



# BMJ Open Rates and risk factors for suicidal ideation, suicide attempts and suicide deaths in persons with HIV: a protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** The prevalence of HIV/AIDS is high and is associated with psychiatric morbidity and suicide risk. The objective of this study will be to assess the rates of suicidal ideation, suicide attempts and suicide deaths in people living with HIV/AIDS (PLWHA).

**Methods and analysis** We present a study protocol for a systematic review and meta-analysis of studies reporting the suicidality outcomes (suicidal ideation, suicide attempts and suicide deaths) in PLWHA. PubMed (MEDLINE), Scopus, EMBASE, Cochrane Library, OVID (HEALTH STAR), OVID (MEDLINE), Joanna Briggs Institute EBP Database, Web of Science and PsychINFO databases will be searched from their inception until 1 January 2020. The primary outcome of interest will be the incidence of suicidality in PLWHA. In addition, we will delineate risk factors associated with suicidality in PLWHA. Citations, full-text articles and abstracts will be screened by four reviewers independently. Disagreements will be resolved through discussion. The study methodological quality (or bias) will be appraised using an appropriate tool. Random-effects meta-analysis will be conducted if we find that the studies are very heterogenous. For the suicidality outcome, probability of suicide risk will be reported. Relative risk ratios (with 95% CIs) will be reported for the effects of the risk factors. Potential publication bias will be assessed by conducting Egger's test and creating funnel plots. We will conduct additional analyses to explore the potential sources of heterogeneity (eg, age, sex and geographical location).

**Ethics and dissemination** No ethics clearance is required as no primary data will be collected. The results of this systematic review and meta-analysis will be presented at scientific conferences and published in a peer-reviewed journal. The results may inform clinical management of PLWHA and may guide future population-specific interventions.

We will search PubMed (MEDLINE), Scopus, EMBASE, Cochrane Library, OVID (HEALTH STAR), OVID (MEDLINE), Joanna Briggs Institute EBP Database, Web of Science and PsychINFO from their inception until 1 January 2020.

**PROSPERO registration number** CRD42020161501.

## Strengths and limitations of this study

- This will be the first comprehensive systematic review and meta-analysis to synthesise the current literature on the epidemiology of suicidality outcomes in people living with HIV/AIDS.
- We adhered to Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines to ensure transparency and reproducibility of the study.
- Heterogeneity in the tools used to assess suicidality outcome may be a limitation.
- Heterogeneity in the cohort selection within each body of work; some studies may limit their work to perinatally infected individuals, pregnant women and/or intravenous drug users.
- To overcome these limitations, we will use meta-regression to statistically explore the sources of heterogeneity in the outcome of interest.

## BACKGROUND

Since its discovery in the 1980s, HIV continues to carry a significant global burden of disease. While the disease remains incurable, antiretroviral therapy (ART) has been effective in controlling disease progression, improving quality of life and prolonging longevity.<sup>1</sup> In 2018, the World Health Organization (WHO) and the United Nations Program on HIV/AIDS (UNAIDS) approximated that 40 million people globally are living with HIV/AIDS (PLWHA).<sup>2</sup> HIV caused an estimated 1 million deaths worldwide and was responsible for the annual 48 disability-adjusted life years per 100 000 population.<sup>3 4</sup> While the UNAIDS and the WHO provide an effective framework in controlling HIV infection, the current strategies fail to adequately address interventions for the psychosocial burden experienced by PLWHA.

Despite the improved prognosis of HIV, studies continue to find an association between HIV and suicide. Carrieri *et al* reported in 2017 that 6.3% of PLWHA are at risk for suicide.<sup>5</sup> Likewise, a cross-sectional study found that 78% of minority PLWHA had suicidal thoughts, and 26% had attempted suicide since diagnosis.<sup>5</sup> Data thus far have shown that patient suicide rates within the first year of HIV diagnosis exceed that of the general population.<sup>6–8</sup> Furthermore, societal factors such as stigma, discrimination and lack of social support have been implicated.<sup>9–10</sup> Because the risk factors implicated in suicidality in PLWHA are multifactorial,<sup>11</sup> identifying the risks correlated to suicidal behaviour in patients with HIV may inform effective preventative measures against suicide. Furthermore, as discussed above, identification of risk factors of suicidal behaviour can improve HIV management in at-risk populations.

