



Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations

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Abstract

Purpose of Review To provide the current state of the development and application of cardiovascular disease (CVD) prediction tools in people living with HIV (PLWH).

Recent Findings Several risk prediction models developed on the general population are available to predict CVD risk, the most notable being the US-based pooled cohort equations (PCE), the Framingham risk functions, and the Europe-based SCORE (Systematic COronary Risk Evaluation). In validation studies in cohorts of PLWH, these models generally underestimate CVD risk, especially in individuals who are younger, women, Black race, or predicted to be at low/intermediate risk. An HIV-specific CVD prediction model, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) model, is available, but its performance is modest, especially in US-based cohorts. Enhancing CVD prediction with novel biomarkers of inflammation or coronary artery calcification is of interest but has not yet been evaluated in PLWH. Finally, studies on CVD risk prediction are lacking in diverse PLWH globally.

Summary While available risk models for CVD prediction in PLWH remain suboptimal, clinicians should remain vigilant of higher CVD risk in this population and should use any of these risk scores for risk stratification to guide preventive interventions. Focus on established traditional risk factors such as smoking remains critical in PLWH. Risk prediction functions tailored to PLWH in diverse settings will enhance clinicians' ability to deliver optimal preventive care.

Keywords HIV · Cardiovascular · Risk · Prediction · Framingham · ASCVD

Introduction

While people living with HIV (PLWH) with access to antiretroviral therapy (ART) continue to live longer and with

improved quality of life, they have a high burden of comorbidities, including cardiovascular disease (CVD) [1, 2]. Compared to the general population, PLWH are at approximately 1.5 to 2 times higher risk of CVD, which they tend to experience at a relatively younger age [2–4]. From 1990 to 2015, the global population-attributable fraction and disability-adjusted life years of HIV-associated CVD have increased nearly 3-fold and are expected to rise with aging of this population [4]. The cause of this increased risk is likely multifactorial: HIV-associated immune dysfunction and inflammation, higher rates of traditional risk factors in PLWH (e.g., smoking), adverse effects of ART including metabolic effects, and higher prevalence of socio-economic disadvantage in this population [5–7]. Particularly intriguing and a core issue in regard to CVD in PLWH is the prospect of unique drivers of CVD risk in HIV that may not be present or contribute to CVD risk in the general population and that are not included in established CVD risk prediction paradigms [8].

In an effort to prevent CVD in the context of unique factors promoting risk in the HIV population, there has been an

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intense interest in the evaluation and development of CVD risk prediction tools in PLWH over the last decade. Cardiovascular risk prediction tools, first developed through the Framingham Heart Study [9–11], can enhance clinical decision-making beyond clinical judgement, especially in less clinically apparent scenarios, such as primary prevention. When used in clinical practice, risk prediction tools may improve clinicians' ability to identify high-risk individuals who could be targeted for interventions while also having the potential to inform further insight into risk level. Moreover, by providing a risk estimate of an outcome, risk prediction can assist in patient behavioral counseling, for example when addressing behavioral risk factors such as smoking. Risk prediction can also advance policy decision-making when surveyed over a large population sample, helping guide investment, education, and focused interventions. Overall, risk assessment holds promise as an important tool in reducing the incidence of CVD in PLWH. While the utility of risk prediction tools in general has not been evaluated in large, prospective randomized trials, they are widely utilized in clinical care and in the context of CVD prevention and are recommended by multiple guidelines [12, 13]. This assumption of benefit, however, is predicated on such predictive tools being accurate, which in the HIV population remains in doubt.

The purpose of this review is to provide an overview of the current state of CVD prediction in PLWH. We first discuss the basics of how to appraise a prediction model. We then consider the characteristics, performance, and current limitations of common CVD risk prediction tools that have been evaluated in PLWH. We focus on prospective studies from the last 3–4 years that have evaluated clinical endpoints for which models were originally developed. Understanding the performance and limitations of cardiovascular risk prediction functions in HIV is critical because established functions do not include novel, HIV-specific risk factors and thus may underestimate risk and incorrectly discriminate. Tailoring risk prediction functions to include HIV-specific factors may improve their ability to accurately classify and predict risk and enhance cardiovascular disease prevention in this population.

