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

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ABSTRACT

Background People living with HIV/AIDS (PLWHA) must contend with a significant burden of disease. However, current studies of this demographic have yielded wide variations in the incidence of suicidality (defined as suicidal ideation, suicide attempt and suicide deaths).

Aims This systematic review and meta-analysis aimed to assess the lifetime incidence and prevalence of suicidality in PLWHA.

Methods Publications were identified from PubMed (MEDLINE), SCOPUS, OVID (MEDLINE), Joanna Briggs Institute EBP and Cochrane Library databases (from inception to before 1 February 2020). The search strategy included a combination of Medical Subject Headings associated with suicide and HIV. Researchers independently screened records, extracted outcome measures and assessed study quality. Data were pooled using a random-effects model. Subgroup and meta-regression analyses were conducted to explore the associated risk factors and to identify the sources of heterogeneity. Main outcomes were lifetime incidence of suicide completion and lifetime incidence and prevalence of suicidal ideation and suicide attempt.

Results A total of 185 199 PLWHA were identified from 40 studies (12 cohorts, 27 cross-sectional and 1 nested case-control). The overall incidence of suicide completion in PLWHA was 10.2/1000 persons (95%CI: 4.5 to 23.1), translating to 100-fold higher suicide deaths than the global general population rate of 0.11/1000 persons. The lifetime prevalence of suicide attempts was 158.3/1000 persons (95%CI: 106.9 to 228.2) and of suicidal ideation was 228.3/1000 persons (95%CI: 150.8 to 330.1). Meta-regression revealed that for every 10-percentage point increase in the proportion of people living with HIV with advanced disease (AIDS), the risk of suicide completion increased by 34 per 1000 persons. The quality of evidence by Grading of Recommendations, Assessment, Development and Evaluations for the suicide deaths was graded as 'moderate' quality.

Conclusions The risk of suicide death is 100-fold higher in people living with HIV than in the general population. Lifetime incidence of suicidal ideation and attempts are substantially high. Suicide risk assessments should be a priority in PLWHA, especially for those with more advanced disease.

INTRODUCTION

Since its discovery in the 1980s, HIV continues to carry a significant global burden of disease. While the disease remains incurable, highly active antiretroviral therapy (HAART) has been effective in controlling disease progression, improving quality of life and prolonging longevity.[1] In 2017, the Global Burden of Disease approximated that globally, 36.8 million people were living with HIV/AIDS (PLWHA).[2 3] HIV caused approximately one million deaths worldwide and was responsible for the annual 48 disability-adjusted life years (DALYs) per 100 000 population.[2 4] While The Joint United Nations Programme on HIV and AIDS (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.

Since the introduction of HAART in 1996, morbidity and mortality have declined in PLWHA,[5] 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 indicative of immunological rebound and decreased depressive symptoms with a temporal relationship.[6] However, other studies have suggested that HAART with efavirenz can induce a neuropsychiatric reaction, potentially increasing depressive symptoms and suicide risk.[7–9] Despite the improved prognosis of HIV, studies continue to find a wide variation in incidence of increased suicidality among PLWHA.[10 11] Marzuk and colleagues found that nearly 9% of suicide victims had HIV in New York City.[12] Likewise, a cross-sectional study found that 78% of women with HIV had suicidal thoughts, and 26% had attempted suicide since their HIV diagnosis.[13] Data thus far have shown

that patient suicide rates within the first year of HIV diagnosis exceed that of the general population.[14–16] While the factors leading to suicide may mirror those seen in depression, identifying the risks correlated to suicidality in patients with HIV will inform effective preventative measures against suicide. Furthermore, as discussed above, identifying risk factors of suicidal behaviour can improve HIV management in at-risk populations. Currently, it is not well established whether: (1) HIV infection itself increases suicide risk; (2) if HAART increases suicide risk because of side effects; (3) other cofactors that are commonly seen in the HIV population such as depression, lack of social support, stigma, loneliness and so on could affect the suicide risk.

To date, there is no systematic review and meta-analysis of the pooled lifetime incidences of suicide in PLWHA and examined associated risk factors. This has, in part, been confounded by the methodological limitations of different studies leading to a wide variety of incidence reports.[17] To fill the knowledge gap, we aimed to explore the relationship between HIV/AIDS and suicide risk. We accomplished this goal by conducting a meta-analysis of published literature. The primary objective was to examine the lifetime incidence of suicide completion in PLWHA and delineate the associated risk factors. Furthermore, we examine the lifetime incidence and prevalence of suicidal ideation and attempts within PLWHA. This comprehensive statistical review of the published literature provides a deeper understanding of the effects of HIV on suicide risk.

METHODS

Database searches, search strategy and terms

This study has been registered with PROSPERO (registration number: CRD42020161501) and the protocol is published.[18] This study is being reported per the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see online supplemental table 1).[17] We used the study protocol (online supplemental text 1). We searched PubMed (MEDLINE), SCOPUS, OVID (MEDLINE), Joanna Briggs Institute EBP and Cochrane Library databases to identify studies reporting suicide rates in PLWHA that have been published from inception to before 1 February 2020. Our keyword search was based on Medical Subject Headings (MeSH) with various combinations of 'Suicide*', OR'Depression*', OR'Suicide Attempt*', OR'Suicidal Ideation*', OR'Suicide Completion*' OR'Mental Illness*' OR 'Anxiety*', AND 'HIV*' OR'Human Immunodeficiency Virus', 'AIDS' OR 'Acquired Immunodeficiency Syndrome'. The full list of search terms is given in online supplemental table 2.

Eligibility criteria

Studies were selected according to the following criteria: participants, condition or outcome(s) of interest, study design and context.

1. *Participants (population):* We included studies involving children, adolescents and adult patients living with HIV (regardless of age or sex). Studies not conducted in humans were excluded.
2. *Condition or outcome(s) of interest:* The primary outcome is the incidence of suicidality outcome indicating the rate of new (or newly diagnosed) cases of suicidal ideations, suicide attempts or suicide deaths in people living with HIV. It is generally reported as the number of new cases occurring within a period of time (eg, per month or per year) or as a fraction of the population at risk of developing the outcome (eg, new cases per 1000 or 10 000). We used author-reported definitions according to accepted diagnostic criteria. Secondary outcomes are the risk factors associated with suicidality outcome (eg, HIV viral lead, CD4 T cell count, age, gender and race, major depression, alcohol or drug abuse and dependence, panic disorder, social phobia and schizophrenia).
3. *Study design and context:* Eligible studies were randomised trials, observational cohort (prospective or retrospective) and cross-sectional studies reporting outcome data and conducted in a wide range of PLWHA. We excluded case series and case reports. No limitations were imposed during the study conduct period and language of publication. Reviews, commentaries and conference/meeting abstracts were excluded.