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, morbidity and mortality rates have declined in PLWHA,<sup>12</sup> although the relationship between HAART and suicide risk remains unclear. A longitudinal study followed 163 PLWHA for 2 years and found that HAART increased CD4 counts and decreased depressive symptoms with a temporal relationship.<sup>13</sup> However, other studies have suggested that HAART combined with clarithromycin or efavirenz can induce a neuropsychiatric reaction, potentially increasing depressive symptoms and suicide risk.<sup>14–16</sup> To our knowledge, there is no systematic review and meta-analysis that estimates the pooled rates of suicidality in PLWHA.

## OBJECTIVES

The objective of this study will be to assess the rates and risk factors of suicidal ideation, suicide attempt and suicide deaths in PLWHA. The specific review questions will be:

1. What is the global incidence of suicide deaths in PLWHA?
2. What is the global prevalence of suicidal ideation and suicide attempt in PLWHA?
3. What are the risk factors associated with suicidality outcomes in PLWHA?

## METHODS

The methods of this protocol are similar to those reported elsewhere.<sup>17</sup> This protocol is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement protocol<sup>18–19</sup> (see PRISMA-P checklist in online supplemental file 1).

## Eligibility criteria

Participants (population): children, adolescents and adult patients living with HIV. No age and sex constraint.

Outcome(s) of interest: the primary outcome will be incidence of suicidality. This includes new cases of suicidal ideations, suicide attempts, or suicide deaths in PLWHA. We will explore risk factors associated with the primary outcomes, including HIV viral load, CD4 T cell count, age, gender, race, major depression disorder, panic disorder, social phobia, schizophrenia, alcohol use, drug abuse and dependence.

Study design: randomised controlled trials, observational cohort (prospective or retrospective) and cross-sectional studies reporting suicidality in people living with HIV. Case reports, case series, meta-analysis and reviews will be excluded.

## Information sources and search strategy

PubMed (MEDLINE), Scopus, EMBASE, Cochrane Library, OVID (HEALTH STAR), OVID (MEDLINE), Joanna Briggs Institute EBP Database, Web of Science and PsychINFO databases will be searched from their inception until 1 January 2020. In addition, grey literature will be searched. We will perform hand-searching of the reference lists of included studies, relevant reviews or other relevant documents. The search will be based on Medical Subject Headings, a broad range of terms and keywords related to: “suicide” and “human immunodeficiency syndrome/acquired immunodeficiency syndrome”. A draft search strategy for MEDLINE is provided in online supplemental file 2.

## Study selection and data extraction

All articles identified from the literature search will be screened by four reviewers (HW, NL, MC and MP) independently.

## Title and abstract screening

In the first stage, four reviewers will independently screen titles and abstracts of articles returned from initial searches based on the eligibility criteria outlined above. They will document, with reasons, the studies excluded from the review. In the case of potential disagreement, the four reviewers will consult a senior reviewer (PS) to reach consensus. The citations will be downloaded into the EndNote software and will exclude duplicate articles.

## Full-text screening and data extraction

In the second stage, full-text versions of selected abstracts will be downloaded/retrieved and assessed independently by the four reviewers. They will extract data from eligible papers identified during the abstract screening step. Disagreements will be resolved through discussion until a consensus is reached. When abstracts and subsequently included papers are not available in English, translators will be sought. The following information will be extracted: first author, country in which the study was conducted, year of publication, study period, research methodology, total sample size, number of patients with suicidal ideation, number of patients with suicide attempt, number of patients with suicide completion, percent of study sample that are male, mean age,

employment, homelessness, partner presence, percent of population on HAART, regimen of HAART, mean CD4 T cell count, median viral load, proportion of PLWHA with major depression, anxiety and other psychiatric illness, proportion with AIDS and AIDS-associated central nervous system conditions. A PRISMA flow chart detailing the study selection process will be provided.

