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Examining the associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses

Sergio Rueda,[1,2,3,4] Sanjana Mitra,[5] Shiyi Chen,[5] David Gogolishvili,[5] Jason Globerman,[5] Lori Chambers,[6] Mike Wilson,[7,8] Carmen H Logie,[9] Qiyun Shi,[5] Sara Morassaei,[4] Sean B Rourke[2,5,10]

For numbered affiliations see end of article.

Correspondence to
Dr Sergio Rueda;
ruedagento@gmail.com

ABSTRACT

Objective: To conduct a systematic review and series of meta-analyses on the association between HIV-related stigma and health among people living with HIV.

Data sources: A structured search was conducted on 6 electronic databases for journal articles reporting associations between HIV-related stigma and health-related outcomes published between 1996 and 2013.

Study eligibility criteria: Controlled studies, cohort studies, case-control studies and cross-sectional studies in people living with HIV were considered for inclusion.

Outcome measures: Mental health (depressive symptoms, emotional and mental distress, anxiety), quality of life, physical health, social support, adherence to antiretroviral therapy, access to and usage of health/social services and risk behaviours.

Results: 64 studies were included in our meta-analyses. We found significant associations between HIV-related stigma and higher rates of depression, lower social support and lower levels of adherence to antiretroviral medications and access to and usage of health and social services. Weaker relationships were observed between HIV-related stigma and anxiety, quality of life, physical health, emotional and mental distress and sexual risk practices. While risk of bias assessments revealed overall good quality related to how HIV stigma and health outcomes were measured on the included studies, high risk of bias among individual studies was observed in terms of appropriate control for potential confounders. Additional research should focus on elucidating the mechanisms behind the negative relationship between stigma and health to better inform interventions to reduce the impact of stigma on the health and well-being of people with HIV.

Conclusions: This systematic review and series of meta-analyses support the notion that HIV-related stigma has a detrimental impact on a variety of health-related outcomes in people with HIV. This review can inform the development of multifaceted, intersectoral interventions to reduce the impact of HIV-related stigma on the health and well-being of people living with HIV.

Strengths and limitations of this study

- This systematic review and series of meta-analyses examined a wide range of associations between stigma and health, supporting the notion that HIV-related stigma has a detrimental impact on a variety of health-related outcomes in people living with HIV.
- It performed a comprehensive search of the literature, used independent reviewers and a consensus approach to select and extract data from relevant papers, performed a detailed quality appraisal of the included studies, used appropriate methods to combine the findings of studies and assessed the likelihood of publication bias where appropriate.
- Substantial heterogeneity was observed for some outcomes, and a small number of studies were available to be pooled in meta-analyses for other outcomes.
- While risk of bias assessments revealed overall good quality for some domains, the majority of studies only presented bivariate associations, potentially obscuring the association between HIV stigma and health outcomes in this review.
- Future reviews should perform a systematic evaluation of the mechanisms involved in the relationship between HIV-related stigma and health, the role a variety of factors play in reducing the negative effects of stigma on health and examine the intersection between stigma and other forms of social exclusion.

BACKGROUND

According to the Global Network of People Living with HIV/AIDS, one of the biggest challenges facing people living with HIV today is stigma and discrimination.[1] HIV-related stigma in this context has been defined as discounting, discrediting and discriminating against people perceived to have HIV.[2] [3] Overall, stigma continues to be

prevalent in the context of HIV, whether measured in terms of the attitudes of those who are not infected[4] or in terms of the experiences of those living with HIV.[5 6] The mechanisms through which stigma may be experienced by those living with HIV include enacted stigma, anticipated stigma and internalised stigma.[5] Enacted stigma refers to discrimination experienced by people with HIV, and may include acts of violence and marginalisation. Anticipated stigma is awareness of negative social perceptions towards HIV and the expectation that a person living with HIV will experience prejudice and discrimination in the future. Internalised stigma refers to the endorsement of negative beliefs, views and feelings of oneself as it relates to one's HIV-positive status.[5] In other words, for those living with HIV, the knowledge that their HIV status is a socially devalued aspect of themselves may be experienced in a variety of ways, ranging from actually being the object of prejudice and discrimination from others to holding negative beliefs and feelings about themselves.[7] Stigma may arise from misconceptions about HIV transmission and from judgmental attitudes towards those social groups that are disproportionately affected by HIV, including men who have sex with men (MSM), Aboriginal people, people from countries where HIV is endemic, ethnic minorities, and injection drug users.[8–10]

Stigma and discrimination negatively affect people living with HIV. A recent review of the qualitative evidence showed that HIV-related stigma is a broad and global social phenomenon that manifests within multiple social domains, including healthcare environments.[11] Studies have reported on HIV discrimination in healthcare environments including denial of care or treatment, HIV testing without consent, confidentiality breaches, negative attitudes and humiliating practices by healthcare workers.[12–14] Models linking the experience to negative outcomes have been developed and tested, especially in the areas of racial discrimination, physical and mental health[15–20] and substance use.[21 22] HIV-related stigma is associated with poorer mental health outcomes, including emotional distress,[23–26] shame,[27] depression,[6 28–30] reduced self-esteem,[31] reduced psychological functioning,[25] poorer psychological adjustment,[32] negative affect,[33] anxiety,[34–36] suicidal ideation,[37 38] life satisfaction,[39] quality of life[40 41] and stress associated with disclosure.[23] Other studies have identified the impact of stigma on a person's self-valuation or mental outlook once his or her status is known.[42 43] Stigma has also been linked with secondary health-related factors including seeking healthcare and adherence to antiretroviral therapy.[44–47] A meta-analysis by Logie and Gadalla (2009) demonstrated that high levels of stigma were consistently and significantly associated with low social support and poorer physical and mental health outcomes in North American contexts.[48]

Given the growing body of research that documents the relationship between stigma and health among people living with HIV, and the limited number of studies that summarise and integrate this body of work, the current systematic review of the quantitative evidence complements our recent review of qualitative research,[11] and further builds on the work of Logie and Gadalla (2009) by including a large number of recent studies from a wider scope of contexts and outcomes, and organising the health outcomes in a more clinically meaningful way. This includes mental health (depressive symptoms, emotional and mental distress, anxiety), quality of life and physical health outcomes. In addition, the present review uniquely examines the association between HIV-related stigma and additional intermediate health-related outcomes such as adherence to antiretroviral medications, social support, access and usage of health and social services, and sexual risk behaviours. This knowledge base informs the need to further develop and evaluate interventions addressing HIV-related stigma for people living with HIV/AIDS.

METHODS
Search strategy
A systematic search of six databases (Medline, EMBASE, PsycInfo, CINAHL Sociological Abstracts and WHOLIS) for journal articles published between January 1996 (with the advent of combination antiretroviral therapy) and September 2013 was conducted. MeSH and/or keyword terms related to HIV/AIDS and stigma were adapted for each specific database (see online supplementary file 1 for search strategies). The search strategy also included literature recommended by content experts, and a citation search of literature included at the stage of full-text article review. The study protocol was peer-reviewed and was funded by the Canadian Institutes of Health Research.

Inclusion/exclusion criteria
All controlled studies (ie, randomised controlled trials and quasiexperimental studies), cohort studies, case–control studies and cross-sectional studies that measured the association between HIV-related stigma and health-related outcomes in people living with HIV were considered for inclusion. Studies were included in this review if they: (1) were published in English, French or Spanish after 1996; (2) included people living with HIV; (3) reported HIV-related stigma as a predictor of health outcomes, such as mental and physical health, access to and usage of care, adherence to antiretroviral therapy, social support, sexual risk behaviours; (4) reported any one of the following statistics: correlation coefficient and sample sizes, ORs and 95% confidence limits, regression coefficients and SE or 95% confidence limits, or other statistics that could be converted into a standardised effect size.

Studies were excluded if: (1) no primary data were reported; (2) full-text articles were not available after exhaustive searches to locate them; (3) there were insufficient or missing data (after contacting authors);

(4) groups of studies had considerable heterogeneity (variation in outcomes between studies). Studies with rare outcomes such as food insecurity, the positive legacy of trauma, sexual compulsivity and affect balance were excluded as these outcomes were unique to one study and therefore not meta-analysable.