Data extraction

Data were extracted from studies using an adapted version of a standard data entry electronic form (table 1). Full-text articles were downloaded and independently reviewed by HW, MP, NL and MC to determine eligibility for inclusion in the analysis. If eligible, data were extracted. Disagreements between extractors were discussed with a fifth author (PS), and a consensus was reached. The incidences of suicidal ideation, attempts and completion were extracted from each publication using a structured data collection spreadsheet. Study-level characteristics included were the year of publication, year or years of study, study methods, mean/median age, gender proportion, proportion on HAART, the proportion with depression and average CD4 count. Studies that do not include enough information to calculate primary outcome (incidence of suicidal ideation, suicide attempt and suicide deaths) were excluded.

Assessment of methodological quality of the papers

Two authors (MP and MC) independently assessed the quality of the papers included in the review. Assessment of methodological quality was conducted using the Newcastle-Ottawa Quality Assessment Scale, a validated tool for assessing cross-sectional, case-control and cohort studies.[19] Scores of 8 to the maximum score of 9 were defined as high quality; scores of 5–7 were defined as intermediate quality and scores of 1–4 were defined as low quality. Discrepancies in scoring were resolved by discussion with a third author (PS). Studies were included regardless of the risk of bias and quality scores, but

Table 1 Study-level characteristics of the articles included in the meta-analysis

Author (year)	Quality score	Study design	Country	Study period	Sample size	Male (%)	Mean/median age (years)
Hentzien *et al* (2018)[15]	8	Nested-case-control	France	2000–2013	34 308	88.9	45.38
Wang *et al* (2019)[44]	5	Cross-sectional	China	2015–2016	523	93.5	34.3
Wang *et al* (2018)[45]	6	Cross-sectional	China	2016 (Jul-Aug)	465	95.1	37.22
Walter and Petry (2016)[31]	7	Cross-sectional	USA	2016	170	61.2	42.9
Shim *et al* (2018)[46]	7	Cross-sectional	South Korea	2016–2017	195	89.1	48.6
Préau *et al* (2008)[47]	7	Cross-sectional	France	2003	2932	71.2	41
Passos *et al* (2014)[48]	9	Cross-sectional	Brazil	2012	211	47.9	40.1
Malbergier and de Andrade (2001)[49]	7	Cross-sectional	Brazil	n.r.	30	77	n.r.
Lopez *et al* (2018)[50]	7	Cross-sectional	USA	2012	648	60.5	40.8
Kelly *et al* (1998)[51]	8	Cross-sectional	Australia	n.r.	164	100	n.r.
Kalungi *et al* (2017)[52]	7	Cross-sectional	Uganda	2010–2012	555	23.6	n.r.
Kalichman *et al* (2000)[53]	4	Cross-sectional	USA	1998–1999	113	75.2	53.4
Lu *et al* (2018)[54]	8	Cross-sectional	China	2015–2016	113	99.1	n.r.
Grassi *et al* (2001)[55]	7	Cross-sectional	Italy	n.r.	81	77.7	31.72
Gielen *et al* (2005)[56]	6	Cross-sectional	USA	n.r.	115	0	n.r.
Ferlatte *et al* (2017)[29]	6	Cross-sectional	Canada	2015–2016	673	100	47.86
de Almeida *et al* (2016)[57]	7	Cross-sectional	Brazil	2007–2011	39	51.3	43
Cooperman and Simoni (2005)[13]	7	Cross-sectional	USA	n.r.	207	0	39.5
Cochand and Bovet (1998)[58]	6	Cross-sectional	Switzerland	1992–1993	65	100	n.r.
Carrieri *et al* (2017)[59]	9	Cross-sectional	France	2011–2012	2973	66.7	47.3
Quinlivan *et al* (2017)[60]	7	Cross-sectional	USA	2011–2012	4099	74.3	n.r.
van Haastrecht *et al* (1994)[30]	5	Prospective cohort	Netherlands	1984–1992	86	73	31.2
Roy (2003)[61]	6	Cross-sectional	USA	n.r.	149	79.9	44.4
Rodriguez *et al* (2019)[27]	4	Prospective cohort	South Africa	2014–2019	681	0	28.37
Protopoescu *et al* (2012)[62]	6	Prospective cohort	France	1997–1999	1095	77.7	37.6
Kreniske *et al* (2019)[63]	4	Prospective cohort	USA	2003–2012	206	45	22.8
Keiser *et al* (2010)[64]	8	Prospective cohort	Switzerland	1998–2008	15 275	71	n.r.
Heckman *et al* (2002)[65]	7	Cross-sectional	USA	1999–2000	201	75.6	39.8
Dannenberg *et al* (1996)[66]	6	Prospective cohort	USA	1985–1993	4147	92	24
Sherr (1995)[67]	6	Prospective cohort	UK	1995	188	88.8	n.r.
Yann Ruffieux *et al* (2019)[28]	8	Retrospective cohort	Switzerland	1988–2017	20 136	72.4	34.8
Scheer *et al* (2001)[11]	7	Cross-sectional	USA	1995–1997	176	89	41
Rice *et al* (2010)[68]	7	Cross-sectional	UK	1981–2008	95 075	87	28.7
Quintana-Ortiz *et al* (2008)[69]	6	Retrospective cohort	USA	2000–2004	717	67.7	40.69
Paparizos *et al* (2017)[70]	6	Retrospective cohort	Greece	1992–2012	1884	96	36.64
May *et al* (2004)[71]	9	Cross-sectional	France	2000	149	74	41
Marzuk *et al* (1997)[10]	7	Cross-sectional	USA	1991–1993	133	87	40
Jovet-Toledo *et al* (2014)[72]	8	Cross-sectional	USA	2010–2012	427	65.3	47.7
Gurm *et al* (2015)[73]	6	Retrospective cohort	Canada	1996–2012	82	78	42
O'Donnell *et al* (2016)[74]	7	Retrospective cohort	USA	2011–2014	289	70.6	45

n.r., not reported.

subgroup analysis was conducted to ascertain the impact of their inclusion (table 1).

