AIDS and Behavior (2022) 26:2559–2573
https://doi.org/10.1007/s10461-022-03591-y

ORIGINAL PAPER

A Systematic Review of Risk Factors for Suicide Among Persons Living with HIV (1996–2020)

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Accepted: 15 January 2022 / Published online: 2 February 2022

Abstract

Persons living with HIV (PWH) are at elevated risk for suicide. We conducted a systematic literature review following PRISMA-P guidelines to examine risk factors associated with suicide as a cause of morbidity among PWH. We searched six electronic databases using search terms (suicide, suicide attempt, self-harm, self-injurious behavior, HIV, AIDS, PWH). We focused on factors that were specific to HIV infection (CD4 count, HIV-1 RNA, and antiretroviral therapy [ART]). The initial search yielded N = 2657 studies. Eligible studies included suicide as an outcome, quantitative study design, and publication in peer-reviewed journals from 1996 through 2020. Fourteen studies met inclusion criteria. PWH share risk factors for suicide found in the general population: psychiatric illness, previous suicide attempt, drug and alcohol misuse. PWH also have HIV-specific risk factors for suicide. HIV diagnosis in the past two years and transmission related to injection drug use were associated with increased risk; HIV-1 RNA, ART, and AIDS-defining illness were not.

Keywords HIV · Mental health · Suicide · Systematic review

Resumen

Las personas viviendo con VIH (PVV) tienen riesgo elevado de suicidio. Realizamos un examen sistemático de la bibliografía, siguiendo las pautas PRISMA-P para examinar los factores de riesgo asociados con suicidio como la causa de morbilidad entre PVV. Realizamos búsquedas en seis bases de datos electrónicas mediante el uso de términos de búsqueda (suicidio, intento de suicidio, autolesiones, comportamiento autolesivo, VIH, AIDS). Nos hemos centrado en factores que eran específicos de la infección por VIH (recuento de CD4, ARN del VIH-1 y la terapia antirretroviral). La búsqueda inicial arrojó N = 2657 estudios. Los estudios seleccionados según criterio incluyeron muerte por suicidio, que el diseño del estudio fuera cuantitativo, y la publicación haya sido entre 1996 y 2020. 14 estudios cumplieron estos criterios de inclusión para el estudio. PVV comparten los mismos factores de riesgo de suicidio que se encuentran en la población general: enfermedad psiquiátrica, intento previo de suicidio, abuso de drogas y alcohol. PVV también poseen factores de riesgo de suicidio propios del VIH. El diagnóstico de VIH en los últimos dos años y la transmisión relacionada con el uso de drogas inyectables se asociaron con un mayor riesgo; mientras que el ARN del VIH-1, la terapia antirretroviral y las enfermedades definidas del SIDA no fueron asociadas con un mayor riesgo de suicidio.

Palabras Clave VIH · Salud mental · Suicidio · Revisión sistemática

Introduction

Persons living with HIV (PWH) are at elevated risk for suicide compared to the general population [1–6]. This risk was highest before the development of antiretroviral therapy (ART) [3, 7–9]. The introduction and advances of ART were instrumental in the transition of HIV from a terminal diagnosis to a manageable chronic disease [1, 4, 9] and the

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attendant decline in the rates of suicide [1–5]. Despite these advances, the risk of suicide remains 3–9 times higher for PWH than for the general population [1–5]. The rate of suicide among PWH is high even when compared to individuals living with other chronic conditions such as cancer or cardiovascular disease [10].

Persistently elevated rates are likely attributable to a constellation of risk factors among PWH. First, well-established risk factors for suicide are prevalent among PWH and include psychiatric illness, substance misuse, chronic illness, and discrimination based on sexual orientation or gender identity [11, 12]. These factors are interrelated, and their associations with suicide are complex. For example, psychiatric illness and substance misuse may precede a diagnosis of HIV or may be precipitated when a person receives a diagnosis. Additionally, multimorbidity is the norm among PWH [13] and results in poor health outcomes and a heightened risk of suicide. Risk factors specific to HIV may also contribute to the risk of suicide, including chronic inflammation, alterations to the central nervous system (CNS), and disease severity [14, 15]. Environmental stressors, persistent social stigma, and isolation experienced by PWH may amplify the risk of suicide [12, 16]. Lastly, improved longevity and the subsequent aging of PWH adds complexity with age-related chronic illnesses, declines in functional status, and ruptured social connectedness [17].

Given the persistently elevated rates of suicide in this population over time and the various potential stressors contributing to these elevated rates, we seek to clarify risk factors for suicide among PWH. A broad understanding of risk factors can inform behavioral health screenings among PWH and help tailor existing suicide prevention and harm reduction programs for this at-risk population. Thus, the goals for this systematic review are to (1) identify key risk factors for suicide among PWH, including those specific to HIV infection: CD4 count, HIV-1 RNA, and ART; and to (2) identify gaps in the literature, provide recommendations for future research and offer suggestions for best practices within the limits of our study findings.

Methods

Protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidelines in conducting this review [18].

Eligibility Criteria

Eligibility criteria included (1) death by suicide as an outcome, (2) study population that included individuals with HIV, (3) study population aged 18 years or older, (4) quantitative study design that examined the association between risk factors and suicide, and (5) publication in English language, peer-reviewed journals from 01/01/1996 through 10/01/2020, corresponding to the introduction of ART.

Information Sources and Search Strategy

A research and data librarian assisted with the search strategy to ensure a comprehensive approach. We searched six electronic databases: Medline, EMBASE, PsycINFO, Web of Science, Scopus, and CINAHL. Search terms included (suicide, suicide attempt, self-harm, self-injurious behavior, HIV, AIDS, PWH). While the study was limited to suicide, we used broader search terms to ensure all relevant studies were identified. Additional information regarding specific search terms pertinent to each database is provided in Online Appendix 1.

Study Selection and Data Extraction

Duplicate studies were removed, and unique studies were uploaded to Covidence Systematic Review Software [19]. Titles and abstracts were screened for inclusion (AS). Three independent reviewers (AS, JW, SB) performed full-text reviews and extracted data from the articles that met inclusion criteria. The following data elements were extracted: (1) bibliographical information; (2) study and sample characteristics (sample size, study design, sex, age, country) and; (3) risk factors categorized into seven domains: (3a) demographic (e.g., age, sex, race/ethnicity); (3b) mental health (e.g., psychiatric illness, previous suicide attempts); (3c) physical health (e.g., chronic illnesses, chronic pain); (3d) substance use (e.g., injection drug use (IDU), illicit drug use, alcohol use, tobacco use); (3e) psychotropic medications (e.g., antidepressants, anxiolytics, antipsychotics); (3f) psychosocial factors (e.g., education, marital status); and (3g) HIV-specific risk factors (e.g., CD4 count, HIV-1 RNA, ART, AIDS-defining illness). These domains (3a–3f) were based on broad categories of risk factors frequently included in the suicide literature [20]. The addition of HIV-specific risk factors (3g) accounted for risk factors pertinent to this population.

