Review Article

Jason Globerman*, Sanjana Mitra, David Gogolishvili, Sergio Rueda, Laura Schoffel, Kira Gangbar, Qiyun Shi, Sean B. Rourke

HIV/STI prevention interventions: A systematic review and meta-analysis

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Abstract: Behavioral interventions can prevent the transmission of HIV and sexually transmitted infections. This systematic review and meta-analysis assesses the effectiveness and quality of available evidence of HIV prevention interventions for people living with HIV in high-income settings. Searches were conducted in MEDLINE, EMBASE, PsycINFO, and CDC Compendium of Effective Interventions. Interventions published between January, 1998 and September, 2015 were included. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Forty-six articles and 63 datasets involving 14,096 individuals met inclusion criteria. Included articles were grouped by intervention type, comparison group and outcome. Few of these had high or moderate quality of evidence and statistically significant effects. One intervention type, group-level health education interventions, were effective in reducing HIV/STI incidence when compared to attention controls. A second intervention type, comprehensive risk counseling and services, was effective in reducing sexual risk behaviors when compared to both active and attention controls. All other intervention types showed no statistically significant effect or had low or very low quality of evidence. Given that the majority of interventions produced low or very low quality of evidence, researchers should commit to rigorous evaluation and high quality reporting of HIV intervention studies.

***Corresponding author: Jason Globerman,** Ontario HIV Treatment Network (OHTN), Toronto, Canada, E-mail: jmgloberman@gmail.com
Sanjana Mitra, David Gogolishvili, Laura Schoffel, Kira Gangbar, Qiyun Shi, Ontario HIV Treatment Network (OHTN), Toronto, Canada
Sergio Rueda, Centre for Addiction and Mental Health (CAMH), Toronto, Canada
Sean B. Rourke, Department of Psychiatry, University of Toronto; Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

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1 Introduction

HIV is a serious health issue in North America. In the United States alone, over 1.2 million people are living with HIV, many of whom are unaware of their infection [1]. While the estimated incidence of HIV in the United States and Canada has remained stable in recent years [1,2], among people living with HIV, there has been a marked increase in the diagnosis of other sexually transmitted infections (STIs), particularly syphilis and gonorrhea [3].

Studies have demonstrated that many people living with HIV do not consistently practice safer sex, placing themselves and others at risk for HIV or STI infection/co-infection [4]. For instance, the prevalence of unprotected anal intercourse (UAI) among HIV-positive men who have sex with men (MSM) with either an unknown HIV-status or HIV-negative partner was 26% (95% CI 21-30%) [5]. Prevalence of UAI was even higher with HIV-positive partners (30%; 95% CI 25–36%) [5].

While most HIV prevention programs target HIV-negative individuals, targeting sexual risk behaviors in HIV-positive people can prevent the transmission of HIV and other STIs to uninfected individuals. For people living with HIV, these interventions can also prevent co-infections with other STIs and the acquisition of other strains of HIV.

The US Centers for Disease Control and Prevention (CDC) maintains an up-to-date Compendium of Evidence Based Interventions and Best Practices for HIV Prevention. The Compendium identifies "evidence-based behavioral interventions proven to reduce HIV risk" [6], however, it does not quantitatively synthesize data across studies or assess the quality of available evidence [6]. Unlike previously conducted systematic reviews and meta-analyses [4,7,8], the present review stands out in three ways: (1) the use of the CDC classifications of behaviroal

HIV interventions; (2) the use of GRADE to summarize the quality of available evidence; and (3) the assessment of outcome measures beyond sexual risk behaviors.

This review aims to assess the effectiveness of behavioral HIV/STI prevention interventions among people living with HIV in high-income settings through quantitative synthesis (meta-analysis) of data from experimental studies (randomized controlled trials and non-randomized trials). It also aims to assess the quality of available evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [9,10]. Only studies conducted in high income countries, as defined by the World Bank [11], were included. Identifying evidence-based HIV prevention interventions from high income settings may help guide decision-makers, including government policymakers, on where best to allocate funding and other resources for program development.

2 Methods

2.1 Protocol and registration

This study has been designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) tool [12]. Analytic methods and inclusion criteria were specified and documented in advance and are available in the systematic review protocol (Supplementary material - file 1).