Statistical analyses

We adopted a narrative approach describing the number of studies, study design, country where the studies were conducted and suicidality diagnostic criteria. We examined three outcomes separately. The first was the lifetime incidence of suicide completion (deaths), the second and third were suicide attempts and suicidal ideation in PLWHA. The metaprop and metagen functions from the R package meta were used to calculate the pooled effect estimates using random-effects models.[20] Random-effect models were built using a generalised linear mixed-effects model with logit transformation of proportions for pooling of studies.[21] The CIs were calculated using the exact binomial (Clopper-Pearson) interval method. We applied the DerSimonian and Laird random-effects method to estimate the pooled between-study variance (heterogeneity).[22] Individual and pooled estimates were graphically displayed using forest plots. A random-effects model assumes the observed estimates can vary across studies because of real differences in the effect in each study as well as sampling variability (chance). Between-study heterogeneity was assessed using I^2 statistics, expressed as a percentage (low (25%), moderate (50%) and high (75%)) and a Cochrane's Qstatistic (significance level <0.05).[23] We assessed the quality of evidence (QoE) using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework using four levels of quality of evidence: very low, low, moderate and high.[24] The following domains were used for the assessment: risk of bias, imprecision, inconsistency, indirectness and publication bias.[25] We reported the overall strength of evidence of the outcome of interest. Potential sources of heterogeneity were investigated further by subgroup or meta-regression analyses according to baseline characteristics and methodological covariates. Additionally, we explored geographical differences in suicide risk. Meta-regression analysis was conducted using the following covariates as regressors: study-level median or mean age (also dichotomised as mean/median age ≥40 years or <40 years), study-level gender proportions, year of study, depression proportions, the proportion of study population with AIDS and patients on HAART, mean/median CD4 count, percentage of the study population with a depression diagnosis and study quality score. Potential ascertainment bias (as might be caused by publication bias) was assessed with funnel plots, by plotting the study effect size against SEs of the effect size and Egger's test.[26] We report absolute differences (per 1000) in the overall rates of suicide.

RESULTS

Our search retrieved 1518 articles, of which 539 full-texts were carefully reviewed and considered as potentially relevant (PRISMA; figure 1). The full-text review identified

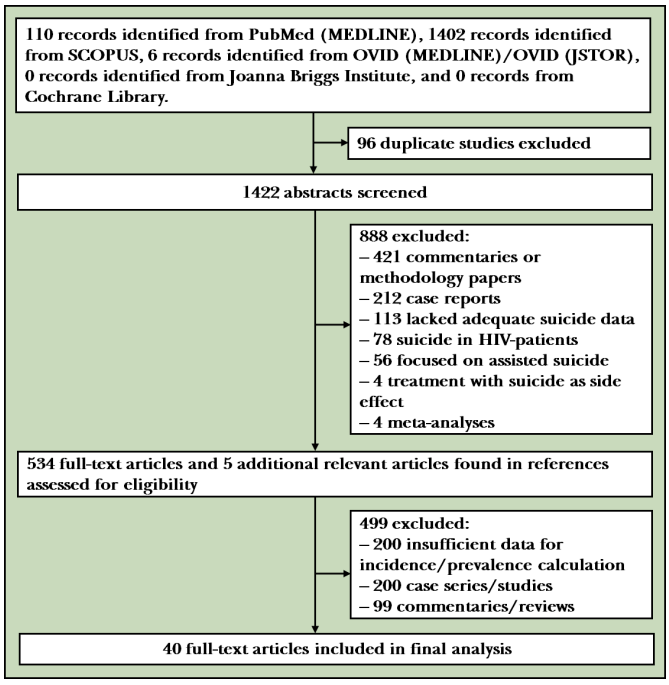

Figure 1 PRISMA flowchart for the meta-analysis of suicidality in PLWHA. Forty full-text articles were incorporated into the review from a total of 1518 titles. PLWHA, people living with HIV/AIDS.

40 eligible articles from 14 countries (table 1): USA 15, France 5, Brazil 3, Switzerland 3, South Africa 1, China 3, Canada 2, Australia 1, Italy 1, South Korea 1, Greece 1, Uganda 1, UK 2 and Netherlands 1. Twenty-seven studies were cross-sectional, while five were retrospective cohorts, seven were prospective cohorts and one was a nested case-control study. Source of participants varied widely between studies from specific subgroups such as pregnant and postpartum women to national databases.[11 27 28] Diagnostic criteria for suicidal ideation and attempts were clinical and assessed by various questionnaires, both formal and informal (eg, MINI, Beck Depression Inventory-II or asking if participants had 'considered ending their lives').[29] Illness duration varied widely between studies, from immediate postdiagnosis period to lifetime risk.[30 31] Suicide completion was reported as the intentional self-infliction of death. There was high heterogeneity in the diagnostic methods used to identify suicide attempts and ideation. The articles included in the final selection comprised a total of 185 199 PLWHA. The articles that reported suicide completion comprised a total of 177 748 PLWHA, and the cumulative number of patients with suicide completion was 973. The median age of the patients included in the study was 39 years. The quality of evidence by Grading of Recommendations, Assessment, Development and Evaluations for the suicide deaths was graded as 'moderate' quality (online supplemental table 3). The median study quality score was 7 out of 9 (range from 4 to 9, table 1 and online supplemental table 3). Study-specific details and references are given in table 1.

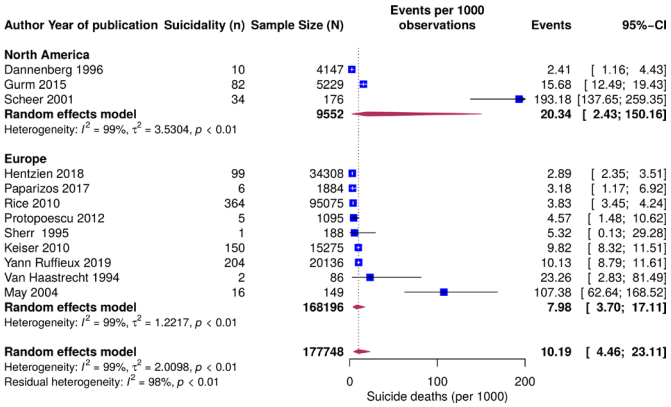

Figure 2 Forest plot of the incidence of suicide deaths per 1000 PLWHA by continent from random-effects model: event values represent the number of suicide deaths per 1000 PLWHA (95%CI). Blue squares and their corresponding lines are the point estimates and 95%CIs per study. Maroon diamonds represent the pooled estimate of the prevalence for each subgroup (width denotes 95%CIs). Heterogeneity by continent: North America (I^2=99%); Europe (I^2=99%); p value for the interaction comparing the different subgroups is 0.41. PLWHA, people living with HIV/AIDS.

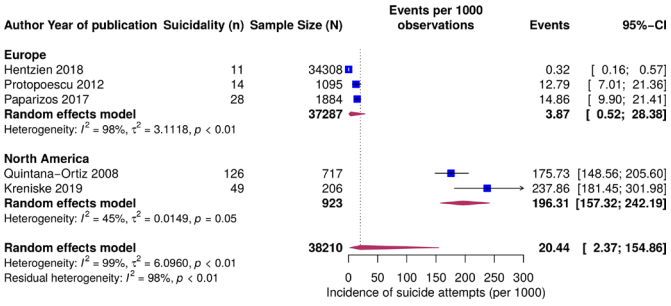

Figure 3 Forest plot of the incidence of suicide attempts per 1000 PLWHA by continent from random-effects model: event values represent the number of new cases of suicide attempts per 1000 PLWHA (95%CI). Blue squares and their corresponding lines are the point estimates and 95%CIs per study. Maroon diamonds represent the pooled estimate of the prevalence for each subgroup (width denotes 95% confidence intervals). Heterogeneity by continent: North America (I^2=45%); Europe (I^2=98%); p value for the interaction comparing the different subgroups is <0.0001. PLWHA, people living with HIV/AIDS.