Risk of Bias

The overall risk of bias in each study was assessed using the Newcastle–Ottawa Scale for assessing the quality of observational studies [21]. The scale ascertains bias in participant selection, comparability of participants, and identification of exposure and outcome. Although included studies were constrained by limitations in available data, they were of good quality (Table 2).

Synthesis of Results

Due to heterogeneity in the study designs, inconsistency in the operationalization of risk factors, and diversity of risk factors included in the studies, a meta-analysis was not feasible. Therefore, we conducted a narrative synthesis of the results.

Results

The initial search yielded 2657 manuscripts after the removal of duplicates. Title and abstract screening excluded 2573 studies. Of the 84 studies proceeding to the full-text review, 14 studies met the inclusion criteria (Fig. 1). These 14 studies included N = 287,094 PWH, of whom 27,781 died during the study period, including 1356 by suicide. Studies that met inclusion criteria are further detailed in Table 1.

Study Characteristics

Studies included an average of 14 years of follow-up. Thirteen studies ascertained deaths from national systems of vital statistics [1–6, 22–27]. One study used medical chart review [28]. Five studies incorporated Coding of Death in HIV (CoDe) [6, 24, 27–29], a standardized method to identify the underlying cause of death among individuals with HIV [30].

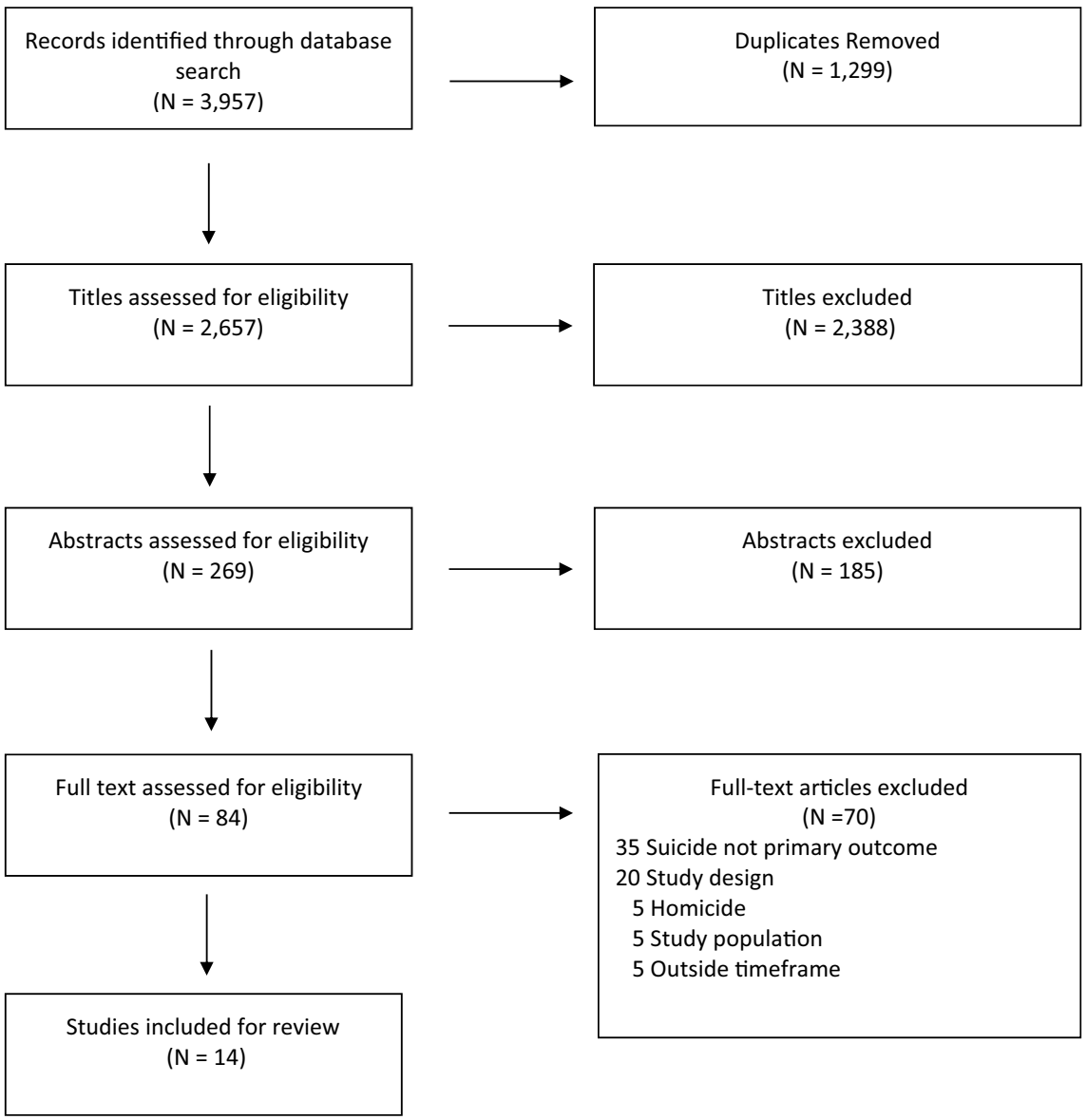

Fig. 1 PRISMA flow diagram

Table 1 Primary characteristics of studies included in the systematic review

Study	Study period	Data	Population characteristics	Outcome assessment	Statistical methods	Study population	Suicide rate/SMR
Aldaz et al. (2011) Spain- Navarra Region	1999–2006	Observational Cohort Epidemiological surveillance system & regional vital statistics	Deceased persons with HIV age 20–59 Reference population: Persons aged 20–59 residing in Navarra, Spain	Vital statistics: ICD-10 X60–X84 (intentional self-harm)	Cox regression model & Standardized Mortality Ratios (SMRs)	HIV + N = 1145 PYs = 7113 Total Deaths N = 210 Suicide N = 7 (3.3%)	98/100,000 PY† SMR 9.6 (3.8–19.7) SMR IDU 10.8 (3.5–25.3)
The Antiretroviral Therapy Cohort Collaboration (2010) North America & Europe	1996–2006	Observational Cohort Cohort: The Antiretroviral Therapy Cohort Collaboration (ART-CC)	Aggregate of 13 cohorts Deceased persons with HIV age 16 + , naïve to ART, initiating combination ART ≥ 3 drugs Comparator Group: Persons with HIV age 16 + , naïve to ART, and starting ART with a combination of ≥ 3 drugs	Coding Causes of Death in HIV (CoDe) protocol (intentional self-harm)	Cox regression model & Poisson regression model	HIV + N = 39,272 PYs = 154,667 Total Deaths N = 1,874 Suicide N = 48 (3.0%)	31/100,000 PY
Croxford et al. (2017) England and Wales	1997–2012	Observational Cohort Public Health England (PHE) national HIV surveillance program & clinical records linked to Office for National Statistics (ONS)	Deceased persons with HIV age 15 + who received services at NHS HIV outpatient clinics Reference population: Persons residing in England and Wales	Office for National Statistics (ONS) death data ICD-10 X60–X84 (intentional self-harm) and Coding Causes of Death in HIV (CoDe) protocol (Suicide)	Cox regression model & Standardized Mortality Ratios (SMRs)	HIV + N = 88,994 PYs = 448,839 Total Deaths N = 5,302 Suicide N = 96 (1.8%)	21/100,000 PY SMR 2.0 (1.6–2.4) SMR First year of diagnosis 4.8 (3.4–6.5)
