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Prognostic prediction models for treatment experienced people living with HIV: a protocol for systematic review and meta-analysis

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Abstract

Background:

Despite the favourable efficacy and safety profile of antiretroviral therapy (ART), HIV/AIDS continues to impose significant disease burdens worldwide. This study aims to systematically review published prognostic prediction models for survival outcomes of treatment experienced people living with HIV (TE-PLHIV), to describe their characteristics, compare their performance, and assess the risk of bias and real-world clinical utility.

Methods:

Studies will be identified through a comprehensive search in PubMed, EMBASE and Scopus databases. Two reviewers will independently conduct selection of eligible studies, data extraction, and critical appraisal. Included studies will be systematically summarized using appropriate tools designed for prognostic prediction modelling studies. Where applicable, evidence will be summarised with meta-analyses.

Discussion:

To the best of our knowledge, it will be the first systematic review to collate and evaluate the available evidence on validated prognostic models in TE-PLHIV. By bridging this gap in knowledge, our review is a crucial step towards facilitating the evidence-based utilization of prognostic factors and risk prediction in the management and care of TE-PLHIV

Systematic review registration: PROSPERO registration number CRD42023412118.

Keywords: HIV; AIDS; antiretroviral therapy (ART); prognostic model; survival

Introduction

Human immunodeficiency virus (HIV) is a viral infection that severely impairs the immune system [1]. Since antiretroviral therapy (ART) first introduction in the mid-1990s, it has led to significant reductions in HIV-associated morbidity and mortality, transforming HIV infection into a manageable chronic condition [2-6].

Despite these advancements, HIV/AIDS continues to impose significant disease burdens worldwide, with 38.4 million people living with HIV (PLHIV) and 650.0 thousand AIDS-related deaths in 2021 [7]. The increasing life expectancy of PLHIV presents new challenges in the treatment and management of this expanding population. Studies indicate that PLHIV face a higher risk of developing concurrent chronic diseases, including cardiovascular disease and non-AIDS-related neoplasms, compared to the general population [8-10]. This heightened risk may be related to HIV-induced immunodeficiency, ART drug toxicities, ageing, and poor lifestyle factors [8, 9]. Moreover, the introduction of regimens such as integrase strand transfer inhibitor (INSTI) in recent decades has presented certain clinical complexities. A recent multicenter study revealed that the initiation of INSTIs was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors [11]. The proportion of deaths from non-AIDS-related illnesses among PLHIV has surpassed that of AIDS-related illnesses in many regions of the world where free ART is available [12, 13]. Furthermore, recent real-world studies have raised doubts about the efficacy of new drugs such as INSTIs, as no significant disparities in mortality rates of PLHIV were observed among different modern ART regimens [14-16]. In light of this scenario, governments and health authorities worldwide must continue to allocate significant medical resources to the treatment and management of HIV-infected populations each year.

Developing an ideal prognostic model for treatment experienced people living with

HIV (TE-PLHIV) is crucial to optimizing HIV care and providing tailored treatment for individual patients, ultimately improving treatment outcomes and facilitating the rational allocation of limited health resources [17]. Given the identification of multiple risk factors associated with HIV/AIDS-related mortality, combining several independent indicators could significantly enhance predictive effectiveness. Existing studies of prognostic model for TE-PLHIV have identified several demographic and laboratory indicators closely linked to the mortality of TE-PLHIV, including age, sex, World Health Organization (WHO) clinical stage, body weight or body mass index (BMI), CD4+ T-cell count, HIV viral load, and haemoglobin [18-30]. However, there are discrepancies in the characteristics of prognostic models of TE-PLHIV, resulting in variations in the selected demographic and clinical features, as well as in the parameters and performance. Publication bias, poor reporting, and extensive heterogeneity are recognised issues in prognostic research [31-33]. Despite the amount of prognostic prediction models established for TE-PLHIV, none of them have been widely accepted as an addition to precision medicine workflows. A systematic review and meta-analysis of these models is therefore essential for enhancing their methodological quality, including better indicators and performance.

Study aim

The aim of this systematic review is to identify, screen, and evaluate all published prognostic prediction models on survival outcomes of TE-PLHIV and inform clinical therapeutic decision-making.

Methods

Study design

The systematic review described in this article is scheduled to be conducted between January 2024 and January 2025. This review was registered on the PROSPERO international registry of systematic reviews on April 8, 2023 (CRD42023412118).

This protocol adheres to a number of reporting guidelines for a systematic review including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline [34] and Cochrane Prognosis Methods Group Protocol Template [35], and guidelines for assessing and reporting prediction model studies including transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [36], PROBAST tool (prediction model risk of bias assessment) [37], and the checklist for corresponding CHARMS checklist (checklist for critical Appraisal and data extraction for systematic reviews of prediction modelling studies) [38]. Key items of this review are clarified with assistance of the PROGnosis RESearch Strategy (PROGRESS) Partnership (Table 1).

Table 1. Framing of this systematic review with key items identified by the CHARMS checklist

Items	Comments
1. Prognostic versus diagnostic prediction model	Prognostic prediction model (aimed to predict future survival outcomes of TE-PLHIV)
2. Intended scope of the review	Prognostic prediction models to inform clinicians' therapeutic decision making regarding the management of HIV/AIDS
3. Type of prediction modelling studies	All study types including prognostic prediction modelling studies with or without external validation and external model validation studies with or without model updating
4. Target population to whom the prediction model applies	TE-PLHIV according to each included study
5. Outcome to be predicted	Survival after ART initiation, including all-cause mortality and/or HIV-related mortality
6. Time span of prediction	Survival outcomes occurring at any time point after ART initiation
7. Intended moment of using the model	At any time point after ART initiation

Notes: TE-PLHIV, treatment experienced people living with HIV/AIDS; ART, antiretroviral therapy.

Eligibility criteria

Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an TE-PLHIV's risk of a future survival outcome (prognostic prediction modelling studies) before January 2024 will be considered for inclusion in the review. Prognostic prediction modelling studies can be either model development, model validation or a combination. Studies that have a single risk factor in the model will be excluded, as they are limited in their utility for individual risk prediction. Editorial comments or letters will be excluded from the review. Eligible studies included in the review will be limited to those conducted in humans by applying The Cochrane Group's filter for Humans not Animals filter[39]. PICOTS (population, index, comparator, outcome, timing, setting) approach will be used to frame the eligibility criteria and to guide the selection of prognostic prediction modes (Table 2) [37, 40].