Pooled incidence of suicide deaths in PLWHA

The pooled incidence of suicide completion was 10.2 per 1000 population (95%CI: 4.5 to 23.1) (figure 2). Between-study heterogeneity for the cumulative incidence was large (I^2=99%; p<0.01). Only North American and European studies reported suicide completion. We carried out subgroup analysis by continent to explore regional differences in suicide completion. The pooled incidence of suicide in studies conducted in North America was twice as high as that in Europe, although the difference was not statistically significant. Egger's test for publication bias was significant (p<0.001) and funnel plots displayed asymmetry (online supplemental figure 1).

Pooled incidence and prevalence of suicide attempts in PLWHA

The overall pooled incidence of suicide attempts per 1000 population was 20.4 (95%CI: 2.4 to 154.9) (figure 3). The incidence in North America was 50 times as high compared with that in Europe. Likewise, in PLWHA, the lifetime prevalence of suicide attempts was 158.3 per 1000 persons (95%CI: 106.9 to 228.2). The prevalence was higher in the Americas and Australia than in Africa and Asia (figure 4). Displayed in online supplemental figure 2 are the country-specific prevalence of suicide attempts. Egger's test for publication bias was significant (p<0.001) and funnel plots displayed asymmetry (online supplemental figure 3).

Pooled prevalence of suicidal ideation in PLWHA

The overall pooled lifetime prevalence of suicidal ideation per 1000 population was 228.3 (95%CI: 150.8 to 330.1) (figure 5). Africa and Europe displayed lower prevalence in suicidal ideation compared with that in North America, South America and Asia. However, these differences were not statistically significant.

Meta-regression

To explore sources of heterogeneity in suicidality, we conducted meta-regression analysis with the following covariates: study-level median or mean age (also dichotomised as mean/median age ≥40 years or <40 years), gender (proportions), year of study, major depression (proportions), AIDS and HAART (proportions), CD4 count (median), depression (proportions) and study quality (high versus low/medium). Summarised in online supplemental table 4 are meta-regression results. The study-level frequency of AIDS was significantly associated with the risk of suicide completion. Per 10-percentage point increase in people living with AIDS, the risk of completing suicide increased by 34 per 1000 persons. The increasing year of the study and increasing study-level mean CD4 count were associated with a lower risk of suicide. However, the associations were not statistically significant (p=0.81 and p=0.32, respectively). High study quality, male gender and increasing age were non-significant risk factors of suicide completion.

On the other hand, no sociodemographic or clinical factors were significantly associated with suicide attempts. HAART use was protective but had wider CI. Per 1-percentage point increase in the PLWHA on HAART, 14 per 1000 persons less had attempted suicide (95% CI: -48.70 to 21.70).

DISCUSSION

Main findings

About 40 million people of the global population are currently living with HIV/AIDS.[3 32] The era of HAART treatment has brought significant improvements in patient longevity and quality of life; however, PLWHA

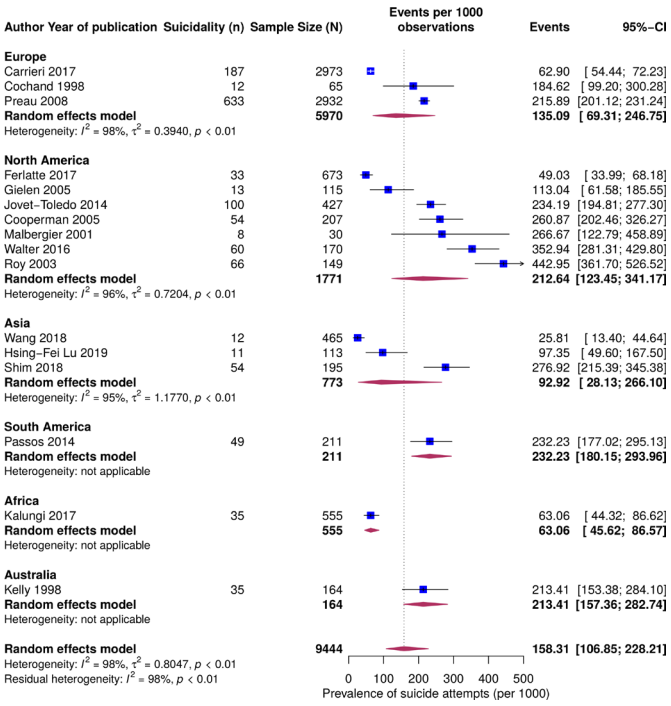

Figure 4 Forest plot of the prevalence of suicide attempts per 1000 PLWHA by continent from random-effects model: event values represent the number of suicide attempts per 1000 PLWHA (95%CI). Blue squares and their corresponding lines are the point estimates and 95%CIs per study. Maroon diamonds represent the pooled estimate of the prevalence for each subgroup (width denotes 95%CIs). Heterogeneity by continent: North America (I^2=96%); Europe (I^2=98%); Asia (I^2=95%); Africa (I^2=not applicable, one study); South America (I^2=not applicable, one study); Australia (I^2=not applicable, one study); p value for the interaction comparing the different subgroups is <0.0001. PLWHA, people living with HIV/AIDS.

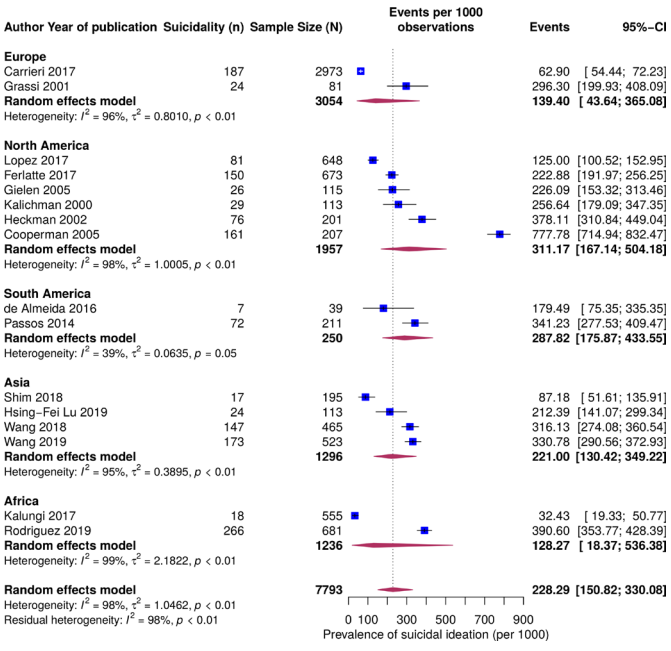

Figure 5 Forest plot of the prevalence of suicidal ideation per 1000 PLWHA by continent from random-effects model: event values represent the number of suicidal ideation per 1000 PLWHA (95%CI). Blue squares and their corresponding lines are the point estimates and 95%CIs per study. Maroon diamonds represent the pooled estimate of the prevalence for each subgroup (width denotes 95%CIs). Heterogeneity by continent: North America (I^2=98%); Europe (I^2=96%); Asia (I^2=95%); Africa (I^2=99%); South America (I^2=39%); p value for the interaction comparing the different subgroups is 0.56. PLWHA, people living with HIV/AIDS.