Fontela1et al. (2020) Spain-Navarra Region	1999–2018	Observational Cohort Epidemiological surveillance system & regional vital statistics	Deceased persons with HIV age 25–74 Reference population: Persons residing in Navarra, Spain	Regional mortality registers ICD-10 X60–X84 (intentional self-harm)	Poisson regression model & Standardized Mortality Ratios (SMRs)	PYs = 16,246 Total Deaths N = 406 Suicide N = 14 (3.4%)	1999–2003: 113/100,000 PY† 2004–2008: 78/100,000 PY† 2009–2013: 72/100,000 PY† 2014–2018: 85/100,000 PY† 2009–2018 SMR 5.3 (2.3–10.6)

Table 1 (continued)

Study	Study period	Data	Population characteristics	Outcome assessment	Statistical methods	Study population	Suicide rate/SMR
Gurm et al. (2015) British Columbia-Canada	1996–2012	Observational Cohort Cohort: HAART Observational Medical and Evaluation (HOMER) cohort	Suicide decedents with HIV age 19 +, initiating ART between 1996 and 2012 Comparator Group: Person with HIV age 19 +, initiating ART between 1996 and 2012	Vital statistics: ICD-10 X60–X84 (intentional self-harm) Plus X41–42, X47 accidental poisoning	Logistic regression & Cox regression models	HIV + N = 5,229 Total Deaths N = 993 Suicide/Overdose N = 82 (8.3%) Suicide N = 20 (2.0%) Overdose N = 62 (6.2%)	1998: 961/100,000 PY 2010: 2.8/100,000 PY
Hentzien et al. (2018) France	2000–2013	Nested-Case Control Cohort: French multicenter Dat'AIDS cohort	Cases: Suicide decedents with HIV Controls: Persons with HIV matched on duration of follow-up & clinical center of care	Vital statistics: ICD-10 X60–X84 (intentional self-harm)	Conditional logistic regression	HIV + N = 349 Suicide N = 70	2000–2006: 45.9/100,000 PY 2007–2013: 46.5/100,000 PY
Hessol et al. (2018) San Francisco, California	1996–2013	Observational Cohort Epidemiological surveillance system: San Francisco Department of Public & Vital statistics National Death Index Plus	Deceased persons with HIV HIV age 15 + Reference population: Persons residing in California age 15–94	Vital statistics: ICD8 E950–959 and ICD-10 X60–X84 (intentional self-harm)	Poisson regression model & Standardized Mortality Ratios (SMRs)	HIV + N = 6268 (Deaths) Suicide N = 165 (2.6%)	SMR 2.72 (2.29–3.14)
Jia et al. (2012) Denmark	1986–2006	Nested-Case Control National longitudinal registers and vital statistics	Cases: Suicide decedents age 23–67 residing in Denmark Controls: Individuals residing in Denmark matched by sex and date of birth	ICD8 E950-959 and ICD-10 X60–X84 (intentional self-harm)	Conditional logistic regression	N = 189,037 HIV + N = 144 Suicide N = 9900 HIV + Suicide N = 44	NR
Keiser et al. (2010) Switzerland	Pre-HAART (1988–1995) HAART (1996–2008)	Observational Cohort Cohort: The Swiss HIV Cohort Study & Swiss National Cohort	Suicide decedents with HIV age 16 + Comparator Group: Person with HIV age 16 + Reference population: Population from the Swiss National Cohort	Vital statistics: ICD-10 X60–X84 (intentional self-harm)	Poisson regression model & Standardized Mortality Ratios (SMRs)	HAART (1996–2008) HIV + N = 7517 Suicide N = 58	1996–2008 Men 90.1/100,000 PY 1996–2008 Female 63.1/100,000 PY SMR 1999–2008 Men 3.5 (2.5–4.8) SMR 1999–2008 Female 5.7 (3.2–10.3)

Table 1 (continued)