### Assessment of methodological quality of the papers

Methodological quality of studies will be conducted using the Newcastle–Ottawa Quality Assessment Scale, which is a validated tool for assessing quantitative cross-sectional, case–control and cohort studies.<sup>20</sup> Scores of 8 to the maximum score of 9 will be defined as high quality; scores of 5–7 will be defined as intermediate quality, and scores of 1–4 will be defined as low quality. Any discrepancy or disagreements in scoring will be resolved by discussion. Further, sensitivity analysis will be carried out using study quality score.

### Data synthesis

The data from each paper (eg, study characteristics, participants, outcomes and findings) will be used to build evidence tables of an overall description of included studies. Incidence and prevalence estimate of suicidality outcome will be presented as cases per 1000 along with 95% confidence intervals (CIs). Relative risk ratios or odds ratios (ORs) with 95% CIs will be used to report the association of suicidality outcome with the risk factors. If feasible and appropriate, data points from primary studies will be used to perform random effects meta-analyses. Since heterogeneity is expected a priori, we will estimate the pooled incidence and its 95% CIs using the random effects model with logit transformation and back transformation. We will use the *meta* package in R Statistical Software for analysis.<sup>21</sup> The CIs will be calculated using the exact binomial (Clopper–Pearson) interval method.<sup>21</sup> The random effects model assumes the study estimates follow a normal distribution, considering both within-study and between-study variation. Forest plots will be used to visualise the extent of heterogeneity among studies. Quantification of statistical heterogeneity will be accomplished by estimating the variance between studies using  $I^2$  statistic, which is the proportion of variation in prevalence estimates that is due to true variation in prevalence rather than sampling (random) error.  $I^2$  ranges between 0% and 100% (with values of 0%–25% and 75%–100% indicating low and considerable heterogeneity, respectively). In addition, we will report  $\text{Tau}^2$  and Cochran  $Q$  test with a  $p$  value of  $<0.05$  considered statistically significant (heterogeneity). Potential publication bias will be explored using Egger's test and funnel plots.

### Additional analyses

Potential sources of heterogeneity will be explored further by subgroup or meta-regression analyses by using baseline characteristics and methodological covariates.

In addition, we plan to conduct analyses by geographical location, age (median), sex (eg, proportion), comorbidities (eg, proportion of major depressive disorder, mean body mass index), CD4 T cell counts (median), HAART (proportion), AIDS (proportion) and quality score of each included study (high vs low/medium score). We will assess publication bias by inspecting the funnel plots for asymmetry and with Egger's test, with the results considered to indicate potential small study effects when  $p$  values  $<0.10$ .

### Software considerations

All analyses will be conducted in meta-package in R Statistical Software for analysis.

### Presentation of results and reporting

The PRISMA guidelines will be followed and the checklist will accompany the publication. Quantitative data will be summarised and presented in tables, forest plots and maps. The prevalence and incidence of suicide in PLWHA will be presented by continents, by study design. We define the prevalence of suicide as the number of existing cases within the described time period, and we define the incidence of suicide as the rate of new cases that occur among cohorts during the described time period. Meta-regression analysis will be reported as absolute differences (per 1000) in the overall probability of suicide. Strength of evidence will be assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework using four levels of quality of evidence: very low, low, moderate and high. We use the following domains GRADE: risk of bias, imprecision, inconsistency, indirectness and publication bias.<sup>22</sup> We will report the overall strength of evidence of the outcome of interest.

### Patient and public involvement

Patients were not involved in the development of this systematic review protocol.

## DISCUSSION

The systematic review and meta-analysis of studies presented in this protocol will identify, collect and evaluate the existing knowledge underlying the incidence, prevalence and risk factors of suicidality associated with HIV infection. We will report the findings of the systematic review and meta-analysis in accordance with the reporting guidance in the PRISMA statement<sup>23</sup> and the Meta-analysis Of Observational Studies in Epidemiology reporting guideline.<sup>24</sup> The results of the proposed systematic review and meta-analysis will be presented at conferences and published in a peer-reviewed journal. The findings of the proposed review will guide interventions to improve the mental health of people living with HIV with the potential of improving their quality of care and overall survival.





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