experience a heavy burden of psychosocial conditions that are frequently undiagnosed and untreated. In our study, the pooled incidence of suicide completion among PLWHA globally was 10.2 per 1000 (95%CI: 4.5 to 23.1), translating to a 100-fold greater suicide completion rate compared with the global population rate of 0.11/1000.[33] While the suicide completion rate was twice as high in North America (20.4/1000, 95%CI: 2.43 to 150.16), compared with that in Europe (8.4/1000, 95%CI: 3.69 to 19), this difference was not significant. Importantly, the most striking difference found was between the prevalence of suicide attempts across the geographic regions. While we found a pooled global prevalence of suicide attempts at 158.3/1000 in PLWHA, the pooled prevalence of suicide attempt in this cohort was highest in North America, South America and Australia at 212.6/1000 (95%CI: 123.5 to 314.2), 232.2/1000 (95%CI: 180.2 to 294.0) and 213.4/1000 (95%CI: 157.4 to 282.7), respectively. This is in striking comparison to a global lifetime suicide attempt prevalence of 3% in the general population.[34] Additionally, the overall pooled prevalence of suicidal ideation in PLWHA was 228.3/1000 (95%CI: 150.8 to 330.1). This is markedly increased compared with the global suicidal ideation rate of 9% in the general population.[34] Collectively, these data suggest that PLWHA are at high risk for attempting suicide. Such observation requires appropriate interventions in those at the highest risk.

Strength and limitations

The major strength of our analysis is the detailed and all-inclusive review of literature without limitation to regions that yielded a very large sample of 177 748 PLWHA assessed for suicide deaths. The cumulative number of patients with suicide completion of 973 was also large. Despite these strengths, the study had some limitations. First, substantial heterogeneity among the included studies in suicide reporting and overall methodology could have resulted in the variations of the reported suicide outcomes. This heterogeneity includes differences in the sampled period and the reporting of suicide attempts over weeks, months or overall lifetime risk. Second, only English language databases were searched, which would have introduced selection bias in the types of studies included in the analysis. A final notable limitation was the cohort selection within each body of work; some studies limited their work to perinatally infected individuals, pregnant women and/or intravenous drug users. These populations may be at higher suicide risk at baseline. To overcome these limitations, we conducted

meta-regression to statistically explore the sources of heterogeneity in the outcome of interest.

Implications

Globally in the general population, one out of every three individuals with suicidal ideation will attempt it, and one out of every 286 attempts will be completed. Our results suggest that in PLWHA for every 2 individuals with suicidal ideations, there is one individual with a suicide attempt, and for every 13 suicide attempts, one person may complete suicide. This is indicative of an increased risk in PLWHA for completed suicide than that of the general population, thus prompting further examination into the characteristics pertinent to these findings.

Determinants for an increased risk of suicide in PLWHA are multifactorial. They include the physiological effects of HAART or decreased CD4 count, neurological symptoms in patients categorised as having neuro HIV, the stigma that is still associated with the disease or the effect of disease on interpersonal relationships.[35 36] In our meta-regression analysis in which we explored the risk factors of suicide, stage V disease (AIDS) was significantly associated with the risk of suicide completion. This relationship is not surprising considering that this stage is associated with high a viral load, fostering a direct effect of the virus on the brain. Previous studies have found a higher CD4 count to have a protective effect on suicide completion. In a recent study exploring seizure frequency in PLWHA, the advanced stage of HIV was significantly associated with new-onset seizures. The author argued that direct brain injury, possibly caused by the virus, could be a potential mechanism of brain injury.[37] Further work should be conducted to determine the mechanisms by which the progression of HIV modulates the risk of suicide completion.

Of note, data have shown that suicide rates are extraordinarily high in PLWHA within the first year of diagnosis.[38] Taking this into consideration with our results, there may be a bimodal distribution for excessive suicide risk within the first year of diagnosis and if the disease progresses to stage V. Given our results, we suggest the most effective actionable targets to reduce the rate of suicidal ideation, attempt and completion is immediate and routine suicide risk assessment, psychological counselling and mental health treatment in conjunction with antiviral treatment to maintain or increase CD4 counts. These intervention strategies have been shown to reduce depression and suicide.[39]

Preliminary studies have shown that brief interventions for suicide prevention can be used shortly after diagnosis, which reduces suicidal ideation when compared with standard post-test counselling.[40] Alternatively, internet-based counselling is effective at reducing depressive symptoms in PLWHA in a randomised control trial in the Netherlands.[41] Furthermore, several studies have found that spiritual engagement has a protective effect against suicidal ideation in PLWHA within different cultural communities.[13 42 43] Health providers should thus consider embracing established interventions, encouraging PLWHA to engage with their preferred form of spirituality in a culturally competent manner and treating to increase or maintain CD4 counts to reduce suicidal ideation and completion. Further work should be done to characterise the efficacy of these interventions to reduce suicidal ideation, attempts and completion in PLWHA.

Conclusion

Within this meta-analysis, we demonstrate for the first time that across an extensive and diverse patient cohort, the rate of suicide deaths in PLWHA is 100-fold higher than the rate that has been reported in the general population. This risk is directly associated with HIV progression; however, antiretroviral treatment and higher CD4 counts seem to be protective against suicide attempts. Lastly, we show that within cohorts of PLWHA, there are regional differences in suicide risk with especially profound rates in North America. We suggest that suicide risk assessment be provided to PLWHA in conjunction with antiviral treatment to improve clinical outcomes, patient longevity and quality of life.

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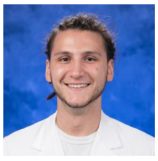
Matt Pelton graduated from Wesleyan University with a bachelor's degree and high honors in the Neuroscience and Behavior major. At present, he is a third year medical student at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. His main research interests include systematic reviews and meta-analyses across many fields of medicine and anticipates entering the field of Neurology after graduating from medical school.



Matthew Ciarletta graduated from York College of Pennsylvania with a major in Biology and a minor in Psychology. At present, he is a third year medical student at the Penn State College of Medicine. His research endeavours include meta-analyses of the psychiatric complications of infectious diseases, as well as behavioural brain mapping in animal models. His research interests centre upon increasing our understanding of the biopsychosocial factors that culminate in the human experience, with a focus on neuropsychological phenomena.