Study	Study period	Data	Population characteristics	Outcome assessment	Statistical methods	Study population	Suicide rate/SMR
McManus et al. (2014) Australia	1999–2012	Nested-Case Control Cohort: Australian HIV Observational Database (AHOD)	Cases: Suicide decedents age 20–59 Controls: Persons with HIV matched on clinical site, age, sex, mode of exposure and date of diagnosis	1999–2005: Adverse events of anti-HIV Drugs (D:A:D) 2005–2012: Coding Causes of Death in HIV (CoDe) protocol	Conditional logistic regression	HIV + N = 81 Suicide/unintentional/violent N = 27 Suicide N = 17 Overdose N = 8 Violent N = 2	NR
Nishijima et al. (2020) Japan	2005–2016	Observational Cohort AIDS Clinical Center, National Center for Global Health and Medicine (NCGM), Tokyo	Deceased persons with HIV age 20 + receiving care at NCGM Comparator Group: persons with HIV age 20 +, receiving care at NCGM Reference population: General population of Japan	Coding Causes of Death in HIV (CoDe) protocol (intentional self-harm)	Cox regression model & Standardized Mortality Ratios (SMRs)	HIV + N = 2797 PYs: 18,858 Total Deaths N = 165 Suicide N = 14 (8.5%)	74/100,000 PY† SMR 3.24 (1.54–4.94)
Pettit et al. (2017) North America & Europe	1996–2014	Observational Cohort Cohort: Antiretroviral Therapy Cohort Collaboration (ART-CC)	Aggregate of 19 cohorts Deceased persons with HIV age 18 +, naive to ART, initiating combination ART ≥ 3 drugs Comparator Group: Persons with HIV age 18 +, naïve to ART, and starting ART with a combination of ≥ 3 drugs	Coding Causes of Death in HIV (CoDe) protocol (intentional self-harm, accident or overdose) or independent clinician classification in absence of death classification	Weighted pooled logistic regression model approximating a Cox regression model	HIV + = 124,587 PYs: 770,259 Total Deaths N = 11,280 Suicide/Accidents/Overdose = 673 (6%) Suicide N = 180 (1.6%) Accidents N = 187 (1.7%) Overdose N = 306 (2.7%)	Suicide/Accidents/Overdose 87/100,000 PY† Suicide 23/100,000 PY† Accidents 24/100,000 PY† Overdose 40/100,000 PY†
Ruffieux et al. (2019) Switzerland	Pre-HAART (1988–1995) HAART (1996–2008) Late cART (2009–2017)	Observational Cohort Cohort: The Swiss HIV Cohort Study & Swiss National Cohort	Suicide decedents with HIV age 16 + Comparator Group: Person with HIV age 16 + Reference population: population from the Swiss National Cohort	Vital statistics: ICD-10 X60–X84 (intentional self-harm)	Cox regression model & Standardized Mortality Ratios (SMRs)	Late cART (2009–2017) HIV + N = 4547 Suicide N = 49	2009–2017 Men 72.4/100,000 PY 2009–2017 Women 34.0/100,000 PY SMR Men 3.1 (2.3–4.3) SMR Female 3.3 (1.5–7.4)

Table 1 (continued)

Study	Study period	Data	Population characteristics	Outcome assessment	Statistical methods	Study population	Suicide rate/SMR
Singh et al. (2019) Baltimore, Maryland	2001–2015	Observational Cohort Cohort: The Johns Hopkins HIV Clinical Cohort	Deceased persons with HIV age 18+ who received care at the Johns Hopkins HIV clinic Comparator Group: Person with HIV age 18+ receiving care at the Johns Hopkins HIV clinic	Vital statistics: ICD-10 X60–X84 (intentional self-harm)	Cox regression model	Person with Injection Drug Use (PWID) HIV+ N = 4796 PYs PWID = 13,505.3 PYs PWID non-IDU = 26,659.4 Total Deaths N = 1283 Suicide N = 9 (0.7%) PWID Suicide N = 6 non-IDU Suicide N = 3	PWID 44 /100,000 PY† non-IDU 11/100,000 PY†

Nine of the fourteen studies used longitudinal HIV cohorts: the HAART Observational Medical and Evaluation (HOMER) cohort [22], the French multicenter Dat'AIDS cohort [1], the Australian HIV Observational Database (AHOD) [27], the Johns Hopkins HIV Clinical Cohort [23], the Swiss HIV Cohort Study (Swiss Cohort) [3, 4], the Antiretroviral Therapy Cohort Collaboration (ART-CC) (a cross-cohort collaboration of HIV studies in Europe and North America) [24, 29], and a cohort obtained from the National Center for Global Health and Medicine (NCGM), Tokyo [28]. The Swiss Cohort and ART-CC were each used in two studies. Keiser et al. and Ruffieux et al. followed individuals in the Swiss Cohort from 1988 to 2008 and from 1988 to 2017, respectively [3, 4]. ART-CC et al. aggregated data from 13 cohorts from 1996–2006. Pettit et al. expanded the study population to include 19 cohorts from 1996–2014 [24, 29]. To reduce duplication, only the Ruffieux et al. (2009–2017) and Pettit et al. (1996–2014) articles were included. The remaining five studies used data from HIV case surveillance systems [5, 6, 25, 26] or electronic health records (EHR) from national health care registries linked to vital statistics [2].

Half of the studies were based in European countries (N = 7) [1–6, 25]. The remaining studies were conducted in North America (N = 3) [22, 23, 26], Australia (N = 1) [27], and Japan (N = 1) [28]. Two studies were cross-cohort analyses that included data from both North America and Europe [24, 29].

No study incorporated risk factors from all seven domains of interest. These domains included demographic characteristics (14/14 studies); substance use (14/14); HIV-specific risk factors (12/14); physical health (8/14); psychosocial risk factors (8/14); mental health (5/14); and psychotropic medications (3/14). A list of risk factors within each of the domains is detailed in Table 2.

Statistical methods used to assess associations between risk factors and suicide included Cox proportional hazards models [4–6, 22–25, 28, 29], Poisson models [3, 24–26], and conditional or unconditional logistic regression [1–4, 22, 27, 29]. Studies also compared rates of suicide among PWH to those among the general population using standardized mortality ratios (SMRs) [3–6, 25, 26, 28].

Rate of Suicide

Suicide accounted for 2.6–8.5% of total deaths among PWH [3, 5, 6, 22, 24–29]. The rate of suicide varied from 2.9 to 112 deaths per 100,000 individuals and declined over time [1, 3–6, 22–25, 28, 29]. The steepest decline in suicide was seen after effective ART became readily available (1996) [4]. Suicide was elevated among PWH compared to the