Table 2. Eligibility criteria for the systematic review framed with the PICOTS system

Items	Inclusion criteria	Exclusion criteria
Population	TE-PLHIV according to criteria in each eligible study included in the review	
Index	Development or external validation of a prognostic prediction model for survival outcomes of TE-PLHIV (e.g., prognostic prediction models of TE-PLHIV to predict survival outcomes)	Diagnostic prediction models (e.g., diagnostic prediction models for diagnosis of HIV/AIDS)
Comparator	No predefined comparator	
Outcomes (primary)	All-cause mortality	
Outcomes (secondary)	HIV-related mortality, if possible	
Timing	Survival outcomes occurring at any time point after ART initiation	
Setting	Prognostic prediction models that are designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of HIV/AIDS, at any time point after ART initiation	

Notes: PLHIV, people living with HIV/AIDS; ART, antiretroviral therapy.

Databases

A comprehensive and systematic literature search will be conducted in two major publicly available electronic medical literature databases: 1) PubMed (covering the period from 1946 to present); 2) EMBASE (covering the period from 1947 to present); 3) Scopus (covering the period from 1996 to present).

Search strategy

The search strategy was built using keywords including HIV-related terms (ie, 'HIV', 'human immunodeficiency virus', 'HIV infection'), AIDS-related terms (ie, 'AIDS', 'acquired immunodeficiency syndrome'), patient-related terms (ie, 'people living with HIV/AIDS', 'PLHIV') and prediction modelling-related terms (ie, 'prognostic tool', 'prognostic model', 'prognostic nomogram', 'prognostic value', 'prognostic risk', 'prognostic score', 'prognostic scoring', 'prognostic marker'). The draft search strategy is provided in Supplementary Appendix. The final search strategy will be iteratively refined.

The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. We will also search for publications which cited the model development studies to identify model validation studies. The included studies will be checked for error or fraud. We will not place any restrictions on language, publication year or publication status when searching the electronic databases. Any non-English studies identified will be translated and assessed for eligibility.

Data collection and analysis

Data management

Retrieved studies included in the review will be imported into Endnote reference manager software (Version 20.4.1, Clarivate Analytics, Philadelphia, USA. Available at: https://endnote.com/). Duplicate records will be identified and excluded using a systematic, rigorous and reproducible method utilizing a sequential combination of fields including author, year, title, journal and pages [41]. Screened records will then be imported into Covidence systematic review software throughout the review (Veritas Health Innovation, Melbourne, Australia. Available at: http://www.covidence.org).

Selection process

Two reviewers (XW and YC) will independently screen and review the abstracts of all studies identified by the final search strategy. For each excluded article, reasons for exclusion will be specified. Disagreement or doubt will be resolved by consensus and if consensus cannot be reached, the full texts of the study will be independently accessed for further evaluation. Any conflict will be resolved through discussion with a senior advisor (HZ), if necessary.

Data extraction

Two reviewers (XW and YC) will independently extract data from eligible studies included in the review, using a standardized electronic form developed with reference to the checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[38].

For each eligible study, we plan to seek information on objective, source of data, participants, survival outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance (discrimination, calibration, clinical utility, and measures of case-mix variation), results including final multivariable models and interpretation of presented models, and model validation[38].

Information not reported in the publications will be obtained from the authors wherever possible, in addition, if insufficient information is obtained the study will be excluded from the review. Any disagreement will be resolved through consultation with a senior advisor (HZ).

Assessment of risk of bias

The methodological quality (risk of bias) and relevance (applicability) reporting the development or validation of a prognostic model will be systematically assessed using the PROBAST [37]. This tool is structured around four key domains: participant selection (e.g. were inclusions and exclusions of participants appropriate); predictors (e.g. were predictors measured blind to outcome data); outcomes (e.g. was the same definition used for outcomes in all patients); sample size and patient flow (e.g. was there a pre-specified sample size based on estimated number of outcome events, handling of missing data); and analysis (e.g. was selection of predictors based on univariable analysis avoided). Each study will be given a rating of high, low, or unclear risk for each of the four domains.

Synthesis

All included studies on prognostic prediction models will be described, with key findings tabulated to facilitate comparison of survival outcomes to be predicted, predictors included in the final model and performance measures [38]. Measures of uncertainty will be reported when published or approximated using published methods[40]. Where reported, classification measures such as sensitivity, specificity, positive predictive value and negative predictive value will also be included[38].

When at least five studies report similar measures of association, a meta-analysis will be conducted for each prognostic factor with reference to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines [42]. The restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman methods will be used to estimate the between-study heterogeneity and 95% confidence intervals for the average

performance [40]. Statistical or clinical homogeneity will be assessed using the I^2 statistics where I^2 values >50% indicate moderate to high heterogeneity [43]. When it is not feasible to conduct a quantitative synthesis, the evidence will be summarized narratively.

Subgroup analyses

Where there are enough eligible studies included in the review, we will conduct subgroup analyses of type of prognostic prediction modelling studies (i.e., development or validation), target population to whom the model applies, whether population was treated (yes/no), treatment type after ART initiation, the follow-up duration, survival outcomes to be predicted, and study quality (risk of bias).

Sensitivity analysis

A sensitivity analysis is a repeat of a meta-analysis. To test the robustness of this review's findings, we would undertake sensitivity analyses to explore the influence on model performance for exclusion of studies at lower and higher risk of bias [40].

Reporting and presentation of findings

Reporting and presentation of findings will be guided by the PRISMA statement[34], and relevant recommendations from the TRIPOD statement[36]. The GRADE approach (grading of recommendations, assessment, development and evaluation) will be utilized to determine confidence in estimates[44-46]. The assessments will be performed by two independent reviewers (XW, YC) independently. Disagreements will be resolved by discussion or third-party adjudication (HZ), when necessary.