Although the importance of understanding the health impact of HIV-related stigma on communities that have been disproportionally impacted by HIV was recognised (eg, MSM, women, people who use drugs, Aboriginal people, racialised communities, immigrants and refugees), the focus of our analysis was on people living with HIV irrespective of cultural identity, sexual orientation, or sexual risk behaviours. This review was also restricted to HIV stigma on health outcomes regardless of the intersecting effects of other types of stigma related to social positioning.

Screening and data extraction

The screening phase was conducted on DistillerSR, an online application specifically designed for knowledge syntheses (DistillerSR [program]. Ottawa, Canada, 2014). A customised checklist reflecting the selection criteria facilitated the selection process. The form was pilot tested using 75 citations each at the title-and-abstract, and full-text article review stages to determine the reliability of the inclusion criteria. Data extracted included author name, year of publication, study jurisdiction (country), study design, sample size, stigma measure, outcome measure, statistical analysis (univariate or multivariate) and key statistical data.

The inclusion process was conducted in three stages: The first stage was title-and-abstract review, where references were reviewed to determine clear exclusions. The second stage was full-text article review, where the paper was retrieved and reviewed to determine general applicability to the review aims. The third stage was methodology review, where the full-text article was reviewed based on inclusion criteria. All three stages were completed by two reviewers independently. Any disagreements between reviewers were resolved by consensus. To determine inter-rater reliability, κ-statistic was used and found to be 0.65, suggesting substantial agreement.

Quality appraisal

The quality appraisal tool was adapted from the Newcastle-Ottawa Scale[49 50] to have a single risk of bias assessment for all study designs. Each study was awarded one rating (good, fair or poor) for each of the three domains: exposure, outcome and comparability. Quality in the exposure domain was considered 'good' if HIV stigma was measured using validated tools; 'fair' if HIV stigma was measured using tools developed by the authors for that particular study; and 'poor' if the authors made no attempts to properly measure stigma. Quality in the outcome domain was considered 'good' if the authors used an objective measure (eg, record linkage, diagnosis made by the clinician, laboratory findings) or used validated self-report measures; 'fair' if the authors used a self-report measure, but limited information regarding reliability and validity was referenced or provided in the paper; and 'poor' if the definition of the outcome was vague, unclear or the measurement of the outcome was poor (eg, questionnaire developed by the authors for that particular study). Quality in the comparability domain was 'good' if studies controlled for at least one demographic or social economic status variable confounder (eg, age, sex, income), and at least one behavioural health indicator; 'fair' if studies controlled for at least one potential demographic or social economic status variable confounder (eg, age, sex, income); and 'poor' if there was lack of adjustment for potential confounders (eg, bivariate analysis). Quality assessments for included studies were completed by two independent reviewers.

Statistical methods
Summary effect size and type of analyses
The effect size statistic was defined as the association between HIV-related stigma and health outcomes. Statistical data such as ORs (with 95% CIs), correlations (with sample sizes) and regression coefficients (with SEs or 95% CIs) were recorded. Summary effect sizes were calculated with inverse variance weighting and presented as univariate analyses and OR, or regression coefficients for the multivariate analyses. No additional data are available to share.

Meta-analysis was conducted separately for studies that reported univariate and multivariate results. If both univariate and multivariate results were provided, multivariate statistics for the meta-analyses were used. For each meta-analysis, we created forest plots to show the magnitude of effects. We used Comprehensive Meta-Analysis-V.2 to perform the statistical analyses (Comprehensive Meta-analysis [program]. 2 version. Englewood New, Jersey: Biostat. 2005).

HIV-related stigma was measured in different studies using a variety of instruments. For studies that reported more than one type of HIV-related stigma (eg, internalised stigma, personalised stigma, self-stigma, enacted stigma), the finding with the highest strength of the association with the outcome was selected. Also, the statistics in table 1 have been adjusted for effect direction. For example, some studies measured the association between HIV-related stigma and delay to healthcare, providing a positive correlation to describe this relationship. In these cases, the direction of this correlation was adjusted to reflect the negative relationship between HIV-related stigma and access to healthcare, as a delay in healthcare may be considered detrimental to health.

Model selection and publication bias
Meta-analyses were performed based on a random effects model because the definitions and measurement scales for the predictor and outcome variables varied across studies, and true effect sizes varied from study to study.

Table 1 Summary of studies included in the meta-analyses by outcomes

Outcomes	Type of analyses in original studies	Number of studies (population)	Summary effect size and 95% CI	Q statistics and p value	I²	Trim-and-fill adjusted effect size	Fail-safe N
Depressive symptoms	Univariate	22 (24)	r: 0.40 (0.35 to 0.45)***	104.07***	77.90	0.33 (0.27 to 0.39)	4774
	Multivariate	9 (9)	β: 0.39 (0.21 to 0.58)***	185.29***	95.68		
Emotional and mental distress	Univariate	4 (4)	r: 0.48 (0.43 to 0.54)***	2.96	0.00		
Anxiety	Univariate	6 (6)	r: 0.32 (0.22 to 0.41)***	13.27*	62.31		
	Multivariate	2 (2)	OR: 1.09 (1.01 to 1.17)*	4.92*	79.67		
Overall quality of life	Univariate	2 (2)	r: −0.26 (−0.45 to −0.06)*	5.09*	80.37		
	Multivariate	3 (3)	β: −0.25 (−0.53 to 0.04)	9.27*	78.43		
Physical health	Univariate	10 (12)	r: −0.19 (−0.26 to −0.11)***	111.54***	90.14	−0.19 (−0.26 to −0.11)	318
Social support	Univariate	14 (16)	r: −0.28 (−0.36 to −0.20)***	104.85***	85.69	−0.28 (−0.36 to −0.20)	1125
	Multivariate	2 (2)	β: −0.31 (−0.56 to −0.06)*	2.22	55.02		
ARV adherence	Univariate	6 (6)	r: −0.08 (−0.17 to 0.01)	27.65***	81.92		
	Multivariate	7 (7)	OR: 0.68 (0.53 to 0.87)***	7.93	24.30		
Access and use of health and social services	Univariate	4 (4)	r: −0.08 (−0.20 to 0.04)	24.92***	87.96		
Risk behaviours	Multivariate	9 (9)	OR: 0.79 (0.68 to 0.93)**	32.69***	75.52		
	Univariate	2 (2)	r: 0.08 (−0.03 to 0.20)	1.53	34.75		
	Multivariate	1 (1)	OR: 1.06 (1.00 to 1.13)				

*p<0.05, **p<0.01, ***p<0.001.

With random effects models, two sources of uncertainty are taken into account: within-study sampling error and between-study variance. Heterogeneity in true effect sizes between studies was indicated by large Cochran's Q statistics with small p values, and large I^2 statistics.[51] Publication bias was assessed for meta-analyses that included more than 10 studies for one particular outcome variable. Funnel plots, trim-and-fill analysis and Rosenthal's fail-safe number were used to assess publication bias.[52 53]

RESULTS

Identification, screening and eligibility

Figure 1 illustrates the study inclusion/exclusion process. A total of 14 010 titles and abstracts were retrieved through electronic databases, and 224 studies identified through experts and reference checking. After removing duplicates, 9284 potentially eligible records remained. After further screening, eligibility assessment was performed with 1067 full-text articles; these were checked against the exclusion criteria and 120 studies remained for inclusion. After removing studies due to heterogeneity (eg, rare outcomes), missing data and duplicate data, 64 studies were included in the final series of meta-analyses.

Description of included studies

Sixty-four studies were included in our meta-analysis (see online supplementary file 2 for the characteristics of the included studies). The total sample size was 20 012. Forty-two of these studies were conducted in the USA, three in India, two each in Canada, Zambia and South Africa, and one each in the Netherlands, Vietnam, Congo, China, Lebanon, Hong Kong, France, Ethiopia, Thailand and Honduras. One study included data from multiple countries. Among these 64 studies, one was a randomised controlled trial, nine used longitudinal study design, one was a case–control study, and 53 had cross-sectional study designs. Separate meta-analyses were performed for different health outcomes and different statistical methods (univariate and multivariate study results). Some of these studies reported more than one health outcome, so the same study may have contributed to different meta-analyses.