Table 2 Risk factors considered in studies included in the systematic review

Domains	Included covariates	Unadjusted	Adjusted
1. Demographics	Sex	*Male/Female reference* RR = 1.83 (0.96–3.47) [1]	Female/Male reference aHR = 0.56 (0.25–1.28) [24] aHR = 0.62 (0.26–1.48) [4] aRR = 0.78 (0.42–1.45) [3] OR = 0.21 (0.07–0.67) [26] Transgender Woman OR = 0.78 (0.29–2.11) [26]
	Age	HR = 0.93 (0.90–0.95) [22] RR = 0.99 (0.97–1.02) [1]	Per 10 yr increase aHR = 1.17 (0.85–1.60) [4] Per 10 yr increase aHR = 1.32 (1.00–1.76) [24] Per 10 yr increase aRR = 1.27 (0.97–1.66) [3]
	Country of birth/citizenship	France RR = 3.50 (1.44–8.50) [1]	Origin Swiss (1996–2008) aRR = 2.70 (1.07–6.80) [3] Origin Swiss (2009–2017) aHR = 1.23 (0.63–2.38) [4]
2. Mental health	Previous Suicide Attempt	RR = 10.27 (3.72–28.35) [1] OR = 2.73 (0.70–10.69) [27]	aRR = 5.93 (1.58–22.24) [1]
	Hx of Anxiety Disorder	RR = 2.60 (1.46–4.62) [1]	
	Hx of Bipolar Disorder	RR = 2.89 (0.56–14.91) [1]	
	Hx of Depressive Disorder	RR = 7.08 (3.71–13.50) [1]	aRR = 3.76 (1.49–9.50) [1]
	Hx of MDD/Anxiety	OR = 1.87 (0.67–5.25) [27]	
	Hx of Schizophrenia	RR = 4.40 (1.50–12.91) [1]	
	Hx of Psychiatric illness	IRR = 18.72 (10.42–33.65) [2]	aIRR = 11.32 (6.26–20.48) [2]
	Psychiatric Treatment		aHR = 2.42 (1.32–4.43) [4] aRR = 3.21 (1.64–6.27) [3]
	Neurocognitive Impairment	OR = 0.84 (0.22–3.26) [27]	
3. Psychotropic medications	Hx Psychotropic Medication	RR = 13.27 (6.18–28.51) [1] OR = 1.76 (0.61–5.08) [27]	aRR = 6.37 (2.56–15.85) [1]
	Recent Psychotropic Medication	OR = 2.47 (0.95–6.41) [27]	
	Antidepressants	RR = 9.55 (4.44–20.55) [1]	
	Anxioltyics	RR = 8.72 (4.21–18.05) [1]	
	Antipsychotics	RR = 5.11 (2.04–12.79) [1]	
4. Substance use	History IDU	HR = 5.86 (2.96–11.60) [22]	aHR = 2.09 (1.03–4.23) [24] aHR = 2.65 (1.09–6.42) [4] aHR = 3.95 (1.99–7.86) [22] aHR = 6.50 (1.51–28.03)[23] aRR = 1.58 (0.88–2.87) [3] aRR = 1.65 (0.5–5.38) [1]
	Active drug use	RR = 3.54 (1.63–7.67) [1] OR = 2.35 (0.64–8.70) [27]	aRR = 3.29 (1.10–9.85) [1]
	ETOH Current	> 20 g/day RR = 4.33 (2.27–8.27) [1] High Etoh OR = 2.31 (0.46–11.54) [27]	> 20 g/day aRR = 3.56(1.43–8.88) [1]
	Smoking Current	RR = 1.56 (0.88–2.77) [1] OR = 0.76 (0.20–2.87) [27]	
5. Physical health	HCV Serology	RR = 1.59 (0.80–3.18) [1]	
	Inpatient Hospitalizations	IRR = 12.47 (8.21–18.93) [2]	aIRR = 5.90 (3.63–9.58) [2]
	Outpatient services only	IRR = 3.71 (1.74–7.88) [2]	aIRR = 1.33 (0.57–3.12) [2]
	Hospitalization < 1 year	IRR = 14.96 (9.04–24.74) [2]	aIRR = 8.53 (4.82–15.09) [2]
	Hospitalization > 1 year	IRR = 5.27 (3.09–9.00) [2]	aIRR = 1.78 (0.97–3.28) [2]
	> 3 Hospital Contacts	IRR = 14.68 (8.24–26.19) [2]	aIRR = 6.07 (3.02–12.18) [2]
	Chronic Pain	OR = 2.68 (0.74–9.68) [27]	

Table 2 (continued)

Domains	Included covariates	Unadjusted	Adjusted
6. HIV-specific	Recent CD4	HR = 0.77 (0.70–0.85) [22] per 50 cells/mm3 increase RR = 0.95 (0.91–1.00) [1] > = 500 cells/mm3 OR = 0.25 (0.07–0.87) [27]	per 100 cells/mm3 decrease aHR = 0.81 (0.67–0.99) [24] per 100 cells/mm3 increase aRR = 0.89 (0.81–0.98) [3] > = 500 cells/mm3 aOR = 0.15 (0.03–0.70) [27]
	CD4 Nadir	RR = 1.01 (0.94–1.09) [1]	
	Recent VL	HR = 3.14 (2.54–3.87) [22] < 200 copies/ml RR = 0.63 (0.35–1.13) [1] > 400 copies/ml RR = 1.63 (0.61–4.36) [27]	≥ 5 log copies aHR = 0.80 (0.43–1.48) [24]
	Adherence > 95%	HR = 0.16 (0.10–0.27) [22]	
	Efavirenz	RR = 1.68 (0.63–4.49) [1] HR = 3.01 (1.37–6.54) [22] OR = 3.78 (0.96–14.87) [27]	
	ART Therapy	RR = 0.73 (0.35–1.56) [1]	
	ART CPE scores > study median	OR = 1.74 (0.68–4.48) [27]	
	Transmission Group	Heterosexual RR = 0.58 (0.33–1.04) [1] MSM RR = 1.29 (0.73–2.29) [1]	MSM aHR = 1.82 (0.8–4.16) [4]
	Diagnosis < 2 years	IRR = 13.70 (7.61–24.70) [2]	aIRR = 8.10 (4.21–15.61) [2]
	Diagnosis 2–5 years	IRR = 12.35 (6.62–23.03) [2]	aIRR = 4.38 (2.12–9.04) [2]
	Diagnosis > 5 years	IRR = 3.83 (1.87–7.82) [2]	aIRR = 1.35 (0.60–3.05) [2]
	AIDS Defining Illness	No AIDS defining illness HR = 4.90 (1.79–13.39) [22] RR = 1.19 (0.66–2.14) [1] OR = 0.29 (0.06–1.34) [27]	No AIDS defining illness aHR = 4.45 (1.62–12.25) [22] aHR = 1.32 (0.61–2.83) [24] aHR = 1.14 (0.78–1.67) [29]
	CDC Clinical Stage (reference C)		CDC stage B aHR = 0.35 (0.16–0.81) [4] CDC stage A aHR = 0.55 (0.28–1.06) [4] CDC stage B aRR = 0.61 (0.26–1.44) [3] CDC stage A aRR = 0.62 (0.31–1.23) [3]
7. Psychosocial	Living alone	RR = 2.01 (1.10–3.66) [1] OR = 3.26 (1.06–10.07) [27]	aOR = 4.66 (1.59–13.68) [27]
	Having children	RR = 0.47 (0.25–0.90) [1]	aRR = 0.26 (0.10–0.70) [1]
	Unemployed	OR = 5.86 (1.69–20.37) [27]	aOR = 14.25 (1.49–136.17) [27]

RR risk ratio, *aRR* adjusted risk ratio, *HR* hazard ratio, *aHR* adjusted hazard ratio, *OR* odds ratio, aOR adjusted odds ratio, *IRR* incident rate ratio, *aIRR* adjusted incident rate ratio

Not included: Aldaz et al., Croxford et al., Fontela et al., & Nishijima et al.

general population, with SMRs ranging from 2.1 to 9.6 [4–6, 25, 28]. SMRs were calculated using national [3, 4, 6, 28] or regional [5, 25, 26] reference populations.