Amendments

Protocol amendments will be listed and made available on the PROSPERO registration. Date, description and rationale will be given for each amendment.

Discussion

This review will provide essential data necessary to evaluate all published prognostic prediction modeling studies on survival outcomes of TE-PLHIV. Recognized systematic review methods will be employed to identify, appraise, and synthesize the existing evidence on prognostic models in TE-PLHIV, ensuring the reliability and validity of the findings. Since the registration of this review on PROSPERO on April 8, 2023, some minor modifications have been made to the protocol. Firstly, the population has been specified as TE-PLHIV. Secondly, the anticipated conduct date has been postponed to allow sufficient time for peer review of this protocol.

HIV/AIDS is a significant global health concern and ranks as the second largest cause of death for the 25-49 year age group worldwide, following road injuries [47]. The derived findings from this review will serve as a foundation to inform future research recommendations regarding model development, validation, and impact assessment. The ideal outcome of this systematic review is to identify a prognostic model of TE-PLHIV with high predictive performance, applicability, and methodological quality. However, if no applicable models are found or the identified models exhibit poor performance and methodological quality, these results will serve as a basis and guidance for model development and updates.

To the best of our knowledge, it will be the first systematic review to collate and evaluate the available evidence on validated prognostic models in TE-PLHIV. By bridging this gap in knowledge, our review is a crucial step towards facilitating the evidence-based utilization of prognostic factors and risk prediction in the management and care of TE-PLHIV.

Ethics and dissemination

Ethical approval is not required for this study because only available published data will be analysed. The findings of this systematic review will be published in an open-access journal to ensure access for all stakeholders and disseminated in various scientific conferences.

Patient and public involvement

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Acknowledgements

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Contributors

HZ conceived and designed the protocol with JW and XW. XW and YC contributed to the manuscript with all authors critically revising the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of interest

The authors declared no conflict of interest.

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Supplementary Appendix - Electronic search term implemented in PubMed, EMBASE and Scopus

PubMed

(((((((HIV[MeSH Terms]) OR (human immunodeficiency virus[Title/Abstract])) OR (HIV infection[Title/Abstract])) OR (AIDS[Title/Abstract])) OR (acquired immunodeficiency syndrome[Title/Abstract])) OR (people living with HIV/AIDS[Title/Abstract])) OR (PLWHA[Title/Abstract]) AND ((prognostic tool) OR (prognostic model) OR (prognostic nomogram) OR (prognostic value) OR (prognostic risk) OR (prognostic score) OR (prognostic scoring) OR (prognostic marker)))

EMBASE

1. 'hiv'/exp OR 'human immunodeficiency virus':ab,ti OR 'hiv infection':ab,ti OR aids:ab,ti OR 'acquired immunodeficiency syndrome':ab,ti OR 'people living with hiv':ab,ti OR plwh:ab,ti
2. 'prognostic tool' OR 'prognostic model' OR 'prognostic nomogram' OR 'prognostic value' OR 'prognostic risk' OR 'prognostic score' OR 'prognostic scoring' OR 'prognostic marker'
3. #1 AND #2

Scopus

1. TITLE-ABS-KEY("hiv") OR TITLE-ABS-KEY('human immunodeficiency virus') OR TITLE-ABS-KEY('hiv infection') OR TITLE-ABS-KEY('aids') OR TITLE-ABS-KEY('acquired immunodeficiency syndrome') OR TITLE-ABS-KEY('people living with hiv') OR TITLE-ABS-KEY('plwh')
2. TITLE-ABS-KEY("prognostic tool") OR TITLE-ABS-KEY("prognostic model") OR TITLE-ABS-KEY("prognostic nomogram") OR TITLE-ABS-KEY("prognostic value") OR TITLE-ABS-KEY("prognostic risk") OR TITLE-ABS-KEY("prognostic score") OR TITLE-ABS-KEY("prognostic scoring") OR TITLE-ABS-KEY("prognostic marker")
3. #1 AND #2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	10
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Prognostic prediction models for treatment experienced people living with HIV: a protocol for systematic review and meta-analysis

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Prognostic prediction models for treatment experienced people living with HIV: a protocol for systematic review and meta-analysis

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Abstract

Introduction:

Despite the favourable efficacy and safety profile of antiretroviral therapy (ART), HIV/AIDS continues to impose significant disease burdens worldwide. This study aims to systematically review published prognostic prediction models for survival outcomes of treatment experienced people living with HIV (TE-PLHIV), to describe their characteristics, compare their performance, and assess the risk of bias and real-world clinical utility.

Methods and analysis:

Studies will be identified through a comprehensive search in PubMed, EMBASE and Scopus databases. Two reviewers will independently conduct selection of eligible studies, data extraction, and critical appraisal. Included studies will be systematically summarized using appropriate tools designed for prognostic prediction modelling studies. Where applicable, evidence will be summarised with meta-analyses.

Ethics and dissemination:

Ethical approval is not required because only available published data will be analysed. The results of this work will be published in an open-access peer-reviewed journal.

Systematic review registration: PROSPERO registration number CRD42023412118.

Keywords: HIV; AIDS; antiretroviral therapy (ART); prognostic model; survival

Strengths and limitations of this study

- This review will be the first systematic review to collate and evaluate the available evidence on validated prognostic models in treatment experienced people living with HIV.
- The results of this review will provide insight that will assist in developing and validating prognostic models in treatment experienced people living with HIV in future studies.
- The main limitation of this study could be the potential heterogeneity among prognostic models included in the analysis.

Introduction

Human immunodeficiency virus (HIV) is a viral infection that severely impairs the immune system [1]. Since antiretroviral therapy (ART) first introduction in the mid-1990s, it has led to significant reductions in HIV-associated morbidity and mortality, transforming HIV infection into a manageable chronic condition [2-6].