Measures of HIV-related stigma and health-related outcomes

The most commonly used HIV-related stigma measures were the Berger Stigma Scale,[28] HIV Stigma Measure,[54] Internalized AIDS-Related Stigma Scale,[55] and Demi-HIV Stigma Scale (A Demi, R Bakeman, R Sowell, *et al.* Psychometric evaluation of the Demi HIV Stigma Scale. Unpublished manuscript. 2001). For mental health outcomes, studies reported on the relationship between HIV-related stigma and depression, emotional and mental distress, and anxiety: (1) depression was commonly measured using the Center for Epidemiologic Studies Depression Scale[56] and the Brief Symptom
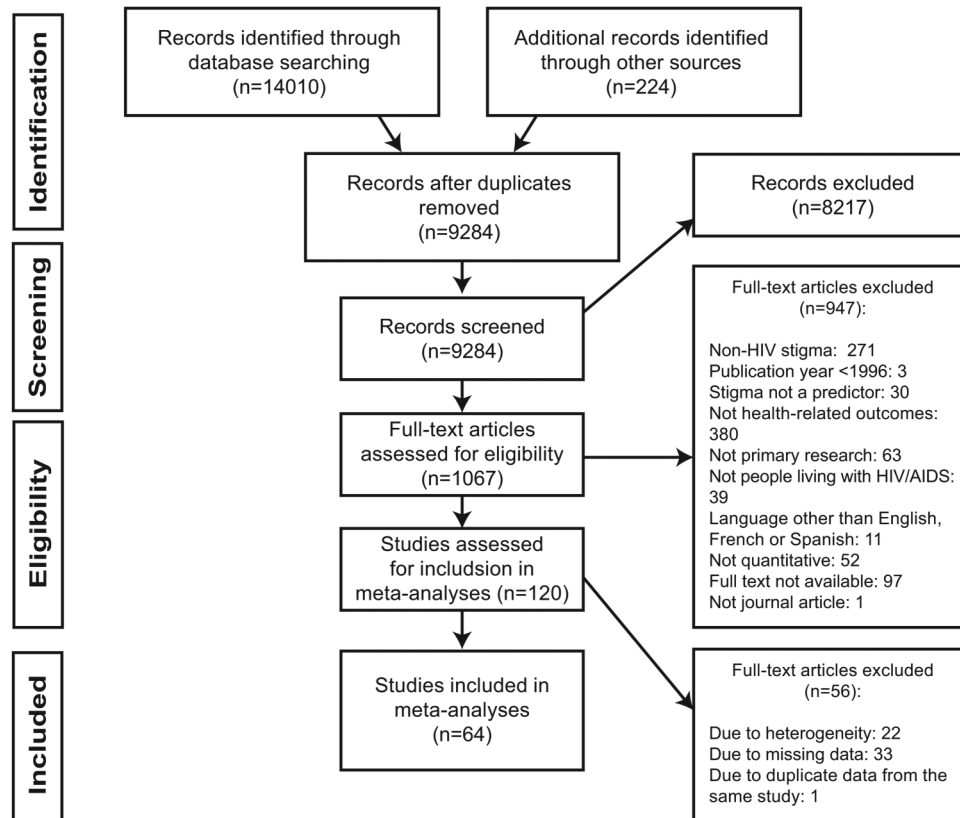
Figure 1 Flow diagram of study included in meta-analysis.

Inventory (BSI) depression subscale;[57] (2) emotional and mental distress reflects the range of emotional and mental symptoms and conditions experienced by people living with HIV (measured by the SF-12 mental health survey[58] or self-reported emotional and distress levels); (c) anxiety was measured using the BSI anxiety subscale,[57] State anxiety[59] and the Symptom Check List-90-R.[60] Overall quality of life was measured using WHO's Quality of Life-HIV BREF,[61] HIV/AIDS Targeted Quality Life instrument[62] and others. Physical health described HIV symptoms and physical well-being of people living with HIV. Instruments included the SF-12 physical health[58] and Medical Outcomes Study HIV Health Survey.[63] Social Support was most commonly measured by the Social Support Questionnaire[64] and the Medical Outcomes Study—Social Support Subscale.[65] Adherence to antiretroviral therapy was measured by self-report or the UCSF Adherence Questionnaire.[66] Access and use of health and social services measured the degree that people living with HIV have access to and use healthcare units, clinics and social services. Measurements include retention in care and seeking medical care. Sexual risk behaviours include unprotected sex. Measures included the NIMH Multisite Cooperative Agreement sexual risk assessment.[67]

Quality appraisal

The risk of bias graph presents the risk of bias in each domain (exposure, outcome and comparability) across all included studies (figure 2). The risk of bias summary (figure 3) presents the assessment of the quality in each domain for each study separately. *Exposure*: Our quality appraisal found that 46 (72%) studies have good quality in the exposure domain. Eleven (17%) and seven (11%) studies have fair and poor quality in the exposure domain respectively. A majority of the studies (k=46) had good exposure quality as they used validated tools to measure exposure. *Outcome*: A majority of studies (k=57) used objective measures of quality in the outcome domain such as validated questionnaires that have been previously published. Fifty-seven (89%) studies were assessed as having good quality in the outcome domain. Three (4%) have fair quality in the outcome domain and four (7%) have poor quality in the outcome domain. *Comparability:* Moreover, eight (12%) studies have good quality in the comparability domain, 18 (29%) have fair quality in the

Figure 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

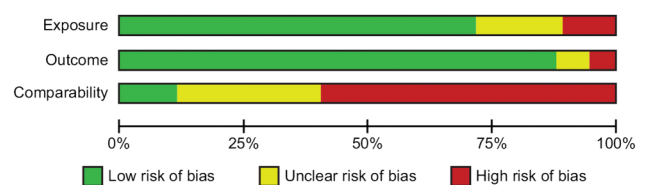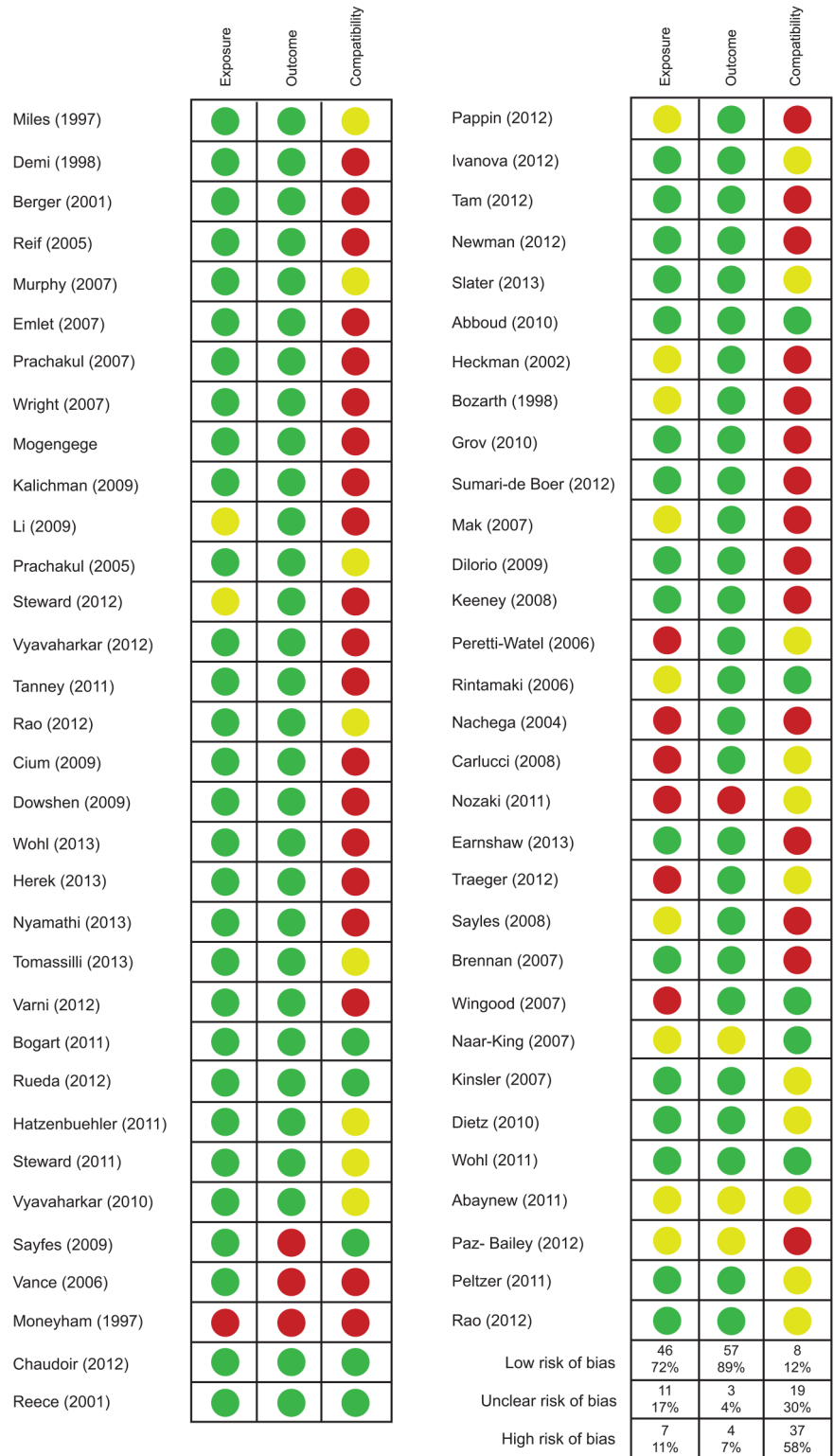|	Exposure	Outcome	Compatibility
Miles (1997)	green	green	yellow
Demi (1998)	green	green	red
Berger (2001)	green	green	red
Reif (2005)	green	green	red
Murphy (2007)	green	green	yellow
Emlet (2007)	green	green	red
Prachakul (2007)	green	green	red
Wright (2007)	green	green	red
Mogengege	green	green	red
Kalichman (2009)	green	green	red
Li (2009)	yellow	green	red
Prachakul (2005)	green	green	yellow
Steward (2012)	yellow	green	red
Vyavaharkar (2012)	green	green	red
Tanney (2011)	green	green	red
Rao (2012)	green	green	yellow
Cium (2009)	green	green	red
Dowshen (2009)	green	green	red
Wohl (2013)	green	green	red
Herek (2013)	green	green	red
Nyamathi (2013)	green	green	red
Tomassilli (2013)	green	green	yellow
Varni (2012)	green	green	red
Bogart (2011)	green	green	green
Rueda (2012)	green	green	green
Hatzenbuehler (2011)	green	green	yellow
Steward (2011)	green	green	yellow
Vyavaharkar (2010)	green	green	yellow
Sayfes (2009)	green	red	green
Vance (2006)	green	red	red
Moneyham (1997)	red	red	red
Chaudoir (2012)	green	green	green
Reece (2001)	green	green	green