Appraising a Prediction Model

A prediction model is a mathematical equation based on risk factor data that predicts the probability of occurrence of an event of interest in a given time period, as usually defined through studies in epidemiologic and other larger cohort studies. Prediction models enable clinicians to estimate an overall risk of an outcome representing a composite of individual risk factors. While details of appraising a prediction model are beyond the scope of this review and are reviewed elsewhere [14–17], we highlight some of the important features referred to in this review.

Model Calibration

Model calibration refers to the ability of a model to predict the actual observed risk of an event over a given time period [16]. The closer the observed risk is to the predicted risk, the better the model is said to be calibrated. If a model predicts the risk of an event to be >10% over a year for a group of individuals with a given set of risk factors, but the observed risk is only 5% in that group, then it would be considered poorly calibrated. A graph of observed risk of an event over categories (e.g., deciles) of predicted risk provides an informative and intuitive assessment of the model performance. Calibration is assessed using a chi-square statistic [18]. Good model calibration is important when an actual estimate of risk is needed, such as when making decisions on preventative interventions.

Model Discrimination

Model discrimination refers to the ability of a model to accurately assess high-risk and low-risk individuals—and perhaps especially intermediate risk individuals—while also distinguishing among these groups. Model discrimination is commonly measured as the area under receiver operating curve (AUC) or concordance (C)-statistic [17]. A C-statistic value of 0.5 indicates that the model cannot discriminate more than at random; a value of ≥ 0.7 is generally considered useful; and a value of ≥ 0.8 is considered excellent and is rarely achieved [17]. For example, the C-statistic of the pooled cohort equations (PCE) score recommended by the American Heart Association (AHA) for predicting CVD ranges between 0.7 and 0.8 in the original cohort depending on race and sex. Arguably, the discrimination of a model is more important than its calibration; clinicians are often interested in identifying intermediate- or high-risk individuals correctly (e.g., 10-year risk of CVD $\geq 7.5\%$ for using lipid-lowering therapies), but not necessarily in accurately predicting risk (e.g., it may not impact clinical decision making if the actual risk is 8% versus 15% in the above example as long as the model correctly identifies the individual as high-risk).

Validation

Ultimately, the true value of a model is assessed by its performance (e.g., calibration and discrimination) when applied to real-world cohorts outside of the settings in which the model was developed [15, 17]. It is accepted that models would perform predictably well in populations similar to those in which the models were derived. External validation of prediction models can yield humbling results, often due to different patient characteristics, frequency of risk factors, and other unknown factors in discrete populations. Poor external validation provides an opportunity to further investigate risk factors for a disease and to consider developing more subgroup-

specific prediction models (e.g., PCE model provides separate equations by race and sex) [19].

Other Key Characteristics of a Prediction Model

The quality of both original and validation studies is understandably important and is reflected in factors such as a representative study population, prospective nature, robust ascertainment of risk factor and outcome measurements, and low loss to follow-up [17]. Finally, a prediction model is only useful if it is simple to use, if risk factors in the model are routinely measured, and if appropriate interventions are available for high-risk individuals (e.g., more intensive behavioral counselling and lipid-lowering therapy in the case of preventing CVD) [13].

Overview of Commonly Used CVD Prediction Models in PLWH

Over 350 models have been developed for CVD risk prediction in the general population [20], of which very few have been evaluated independently in cohorts of PLWH. The Framingham Heart Study (FHS) risk prediction models, developed on a multi-generational population from Framingham, Massachusetts (USA), have now been widely used for several decades [8, 9, 21, 22]. The Framingham group developed and evaluated CVD risk prediction functions, addressing the question of whether individual risk factors could be combined into a multifactorial function to assess CVD risk over a given time period and representing a paradigm shift in conceptualizing risk. Framingham risk functions have been developed for multiple endpoints that include hard coronary heart disease, stroke, and global cardiovascular disease. The updated FHS model for the composite endpoint of cardiovascular disease (FHS-CVD in Table 1) in 2008 has been adopted by contemporary guidelines [21]. More recently, the American College of Cardiology (ACC) and the AHA developed the PCE in 2013, based on several large diverse community-based US cohorts (PCE in Table 1) and validated externally [19]. The prediction tools built on the Framingham functions by including stroke in addition to hard coronary events and by generating separate equations by race in addition to by sex. The PCE have been endorsed by multiple guidelines, although not without extensive discussion regarding possible over- and under-estimation of risk [25]. Similarly, the SCORE (Systematic CORonary Risk Evaluation) model was developed by the European union based on multiple European cohorts [23]. All of these prediction tools predict hard CVD endpoints: a composite of myocardial infarction, stroke (fatal or nonfatal for PCE; fatal only for SCORE) and in the case of FHS-CVD, other atherosclerotic endpoints (Table 1). The FHS-CVD, PCE, and SCORE models have