Despite these advancements, HIV/AIDS continues to impose significant disease burdens worldwide, with 38.4 million people living with HIV (PLHIV) and 650.0 thousand AIDS-related deaths in 2021 [7]. The increasing life expectancy of PLHIV presents new challenges in the treatment and management of this expanding population. Studies indicate that PLHIV face a higher risk of developing concurrent chronic diseases, including cardiovascular disease and non-AIDS-related neoplasms, compared to the general population [8-10]. This heightened risk may be related to HIV-induced immunodeficiency, ART drug toxicities, ageing, and poor lifestyle factors [8, 9]. Moreover, the introduction of regimens such as integrase strand transfer inhibitor (INSTI) in recent decades has presented certain clinical complexities. A recent multicenter study revealed that the initiation of INSTIs was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors [11]. The proportion of deaths from non-AIDS-related illnesses among PLHIV has surpassed that of AIDS-related illnesses in many regions of the world where free ART is available [12, 13]. Furthermore, recent real-world studies have raised doubts about the efficacy of new drugs such as INSTIs, as no significant disparities in mortality rates of PLHIV were observed among different modern ART regimens [14-16]. In light of this scenario, governments and health authorities worldwide must continue to allocate significant medical resources to the treatment and management of HIV-infected populations each year.

Developing an ideal prognostic model for treatment experienced people living with

HIV (TE-PLHIV) is crucial to optimizing HIV care and providing tailored treatment for individual patients, ultimately improving treatment outcomes and facilitating the rational allocation of limited health resources [17]. Given the identification of multiple risk factors associated with HIV/AIDS-related mortality, combining several independent indicators could significantly enhance predictive effectiveness. Existing studies of prognostic model for TE-PLHIV have identified several demographic and laboratory indicators closely linked to the mortality of TE-PLHIV, including age, sex, World Health Organization (WHO) clinical stage, body weight or body mass index (BMI), CD4+ T-cell count, HIV viral load, and haemoglobin [18-30]. However, there are discrepancies in the characteristics of prognostic models of TE-PLHIV, resulting in variations in the selected demographic and clinical features, as well as in the parameters and performance. Publication bias, poor reporting, and extensive heterogeneity are recognised issues in prognostic research [31-33]. Despite the amount of prognostic prediction models established for TE-PLHIV, none of them have been widely accepted as an addition to precision medicine workflows. A systematic review and meta-analysis of these models is therefore essential for enhancing their methodological quality, including better indicators and performance.

Study aim

The aim of this systematic review is to identify, screen, and evaluate all published prognostic prediction models on survival outcomes of TE-PLHIV and inform clinical therapeutic decision-making.

Methods

Study design

The systematic review described in this article is scheduled to be conducted between January 2024 and January 2025. This review was registered on the PROSPERO international registry of systematic reviews on April 8, 2023 (CRD42023412118).

This protocol adheres to a number of reporting guidelines for a systematic review including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline [34] and Cochrane Prognosis Methods Group Protocol Template [35], and guidelines for assessing and reporting prediction model studies including transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [36], PROBAST tool (prediction model risk of bias assessment) [37], and the checklist for corresponding CHARMS checklist (checklist for critical Appraisal and data extraction for systematic reviews of prediction modelling studies) [38]. Key items of this review are clarified with assistance of the PROGnosis RESearch Strategy (PROGRESS) Partnership (Table 1).

Table 1. Framing of this systematic review with key items identified by the CHARMS checklist

Items	Comments
1. Prognostic versus diagnostic prediction model	Prognostic prediction model (aimed to predict future survival outcomes of TE-PLHIV)
2. Intended scope of the review	Prognostic prediction models to inform clinicians' therapeutic decision making regarding the management of HIV/AIDS
3. Type of prediction modelling studies	All study types including prognostic prediction modelling studies with or without external validation and external model validation studies with or without model updating
4. Target population to whom the prediction model applies	TE-PLHIV according to each included study
5. Outcome to be predicted	Survival after ART initiation, including all-cause mortality and/or HIV-related mortality
6. Time span of prediction	Survival outcomes occurring at any time point after ART initiation
7. Intended moment of using the model	At any time point after ART initiation

Notes: TE-PLHIV, treatment experienced people living with HIV/AIDS; ART, antiretroviral therapy.

Eligibility criteria

Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an TE-PLHIV's risk of a future survival outcome (prognostic prediction modelling studies) before January 2024 will be considered for inclusion in the review. Prognostic prediction modelling studies can be either model development, model validation or a combination. Studies that have a single risk factor in the model will be excluded, as they are limited in their utility for individual risk prediction. Editorial comments or letters will be excluded from the review. Eligible studies included in the review will be limited to those conducted in humans by applying The Cochrane Group's filter for Humans not Animals filter[39]. PICOTS (population, index, comparator, outcome, timing, setting) approach will be used to frame the eligibility criteria and to guide the selection of prognostic prediction modes (Table 2) [37, 40].

Table 2. Eligibility criteria for the systematic review framed with the PICOTS system

Items	Inclusion criteria	Exclusion criteria
Population	TE-PLHIV according to criteria in each eligible study included in the review	
Index	Development or external validation of a prognostic prediction model for survival outcomes of TE-PLHIV (e.g., prognostic prediction models of TE-PLHIV to predict survival outcomes)	Diagnostic prediction models (e.g., diagnostic prediction models for diagnosis of HIV/AIDS)
Comparator	No predefined comparator	
Outcomes (primary)	All-cause mortality	
Outcomes (secondary)	HIV-related mortality, if possible	
Timing	Survival outcomes occurring at any time point after ART initiation	
Setting	Prognostic prediction models that are designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of HIV/AIDS, at any time point after ART initiation	

Notes: PLHIV, people living with HIV/AIDS; ART, antiretroviral therapy.

Databases

A comprehensive and systematic literature search will be conducted in two major publicly available electronic medical literature databases: 1) PubMed (covering the period from 1946 to present); 2) EMBASE (covering the period from 1947 to present); 3) Scopus (covering the period from 1996 to present); 4) the Cochrane Library; 5) OpenGrey (www.opengrey.eu/), which is a database containing conference abstracts that has not been published.