2.2 Eligibility criteria

Included studies addressed interventions to prevent HIV and/or STIs in people living with HIV. Only randomized-controlled trials (RCTs) and non-randomized trials (quasi-experimental studies) were analyzed. Studies were grouped by intervention category, comparison group, and outcome. Effectiveness was assessed by a series of meta-analyses. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [9,13,14]. Only studies conducted in high-income countries, as defined by the World Bank, were included [11]. The following STIs (in addition to HIV) were included in this review: syphilis, chlamydia, gonorrhea, trichomoniasis, genital or anal warts, genital herpes, lymphogranuloma venereum (LGV), and hepatitis B and C. Studies addressing biomedical interventions (e.g., pre-exposure prophylaxis, microbicides, and vaccination/immunization) were excluded.

A prevention intervention was defined as a "specific activity (or set of related activities) intended to change the knowledge, attitudes, beliefs, behavior, or practices of individuals and populations, to reduce their health risk. An intervention has a distinct process, outcome objectives, and a protocol outlining the steps for implementation" [15,16].

The US CDC categorization of behavioral interventions was used to classify interventions [15-18]. (Supplementary material - file 2). To our knowledge, this classification system is the most comprehensive method of categorizing studies by intervention type.

Comparison groups in all identified studies were categorized as 'attention' controls (comparing the effectiveness of the intervention with no intervention or with general health information) or 'active' controls (comparing the effectiveness of the intervention with another HIV/STI prevention intervention). These two groups were analyzed separately since it is more difficult to detect a statistically significant difference between groups when an intervention is compared to an active control versus an attention control.

Data from included studies were classified into the following outcomes to evaluate their effectiveness (in order of importance): i) change in HIV/STI incidence; ii) change in self-reported or observed risk behavior; iii) change in knowledge, attitudes and beliefs regarding the HIV/STI prevention.

In cases where a study reported multiple measures of the same outcome, only one measure was selected. For example, specific to changes in self-reported or observed risk behavior, the hierarchy used was as follows: unprotected anal intercourse, unprotected vaginal intercourse, unprotected oral intercourse, condom use, multiple partners, and frequency of sexual encounters [19].

This review includes peer-reviewed articles published in English between January 1, 1998 and September 30, 2015.

2.3 Information sources

Databases consulted included: the Cochrane Database of Systematic Reviews, MEDLINE (1996-present); MEDLINE In-Process & Other Non-Indexed Citations, PsycINFO (1806-present); and EMBASE (1980-present). The US CDC's Compendium of Evidence Based HIV Behavioral Interventions [6] and Effective Interventions [20] were also searched.

Electronic search strategies were developed in consultation with a reference librarian at Robarts Library,

University of Toronto. Reference lists of identified systematic reviews and meta-analyses were further searched to locate additional papers.

2.4 Search

The following terms, in various combinations, were searched: prevent*, HIV, sexually transmitted diseases, hepatitis B, hepatitis C, syphilis, gonorrhea, chlamydia, papillomavirus, wart*, condyloma*, genital herpes, trichomon*, lymphogranuloma, LGV (Supplementary material - file 3). Searches were not limited by study designs, publication types, populations, intervention categories, comparison groups or outcome measures.

2.5 Study selection

Titles and abstracts of all references were screened by two independent reviewers using Distiller SR [21]. Inclusion was based on study type, population, intervention, disease, outcome measure, study jurisdiction, publication year and publication language. Full-text versions of all references identified as "include" or "unclear" were retrieved and additional inclusion assessments of those identified as "unclear" completed. Disagreements between reviewers were resolved by consensus.

2.6 Data collection process

The data extraction form was designed and pilot tested using ten randomly selected studies. Data were extracted by one reviewer and checked independently for accuracy by a second reviewer. Discrepancies were resolved through discussion with a third reviewer. Data were processed using DistillerSR [21]. When data were missing or unclear, the authors of the original papers were contacted to obtain further details.

2.7 Data items

The following information was extracted from each included study: study design, objectives, country/city, sample sizes (intervention and control groups), intervention category (Supplementary material - file 2), duration of intervention, comparison group (active vs. attention control), length of follow-up, and outcome measure(s) with corresponding effect sizes.