Domain 1: Demographics

Sex

Study participants were predominately male (66–96%) [1, 3–6, 22–26, 28, 29]. Two studies excluded females due to insufficient sample size [2, 27]. Four studies adjusted for sex

and age in SMRs [5, 6, 25, 28]; two studies controlled for sex in fully adjusted models but did not present associations [24, 29]. In one study, women were diagnosed with HIV at a younger age than men (median of 32 vs. 36 years). Women in this study were predominately from sub-Saharan Africa with reported heterosexual transmission, while men were predominantly born in the UK with transmission reported from sex with other men [6]. Only one study observed a lower risk of suicide among females [26]. Otherwise, sex was not associated with suicide, possibly due to limitations related to power [1, 3, 4, 22].

Age

Six studies reported age-related metrics related to suicide. The median age of individuals at entry into the cohort ranged from 32 to 47 years [3, 4, 6, 22–29]. Median age at suicide ranged from 34 to 42 years [3, 4, 6, 22]; two reported a mean age at suicide of 41.4 (±1.5) [27] and 44.9 (±9.3) years [1]. Younger age was positively associated with suicide in unadjusted models [22], but no association was observed between age and suicide in fully adjusted models [1, 3, 4].

Race/Ethnicity

Three North American studies included race and/or ethnicity [22, 23, 26]; eight European studies reported citizenship or country of origin [1–6, 25]. Three studies did not report race, ethnicity, or citizenship [24, 27, 29]. Two U.S.-based studies adjusted for race but did not report the association [23, 26]. Indigenous peoples were included in a study based in British Columbia [22]. Although Indigenous peoples did not appear to be at elevated risk for suicide, the small sample size limited the ability of this study to detect an association. Indigenous peoples represented 20% of suicide decedents (N = 16) and 11% of the study population (N = 489) [22]. In European studies, 11 to 40% of the study population was born abroad or was a citizen of another country [1–6, 25]. These populations displayed either no difference [4] or a reduced risk of suicide relative to those born in the country of interest [3, 6].

Domain 2: Mental Health

Mental health comorbidity was assessed in different ways: a previous suicide attempt [1, 3, 27], specific psychiatric illnesses [1–3, 27], past psychiatric treatment history [4], and neurocognitive impairment [27]. Mental health comorbidities were primarily identified by chart review and ICD-9/10 diagnostic codes [1, 3, 4, 27]. One study used ICD-9/10 codes alone to identify comorbidities from medical records [2].

Prior suicide attempts were documented in 22 to 35% of suicide decedents [1, 3, 27] and were associated with a substantial increase in the risk of suicide (adjusted relative risk [aRR] = 5.93, 95% confidence interval [CI] 1.58–22.24) [1]. Among suicide decedents, the prevalence of psychiatric comorbidities was high and included depressive disorders (60–64%), anxiety (25–41%), and schizophrenia (11–13%) [1, 3]. Psychiatric comorbidities were associated with an increased risk of suicide in unadjusted models [1, 2, 27]. A history of depressive disorder was the only psychiatric comorbidity included in adjusted models and was associated with an increased risk of suicide (aRR 3.76, 95% CI 1.49–9.50) [1].

Domain 3: Psychotropic Medications

The use of psychotropic medications (e.g., antidepressants, anxiolytics, antipsychotics) was prevalent among suicide decedents (48–63%) [1, 3, 27]. Individuals with a recent prescription for psychotropic medication were six times as likely to die by suicide compared to individuals without (aRR = 6.37, 95% CI 2.56–15.85) [1].

Domain 4: Substance Use

A history of injection drug use (IDU) was addressed in 13 studies [1, 3–6, 22–29]. In ten studies, historical IDU was identified from the route of transmission at diagnosis [3–6, 22–26, 29]. A history of IDU was strongly associated with suicide [3–6, 22–29]. Current illicit drug use was considered in two studies with a prevalence of 12–16% [1, 27]. The relative risk of suicide was three times higher among individuals with current drug use (aRR = 3.29, 95% CI 1.10–9.85) compared to those without current drug use [1]. Elevated daily alcohol consumption (> 20 g/day) was more prevalent among suicide decedents than among controls (31% vs. 13%, respectively, χ^2 $P = 0.01$) [1]. Elevated alcohol consumption increased the risk of suicide, even after accounting for current drug use (aRR = 3.56, 95% CI 1.43–8.88) [1]. No relationship was observed between current smoking and suicide [1, 27].

Domain 5: Physical Health

Hepatitis C Virus (HCV)

HCV frequently co-occurs with psychiatric illness and substance misuse and has been associated with an increased risk of suicide in the general population [31, 32]. Within the reviewed studies, HCV was common among PWH with a history of IDU (71.4–93.7%) [1, 22]. One study examined the association between HCV and suicide, with no significant association reported [1].

Physical Health Comorbidities

Physical health comorbidities were generally not considered in the reviewed studies. Measures of physical health were limited to health services utilization as a proxy for morbidity [2]. Compared to individuals without HIV, Jia et al. observed an increase in risk of suicide among PWH with more frequent health care utilization, including inpatient hospitalization (adjusted incidence rate ratio [aIRR] = 5.9, 95% CI 3.63–9.58) [2], hospitalization in the past year (aIRR = 8.53, 95% CI 4.82–15.09) [2], and frequent hospitalization (aIRR = 6.07, 95% CI 3.02–12.18) [2].

Domain 6: HIV-Specific Risk Factors

All studies included at least one HIV-specific risk factor: ART, presence of an AIDS-defining illness, CD4 count, HIV-1 RNA, mode of transmission of HIV, and/or time since diagnosis of HIV.

ART Use and Adherence

The association between ART use and suicide was examined in three of the 14 studies reviewed [1, 22, 27]. Three additional studies stratified the analysis by three time periods (i.e., pre-combination therapy (< 1997), early combination therapy (1996–2008), and current treatment era (2009–2018) but not by individual ART use [3, 4, 25]. Most individuals included in these studies were on some form of ART (86–100%) [1, 22, 25, 27]. ART was not associated with suicide in unadjusted analyses (relative risk [RR] = 0.73, 95% CI 0.35–1.56) [1]. The association was not explored in fully adjusted models [22, 27].