Search strategy

The search strategy was built using keywords including HIV-related terms (ie, 'HIV', 'human immunodeficiency virus', 'HIV infection'), AIDS-related terms (ie, 'AIDS', 'acquired immunodeficiency syndrome'), patient-related terms (ie, 'people living with HIV/AIDS', 'PLHIV') and prediction modelling-related terms (ie, 'prognostic tool', 'prognostic model', 'prognostic nomogram', 'prognostic value', 'prognostic risk', 'prognostic score', 'prognostic scoring', 'prognostic marker', 'disease progression score', 'risk index for mortality', 'multivariate models for predicting progression'). The draft search strategy is provided in Supplementary Appendix. The search strategy, specifically, subject indexing terms will be translated appropriately for the Cochrane Library and OpenGrey. The final search strategy will be iteratively refined.

The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. We will also search for publications which cited the model development studies to identify model validation studies. The included studies will be checked for error or fraud. We will not place any restrictions on language, publication year or publication status when searching the electronic databases. Any non-English studies identified will be translated and assessed for eligibility.

Data collection and analysis

Data management

Retrieved studies included in the review will be imported into Endnote reference manager software (Version 20.4.1, Clarivate Analytics, Philadelphia, USA. Available at: https://endnote.com/). Duplicate records will be identified and excluded using a systematic, rigorous and reproducible method utilizing a sequential combination of fields including author, year, title, journal and pages [41]. Screened records will then be imported into Covidence systematic review software throughout the review (Veritas Health Innovation, Melbourne, Australia. Available at: http://www.covidence.org).

Selection process

Two reviewers (XW and YC) will independently screen and review the abstracts of all studies identified by the final search strategy. For each excluded article, reasons for exclusion will be specified. Disagreement or doubt will be resolved by consensus and if consensus cannot be reached, the full texts of the study will be independently accessed for further evaluation. Any conflict will be resolved through discussion with a senior advisor (HZ), if necessary.

Data extraction

Two reviewers (XW and YC) will independently extract data from eligible studies included in the review, using a standardized electronic form developed with reference to the checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[38].

For each eligible study, we plan to seek information on objective, source of data, participants, survival outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance (discrimination, calibration, clinical utility, and measures of case-mix variation), results including final multivariable models and interpretation of presented models, and model validation[38].

Information not reported in the publications will be obtained from the authors wherever possible, in addition, if insufficient information is obtained the study will be excluded from the review. Any disagreement will be resolved through consultation with a senior advisor (HZ).

Assessment of risk of bias

The methodological quality (risk of bias) and relevance (applicability) reporting the development or validation of a prognostic model will be systematically assessed using the PROBAST [37]. This tool is structured around four key domains: participant selection (e.g. were inclusions and exclusions of participants appropriate); predictors (e.g. were predictors measured blind to outcome data); outcomes (e.g. was the same definition used for outcomes in all patients); sample size and patient flow (e.g. was there a pre-specified sample size based on estimated number of outcome events, handling of missing data); and analysis (e.g. was selection of predictors based on univariable analysis avoided). Each study will be given a rating of high, low, or unclear risk for each of the four domains.

Synthesis

All included studies on prognostic prediction models will be described, with key findings tabulated to facilitate comparison of survival outcomes to be predicted, predictors included in the final model and performance measures [38]. Measures of uncertainty will be reported when published or approximated using published methods[40]. Where reported, classification measures such as sensitivity, specificity, positive predictive value and negative predictive value will also be included[38].

When at least five studies report similar measures of association, a meta-analysis will be conducted for each prognostic factor with reference to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines [42]. The restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman methods will be used to estimate the between-study heterogeneity and 95% confidence intervals for the average

performance [40]. Statistical or clinical homogeneity will be assessed using the I^2 statistics where I^2 values >50% indicate moderate to high heterogeneity [43]. When it is not feasible to conduct a quantitative synthesis, the evidence will be summarized narratively.

Subgroup analyses

Where there are enough eligible studies included in the review, we will conduct subgroup analyses of type of prognostic prediction modelling studies (i.e., development or validation), target population to whom the model applies, whether population was treated (yes/no), treatment type after ART initiation, the follow-up duration, survival outcomes to be predicted, and study quality (risk of bias).

Sensitivity analysis

A sensitivity analysis is a repeat of a meta-analysis. To test the robustness of this review's findings, we would undertake sensitivity analyses to explore the influence on model performance for exclusion of studies at lower and higher risk of bias [40].

Reporting and presentation of findings

Reporting and presentation of findings will be guided by the PRISMA statement[34], and relevant recommendations from the TRIPOD statement[36]. The GRADE approach (grading of recommendations, assessment, development and evaluation) will be utilized to determine confidence in estimates[44-46]. The assessments will be performed by two independent reviewers (XW, YC) independently. Disagreements will be resolved by discussion or third-party adjudication (HZ), when necessary.

Amendments

Protocol amendments will be listed and made available on the PROSPERO registration. Date, description and rationale will be given for each amendment.

Patient and public involvement

None.

Consent for publication

Not applicable.

Contributorship statement

HZ conceived and designed the protocol with JW and XW. XW and YC contributed to the manuscript with all authors (XW, YC, ZL, JW and HZ) critically revising the manuscript. All authors have read and approved the final version of the manuscript. HZ is the guarantor.

Competing interests

The authors declared no conflict of interest.

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Data sharing statement

The findings of this systematic review will be published in an open-access journal to ensure access for all stakeholders and disseminated in various scientific conferences.

Ethics statement

Ethical approval is not required for this study because only available published data will be analysed. No patients, public or service users were involved in the design of this review protocol.