Supplemental text 1. Systematic Review Protocol

Suicidal ideation, suicide attempts, and suicide deaths in persons with HIV: a systematic review and meta-analysis

Background

Since its discovery in the 1980s, Human Immunodeficiency Virus (HIV) continues to carry a significant global burden of disease. While the disease remains incurable, anti-retroviral therapy (ART) has been effective in controlling disease progression, improving quality of life, and prolonging longevity. In 2018, the World Health Organization and United Nations Program on HIV/AIDS (UNAIDS) approximated that globally approximately 40 million people are living with HIV/AIDS (PLWHA). Depression is one of the most common comorbidities of PLWHA, with seropositive individuals reporting higher rates of depression than seronegative counterparts [1-3]. Depression in affected individuals remains cyclical, chronic, poorly-treated and is correlated with poorer clinical outcomes with lack of care retention, higher viral load, and increased mortality rates [1,4]. Unfortunately, untreated depression has led to exceptionally high rates of suicide within this vulnerable population. Data shows that patient suicide rates within the first year of HIV diagnosis exceed that of the general population [5-7]. In this meta-analysis, we sought to explore the relationship between HIV and suicide risk. The primary objective was to examine the incidence of suicide completion in PLWHA and to delineate the associated risk factors. Furthermore, we examined the incidence and prevalence of suicide ideation and attempts within PLWHA. This comprehensive statistical review provides a snapshot of the global health burden associated with the psychosocial effects of HIV on affected patients.

PROSPERO registration number: CRD42020161501

Objectives

The objective of this review was to ascertain the incidence of suicide ideation, attempt, and completion in PLWHA. Specific aims were:

(i) To examine the global incidence of suicide completion in PLWHA
(ii) To examine the global prevalence of suicide ideation, attempt, and completion in PLWHA
(iii) To delineate risk factors associated with suicide ideation, attempt and completion in PLWHA

Search Strategy

Inclusion criteria

- Reported on the reporting suicide rates in PLWHA
- Published from inception to before February 1, 2020
- Published in any language

Exclusion criteria

- Not conducted in humans
- Case reports and studies that did not report the incidence of suicide, suicide attempts, or suicide ideations were excluded
- Meeting abstracts, review papers, and commentaries

Database searches

The databases searched included:

- PubMed
- MEDLINE
- Cochrane Library

Search Terms

Pelton M, *et al. General Psychiatry* 2021; 34:e100247. doi: 10.1136/gpsych-2020-100247

Our keyword search was based on Medical Subject Headings (MeSH) with various combinations of "Suicide*", OR "Depression*", OR "Suicide attempt*", OR "Suicidal Ideation*", OR "Suicide Completion*"OR "Mental Illness*" OR "Anxiety*", AND "HIV*" "Human immunodeficiency syndrome" "AIDS" or "Acquired Immunodeficiency Syndrome".

Title and abstract screening

We searched the databases listed above. The citations were downloaded into the Endnote software. We excluded duplicate articles. Four reviewers independently screened titles and abstracts and documented, with reasons, studies were excluded from the review.

Full-text screening and data extraction

We extracted data from eligible the papers identified during the abstract screening step. We extracted the following information: country of study, year published, study period, total sample size, number of patients with suicidal ideation, number of patients with suicidal attempt, number of patients with suicidal completion, percent of study sample that was male, mean age, percent of population with HAART, average CD4 count, mean viral load, percent with reported depression and percent of individuals with AIDS.

Assessment of Methodological Quality of the Papers

Four reviewers independently assessed the quality of the papers included in the review using a standardized form.

Data Analysis

We used the metaprop function of the *meta*-package in R Statistical Software for analysis. The primary outcome was the overall rate of suicide completion, suicide attempts, and suicide ideation in PLWHA. We extracted rates from each manuscript. The R package was used to create a random-effects model with logit transformation of proportions for pooling of studies. The confidence intervals were calculated using the exact binomial (Clopper-Pearson) interval method. The between-study heterogeneity was assessed using the I^2 statistic, expressed as % (low (25%), moderate (50%), and high (75%)) and Cochrane's Q statistic (significance level < 0.05). We performed subgroup meta-analyses to look at geographical differences in the suicide risk. We conducted a meta-regression analysis, using study level median age, and study level gender proportions, year of study, the proportion of study population with AIDS, HAART proportions, mean/median CD4 counts and percentage of the study population with depression diagnosis. We report absolute differences (per 1000) in the overall probability of suicide. The Egger's test and funnel plots were used to assess small sample size bias.

Supplemental Table 1: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S1Text
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.6 and p.7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.6 and p.7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 6 and p.7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p. 6 and p.7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p. 6 and p.7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.6 and p.7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 7 and p.8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.6 and p.7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p.8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). – not addressed as much in methods – should we add more?	Suppl Fig 2 and 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p.7, p.8 and p.11
RESULTS			
Study selection	17	Give numbers of studies screened (should be in methods), assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.6 p.7 and Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. – this would be all figures correct?	p.8 and S3 Table
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2, Fig 3, Fig 4, Fig 5, Fig 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p.9 and p.10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl Figure 2 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p.7, p.8 and Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 13, p.14 and p.15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.14 and p.15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p. 13,14 and p.15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p. 17

Supplemental Table 2: Literature search strategy

Database	Search Terms
MEDLINE	PubMed and OVID (MEDLINE) search terms 1. (("HIV"[Mesh] OR "Acquired Immunodeficiency Syndrome"[Mesh])) 2. (("Suicide"[Mesh] OR "Suicide, Attempted"[Mesh] OR "Suicide, Completed"[Mesh] OR "Suicidal, Ideation"[Mesh) 3. (("Mental Disorder "[Majr] OR "Depressive Disorders"[Majr])) 4. 1 AND 2 5. 1 AND 3
Cochrane Library	1. (("HIV"[Keyword] OR "Acquired Immunodeficiency Syndrome"[Keyword])) 2. (("Suicide"[Keyword] OR "Suicide, Attempted"[Keyword] OR "Suicide, Completed"[Keyword] OR "Suicidal, Ideation"[Keyword) 3. (("Mental Disorder "[Majr] OR "Depressive Disorders"[Majr])) 4. 1 AND 2 5. 1 AND 3
SCOPUS	1. (("HIV"[Keyword] OR "Acquired Immunodeficiency Syndrome"[Keyword])) 2. (("Suicide"[Keyword] OR "Suicide, Attempted"[Keyword] OR "Suicide, Completed"[Keyword] OR "Suicidal, Ideation"[Keyword) 3. (("Mental Disorder "[Majr] OR "Depressive Disorders"[Majr])) 4. 1 AND 2 5. 1 AND 3
JOANNA BRIGGS INSTITUTE	1. (("HIV"[Keyword] OR "Acquired Immunodeficiency Syndrome"[Keyword])) 2. (("Suicide"[Keyword] OR "Suicide, Attempted"[Keyword] OR "Suicide, Completed"[Keyword] OR "Suicidal, Ideation"[Keyword) 3. (("Mental Disorder "[Majr] OR "Depressive Disorders"[Majr])) 4. 1 AND 2 5. 1 AND 3