	Exposure	Outcome	Compatibility
Pappin (2012)	yellow	green	red
Ivanova (2012)	green	green	yellow
Tam (2012)	green	green	red
Newman (2012)	green	green	red
Slater (2013)	green	green	yellow
Abboud (2010)	green	green	green
Heckman (2002)	yellow	green	red
Bozarth (1998)	yellow	green	red
Grov (2010)	green	green	red
Sumari-de Boer (2012)	green	green	red
Mak (2007)	yellow	green	red
Dilorio (2009)	green	green	red
Keeney (2008)	green	green	red
Peretti-Watel (2006)	red	green	yellow
Rintamaki (2006)	yellow	green	green
Nachega (2004)	red	green	red
Carlucci (2008)	red	green	yellow
Nozaki (2011)	red	red	yellow
Earnshaw (2013)	green	green	red
Traeger (2012)	red	green	yellow
Sayles (2008)	yellow	green	red
Brennan (2007)	green	green	red
Wingood (2007)	red	green	green
Naar-King (2007)	yellow	yellow	green
Kinsler (2007)	green	green	yellow
Dietz (2010)	green	green	yellow
Wohl (2011)	green	green	yellow
Abaynew (2011)	yellow	yellow	yellow
Paz-Bailey (2012)	yellow	yellow	red
Peltzer (2011)	green	green	yellow
Rao (2012)	green	green	yellow

	Exposure	Outcome	Compatibility
Low risk of bias	46 72%	57 89%	8 12%
Unclear risk of bias	11 17%	3 4%	19 30%
High risk of bias	7 11%	4 7%	37 58%

comparability domain and 37 (58%) have poor quality in the comparability domain. Few studies (k=19) controlled for at least one demographic variable and social-economic status variable, and a majority (k=37) did not control for any confounder at all. Seven longitudinal studies were also assessed for follow-up quality; however, this result was not included in the quality appraisal graph.

Effect sizes and heterogeneity

For each meta-analysis, table 1 reports the summary effect size and 95% CI, Q test of homogeneity, the heterogeneity of between-study variance (measured by I^2 statistics), and publication bias assessments including the calculated 'trim-and-fill' statistics and fail-safe N. For I^2 statistics, 25%, 50% and 75% represents low, medium and high heterogeneity, respectively.

Mental health: depressive symptoms

Meta-analysis of 22 articles (24 studies, figure 4) that reported univariate results showed a moderate correlation between HIV-related stigma and depressive symptoms. High heterogeneity was observed for univariate analysis. The eight studies that controlled for potential confounders (multivariate analysis) found that people living with HIV who experienced HIV-related stigma were at a greater risk of higher depressive symptoms. High heterogeneity was observed for multivariate analysis.

Mental health: emotional and mental distress

Meta-analysis on four studies (figure 5) that reported univariate results found a moderate correlation between HIV-related stigma and increased emotional and mental distress. Although there was no evidence of heterogeneity, the random effect model was still used to be consistent with the statistical analyses adopted throughout this study.[51]

Mental health: anxiety

Meta-analysis on six studies (figure 6) that reported univariate results showed a moderate correlation between HIV-related stigma and heightened anxiety. Medium heterogeneity was observed for univariate analysis. The two studies that controlled for potential confounders found that people who experienced HIV-related stigma were 1.09 times more likely to experience anxiety. High heterogeneity was observed for multivariate analysis.

Overall quality of life

Meta-analysis on two studies (figure 7) that reported univariate results showed a weak correlation between HIV-related stigma and lower overall quality of life. The three studies that controlled for potential confounders found that people who experienced HIV-related stigma were at higher risk of worse overall quality of life, but the results were not statistically significant. High heterogeneity was observed for both univariate and multivariate analyses.

Univariate Results — Statistics for Each Study — Correlation and 95% CI

	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Miles (1997)	0.500	0.268	0.677	3.923	0.000
Demi (1998)	0.520	0.415	0.611	8.372	0.000
Berger (2001)	0.630	0.559	0.692	13.159	0.000
Reece (2001)	0.520	0.383	0.634	6.546	0.000
Relf (2005)	0.280	0.074	0.463	2.637	0.008
Emlet (2007)	0.630	0.313	0.821	3.478	0.001
Prachakul (2007)	0.460	0.120	0.704	2.584	0.010
Wright (2007)	0.350	0.114	0.549	4.219	0.004
Mogengage (2008)	0.500	0.286	0.667	10.568	0.000
Kalichman (Swaziland 2009)	0.310	0.255	0.363	5.880	0.000
Kalichman (Atlanta 2009)	0.380	0.261	0.488	9.035	0.000
Kalichman (Cape Town 2009)	0.270	0.213	0.325	8.526	0.000
Li (2009)	0.400	0.315	0.479	11.665	0.000
Steward (2012)	0.360	0.304	0.414	5.725	0.000
Vyavahakar (2012)	0.280	0.187	0.368	6.388	0.000
Tanney (2011)	0.440	0.316	0.549	3.900	0.000
Clum (2009)	0.314	0.160	0.453	2.325	0.000
Dowshen (2009)	0.356	0.058	0.595	5.461	0.020
Herek (2013)	0.374	0.247	0.489	0.242	0.000
Nyamanthi (2013)	0.030	-0.210	0.267	5.461	0.809
Tomassilli (2013)	0.350	0.105	0.555	2.759	0.006
Wohl (2013)	0.470	0.301	0.610	5.024	0.000
Varni (2012)	0.340	0.211	0.457	4.970	0.000
Bozarth (1998)	0.758	0.565	0.873	5.520	0.000
Summary Measure	0.403	0.351	0.453	13.629	0.000