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Supplementary Appendix - Electronic search term implemented in PubMed, EMBASE and Scopus

PubMed

(((((((HIV[MeSH Terms]) OR (Acquired Immunodeficiency Syndrome[Mesh]) OR (human immunodeficiency virus[Title/Abstract])) OR (HIV infection[Title/Abstract])) OR (AIDS[Title/Abstract])) OR (acquired immunodeficiency syndrome[Title/Abstract])) OR (people living with HIV/AIDS[Title/Abstract])) OR (PLWHA[Title/Abstract]) AND ((prognostic tool) OR (prognostic model) OR (prognostic nomogram) OR (prognostic value) OR (prognostic risk) OR (prognostic score) OR (prognostic scoring) OR (prognostic marker) OR (disease progression score) OR (risk index for mortality) OR (multivariate models for predicting progression)))

EMBASE

1. 'hiv'/exp OR 'human immunodeficiency virus':ab,ti OR 'hiv infection':ab,ti OR aids:ab,ti OR 'acquired immunodeficiency syndrome':ab,ti OR 'people living with hiv':ab,ti OR plwh:ab,ti
2. 'prognostic tool' OR 'prognostic model' OR 'prognostic nomogram' OR 'prognostic value' OR 'prognostic risk' OR 'prognostic score' OR 'prognostic scoring' OR 'prognostic marker' OR 'disease progression score' OR 'risk index for mortality' OR 'multivariate models for predicting progression'
3. #1 AND #2

Scopus

1. TITLE-ABS-KEY('hiv') OR TITLE-ABS-KEY('human immunodeficiency virus') OR TITLE-ABS-KEY('hiv infection') OR TITLE-ABS-KEY('aids') OR TITLE-ABS-KEY('acquired immunodeficiency syndrome') OR TITLE-ABS-KEY('people living with hiv') OR TITLE-ABS-KEY('plwh')
2. TITLE-ABS-KEY('prognostic tool') OR TITLE-ABS-KEY('prognostic model') OR TITLE-ABS-KEY('prognostic nomogram') OR TITLE-ABS-KEY('prognostic value') OR TITLE-ABS-KEY('prognostic risk') OR TITLE-ABS-KEY('prognostic score') OR TITLE-ABS-KEY('prognostic scoring') OR TITLE-ABS-KEY('prognostic marker') OR TITLE-ABS-

KEY(‘disease progression score’) OR TITLE-ABS-KEY(‘risk index for mortality’) OR TITLE-ABS-KEY(‘multivariate models for predicting progression’)

3. #1 AND #2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Prognostic prediction models for treatment experienced people living with HIV: a protocol for systematic review and meta-analysis

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Prognostic prediction models for treatment experienced people living with HIV: a protocol for systematic review and meta-analysis

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Abstract

Introduction:

Despite the favourable efficacy and safety profile of antiretroviral therapy (ART), HIV/AIDS continues to impose significant disease burdens worldwide. This study aims to systematically review published prognostic prediction models for survival outcomes of treatment experienced people living with HIV (TE-PLHIV), to describe their characteristics, compare their performance, and assess the risk of bias and real-world clinical utility.

Methods and analysis:

Studies will be identified through a comprehensive search in PubMed, EMBASE and Scopus databases. Two reviewers will independently conduct selection of eligible studies, data extraction, and critical appraisal. Included studies will be systematically summarized using appropriate tools designed for prognostic prediction modelling studies. Where applicable, evidence will be summarised with meta-analyses.

Ethics and dissemination:

Ethical approval is not required because only available published data will be analysed. The results of this work will be published in an open-access peer-reviewed journal.

Systematic review registration: PROSPERO registration number CRD42023412118.

Keywords: HIV; AIDS; antiretroviral therapy (ART); prognostic model; survival

Strengths and limitations of this study

- A highly sensitive search strategy and robust quality assessment criteria (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) will be used to appraise existing prognostic prediction models for treatment experienced people living with HIV.
- The main limitation of this study could be the potential heterogeneity among prognostic models included in the analysis.

Introduction

Human immunodeficiency virus (HIV) is a viral infection that severely impairs the immune system [1]. Since antiretroviral therapy (ART) first introduction in the mid-1990s, it has led to significant reductions in HIV-associated morbidity and mortality, transforming HIV infection into a manageable chronic condition [2-6].

Despite these advancements, HIV/AIDS continues to impose significant disease burdens worldwide, with 38.4 million people living with HIV (PLHIV) and 650.0 thousand AIDS-related deaths in 2021 [7]. The increasing life expectancy of PLHIV presents new challenges in the treatment and management of this expanding population. Studies indicate that PLHIV face a higher risk of developing concurrent chronic diseases, including cardiovascular disease and non-AIDS-related neoplasms, compared to the general population [8-10]. This heightened risk may be related to HIV-induced immunodeficiency, ART drug toxicities, ageing, and poor lifestyle factors [8, 9]. Moreover, the introduction of regimens such as integrase strand transfer inhibitor (INSTI) in recent decades has presented certain clinical complexities. A recent multicenter study revealed that the initiation of INSTIs was associated with an early onset, excess incidence of cardiovascular disease in the first 2 years of exposure, after accounting for known cardiovascular disease risk factors [11]. The proportion of deaths from non-AIDS-related illnesses among PLHIV has surpassed that of AIDS-related illnesses in many regions of the world where free ART is available [12, 13]. Furthermore, recent real-world studies have raised doubts about the efficacy of new drugs such as INSTIs, as no significant disparities in mortality rates of PLHIV were observed among different modern ART regimens [14-16]. In light of this scenario, governments and health authorities worldwide must continue to allocate significant medical resources to the treatment and management of HIV-infected populations each year.

Developing an ideal prognostic model for treatment experienced people living with

HIV (TE-PLHIV) is crucial to optimizing HIV care and providing tailored treatment for individual patients, ultimately improving treatment outcomes and facilitating the rational allocation of limited health resources [17]. Given the identification of multiple risk factors associated with HIV/AIDS-related mortality, combining several independent indicators could significantly enhance predictive effectiveness. Existing studies of prognostic model for TE-PLHIV have identified several demographic and laboratory indicators closely linked to the mortality of TE-PLHIV, including age, sex, World Health Organization (WHO) clinical stage, body weight or body mass index (BMI), CD4+ T-cell count, HIV viral load, and haemoglobin [18-30]. However, there are discrepancies in the characteristics of prognostic models of TE-PLHIV, resulting in variations in the selected demographic and clinical features, as well as in the parameters and performance. Publication bias, poor reporting, and extensive heterogeneity are recognised issues in prognostic research [31-33]. Despite the amount of prognostic prediction models established for TE-PLHIV, none of them have been widely accepted as an addition to precision medicine workflows. A systematic review and meta-analysis of these models is therefore essential for enhancing their methodological quality, including better indicators and performance.

Study aim

The aim of this systematic review is to identify, screen, and evaluate all published prognostic prediction models on survival outcomes of TE-PLHIV and inform clinical therapeutic decision-making.