been most commonly evaluated in HIV cohorts. There are subtle variations in the risk factors incorporated and in the CVD outcomes predicted. Table 1 reviews the key features of these models and population characteristics in the original publication. Of note, the PCE model was disseminated in updated guidelines that incorporated a clinical approach to risk assessment, identifying four patient groups who warranted LDL-C lowering and statin therapy independent of any risk score: known ASCVD, diabetes, LDL-C > 190 mg/dL, or primary prevention with calculated risk of 7.5% or greater over 10 years [26]. This strategy highlights the complexity of the clinical application of risk prediction scores in the general population, a process likely to be even more complicated in the setting of HIV where risk factors differ and where the role of statins—especially in low to moderate risk individuals—is still being delineated.

Performance of General Population CVD Prediction Models in Cohorts of PLWH

While multiple studies have applied CVD risk prediction models in PLWH or assessed concordance among models, relatively few studies have formally assessed model performance in cohorts of PLWH. Table 2 summarizes key prospective studies that have evaluated CVD prediction models in PLWH. The performance of these models in cohorts of PLWH has generally demonstrated suboptimal discrimination and calibration, although performance varies by model and within subgroups. In a large, multi-site, US-based cohort, Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), the PCE showed good discrimination of CVD risk overall (C-statistic 0.75), but only modest calibration in regard to accuracy [28•]. Overall, in HIV, the PCE underestimated the risk of CVD, particularly in individuals who were female, Black, or predicted to be at low/moderate risk of CVD. In a Boston-based cohort of over 1200 men, FHS-CVD and PCE showed modest discrimination (C-statistic of 0.67 and 0.65, respectively), and both systematically underestimated CVD risk, particularly in low/moderate risk groups (Fig. 1) [29••]. Notably, recalibrating the original FHS-CVD or PCE equations did not significantly improve model performance, suggesting that unique HIV-associated risk factors could be conferring risk. In another US-based study of the HIV Outpatients Study (HOPS) cohort, PCE and the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) model (discussed in detail below) underestimated risk, and FHS-CVD and SCORE showed modest and poor discrimination (Table 2) [27]. Most recently, in a large population-based Dutch cohort which was predominantly White with high rates of viral suppression, all of the prediction scores discriminated well, with acceptable C-statistics (e.g., 0.76 for PCE) [30••]. All models demonstrated statistically significant chi-square P values indicating inadequate calibration, but model

Table 1 Summary of CVD risk prediction models commonly used in PLWH

Model	Source population	Mean age (years)	Females	Black race	Current or former smoker	Risk factors	Predicted outcome
Framingham Heart Study (FHS)- CVD [21]	US adults from the Framingham Heart Study Original and Offspring Cohorts (Frammingham, MA, USA)	49	50%	<10%	35%	Age, SBP, BP Rx, smoking, total cholesterol, HDL-C, diabetes (sex-specific estimates)	Composite CHD (coronary death, MI, coronary insufficiency, angina), cerebrovascular events (stroke, TIA), PAD, heart failure
ACC/AHA pooled cohort equations (PCE) [19]	US adults from 4 cohorts	40–70 (variable by cohort)	56%	21%	24–30%	Age, SBP, BP Rx, smoking, total cholesterol, HDL-C, diabetes (sex- and race-specific estimates)	MI, fatal or nonfatal stroke, CHD death
Systematic Coronary Risk Evaluation (SCORE) high-risk equation (SCORE) [23]	Adults from 12 European countries	Variable by cohort	43%	Not reported	20–40% in women, 40–60% in men	Age, sex, SBP, smoking, total cholesterol	CHD death, fatal stroke
Data Collection on Adverse Effects of Antiretroviral Drugs (D:A:D) Study model [24]	HIV-infected adults from clinics in the USA, Europe, Argentina, and Australia	39	26%	Not reported	69%	Age, sex, SBP, smoking, total cholesterol, diabetes, ever smoke, family history of CVD, CD4 count, years of use of PIs and NRTIs, current abacavir use	Composite CVD (fatal or nonfatal MI including sudden death, stroke, TIA, invasive coronary artery procedures including CABG, angioplasty, death from other CHD)