Multivariate Results — Point Estimate and 95% CI
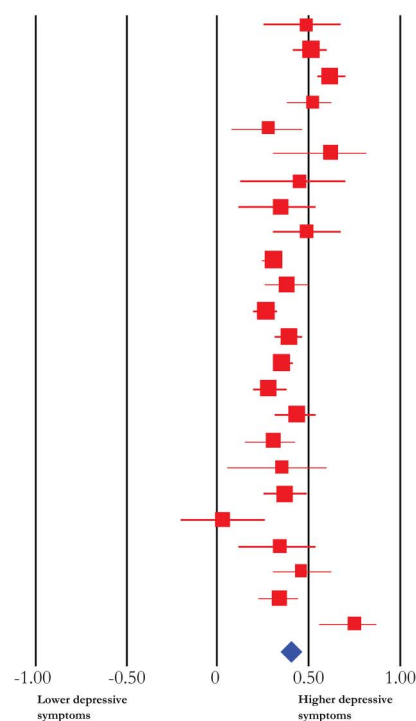
	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Prachakul (2005)	0.440	0.256	0.624	4.681	0.000
Murphy (2007)	0.361	0.208	0.514	4.628	0.000
Bogart (2011)	0.000	-0.098	0.098	0.000	1.000
Rueda (2011)	0.130	0.065	0.195	3.920	0.000
Hatzenbuehler (2011)	0.160	0.101	0.219	5.333	0.000
Rao (2012)	0.670	0.572	0.768	13.400	0.000
Steward (2011)	10.985	7.196	14.774	5.682	0.000
Vyavaharkar (2010)	0.220	0.122	0.318	4.400	0.000
Summary Measure	0.301	0.127	0.476	3.381	0.001
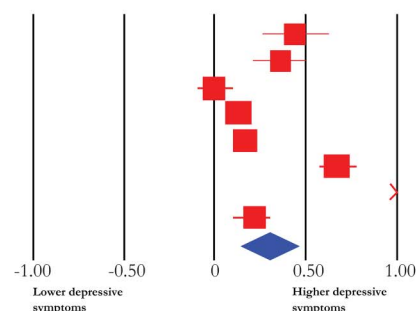
Figure 4 Stigma is associated with higher depressive symptoms (univariate and multivariate results).

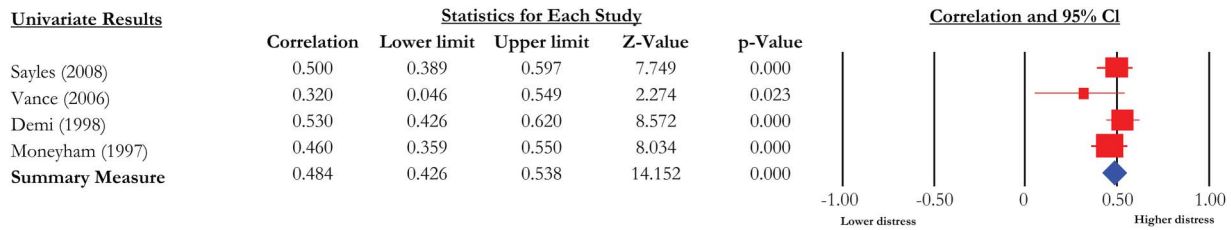| Univariate Results	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Sayles (2008)	0.500	0.389	0.597	7.749	0.000
Vance (2006)	0.320	0.046	0.549	2.274	0.023
Demi (1998)	0.530	0.426	0.620	8.572	0.000
Moneyham (1997)	0.460	0.359	0.550	8.034	0.000
Summary Measure	0.484	0.426	0.538	14.152	0.000

Figure 5 Stigma is associated with higher emotional and mental distress (univariate results).

Univariate Results	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Wright (2007)	0.240	-0.006	0.459	1.912	0.056
Reece (2001)	0.480	0.337	0.602	5.940	0.000
Herek (2013)	0.367	0.239	0.482	5.348	0.000
Vami (2012)	0.320	0.190	0.439	4.655	0.000
Hatzenbuehler (2011)	0.170	0.060	0.276	3.027	0.002
Tomassilli (2013)	0.320	0.072	0.531	2.504	0.012
Summary Measure	0.317	0.215	0.413	5.849	0.000

Multivariate Results	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Pappin (2012)	1.140	1.072	1.212	4.177	0.000
Ivanova (2012)	1.060	1.040	1.080	6.052	0.000
Summary Measure	1.093	1.018	1.172	2.469	0.014

Figure 6 Stigma is associated with higher anxiety symptoms (univariate and multivariate results).

Univariate Results	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Tam Van (2012)	-0.360	-0.468	-0.241	-5.653	0.000
Newman (2012)	-0.160	-0.284	-0.027	-2.361	0.018
Summary Measure	-0.263	-0.447	-0.058	-2.503	0.012

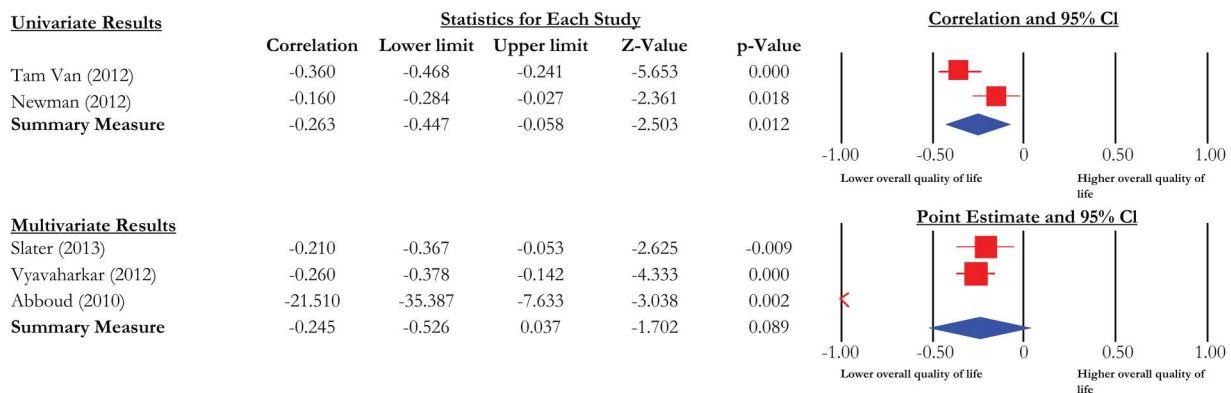| Multivariate Results					
Slater (2013)	-0.210	-0.367	-0.053	-2.625	-0.009
Vyavaharkar (2012)	-0.260	-0.378	-0.142	-4.333	0.000
Abboud (2010)	-21.510	-35.387	-7.633	-3.038	0.002
Summary Measure	-0.245	-0.526	0.037	-1.702	0.089

Figure 7 Stigma is associated with lower quality of life (univariate and multivariate results).

Physical health

A weak correlation was found between HIV-related stigma and greater number of physical symptoms (figure 8). Meta-analysis indicated that people who experienced HIV-related stigma were at a greater risk of poorer physical health. High heterogeneity was observed.

Social support

For meta-analysis based on univariate results (figure 9), a moderate correlation was found between HIV stigma and lower level of social support. High heterogeneity was observed for this analysis. The two studies that controlled for potential confounders gave the summary point estimate of −0.31 with 95% CI (−0.56 to −0.06). There was no conclusive evidence of heterogeneity for the multivariate analysis.

Adherence to antiretroviral therapy

Meta-analysis based on univariate results (figure 10) showed a weak correlation between HIV-related stigma and poor adherence to treatment across five studies. However, this correlation was not statistically significant. High heterogeneity was found among the studies. In addition, the seven studies that controlled for potential confounders found that people who experienced HIV-related stigma were 32% less likely to adhere to antiretroviral therapy. There was no conclusive evidence of heterogeneity.