Ethical approval: The conducted research is not related to either human or animals use.

2.8 Risk of bias in individual studies

Risk of bias assessments were completed for all individual studies using the Cochrane risk of bias tool [22,23]. A judgment of high, low or unclear was assigned for each of the seven criteria for every included study. Non-randomized trials automatically scored "high risk of bias" in at least one domain ("random sequence generation").

2.9 Summary measures

Effectiveness of interventions was evaluated based on results of meta-analyses conducted for each combination of intervention, comparison group and outcome. Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA) version 2 [24]. Odds ratios were used when the outcome was HIV/STI incidence, and standardized mean differences (SMD) were used when the outcomes were risk behavior and/or knowledge, attitudes, and beliefs.

2.10 Synthesis of results

For HIV/STI incidence, most included studies reported their results in the form of event rates. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated for this outcome. We judged that reduction of 25% or more in odds of acquiring HIV infection was an appreciable benefit, and an OR ≤ 0.75 was considered as effective. This is in line with the GRADE handbook suggestion that default threshold for appreciable benefit is relative risk reduction of 25% or more [9]. For the other two outcomes, included studies reported results in ORs, Chi-squared statistics or means/standard deviations. CMA was used to convert different statistics into SMDs. Random effect models were used to calculate pooled SMDs and 95% CIs for these outcomes. Following widely used standards, SMDs of 0.20 were interpreted as small effect sizes, those above 0.50 as medium effect sizes, and those above 0.80 as large effect sizes [25]. The I^2 index was used to assess the heterogeneity between studies.

2.11 Risk of bias across studies

Random effect models were selected for meta-analyses under the assumption that true effect sizes varied from study to study, and because definitions and measurement scales for outcome variables were different across studies. Publication bias was examined using funnel plots.

2.12 Assessment of quality of available evidence

Quality of available evidence for each intervention category was assessed using the GRADE tool [9,13,14]. Quality of evidence in this context refers to the extent to which one can be confident that an estimate of effect is correct. GRADE's approach to rating the quality of evidence begins with the study design and then addresses five reasons to 'downgrade' the quality of evidence (risk of bias, imprecision, inconsistency, indirectness, and publication bias) followed by three reasons to 'upgrade' the quality of evidence (large effect, dose response, plausible residual confounding) [9,14].

For HIV/STI incidence, summary of findings tables included the number of studies and number of participants, length of follow-up, confidence in effect estimates (quality of evidence) and the best estimates of relative and absolute effect. ORs were used as the measure of relative effect applied to the control group to generate absolute risk [26]. For continuous outcomes (risk behavior and knowledge, attitude and beliefs) pooled results were presented as SMDs [27]. As a final step on *GRADEproGDT*, quality of evidence was rated as high, moderate, low or very low for all intervention, comparison group and outcome combinations [9,10,14].

3 Results

3.1 Study selection

Figure 1 illustrates study inclusion and exclusion processes. After database searches, duplicate removal, and the review of other sources and reference checks were complete, 25,865 titles and abstracts were reviewed. Initial screening resulted in 544 full text articles being further assessed for eligibility. Of these, 46 studies met inclusion criteria. Some studies contributed more than one data set, resulting in a total of 63 (k=63) datasets for meta-analyses. Datasets were grouped by intervention, comparison group and outcomes resulting in 17 groups (Supplementary material - file 4).

3.2 Study characteristics

Of the 46 studies included in the meta-analysis, 40 were randomized controlled trials [28-67], while the remaining six were non-randomized trials [68-73]. All included studies were conducted in the United States.

The total sample size of included studies was 14,096 (range 25 to 2,135). In addition to being HIV-positive, study participants belonged to a variety of other groups. Twenty-four percent (n=11) of studies were conducted among men who have sex with men (MSM), 17% (n=8) among ethnocultural minorities, and 15% (n=7) among people who use drugs. There were four studies among women, four among older adults, three studies among youth, three among individuals with childhood sexual abuse histories, and two studies among individuals who were unstably housed. One study included prisoners, one study focused on rural populations. Eight studies included general HIV-positive populations with no other characteristics specified.