Reduced ART adherence (< 95%) was common among suicide decedents versus comparators (77% vs. 37%). ART adherence (≥ 95%) was associated with a reduction in the risk of suicide in unadjusted models (HR 0.16, 95% CI 0.10–0.27) [22]. Efavirenz (EFV)—a nucleoside reverse transcriptase inhibitor (NNRTI) with known adverse psychiatric side effects [33, 34]—was included in unadjusted analyses in three studies with mixed findings [1, 22, 27]. Two studies did not find an association [1, 27]. Gurm et al. observed an increase in risk in univariate analysis (hazard ratio [HR] = 3.01, 95% CI 1.37–6.54) [22]. However, the small number of individuals receiving EFV precluded examining the association in fully adjusted models.

AIDS-Defining Illnesses

AIDS-defining illnesses were documented in 13.7–35.5% of PWH [1, 3, 4, 22, 24, 25, 27, 29] and were not associated with an increased risk of suicide [1, 3, 4, 22, 24, 27, 29]. Gurm et al., however, observed an increased risk of suicide among individuals who never experienced an AIDS-defining illness (HR = 4.90, 95% CI 1.79–13.39) [22], as did Nishijima et al. (SMR 3.24, 95% CI 1.54–4.94) [28].

CD4 Count/HIV-1 RNA

Nine of the 14 studies included a measure of CD4 count assessed at baseline [3, 4, 6, 22–24, 28], nadir [1, 22, 28], and/or proximal to the date of suicide death [1, 3, 4, 22, 23, 27]. Six studies reported HIV-1 RNA measured at baseline [23, 28] and proximal to the date of death [1, 22, 24, 27, 28].

Associations between CD4 count/HIV-1 RNA and suicide were mixed. In some studies, high CD4 counts proximal to the date of death were associated with a lower risk of suicide in unadjusted [3, 22, 27] and adjusted models [27]. Other studies found no association between recent low CD4 counts and suicide [1]. One study found that a recent decrease in CD4 count was associated with a reduced risk of suicide (adjusted hazard ratio [aHR] = 0.81, 95% CI 0.67–0.99) [24]. The association between HIV-1 RNA and suicide was mixed in unadjusted models [1, 24, 27]. However, in the one study that explored the fully adjusted association between individuals with HIV-1 RNA ≥ 5 log copies and suicide, no association was found [24].

Mode of Transmission of HIV

The mode of transmission of HIV was considered in 12 of the 14 studies. Route of transmission was defined as men who have sex with men (MSM) (35–92%) [1, 3–6, 23–29], heterosexual transmission (39–57%) [1, 3, 4, 6], IDU (0.5–71%) [1–6, 22, 23, 25–28], and blood products (4.4%) [28]. No association between heterosexual transmission, MSM, and suicide was observed in unadjusted [1] or adjusted models [4]. Conversely, transmission of HIV via IDU was associated with a twofold to 6.5-fold increased risk of suicide [1, 4, 22–24].

Time Since Diagnosis of HIV

Suicide risk was elevated in the first year following diagnosis with HIV [2, 6]. Croxford et al. found that 40% of suicides occurred in the first year following diagnosis [6]. These deaths were mostly found in individuals not linked to care (79%) [6]. Jia et al. also observed that individuals who died by suicide, compared with those who had not, had received a diagnosis of HIV in the previous two years (aIRR = 8.10, 95% CI 4.21–15.61) [2]. While the risk of suicide declined in the five years following diagnosis, it remained elevated (aIRR = 4.38, 95% CI 2.12–9.04) [2].

Domain 7: Psychosocial

Psychosocial risk factors included income [2, 22, 26], employment status [1, 4, 27], cohabitation or marital status [1–4, 27], having children [1], and educational attainment [1, 3, 4]. Among the psychosocial factors considered, living alone (adjusted odds ratio [aOR] = 4.66, 95% CI 1.59–13.68) [27] and unemployment (aOR = 14.25, 95% CI 1.49–136.17) [27] were associated with an increased risk of suicide, whereas having children reduced the risk of suicide (aRR = 0.26, 95% CI 0.10–0.70) [1].

Discussion

This systematic review established that the key risk factors for suicide identified among PWH were consistent with those found in the general population: a previous suicide attempt, substance misuse, psychiatric illness, and social factors such as living alone and not having children.

Notably, PWH had a higher prevalence of these risk factors than individuals in the general population [35, 36].

We hypothesized that HIV-specific risk factors—low CD4 count and high HIV-1 RNA—would be associated with an elevated risk of suicide, yet neither of these factors significantly increased risk. Lack of power could have reduced the ability of the studies to detect an association between suicide and CD4 count and HIV-1 RNA. While CD4 count and HIV-1 RNA—as biological markers—may not be associated with an increased risk of suicide, they may serve as proxies for treatment engagement and general psychosocial wellbeing. Reductions in CD4 count [37], increases in HIV-1 RNA [37], and reduced treatment adherence [38, 39] are influenced by psychosocial factors that are also correlated with risk of suicide, such as substance use, psychiatric illness, and environmental stressors [20]. Additional consideration of psychosocial and behavioral variables is needed and should be a focus of future research.

The presence of an AIDS-defining condition was not associated with risk of suicide. In contrast, a study by Gurm et al. observed an increased risk of suicide among individuals who had never experienced an AIDS-defining illness [22]. It is possible that those who died from suicide died before developing an AIDS-defining condition.

Substance misuse emerged as one of the strongest risk factors for suicide among PWH. Substance misuse in the reviewed studies was predominately limited to historical IDU ascertained from the route of transmission for HIV. Current substance use was largely unspecified [40]. Yet, the inclusion of historical IDU alone failed to capture the breadth of substance misuse. Current substance use, inclusive of illicit drug use and alcohol use, is a strong risk factor for suicide in the general population [41, 42]. In the two studies that explored substance use in more detail, current illicit drug use and current alcohol use were two of the strongest risk factors for suicide among PWH [1, 27]. Furthermore, the risk of suicide was likely differentially affected by the number and type of substances used [43, 44], such as opioids, cocaine, marijuana, and methamphetamines [41, 45]. Based on this observed relationship in the general population, a more comprehensive accounting of substance use could help to explain the elevated risk of suicide among PWH.