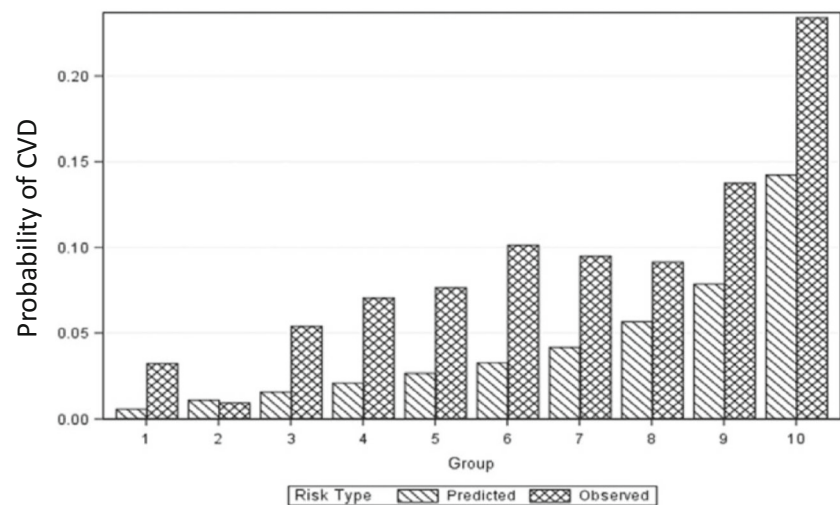
Note: Summary statistics provided are approximate and are taken from source publications of the study. CHD death included fatal MI, peripheral vascular disease, (PVD), or coronary artery disease, (CAD), PVD and CAD diagnoses were confirmed on the basis of aortography, angiography, or arterial Doppler. Abbreviations: ACC/AHA American College of Cardiology/American Heart Association, BP Rx blood pressure treatment, CABG coronary artery bypass graft, CHD coronary heart disease, CVD cardiovascular disease, HDL-C high-density lipoprotein cholesterol, HIV human immunodeficiency virus, LDL-C low-density lipoprotein cholesterol, MI myocardial infarction, PAD peripheral arterial disease, SBP systolic blood pressure, TIA transient ischemic attack, NRTIs nucleoside reverse transcriptase inhibitors, PIs protease inhibitors

Table 2 Summary of published validation studies for CVD risk prediction models in PLWH

Study	Year	Setting	N	Age (mean) (%)	Female (%)	Black race (%)	Current or former smoker (%)	Virologically suppressed (%) or viral load (median, IQR)	Mean follow-up (years)	Events (N)	C-statistic (discrimination) Chi square P value (calibration)			Summary findings	
											FHS-CVD	PCE	D:A:D		
Thompson-Paul et al. [27]	2016	HOPS; multiple US sites	2283	42	24	34	42	490 (25–21,600)	6.5	195	0.66	0.71	0.59	0.72	-PCE and D:A:D models underestimated risk by nearly 20%
Feinstein et al. [28]	2017	CNICS; 5 US sites	11288	40–43	18	38	25–32	64–9	4	247	0.89	<0.001	0.48	<0.001	-Only the FRS accurately estimated risk
Triant et al. [29]	2018	Partners; Boston healthcare system	1272	51	0	20	45	77	4	78	-	0.16	-	-	-Only evaluated myocardial infarction endpoint
van Zoest et al. [30]	2019	ATHENA; 26 Netherlands clinics	16070	43	18	19	59	89	5.5	~550	0.0004	0.001	-	-	-PCE model underestimated risk, especially in female, Black, and low/intermediate risk
											0.0004	0.001	-	-	-Both FHS-CVD and PCE models underestimated risk (Fig. 1)
											0.75	0.76	0.73	0.77	-Recalibration did not improve model fit
											<0.0001	0.0035	<0.0001	0.0004	-Large cohort accounting for ~63% of population of the Netherlands
											<0.0001	0.0001	0.0004	-	-All models discriminated well
															-PCE, SCORE, D:A:D underestimated risk in low/intermediate

Note: Summary statistics are best approximate from available published data. Abbreviations: *FHS-CVD* Framingham Heart Study (FHS) model for composite cardiovascular disease (CVD) outcome (2008), *PCE* American College of Cardiology (ACC) and American Heart Association (AHA) pooled cohort equations (PCE) (2013), *SCORE* Systematic Coronary Risk Evaluation, *D:A:D* Data Collection on Adverse Events of Anti-HIV Drugs. See text for details on these models

Fig. 1 Observed vs predicted CVD risk over deciles of predicted risk by pooled cohort equation (PCE) in a US cohort. Taken with permission from Triant et al. [29••] Figure illustrates underestimation of CVD risk by pooled cohort equation (PCE) model in people living with HIV (PLWH). See text for details



fit was poorest for SCORE. PCE, D:A:D, and SCORE underestimated risk in low/moderate predicted risk groups, whereas FHS-CVD overestimated risk, especially in groups with high predicted risk [30••].