Intervention follow-ups ranged from two to 25 months. Five studies collected outcome measures on the change in HIV/STI incidence rates, 45 studies collected data on changes in sexual risk behavior, while five studies collected data on changes in HIV knowledge, attitudes, and beliefs. Intervention categories included: individual-level health education; group-level health education; counseling testing and referral services; and comprehensive risk counseling and services. There were two additional categories: combined individual- and group-level interventions, and interventions not classified elsewhere (housing assistance, and spiritual therapy).

3.3 Results of individual studies

Descriptive characteristics of included studies and interventions are presented in Table 1.

3.4 Synthesis of results

Results of pooled effect sizes and quality of evidence of HIV/STI prevention interventions for people living with HIV have been summarized in Table 2.

Few intervention, comparison group and outcome combinations had high or moderate quality of evidence and statistically significant summary effects (Supplementary material - file 5).

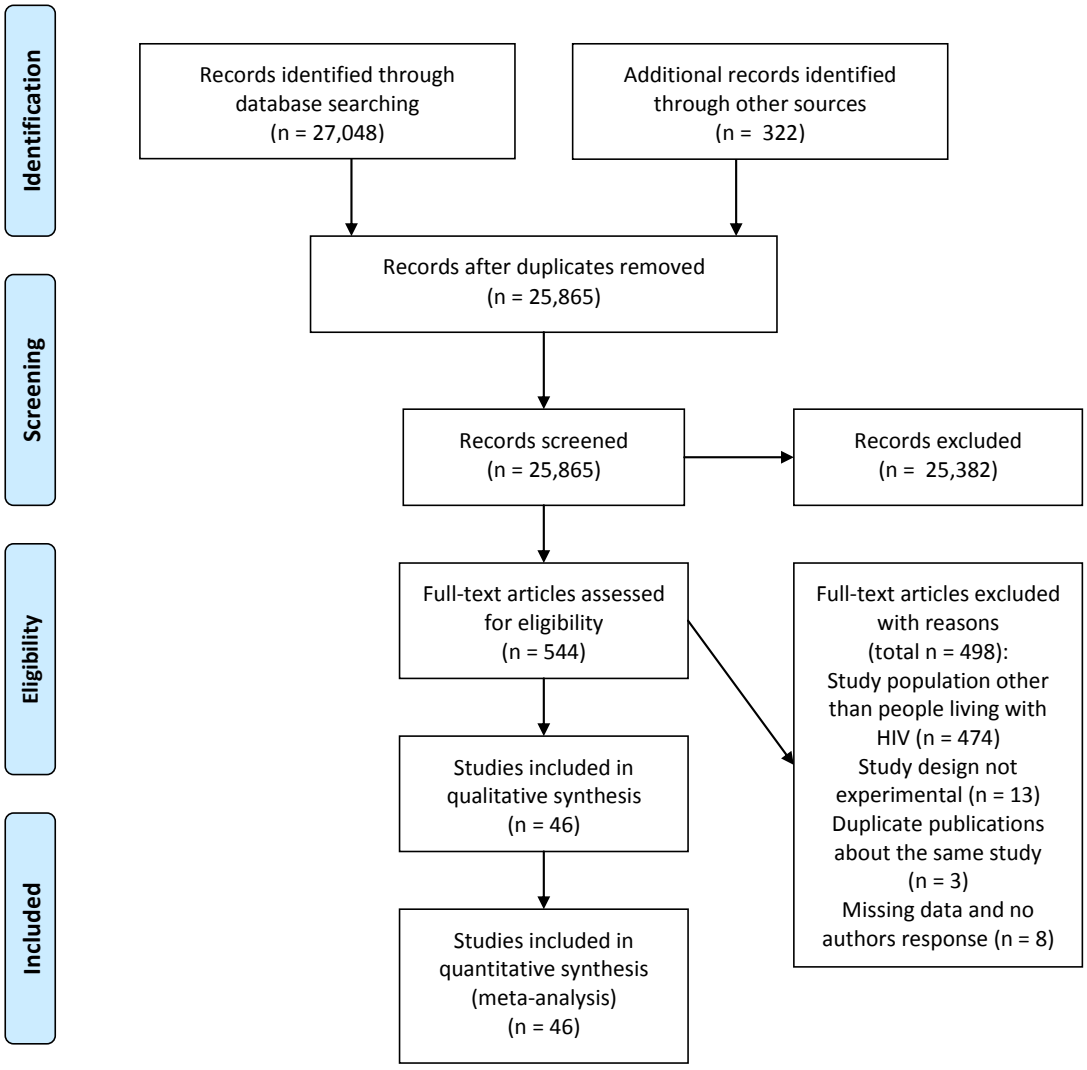

Figure 1: Flow chart of study selection process

3.5 High and Moderate Quality of Evidence and Statistically Significant Summary Effects

Quality of evidence was high and summary effect was statistically significant although minimal (k=7; SMD=-0.15, 95%CI=-0.25, -0.05; p=0.003; I^2=0) for comprehensive risk counseling in reducing sexual risk behavior when compared to active control. Moderate quality of evidence and statistically significant summary effects (k=14; SMD: -0.35, 95%CI=-0.49, -0.20; p=0.000; I^2=72) were observed for comprehensive risk counseling in reducing sexual risk behavior when compared to attention controls. Similar results (k=2; OR: 0.26, 95%CI=0.12, 0.56; p=0.001) were found for group level health education interventions aimed at reducing HIV incidence when compared to attention controls (Supplementary material - file 5).

3.6 Moderate Quality of Evidence and Statistically Non-Significant Summary Effects

Moderate quality of evidence and statistically non-significant summary effects were observed for two interventions: individual level health education and housing assistance. Both interventions were found to reduce sexual risk behavior when compared to attention controls (k=5; SMD: -0.08, 95%CI=-0.17, 0.004; p=0.063; I^2=0; and k=1; SMD: -0.17, 95%CI=-0.42, 0.09; p=0.208 respectively). Similar results (k=8; SMD: -0.09, 95%CI=-0.20, 0.02; p=0.114; I^2=0) were observed for group level health education interventions aimed at reducing sexual risk behavior when compared to active control (Supplementary material - file 5).

Table 1: Descriptive characteristics of 46 behavioural interventions for people living with HIV

Experimental studies of individual-level interventions among people living with HIV/AIDS					