Access to and usage of health and social services

Meta-analysis based on univariate results (figure 11) showed a weak correlation between HIV stigma and lower access and usage of services across four studies, although this association was not statistically significant. The nine studies that controlled for potential
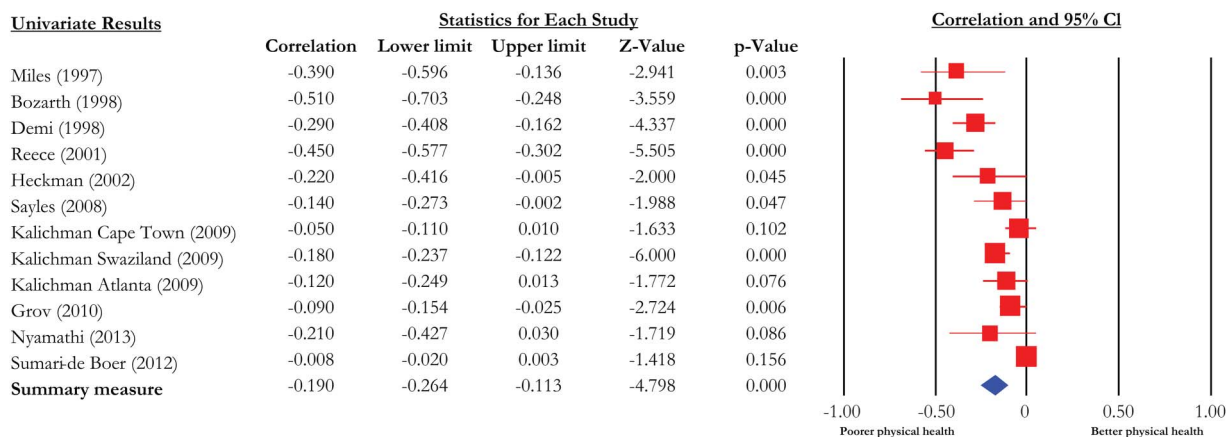
Univariate Results	Statistics for Each Study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Miles (1997)	-0.390	-0.596	-0.136	-2.941	0.003	
Bozarth (1998)	-0.510	-0.703	-0.248	-3.559	0.000	
Demi (1998)	-0.290	-0.408	-0.162	-4.337	0.000	
Reece (2001)	-0.450	-0.577	-0.302	-5.505	0.000	
Heckman (2002)	-0.220	-0.416	-0.005	-2.000	0.045	
Sayles (2008)	-0.140	-0.273	-0.002	-1.988	0.047	
Kalichman Cape Town (2009)	-0.050	-0.110	0.010	-1.633	0.102	
Kalichman Swaziland (2009)	-0.180	-0.237	-0.122	-6.000	0.000	
Kalichman Atlanta (2009)	-0.120	-0.249	0.013	-1.772	0.076	
Grov (2010)	-0.090	-0.154	-0.025	-2.724	0.006	
Nyamathi (2013)	-0.210	-0.427	0.030	-1.719	0.086	
Sumari-de Boer (2012)	-0.008	-0.020	0.003	-1.418	0.156	
Summary measure	**-0.190**	**-0.264**	**-0.113**	**-4.798**	**0.000**	

Figure 8 Stigma is associated with lower physical health (univariate results).

Univariate Results	Statistics for Each Study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Bozarth (1998)	-0.540	-0.723	-0.286	-3.821	0.000	
Berger (2001)	-0.540	-0.614	-0.457	-10.723	0.000	
Heckman (2002)	-0.110	-0.318	0.108	-0.988	0.323	
Prachakul (2007)	-0.490	-0.723	-0.158	-2.785	0.005	
Wright (2007)	-0.200	-0.425	0.048	-1.583	0.113	
Sayles (2008)	-0.430	-0.536	-0.310	-6.488	0.000	
Kalichman Cape Town (2009)	-0.320	-0.373	-0.265	-10.823	0.000	
Kalichman Swaziland (2009)	-0.080	-0.139	-0.021	-2.643	0.008	
Kalichman Atlanta (2009)	-0.260	-0.379	-0.132	-3.911	0.000	
Li (2009)	-0.190	-0.282	-0.095	-3.871	0.000	
Vyavaharkar (2012)	-0.220	-0.311	-0.125	-4.451	0.000	
Rao (2012)	-0.260	-0.420	-0.085	-2.878	0.004	
Clum (2009)	-0.367	-0.499	-0.218	-4.619	0.000	
Dowshen (2009)	-0.316	-0.566	-0.013	-2.043	0.041	
Newman (2012)	-0.170	-0.294	-0.040	-2.558	0.011	
Dilorio (2009)	-0.130	-0.253	-0.002	-1.996	0.046	
Summary Measure	**-0.282**	**-0.358**	**-0.202**	**-6.692**	**0.000**	

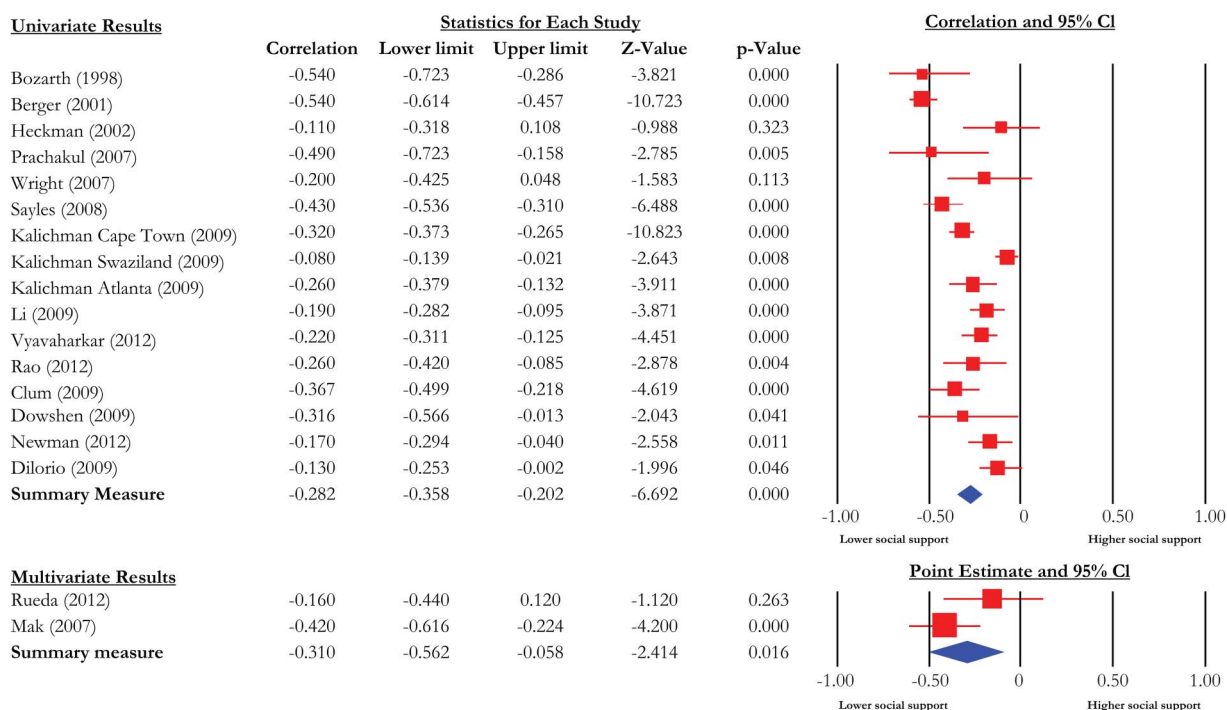| Multivariate Results						Point Estimate and 95% CI
Rueda (2012)	-0.160	-0.440	0.120	-1.120	0.263	
Mak (2007)	-0.420	-0.616	-0.224	-4.200	0.000	
Summary measure	**-0.310**	**-0.562**	**-0.058**	**-2.414**	**0.016**	

Figure 9 Stigma is associated with lower social support (univariate and multivariate results).

confounders found that people who experienced HIV-related stigma were 21% less likely to access or use health and social services. High heterogeneity was found in both univariate and multivariate analyses, respectively.

Risk behaviour

A statistically significant correlation between HIV-related stigma and unprotected sex was not found in univariate results (figure 12). There was no conclusive evidence of heterogeneity. One study that controlled for potential confounders did not find an association between HIV-related stigma and risk behaviour.

Publication bias

Publication bias was assessed for three meta-analyses with greater than 10 studies: depressive symptoms,

physical health and social support (see online supplementary file 3 for funnel plots).

