentina, and Australia, with algorithms developed specifically for this population. The DAD score was formulated from Cox regression models for HIV-positive patients who have no pre-existing CVD and are under exposure to adverse events of ART. It was first published in 2010 and considered CD4 count, Abacavir use, and time of exposure to protease inhibitors and nucleoside reverse transcriptase inhibitors, in addition to the classical CVR factor. In 2016, to simplify the risk stratification of HIV-positive patients and because of the difficulty in assessing previous ART regimens, such as information retrieval, a modification of the DAD score was published, assessing the same clinical outcomes at five years, but not using the classes and time of ART exposure.39-40 The DAD score is one of the most used instruments in people living with HIV, because this score uses HIV-related factors such as CD440-41 lymphocyte count.

The risk measurement in this instrument is validated by the variables presented in Chart 2.42 Despite the use of these variables, in clinical practice it is recommended to verify the risk factors that may influence the increase in CVR, highlighting, among these factors, the history of antiretroviral treatment and drugs used in treatment.40

Through the data survey, it was possible to identify that the Framingham Heart Study and DAD are the most widely used tools in people living with HIV today, because of the ease of applicability and accuracy of the results presented. When compared with DAD, the FRS shows a 2.9% increase in the number of individuals present in the high-risk group for CVD development, totaling 5.7%. This increase is mainly due to the high-sensitivity C-reactive protein (hsCRP), which is a marker for inflammation independent of the CVR.18

The application of these two tools for measuring the CVR was performed in a cohort study in Thailand as a comparative method. The study used 785 individuals and found that the Thai population living with HIV has a low CVR, which is explained by the almost non-existent cardiovascular risk factors, since the study population already has professional follow-up for maintenance and control of CVR. Moreover, through the study, it was possible to identify that the FRS predicted a higher cardiovascular risk when compared to the DAD, however, the analyzed results did not have a great impact for the individual.23

In Denmark, a matched case-control study of 54 cases and 54 controls used the FRS and DAD to assess the association of biomarkers with acute myocardial infarction (AMI) in people living with HIV, considering factors such as age, sex, smoking, and duration of ART adherence. After analysis, the study identified that C-reactive protein (CRP), a biomarker, at high levels was associated with the risk of developing AMI and, according to the authors, the use of biomarkers for CVD should be taken into consideration in the applications of CVR measuring tools.25

Given the above, it is noteworthy that the Brazilian Ministry of Health (MH) recommends that the CVR be assessed in all people living with HIV/AIDS, both in the initial approach and at each change in ART, via Framingham risk score5. In contrast, the literature points to the possibility that this measure does not perform as expected in this population, because the CVR spectrum in people living with HIV differs from that of patients in usual primary prevention.43
This may be derived from the type of population in which the Framingham study was developed, as well as the definition of events and follow-up time of the cohorts.\textsuperscript{44,45} In addition, one finds the DAD score, which was developed from a global equation of predictive CVD risk, specially adapted for people with HIV. On the other hand, the DAD study population is slightly young and predominantly European.\textsuperscript{39} Thus, it is evident that there is no instrument to measure CVR, specifically directed to people living with HIV in Brazil. Therefore, it is a priority for public health, since the determination of the CVR, through tools adapted to this population, should be seen as routine in the care provided.\textsuperscript{45}

The use of cardiovascular risk measurement tools has become indispensable in health services, especially in primary care, which works as the individual's gateway to health services, especially for people living with HIV, especially those who are in a situation of vulnerability, in different spheres.\textsuperscript{8} Its use benefits the early detection of CVR, which consequently favors the development of individual and collective preventive measures that are effective for the control of this risk, such as the control of modifiable/non-modifiable risk factors, contributing to the well-being of the person.\textsuperscript{23}

Finally, the limitations of this scope review are since the methodological quality of the evidence that used the selected scores was not evaluated, because, for scope reviews, this is not recommended.\textsuperscript{12} Moreover, in future studies, it is recommended to conduct searches with greater refinement and expansion of databases, as well as the use of other descriptors and other cross-references.

\textbf{CONCLUSION}

This review mapped scientific evidence that presented scores for measuring the CVR in people living with HIV. Five different tools were found, among which the FRS stands out because it is used worldwide and is the measure adopted by the Brazilian health system. We also identified a single tool developed specifically for the HIV population, the DAD score, based on a global equation of predictive risk of CVD.

The findings of this study contribute significantly to the performance of health professionals and managers, since the main CVR tools used in people with HIV were evidenced, besides highlighting the importance of using these tools in the care offered to this public.

We emphasize the relevance, for Brazilian public health, of building specific instruments to measure the CVR in people living with HIV, adopting more robust statistical techniques.

\textbf{CONTRIBUTIONS}

Conception, project, analysis and interpretation of data, writing of the work and final approval of the version to be published: Mayara Nascimento Vasconcelos, Alana Eufrásio de Castro Lima, Emilly Alves Pereira Vidal and Nayara Wennya Cavalcante de Sousa; Data analysis and interpretation, relevant critical review of the intellectual content and final approval of the version to be published: Mayara Nascimento Vasconcelos, Thereza Maria Magalhães Moreira and Maria Lúcia Duarte Pereira.
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