Reference, date; location	**Study design, comparison group**	**Sample characteristics (sample size at follow-up)**	**Description of intervention**	**Follow-up**	**Outcome measure**
Sikkema et al., 2014; [41] New York, NY	RCT, active control	Newly-diagnosed MSM (n=80)	Individual, brief sexual risk reduction through enhanced decision-making and disclosure skills Duration: 3 sessions, 60 minutes each	9 months	Sexual risk behaviour: Decreased counts of UAI with serodiscordant partners
Klein et al., 2013; [33] Six sites (USA)	RCT, active control	African-American women (n=168)	Multimedia adaptation of WiLLOW, an educational and skills building intervention aimed at enhancing risk behaviour and psychosocial mediators Duration: 2 sessions, 60 minutes each	3 months	Sexual risk behaviour: Decreased unprotected vaginal/anal sex in the past 30 days *
Safren et al., 2013; [39] Boston, MA	RCT, attention control	MSM (n=201)	Proactive case management for psychosocial problems, counseling, and sexual risk reduction provided by a medical social worker Duration: 5 sessions, 50-90 minutes each	12 months	Sexual risk behaviour: Decreased chance of engaging in risk behaviour
Lovejoy et al., 2011; [34] New York, NY; Atlanta, GA; Philadelphia, PA; Cincinnati, OH; Columbus, OH	RCT, attention control	Older adults (n=62)	Telephone-delivered motivational interviewing intervention aimed at reducing risky sexual behaviour Duration: 4 session, 50 minutes each	6 months	Sexual risk behaviour: Increased number of unprotected sex acts
McKirnan et al., 2010; [36] Chicago, IL	RCT, attention control	MSM (n=251)	Primary-care based, individual counseling led by HIV-positive MSM peer advocates aimed at reducing unprotected sex Duration: 4 sessions	12 months	Sexual risk behaviour: Greater decline in risk
Richardson et al., 2004; [37] California, USA	RCT, attention control	People living with HIV (n=572)	Brief, safer-sex counseling by medical providers. Participants were randomized to either "gain-framed messages" arm or "loss-framed messages" arm Duration: 3-5 minutes at every visit	7 months	Sexual risk behaviour: Decreased unprotected intercourse for participants with ≥2 partners at baseline in "loss-framed message" arm *
Experimental studies of group-level interventions among people living with HIV/AIDS					
Reference, date; location	**Study design, comparison group**	**Sample characteristics (sample size at follow-up)**	**Description of intervention**	**Follow-up**	**Outcome measure**
Lovejoy et al, 2015; [63] New York, NY; Cincinnati, OH; Columbus, OH	RCT, attention control	Older adults (n=295)	Coping improvement arm: intervention aimed to reduce depression Interpersonal support arm: similar to coping improvement arm, but conducted separately for men who have sex with men, heterosexual men, and women, and addressed sexual safety for HIV-infected adults Duration: 12 sessions, 90 minutes each	12 months	Sexual risk behaviour: Decreased unprotected sex with HIV-negative or unknown serostatus partners in both intervention arms.