Mental health—depressive symptoms

Both funnel plot and 'trim-and-fill' analysis suggested that publication bias existed, and that people who experienced HIV-related stigma were at higher risk of depression.

Physical health

Despite publication bias, the key finding remains unchanged: people who experience HIV-related stigma were at higher risk of poorer physical health. Fail-safe N indicated that the association between HIV-related stigma and physical health likely existed.
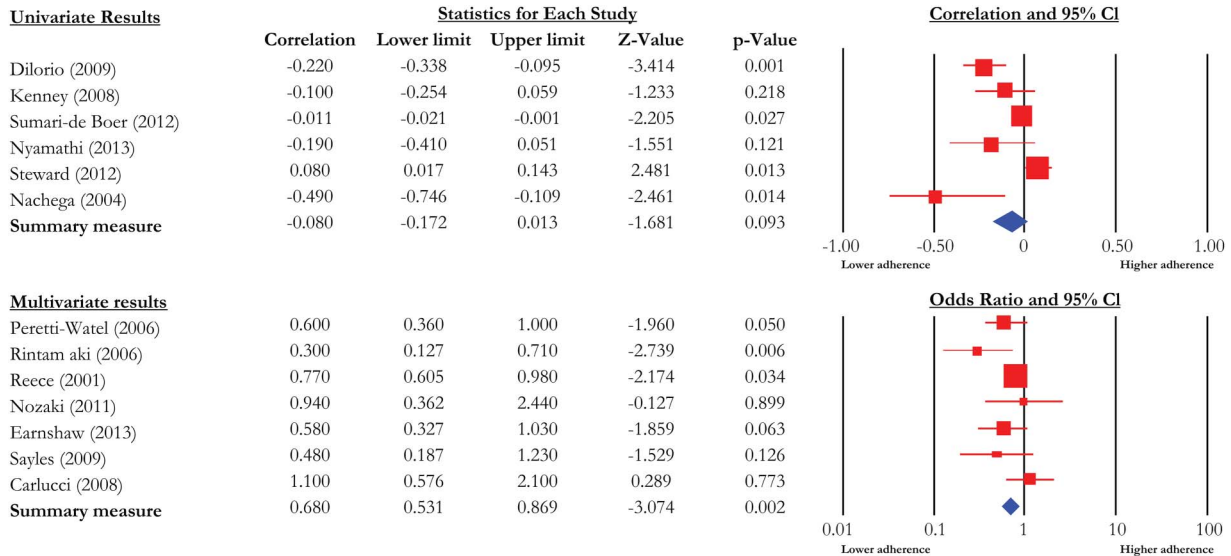
Univariate Results	Statistics for Each Study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Dilorio (2009)	-0.220	-0.338	-0.095	-3.414	0.001	
Kenney (2008)	-0.100	-0.254	0.059	-1.233	0.218	
Sumari-de Boer (2012)	-0.011	-0.021	-0.001	-2.205	0.027	
Nyamathi (2013)	-0.190	-0.410	0.051	-1.551	0.121	
Steward (2012)	0.080	0.017	0.143	2.481	0.013	
Nachega (2004)	-0.490	-0.746	-0.109	-2.461	0.014	
Summary measure	-0.080	-0.172	0.013	-1.681	0.093	

Multivariate results						Odds Ratio and 95% CI
Peretti-Watel (2006)	0.600	0.360	1.000	-1.960	0.050	
Rintam aki (2006)	0.300	0.127	0.710	-2.739	0.006	
Reece (2001)	0.770	0.605	0.980	-2.174	0.034	
Nozaki (2011)	0.940	0.362	2.440	-0.127	0.899	
Earnshaw (2013)	0.580	0.327	1.030	-1.859	0.063	
Sayles (2009)	0.480	0.187	1.230	-1.529	0.126	
Carlucci (2008)	1.100	0.576	2.100	0.289	0.773	
Summary measure	0.680	0.531	0.869	-3.074	0.002	

Figure 10 Stigma is associated with lower antiretroviral adherence (univariate and multivariate results).

Univariate Results	Statistics for Each Study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Heckman (2002)	-0.420	-0.583	-0.225	-4.004	0.000	
Nyamathi (2013)	0.130	-0.112	0.357	1.054	0.292	
Dietz (2010)	0.000	-0.003	0.003	0.000	1.000	
Steward (2012)	-0.090	-0.152	-0.027	-2.793	0.005	
Summary measure	-0.083	-0.199	0.035	-1.385	0.166	

Multivariate results						Odds Ratio and 95% CI
Wingood (2007)	0.400	0.191	0.836	-2.436	0.015	
Reece (2001)	0.780	0.615	0.989	-2.054	0.040	
Naar-King (2007)	0.970	0.733	1.284	-0.213	0.832	
Kinsler (2007)	0.350	0.130	0.941	-2.080	0.038	
Wohl (2011)	0.900	0.810	1.000	-1.960	0.050	
Sayles (2009)	0.230	0.100	0.529	-3.454	0.001	
Abaynew (2011)	0.320	0.113	0.906	-2.146	0.032	
Brennan (2007)	0.980	0.960	1.000	-1.940	0.052	
Traeger (2011)	0.740	0.453	1.208	-1.203	0.229	
Summary measure	0.792	0.675	0.930	2.845	0.004	

Figure 11 Stigma is associated with lower access and usage of health and social services (univariate and multivariate results).

Multivariate Results	Statistics for each study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Clum (2009)	0.006	-0.156	0.168	0.072	0.943	
Paz-Balley (2012)	0.128	0.023	0.232	2.375	0.018	
Summary Measure	0.084	-0.033	0.198	1.409	0.159	

Multivariate Results	Statistics for each study					Correlation and 95% CI
	Correlation	Lower limit	Upper limit	Z-Value	p-Value	
Hatzenbuehler (2011)	0.017	0.000	0.033	2.007	0.045	
	0.017	0.000	0.033	2.007	0.045	

Figure 12 Stigma is associated with higher risk behaviour (univariate and multivariate results).

Social support

Despite publication bias, the main message remained unchanged: people who experienced HIV-related stigma were at greater risk of lower social support. Moreover, the fail-safe N suggested that the observed association was robust.

DISCUSSION
Summary of main findings

This review examined the relationship between HIV-related stigma and a variety of health and intermediate health-related outcomes by conducting a series of meta-analyses and pooling data from 64 studies of people living with HIV published after the advent of combination antiretroviral therapy. One key finding of this review is that experiencing HIV-related stigma is associated with higher levels of depression and lower levels of social support. Cross-sectional associations between HIV-related stigma and both depression and social support are reasonably well established given the large number of published studies included in this review and the corresponding strength of these associations. These findings are in agreement with those reported by a previous meta-analysis on the relationship between stigma, health and demographic factors in people living with HIV in North America.[48] However, there are fewer studies examining the longitudinal associations between HIV-related stigma and depression or social support.

Some evidence suggests that various coping strategies have been shown to moderate the effect of HIV-related stigma on depression. For instance, disengagement coping (avoidant strategies including disengagement from the stressor, denial and/or wishful thinking) was found to moderate the relationship between stigma and depression,[68] whereas mastery (a psychological resource related to personal control and self-efficacy) was found to be associated with lower levels of depression.[69]

There was also some evidence examining how the association between HIV-related stigma and depression may intersect with other forms of stigmatisation, such as homophobia, racism and gender discrimination. One recent study examining the role of stigma on MSM not only reported a strong correlation between HIV-related stigma and MSM-stigma, but also found an association between HIV-related stigma, sexual-stigma and depression.[70] HIV-positive gay men reported considerable effects on mental health through increased levels of anxiety, depressive symptoms and avoidant-coping strategies. These men also experience higher levels of risk-taking behaviours[71 72] and decreased uptake of HIV prevention and testing programmes.[72] Among African, Caribbean and Black women in Canada, HIV-related stigma, depression, racism and gender discrimination were significantly correlated with each other, emphasising the importance of exploring the intersection of different types of stigmas.[73]

With respect to the relationship between HIV-related stigma and social support, previous research indicates that disclosure of one's HIV status to family, friends or healthcare professionals may be a stigmatising social process that can result in fear of rejection,[28] or isolation and exclusion by support networks.[7 48] Research examining social support as moderating the relationship between HIV-related stigma and depression,[6 74–76] points to the role of social support in buffering depression

among people living with HIV. However, the extent to which people who experience a high degree of anticipated stigma may be less likely to disclose their HIV status for fear of social exclusion is unknown.[7 48] Consequently, as questions surrounding the complex relationship between HIV-related stigma, depression and social support still remain, conducting longitudinal studies and exploring the role of potential moderating factors is warranted.