Suboptimal performance of established risk prediction models in PLWH is likely due to multiple factors. The demographic and comorbidity profiles of HIV populations are likely to differ from those of the populations on which the prediction models were developed. PLWH tend to be younger with a higher proportion of non-White individuals, have higher smoking rates, and have a higher comorbidity burden [2, 31]. The role of HIV infection itself cannot be overstated. Importantly, inflammation and immune dysfunction are likely play integral roles in increasing CVD risk in the setting of HIV and are not reflected in widely used prediction functions [32, 33]. Embedded in this issue is the related possibility that HIV additionally confers unique drivers of risk that may not be present, or as present, in the general population, including for example other concomitant viral infections or other aspects of immune dysregulation [34]. Additional limitations of these studies should be acknowledged. All of the general population models discussed above had their enrollment periods in the 1970s to 1980s, when smoking rates were higher, and preventive care has improved since that time period. Most validation studies have been relatively small with shorter follow-up periods of approximately 4–5 years and relatively small numbers of events (Table 2). Risk prediction models on contemporary cohorts with longer follow-up periods are therefore needed, both in the general population and in PLWH. Finally, CVD risk prediction models, including non-laboratory-based risk functions, are yet to be properly evaluated in prospective studies in PLWH living in low- and middle-income countries, especially sub-Saharan Africa, where a larger burden of HIV-associated CVD lies [4•].

HIV-Specific Risk-Prediction Models

The D:A:D model is the primary existing HIV-specific risk prediction model, initially developed in 2010 [35] and updated in 2016 [24•]. The D:A:D study developed a model for predicting 5-year CVD risk based on a large cohort of predominantly European PLWH (N>30,000) with prospective collection of CVD- and HIV-related risk factors and adjudication of CVD outcomes. In addition to traditional CVD risk factors, the full D:A:D model incorporates HIV-related factors including CD4 count, recent use of abacavir, and cumulative use of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) [24•]. Its performance in validation studies has been similar to the FHS-CVD, PCE, and SCORE models (Table 2): Performance was generally modest in US cohorts [27, 28•], while the prediction score performed better in a Dutch cohort with a similar population to the D:A:D derivation cohort [30••]. Evaluation of the D:A:D model has been limited in part by inclusion of family history of CVD, a variable which is not available in many cohorts of PLWH. Several de novo HIV-specific risk scores were also developed from the CNICS cohort that included variables from the ASCVD risk score in addition to HIV-specific variables and utilized a derivation and holdout cohort for internal validation [28•]. The two scores that were developed discriminated adequately but demonstrated worse calibration than PCE [28•].

Role of Novel Risk Factors to Improve CVD Prediction

Over the last two decades, there have been intensive efforts in identifying novel risk factors and biomarkers to improve CVD risk prediction. The main interest in evaluating novel biomarkers has been to more accurately identify individuals predicted to have low/intermediate risk by traditional risk prediction models but who go on to develop clinical CVD in the

future. Some biomarkers or indicators of interest have included coronary artery calcium (CAC) scoring (quantification of calcification of coronary vessels measured on a CT scan), high-sensitivity C reactive protein (hsCRP), ankle-brachial index (ABI), advanced lipoprotein testing, and lipoprotein-a (LPa). Of these, CAC has demonstrated strong data on the negative predictive value for CVD risk with a CAC value of zero over subsequent windows of time; of relevance to HIV, CAC testing may be limited in regard to its use in younger individuals [13]. While these additional measures are not currently endorsed for routine use in primary prevention of CVD by the AHA, United States Preventive Services Task Force, or European guidelines [12, 13, 36], use of these biomarkers and additional measures are now discussed, especially in those with intermediate predicted risk of CVD by traditional models where therapeutic intervention is uncertain and in clinical scenarios such as strong family history of premature CAD where concern is heightened [12, 13].