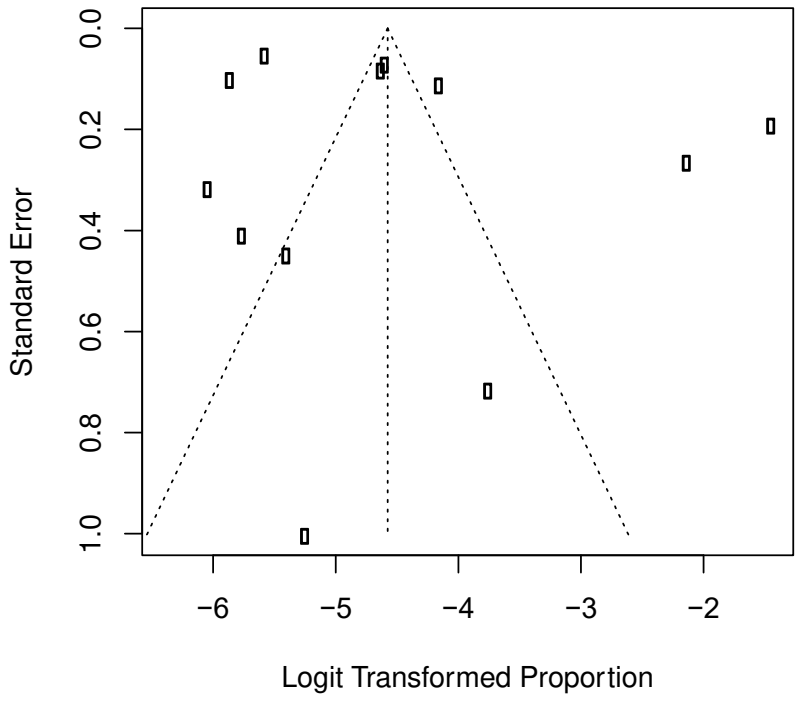
Supplemental Table 3. Depicts the quality assessment of studies using the Newcastle-Ottawa Scale and the GRADE quality of evidence. This includes 27 cross-sectional, 7 prospective cohort, 5 retrospective cohort, and 1 nested case-control study.

				Selection				Comparability	Outcome/Exposure			GRADE QoE
Author Year of Publication	Type of Study	Sum	Quality	1	2	3	4	5	6	7	8	
Carrieri 2017	Cross-sectional	9	High (>7)	1	1	1	2	2	1	1	0	Moderate
Cochand 1998	Cross-sectional	6	Moderate (5-7)	0	0	1	2	1	1	1	0	Low
Cooperman 2005	Cross-sectional	7	Moderate (5-7)	1	0	1	2	2	1	0	0	Low
Dannenberg 1996	Prospective	6	Moderate (5-7)	0	1	1	1	1	1	0	1	Moderate
de Almeida 2016	Cross-sectional	7	Moderate (5-7)	1	0	0	2	2	1	1	0	Very low
Ferlatte 2017	Cross-sectional	6	Moderate (5-7)	1	0	1	1	1	1	1	0	Low
Gielen 2005	Cross-sectional	6	Moderate (5-7)	1	0	1	2	1	1	0	0	Low
Grassi 2001	Cross-sectional	7	Moderate (5-7)	1	0	1	2	1	1	1	0	Low
Gurm 2015	Retrospective	6	Moderate (5-7)	1	1	1	0	2	1	0	0	Moderate
Heckman 2002	Cross-sectional	7	Moderate (5-7)	1	1	1	2	1	1	0	0	Low
Hentzien 2018	Nested Case-Control	8	High (>7)	1	1	1	0	2	1	1	1	Moderate
Hsing-Fei Lu 2018	Cross-sectional	8	High (>7)	1	0	1	2	2	1	1	0	Moderate
Jovet-Toledo 2014	Cross-sectional	8	High (>7)	1	1	1	2	1	1	1	0	Moderate
Kalichman 2000	Cross-sectional	4	Low (1-4)	0	0	0	2	1	1	0	0	Moderate
Kalungi 2017	Cross-sectional	7	Moderate (5-7)	1	1	0	2	1	1	1	0	Low
Keiser 2010	Prospective	8	High (>7)	1	1	1	1	2	1	1	0	Moderate
Kelly 1998	Cross-sectional	8	High (>7)	1	0	1	2	2	1	1	0	Moderate
Kreniske 2019	Prospective	4	Low (1-4)	1	1	1	0	0	0	0	1	Low
López 2018	Cross-sectional	7	High (>7)	1	0	0	2	2	1	1	0	Very Low
Malbergier 2001	Cross-sectional	7	High (>7)	0	0	1	2	2	1	1	0	Moderate
Marzuk 1997	Cross-sectional	7	Moderate (5-7)	1	1	0	2	1	1	1	0	Moderate
May 2004	Cross-sectional	9	High (>7)	1	1	1	2	2	1	1	0	Moderate
Paparizos 2017	Retrospective	6	Moderate (5-7)	1	1	1	0	1	1	0	1	Low
Passos 2014	Cross-sectional	9	High (>7)	1	1	1	2	2	1	1	0	Moderate
Preau 2008	Cross-sectional	7	Moderate (5-7)	1	0	1	1	2	1	1	0	Low
Protopoescu 2012	Prospective	6	Moderate (5-7)	1	1	1	1	1	1	0	0	Low
Quintana-Ortiz 2008	Retrospective	6	Moderate (5-7)	1	1	1	0	2	0	0	1	Moderate
Rice 2010	Cross-sectional	7	Moderate (5-7)	1	1	1	2	0	1	1	0	Moderate
Rodriguez 2019	Prospective	4	Low (1-4)	0	1	1	0	1	1	0	0	Low
Roy 2003	Cross-sectional	6	Moderate (5-7)	0	1	1	2	0	1	1	0	Low
Scheer 2001	Cross-sectional	7	Moderate (5-7)	1	1	1	2	0	1	1	0	Moderate
Shim 2018	Cross-sectional	7	Moderate (5-7)	1	0	0	2	2	1	1	0	Moderate
Van Haastrecht 1994	Prospective	5	Moderate (5-7)	0	1	1	1	1	1	0	0	Very low
Walter 2016	Cross-sectional	7	Moderate (5-7)	0	0	0	2	2	1	1	0	Low
Wang 2018	Cross-sectional	6	Moderate (5-7)	1	0	0	2	1	1	1	0	Low
Wang 2019	Cross-sectional	5	Moderate (5-7)	1	0	0	1	1	1	1	0	Low
Yann Ruffieux 2019	Retrospective	8	High (>7)	1	1	1	0	2	1	1	1	Moderate
O'Donnell 2016	Retrospective	7	Moderate (5-7)	1	1	1	0	2	1	0	1	Moderate
Sherr 1995	Prospective	6	Moderate (5-7)	1	1	1	1	0	1	0	1	Moderate
Quinlivan 2017	Cross-sectional	7	Moderate (5-7)	0	0	1	2	2	1	1	0	Moderate