This review also found evidence suggesting the negative association between HIV-related stigma and intermediate health-related outcomes, including adherence to antiretroviral therapy, and access to and usage of health and social services. Although meta-analysis of univariate data for both adherence to antiretroviral therapy, and access to and usage of health and social services did not show a statistically significant correlation with HIV-related stigma, pooling data from studies that used multivariate models found significant associations. In support of our findings on the relationship between HIV-related stigma and adherence, a systematic review and meta-analyses specific to this topic similarly concluded that HIV-related stigma compromised the ability of people with HIV to adhere to antiretroviral therapy.[77] Specifically, this review found that HIV-related stigma may compromise adherence by undermining social support and adaptive coping.[77] Depression was also found to have a partial mediating effect on the negative association between HIV-related stigma and adherence.[47] Additionally, stigma diminishes adherence through psychosocial processes, as people living with HIV who experience enacted and anticipated stigma may adopt strategies to conceal their status, leading to delayed treatment initiation or treatment interruptions.[77 78] Despite a few studies that do not support the association between HIV-related stigma and access to and usage of health and social services,[79 80] other studies support the notion that perceived stigma of people living with HIV was associated with low access to care,[81] or delayed presentation in care,[82] possibly stemming from perceived discrimination by healthcare providers.[45 83]

Some evidence to support the negative association between HIV-related stigma and both anxiety and health-related quality of life was found, but more research in these areas is necessary. While meta-analyses of univariate data between HIV-related stigma and anxiety showed a significant correlation, no significant associations were found when results of multivariate studies were pooled. Similarly, pooling univariate data for health-related quality of life showed a significant correlation with HIV-related stigma, while pooling data from multivariate studies failed to show a significant association. These findings may be explained by the observation that univariate data may be more comparable across studies—relative to multivariate data, which includes different sets of covariates. In addition, the low number of both univariate and multivariate studies included in these analyses suggest that the evidence on the cross-sectional associations

between HIV-related stigma and both anxiety and quality of life are not well established, and highlights the need for more studies to elucidate these associations. It is important to note that one study with multivariate data that was excluded due to insufficient data required for meta-analysis found, however, that after adjusting for potential confounders, negative public attitudes toward HIV were associated with poorer quality of life and mental health problems.[84]

Multivariate data could not be pooled for the outcomes of physical health, emotional and mental distress and sexual risk behaviours. Pooled univariate findings limited the ability to draw more conclusive evidence between HIV-related stigma and these outcomes as these studies were not adjusted for potential confounders. Pooled univariate data for physical health was statistically significant, providing support for the negative association between HIV-related stigma and physical health. Of note, one study with multivariate data among HIV-positive women found that physical health variables (ie, viral load and CD4 counts) were not associated with HIV-related stigma.[85] However, this study was not included for meta-analysis as it lacked sufficient information required for meta-analysis. Meta-analysis of univariate data for the relationship between HIV-related stigma and both emotional and mental distress and sexual risk behaviours showed non-significant associations, possibly due to the limited number of studies published to date with complete meta-analysable data. The dearth of literature in these areas suggest the need for additional studies examining these association, particularly those that control for potential confounders such as substance use, sexual orientation and health status.

Findings from this meta-analysis and our recent review of the qualitative evidence[11] could be used to inform practitioners of the negative associations between HIV-related stigma and health-related outcomes, and they draw attention to the need to develop, test, implement and scale-up HIV stigma-reduction interventions. A recent systematic review of interventions to reduce the impact of HIV-related stigma found that while many individual-level and community-based interventions have been tested, only a handful of organisational interventions have been assessed for effectiveness.[86] While there has been an increase in socioecological strategies to reduce stigma over the last decade,[86] there still remains a need for complex structural, and intersectional approaches to address the synergistic effects of multiple stigmatised identities.[86–88] Finally, the few studies[68 69 74 75] available on moderating factors point to focusing on strategies that improve coping and strengthen social support networks among people living with HIV.

Strengths and limitations
The main strength of this systematic review and series of meta-analyses is that it examines a broad set of relationships between HIV-related stigma and health outcomes. It also performed a comprehensive search of the literature, used independent reviewers and a consensus approach to select and extract data from relevant papers, presented detailed information of included studies, performed a detailed quality appraisal of the included studies, used appropriate methods to combine the findings of studies and assessed the likelihood of publication bias where appropriate.

The most important limitation was the lack of a systematic evaluation of the mechanisms involved in the relationship between HIV-related stigma and health (mediation models), the role a variety of factors play in reducing the negative effects of HIV-related stigma on health (moderating models), and the intersection between HIV-related stigma and inter-related forms of social exclusion, as the stigma experienced by people living with HIV may be compounded by homophobia, racism, sexism and immigration status.[10] These topics prevented a more nuanced evaluation of the complexity of HIV-related stigma, but they were outside the scope of the present review. These factors, however, are critical to the development of interventions, and they warrant focused reviews on their own merit. Other limitations included a search limited to papers published until September 2013, and the small number of studies that were pooled in meta-analyses for outcomes such as overall quality of life, anxiety, emotional and mental distress, adherence to antiretroviral therapy, access to and usage of health and social services and risk behaviours. Publication bias was not assessed for these outcomes as they included <10 studies. In addition, substantial heterogeneity was observed for depression, anxiety, physical health, social support and access to and usage of health and social services. Moreover, a lack of sensitivity, or subgroup analyses, taking into account the income levels of the countries where the primary studies took place, or based on the quality of the studies, may distort the applicability of this review's findings across different settings and jurisdictions, but this was also beyond the scope of this review.

In addition, while quality assessments revealed overall good quality in the domains of 'exposure' and 'outcome' for the included studies, low quality in the 'comparability' domain among individual studies was observed. This suggests that some studies controlled for at least one potential confounder, while the majority only presented bivariate associations. Consequently, this may have obscured the association between HIV stigma and health outcomes in this review. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and performed the identification, screening, selection and evaluation of papers in duplicate, but as with any systematic review, we cannot guarantee that we did not miss any papers.

CONCLUSIONS
This systematic review and series of meta-analyses support the notion that HIV-related stigma has a

detrimental impact on a variety of health-related outcomes in people living with HIV. This body of work found significant associations between HIV-related stigma and depression, social support, adherence to antiretroviral therapy and access and usage of health and social services. Weaker relationships were observed between HIV-related stigma and anxiety, quality of life, physical health, emotional and mental distress and sexual risk practices. Few studies in these areas point to a greater need to conduct additional studies that explore HIV-related stigma as a predictor of health-related outcomes, and the potential moderating and mediating effects of other variables that may diminish these negative relationships. Future research should specifically focus on elucidating the mechanisms behind the detrimental relationship between HIV-related stigma and health outcomes to better inform multifaceted intersectoral interventions to reduce the impact of HIV-related stigma on the health and well-being of people living with HIV.

Author affiliations
[1]Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[2]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
[4]Institute for Work and Health, Toronto, Ontario, Canada
[5]The Ontario HIV Treatment Network, Toronto, Ontario, Canada
[6]School of Social Work, McMaster University, Hamilton, Ontario, Canada
[7]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[8]McMaster Health Forum, McMaster University, Hamilton, Ontario, Canada
[9]Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, Ontario, Canada
[10]Centre for Research on Inner City Health, Keenan Research Center, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

Contributors SR originated the project; designed and oversaw screening, data extraction, quality appraisal and synthesis, and was the principal writer. SM contributed substantially to data synthesis, interpretation of findings and writing the article. DG, JG, LC and SM contributed to screening, data synthesis and interpretation of the results. SC, QS and CL contributed to statistical analyses and interpretations of findings. MW and SBR contributed to the design of the study and provided critical revisions to the article for important intellectual content. All authors conceptualised ideas, interpreted findings, reviewed drafts of the article, and approved the final version.

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