In the context of HIV infection, novel biomarkers or disease indicators have not been formally evaluated with regard to their capacity to improve discrimination or calibration in prospective studies employing hard CVD endpoints. Biomarkers of inflammation and coagulation activation, such as hsCRP, interleukin-6, and D-dimer, have been linked to CVD and subclinical atherosclerosis in PLWH but have not been formally evaluated as components of risk prediction models, given they are not routinely obtained clinically [37, 38]. The CAC score has also been of interest, and in one recent cross-sectional study in PLWH aged >50 years, use of CAC reclassified 20% of individuals in low-risk groups identified by the PCE model to a higher-risk group [39]. However, in the absence of prospective data on clinical endpoints, it was unclear whether this reclassification was correct. Future studies on CAC, biomarkers of inflammation and immune activation, and HIV-specific factors will be important to improve our understanding of the role of novel risk factors in CVD risk prediction in PLWH.

Clinical Implications of Data on CVD Risk Prediction in HIV

Underestimation of CVD risk in PLWH by established risk prediction models is an important problem which can defer appropriate implementation of preventive measures, in particular in Black individuals, women, and in those predicted to be at low/moderate risk. Even with current suboptimal risk stratification strategies, implementation of CVD prevention is limited in HIV clinics globally; in a large international survey of PLWH, only 19% ever had CVD discussed by their physician, and 42% of smokers reported never having discussed smoking [40]. In recognition of potential underestimation of CVD risk in the HIV population, the AHA released a scientific statement on this topic in 2019, providing guidance on CVD prevention

in PLWH [41••] based on the 2018 cholesterol guidelines [13] and the 2013 AHA guidelines [19]. Notably, the guidance indicated that a clear best risk estimation model for HIV has not been established. For those who do not qualify for lipid-lowering therapy from other indications, the guidance suggests using the FHS-CVD, PCE, or D:A:D model and considering HIV as a “risk enhancing factor” that increases risk by 1.5 to 2 times, particularly in those PLWH with history of delayed ART initiation/prolonged viremia, low CD4 count, or hepatitis C co-infection. The guidance cautions against routinely using risk enhancers such as CAC or hsCRP in PLWH as they would be used in the general population given the relative scarcity of data in HIV. Moreover, risk enhancers which might aid in calibration or discrimination in the general population may not similarly enhance models in HIV; for example, CAC alone may not reflect underlying coronary artery disease among PLWH, who tend to have more noncalcified plaque compared with uninfected individuals. Ultimately, it remains to be seen whether PLWH predicted to be at low/intermediate CVD risk by established prediction models will merit aggressive prevention therapies due to elevated CVD risk from HIV infection itself. An ongoing, large randomized trial, REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV), is investigating this question and has enrolled a diverse group including participants from sites in Asia and sub-Saharan Africa [42••]. While awaiting REPRIEVE data, as outlined in the 2019 AHA Scientific Statement, primary CVD prevention in PLWH should focus on identifying high-risk individuals, implementing interventions on dietary and lifestyle factors—particularly smoking which occurs at elevated rates in PLWH—and using lipid-lowering therapies when indicated by current guidance [26, 41••].

Conclusions and Future Directions

In summary, accurate prediction of CVD risk is one of the important tools in mitigating morbidity and mortality from CVD in PLWH, yet established risk prediction models have been shown to be inaccurate in this group. Risk prediction models used in the general population, first developed and refined by the Framingham Heart Study group [9–11] and including FHS-CVD, PCE, and SCORE, are based on traditional CVD risk factors combined into a multifactorial function to estimate risk. While they serve as a cornerstone of CVD preventive care for the general population, current established functions may misrepresent the relative contributions of traditional CVD risk factors in PLWH and do not incorporate novel risk factors related to HIV-associated inflammation and immune dysregulation which may drive excess CVD risk in this group. While established prediction models do a fair to acceptable job of discriminating between

high- and low-risk individuals, they have been shown to underestimate CVD risk in PLWH, particularly in individuals with low/intermediate predicted risk in whom accurate risk estimation to guide clinical decision-making is arguably most important. Future studies should focus on the inclusion of novel and HIV-specific risk factors to refine risk prediction models and should include diverse populations, including women, Black individuals, and PLWH in low- and middle-income countries. Optimizing the performance of risk prediction models in PLWH will be critical to reduce disparities in the receipt of appropriate CVD preventative care and to enhance the long-term health of this group.

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