The studies we reviewed did not report the impact of substance misuse co-occurring with psychiatric illness (dual-diagnosis) on excess risk for suicide. However, evidence from the general population demonstrates a heightened risk of suicide among individuals with a dual-diagnosis [46]. The addition of HIV (triple-diagnosis) adds further complexity. The relation between substance use, psychiatric illness, and HIV is complex and multidirectional and enhances the likelihood of adverse outcomes. Individuals with a triple-diagnosis, relative to those without, report less adherence to treatment regimens, poorer mental and physical health, and reduced social and emotional wellbeing [47]. This suggests that the risk of suicide may be elevated among PWH with co-occurring psychiatric illness and substance misuse.

While most risk factors for suicide among PWH were similar to those identified in the general population, risk of suicide associated with sex was not [1, 3, 4, 24]. In the general population, the risk of suicide is lower among women than among men [48]. In the studies that we reviewed, no difference in risk by sex among PWH was observed. This may be an artifact of insufficient power: few women were included in these studies. If we consider that women with HIV experience a disproportionately high burden of stressors—they are frequently victims of violence [49], engage in substance misuse [49], are economically disadvantaged [50], and are from marginalized communities [50]—we might expect that such experiences could amplify their risk of suicide [49, 51, 52]. Differences in risk associated with sex remain an open question for further investigation.

Gaps in the Literature

Absent from the reviewed studies were risk factors associated with non-AIDS-related chronic illnesses and multimorbidity. Chronic inflammation due to HIV infection is associated with an accelerated development of chronic diseases and multimorbidity [15, 53]. With improved longevity, the prevalence of chronic illnesses such as liver disease, cardiovascular disease, renal disease, and non-AIDS-related cancers is increasing [13, 54]. A growing proportion of PWH will confront complications associated with the aging process, including polypharmacy, alterations in physical functioning [55], and cognitive changes [56]. These factors will

be important to incorporate in future studies. The current longitudinal cohorts are well-positioned to extract relevant diagnostic information pertaining to chronic illnesses in future studies.

Also largely absent from the reviewed studies were psychosocial risk factors associated with living with HIV. Given data limitations, only a few studies were able to include such factors (e.g., living alone, employment, having children). When included, these factors were consistently associated with an elevated risk of suicide. Critical risk factors absent from most studies include measures for discrimination based on gender, sexuality, ethnicity [57, 58], ruptured social connections [59], and exposure to trauma and violence [12]. The recognition of the importance of psychosocial risk factors has led to recommendations by the Institute of Medicine to capture social determinates of health within EHRs [60].

Lastly, there were concerns that the reviewed studies may not be generalizable to all PWH, as the samples may not be representative of the underlying population of PWH. Observational cohorts and health registries reflect individuals who access clinical services and are engaged with the health care system [1–4, 6, 22–24, 27–29]. Those with reduced access, including individuals with IDU, severe mental illness, and those struggling with homelessness or other significant socioeconomic stressors [31, 32], would be under-represented. Studies that used population-based HIV surveillance data linked to vital statistics have the advantage of identifying individuals at the point of HIV diagnosis. While these studies include individuals not accessing HIV-related care, they exclude those who have not been tested.

Future Directions

To advance our knowledge of key risk factors that drive suicide among PWH, more diverse methodologies are needed. The low base-rate of suicide compared to the number at risk constrains the detection of associations and limits the examination of complex relationships between risk factors and suicide. Given this limitation, the examination of smaller, at-risk populations is frequently impossible. Large datasets (e.g., longitudinal cohorts, national health care registries, and surveillance systems) are necessary to identify an adequate number of suicide deaths. While these datasets are rich in clinical information, contextual information, including social and environmental factors are often absent from them.

The complexity and multidimensionality of suicide could be better understood by including qualitative analyses. A major strength of qualitative methods is the inclusion of factors that are not easily enumerated or available in current datasets. Qualitative studies among PWH who have survived a suicide attempt would make it possible to explore the individual, social, and environmental factors that lead to a suicidal crisis. This approach could identify new risk factors and illuminate how risk factors precipitate a suicidal crisis. Thus, incorporating qualitative approaches, particularly using a mixed methods approach, would better describe the experiences of PWH who have attempted suicide and better evaluate the risk factors they face.

Strengths and Limitations

The study was designed in collaboration with a medical research librarian, which ensured a comprehensive search strategy. We identified relevant literature by querying several bibliographic databases. The methodological approach to this systematic review introduced two potential limitations. First, we restricted studies to English-language publications, thus possibly excluding relevant studies on suicide. Second, we limited the primary outcome to suicide deaths rather than using an expanded definition of suicide deaths and attempts. The latter would improve sample sizes and the number of studies. However, evidence suggests that the risk factors for suicide are different than those associated with suicide attempts [61].

Conclusion

Despite advances in treatment, suicide remained elevated among PWH compared to the general population. Psychiatric illness, suicide attempts, IDU, current substance misuse, and alcohol use were strongly associated with suicide, while most HIV-specific risk factors were not. There is a clear need for additional studies of suicide risk among PWH. Future studies should consider a qualitative or mixed methods approach. The addition of qualitative methods would capture the subjective experience of PWH and contribute to our understanding of the drivers of suicide in this population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10461-022-03591-y.

Acknowledgements We thank Kate Nyhan, Research, and education data librarian at the Yale School of Medicine, for assisting with the design of our search strategy. This work was supported by the Robert Wood Johnson, Future of Nursing Scholars program; Yale Center for Clinical Investigation Multidisciplinary Pre-Doctoral Training Program in Translational Research; and NIH National Institute on Alcohol Abuse and Alcoholism U24 AA020794, U01 AA020790, U24 AA022001, U10 AA013566.

Author Contributions Conception or design of the work. AS, JW. Data collection: AS, JW, SB. Data analysis and interpretation: AS, JW. Drafting the article: AS, JW. Critical revision of the article: AS, JW, SB, JG, AJ, DV. Final approval of the version to be published: AS, JW, SB, JG, AJ, DV.

Funding Robert Wood Johnson, Future of Nursing Scholars; Yale Center for Clinical Investigation Multidisciplinary Pre-Doctoral

Training Program in Translational Research; NIH National Institute on Alcohol Abuse and Alcoholism U24 AA020794, U01 AA020790, U24 AA022001, U10 AA013566-completed and in kind by the US Department of Veterans Affairs.

Data Availability Literature extracted during each search stage, data extraction form and extracted data will be made available.

Code Availability Searches uploaded to Covidence. Included publications will be made available.

Declarations

Conflict of interest No conflicts of interest.

Ethical Approval Exempt.

Consent to Participate Not applicable, use of publicly available data.

Consent for Publication Not applicable, use of publicly available data.

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