Methods

Study design

The systematic review described in this article is scheduled to be conducted between January 2024 and January 2025. This review was registered on the PROSPERO international registry of systematic reviews on April 8, 2023 (CRD42023412118).

This protocol adheres to a number of reporting guidelines for a systematic review including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline [34] and Cochrane Prognosis Methods Group Protocol Template [35], and guidelines for assessing and reporting prediction model studies including transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [36], PROBAST tool (prediction model risk of bias assessment) [37], and the checklist for corresponding CHARMS checklist (checklist for critical Appraisal and data extraction for systematic reviews of prediction modelling studies) [38]. Key items of this review are clarified with assistance of the PROGnosis RESearch Strategy (PROGRESS) Partnership (Table 1).

Table 1. Framing of this systematic review with key items identified by the CHARMS checklist

Items	Comments
1. Prognostic versus diagnostic prediction model	Prognostic prediction model (aimed to predict future survival outcomes of TE-PLHIV)
2. Intended scope of the review	Prognostic prediction models to inform clinicians' therapeutic decision making regarding the management of HIV/AIDS
3. Type of prediction modelling studies	All study types including prognostic prediction modelling studies with or without external validation and external model validation studies with or without model updating
4. Target population to whom the prediction model applies	TE-PLHIV according to each included study
5. Outcome to be predicted	Survival after ART initiation, including all-cause mortality and/or HIV-related mortality
6. Time span of prediction	Survival outcomes occurring at any time point after ART initiation
7. Intended moment of using the model	At any time point after ART initiation

Notes: TE-PLHIV, treatment experienced people living with HIV/AIDS; ART, antiretroviral therapy.

Eligibility criteria

Any study design including primary research (e.g., randomized controlled trial, cohort study, case-control study) that reports on one or more statistical models, tools or scores with at least two predictors proposed to predict an TE-PLHIV's risk of a future survival outcome (prognostic prediction modelling studies) before January 2024 will be considered for inclusion in the review. Prognostic prediction modelling studies can be either model development, model validation or a combination. Studies that have a single risk factor in the model will be excluded, as they are limited in their utility for individual risk prediction. Editorial comments or letters will be excluded from the review. Eligible studies included in the review will be limited to those conducted in humans by applying The Cochrane Group's filter for Humans not Animals filter[39]. PICOTS (population, index, comparator, outcome, timing, setting) approach will be used to frame the eligibility criteria and to guide the selection of prognostic prediction modes (Table 2) [37, 40].

Table 2. Eligibility criteria for the systematic review framed with the PICOTS system

Items	Inclusion criteria	Exclusion criteria
Population	TE-PLHIV according to criteria in each eligible study included in the review	
Index	Development or external validation of a prognostic prediction model for survival outcomes of TE-PLHIV (e.g., prognostic prediction models of TE-PLHIV to predict survival outcomes)	Diagnostic prediction models (e.g., diagnostic prediction models for diagnosis of HIV/AIDS)
Comparator	No predefined comparator	
Outcomes (primary)	All-cause mortality	
Outcomes (secondary)	HIV-related mortality, if possible	
Timing	Survival outcomes occurring at any time point after ART initiation	
Setting	Prognostic prediction models that are designed to be used by healthcare professionals in the clinical setting to inform their therapeutic decision making regarding the management of HIV/AIDS, at any time point after ART initiation	

Notes: PLHIV, people living with HIV/AIDS; ART, antiretroviral therapy.

Databases

A comprehensive and systematic literature search will be conducted in five major publicly available electronic medical literature databases: 1) PubMed (covering the period from 1946 to present); 2) EMBASE (covering the period from 1947 to present); 3) Scopus (covering the period from 1996 to present); 4) the Cochrane Library; 5) OpenGrey (www.opengrey.eu/), which is a database containing conference abstracts that has not been published.

Search strategy

The search strategy was built using keywords including HIV-related terms (ie, 'HIV', 'human immunodeficiency virus', 'HIV infection'), AIDS-related terms (ie, 'AIDS', 'acquired immunodeficiency syndrome'), patient-related terms (ie, 'people living with HIV/AIDS', 'PLHIV') and prediction modelling-related terms (ie, 'prognostic tool', 'prognostic model', 'prognostic nomogram', 'prognostic value', 'prognostic risk', 'prognostic score', 'prognostic scoring', 'prognostic marker', 'disease progression score', 'risk index for mortality', 'multivariate models for predicting progression'). The draft search strategy is provided in Supplementary Appendix. The search strategy, specifically, subject indexing terms will be translated appropriately for the Cochrane Library and OpenGrey. The final search strategy will be iteratively refined.

The reference lists of included model development studies and relevant systematic reviews for further studies will be hand searched for additional potentially relevant citations. We will also search for publications which cited the model development studies to identify model validation studies. The included studies will be checked for error or fraud. We will not place any restrictions on language, publication year or publication status when searching the electronic databases. Any non-English studies identified will be translated and assessed for eligibility.

Data collection and analysis

Data management

Retrieved studies included in the review will be imported into Endnote reference manager software (Version 20.4.1, Clarivate Analytics, Philadelphia, USA. Available at: https://endnote.com/). Duplicate records will be identified and excluded using a systematic, rigorous and reproducible method utilizing a sequential combination of fields including author, year, title, journal and pages [41]. Screened records will then be imported into Covidence systematic review software throughout the review (Veritas Health Innovation, Melbourne, Australia. Available at: http://www.covidence.org).

Selection process

Two reviewers (XW and YC) will independently screen and review the abstracts of all studies identified by the final search strategy. For each excluded article, reasons for exclusion will be specified. Disagreement or doubt will be resolved by consensus and if consensus cannot be reached, the full texts of the study will be independently accessed for further evaluation. Any conflict will be resolved through discussion with a senior advisor (HZ), if necessary.

Data extraction

Two reviewers (XW and YC) will independently extract data from eligible studies included in the review, using a standardized electronic form developed with reference to the checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[38].

For each eligible study, we plan to seek information on objective, source of data, participants, survival outcome(s) to be predicted, candidate predictors, sample size, missing data, model development, model performance (discrimination, calibration, clinical utility, and measures of case-mix variation), results including final multivariable models and interpretation of presented models, and model validation[38].