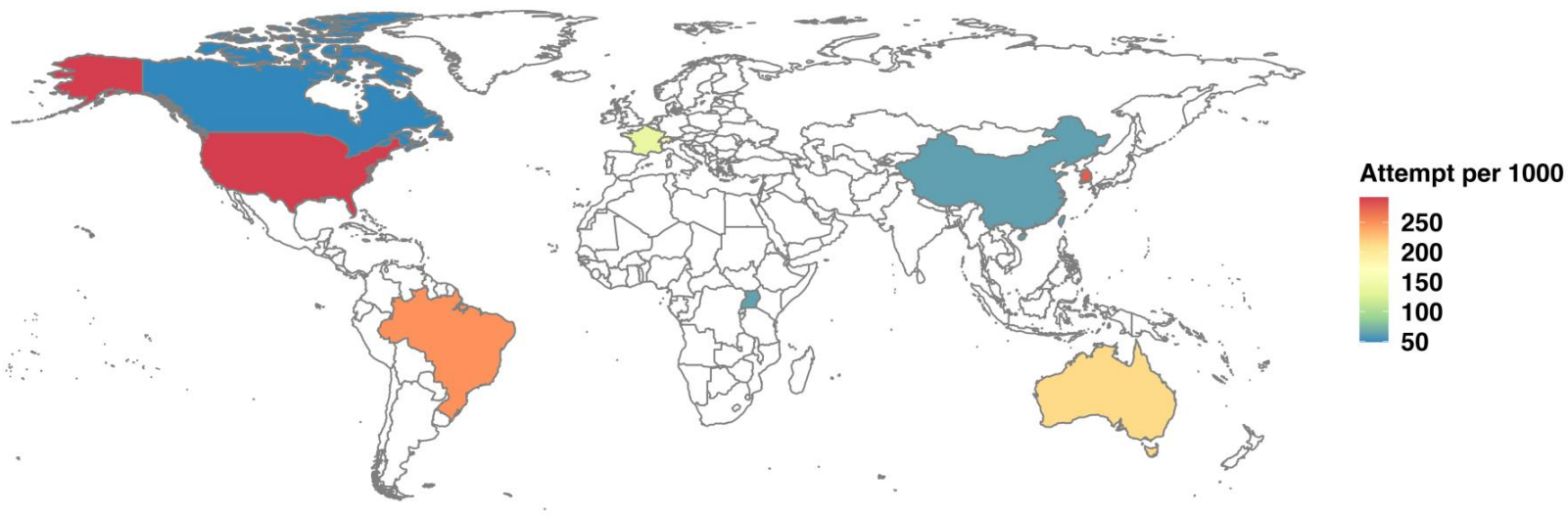
Supplemental Table 4: Meta-regression results: Advanced HIV disease (AIDS) was significantly associated with suicide completion.

Study-Level Predictors	Univariate absolute difference (per 1000) (95%CI) in incidence rate of suicide completion	p-value	Univariate absolute difference (per 1000) (95%CI) in prevalence of suicide attempts	p-value
Year of study	-0.8 (-7.5 to 5.9)	0.81	-1.7 (-9 to 5.6)	0.66
Study level-Male Gender (%)	0.25 (-4.2 to 4.7)	0.91	-0.3 (-1.9 to 1.3)	
Study-Level Mean or Median Age (y)	3.4 (-2.7 to 9.6)	0.28	-1.8 (-24.3 to 20.7)	0.88
Mean Age >40 years	2.3 (-1.4 to 4.2)	0.32	3 (-2 to 4.9)	0.43
Study-level AIDS frequency (%)	**3.4 (1.3 to 5.5)**	**0.001**	-0.3 (-2.4 to 1.8)	0.77
Study-level HAART (%)	N/A		-13.5 (-48.7 to 21. 70)	0.45
Study-level mean CD4 count	-0.3 (-0.9 to 0.3)	0.32	N/A	
Study-level % of depression	N/A		0.94 (-5.7 to 7.5)	0.28
Study-quality, high versus low/medium	2.2 (-1.3 to 3.2)	0.40	1.3 (-2.3 to 4.3)	0.23

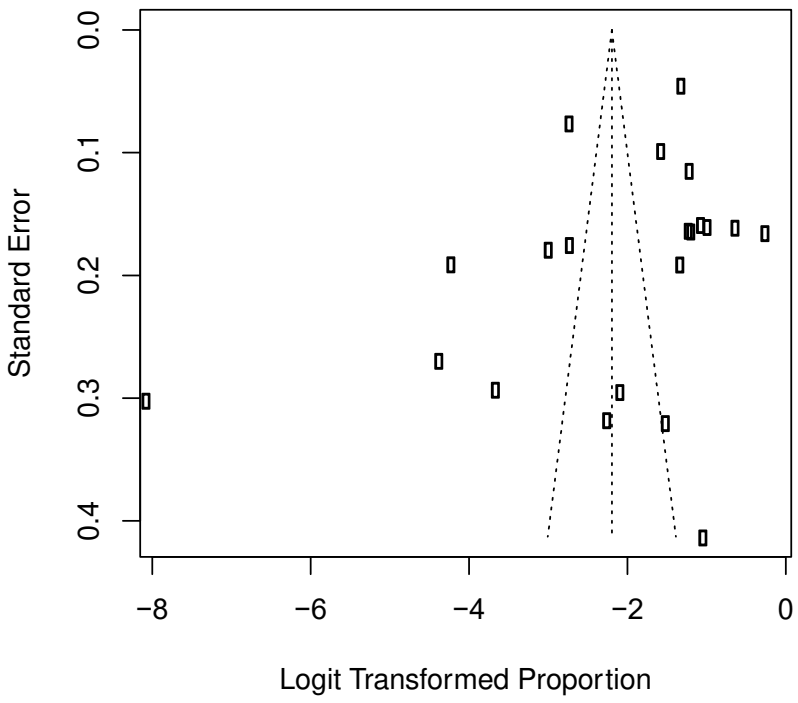
Supplemental Figure 1: Funnel plot of the studies on suicide completion. There is asymmetry indicative of small study bias.



Supplemental Figure 2: Country-specific prevalence of suicide attempts in people living with HIV/AIDS.



Supplemental Figure 3: Funnel plot of the studies on suicide attempts. There is asymmetry indicative of small study bias



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