Information not reported in the publications will be obtained from the authors wherever possible, in addition, if insufficient information is obtained the study will be excluded from the review. Any disagreement will be resolved through consultation with a senior advisor (HZ).

Assessment of risk of bias

The methodological quality (risk of bias) and relevance (applicability) reporting the development or validation of a prognostic model will be systematically assessed using the PROBAST [37]. This tool is structured around four key domains: participant selection (e.g. were inclusions and exclusions of participants appropriate); predictors (e.g. were predictors measured blind to outcome data); outcomes (e.g. was the same definition used for outcomes in all patients); sample size and patient flow (e.g. was there a pre-specified sample size based on estimated number of outcome events, handling of missing data); and analysis (e.g. was selection of predictors based on univariable analysis avoided). Each study will be given a rating of high, low, or unclear risk for each of the four domains.

Synthesis

All included studies on prognostic prediction models will be described, with key findings tabulated to facilitate comparison of survival outcomes to be predicted, predictors included in the final model and performance measures [38]. Measures of uncertainty will be reported when published or approximated using published methods[40]. Where reported, classification measures such as sensitivity, specificity, positive predictive value and negative predictive value will also be included[38].

When at least five studies report similar measures of association, a meta-analysis will be conducted for each prognostic factor with reference to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group guidelines [42]. The restricted maximum likelihood and Hartung-Knapp-Sidik-Jonkman methods will be used to estimate the between-study heterogeneity and 95% confidence intervals for the average

performance [40]. Statistical or clinical homogeneity will be assessed using the I^2 statistics where I^2 values >50% indicate moderate to high heterogeneity [43]. When it is not feasible to conduct a quantitative synthesis, the evidence will be summarized narratively.

Subgroup analyses

Where there are enough eligible studies included in the review, we will conduct subgroup analyses of type of prognostic prediction modelling studies (i.e., development or validation), target population to whom the model applies, whether population was treated (yes/no), treatment type after ART initiation, the follow-up duration, survival outcomes to be predicted, and study quality (risk of bias).

Sensitivity analysis

A sensitivity analysis is a repeat of a meta-analysis. To test the robustness of this review's findings, we would undertake sensitivity analyses to explore the influence on model performance for exclusion of studies at lower and higher risk of bias [40].

Reporting and presentation of findings

Reporting and presentation of findings will be guided by the PRISMA statement[34], and relevant recommendations from the TRIPOD statement[36]. The GRADE approach (grading of recommendations, assessment, development and evaluation) will be utilized to determine confidence in estimates[44-46]. The assessments will be performed by two independent reviewers (XW, YC) independently. Disagreements will be resolved by discussion or third-party adjudication (HZ), when necessary.

Amendments

Protocol amendments will be listed and made available on the PROSPERO registration. Date, description and rationale will be given for each amendment.

Patient and public involvement

None.

Consent for publication

Not applicable.

Contributorship statement

HZ conceived and designed the protocol with JW and XW. XW and YC contributed to the manuscript with all authors (XW, YC, ZL, JW and HZ) critically revising the manuscript. All authors have read and approved the final version of the manuscript. HZ is the guarantor.

Competing interests

The authors declared no conflict of interest.

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Data sharing statement

The findings of this systematic review will be published in an open-access journal to ensure access for all stakeholders and disseminated in various scientific conferences.

Ethics statement

Ethical approval is not required for this study because only available published data will be analysed. No patients, public or service users were involved in the design of this review protocol.

Acknowledgements

We thank all authors, Editors, and reviewers for carefully reading and commenting on the manuscript.

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Supplementary Appendix - Electronic search term implemented in PubMed, EMBASE and Scopus

PubMed

(((((((HIV[MeSH Terms]) OR (Acquired Immunodeficiency Syndrome[Mesh]) OR (human immunodeficiency virus[Title/Abstract])) OR (HIV infection[Title/Abstract])) OR (AIDS[Title/Abstract])) OR (acquired immunodeficiency syndrome[Title/Abstract])) OR (people living with HIV/AIDS[Title/Abstract])) OR (PLWHA[Title/Abstract]) AND ((prognostic tool) OR (prognostic model) OR (prognostic nomogram) OR (prognostic value) OR (prognostic risk) OR (prognostic score) OR (prognostic scoring) OR (prognostic marker) OR (disease progression score) OR (risk index for mortality) OR (multivariate models for predicting progression)))

EMBASE

1. 'hiv'/exp OR 'human immunodeficiency virus':ab,ti OR 'hiv infection':ab,ti OR aids:ab,ti OR 'acquired immunodeficiency syndrome':ab,ti OR 'people living with hiv':ab,ti OR plwh:ab,ti
2. 'prognostic tool' OR 'prognostic model' OR 'prognostic nomogram' OR 'prognostic value' OR 'prognostic risk' OR 'prognostic score' OR 'prognostic scoring' OR 'prognostic marker' OR 'disease progression score' OR 'risk index for mortality' OR 'multivariate models for predicting progression'
3. #1 AND #2

Scopus

1. TITLE-ABS-KEY("hiv") OR TITLE-ABS-KEY("human immunodeficiency virus") OR TITLE-ABS-KEY("hiv infection") OR TITLE-ABS-KEY("aids") OR TITLE-ABS-KEY("acquired immunodeficiency syndrome") OR TITLE-ABS-KEY("people living with hiv") OR TITLE-ABS-KEY("plwh")
2. TITLE-ABS-KEY("prognostic tool") OR TITLE-ABS-KEY("prognostic model") OR TITLE-ABS-KEY("prognostic nomogram") OR TITLE-ABS-KEY("prognostic value") OR TITLE-ABS-KEY("prognostic risk") OR TITLE-ABS-KEY("prognostic score") OR TITLE-ABS-KEY("prognostic scoring") OR TITLE-ABS-KEY("prognostic marker") OR TITLE-ABS-

KEY("disease progression score") OR TITLE-ABS-KEY("risk index for mortality") OR TITLE-ABS-KEY("multivariate models for predicting progression")

3. #1 AND #2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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