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Marhefka et al., 2014; [35] Four counties in Florida (USA)	RCT, attention control	Women (n=59)	Internet-based group videoconferencing adaptation of intervention designed to promote safer sexual behaviour through discussions, videos, and role playing Duration: 6 sessions, 2 hours each	6 months	Sexual risk behaviour: Fewer unprotected sex occasions *
Jones et al., 2013; [31] Miami, FL	RCT, active control	Multicultural serodiscordant and discordant couples (n=432)	Gender-matched intervention aimed at enhancing sexual risk reduction and conflict resolution Duration: 4 weekly, 2-hour sessions	12 months	Knowledge, attitude, and beliefs: Increased male condom acceptability *
Kalichman et al., 2011; [32] Atlanta, GA	RCT, attention control	African-American people (n=436)	Theory-based intervention focused on medication adherence and reduced sexual transmission risk behaviour Duration: Not reported	9 months	Incidence of HIV/STI: Fewer new STIs * Sexual risk behaviour: Reduced unprotected anal intercourse
Teti et al., 2010; [42] Philadelphia, PA	RCT, attention control	African-American women (n=55)	Intervention addressing sexual risk reduction education and skill-building, women's challenges and opportunities, and HIV status disclosure Duration: 5 weekly, 90 minute sessions	18 months	Sexual risk behaviour: Increased sexual acts with condom
Cosio et al., 2010; [29] Northeast states, South states, Midwest states, and West states (USA)	RCT, active control	Rural persons (n=79)	Motivational interviewing and skills-building intervention Duration: 2 sessions	2 months	Knowledge, attitudes, and behaviour: Increased risk behaviour information Sexual risk behaviour: Increased incidence of condom use when having vaginal/anal intercourse
Illa et al., 2010; [30] Miami, FL	RCT, active control	Older adults (n=241)	Behavioural intervention guided by information-motivation-behaviour skills model and self-efficacy theory aimed at reducing sexual risk behaviours Duration: 4 sessions, 60-90 minutes each	6 months	Sexual risk behaviour: Decreased unprotected anal intercourse
Rosser et al., 2010; [38] Seattle, WA; Washington, D.C.; Boston, MA; New York, NY; Los Angeles, CA; Houston, TX	RCT, active control	MSM (n=527)	Man2Man (M2M): Seminar to address sexual health and HIV risk concerns through the use of multimedia, behavioural modeling, and small group discussions Duration: 2 consecutive days, 14-15 hours Positive Sexual Health (PoSH): designed after M2M, but addresses HIV risk from an HIV+ MSM's perspective Duration: 2 consecutive days, 14-15 hours	18 months	Sexual risk behaviour: No difference in serodiscordant unprotected anal intercourse in either arm
Coleman et al., 2009; [28] USA	RCT, attention control	Older African-American MSM (n=60)	HIV risk reduction intervention aimed at increasing condom use Duration: 4 sessions, 2 hours each	3 months	Sexual risk behaviour: Increased likelihood to report condom use
Sikkema et al., 2008; [40] New York, NY	RCT, active control	Men and women with childhood sexual abuse histories (n=247)	Therapeutic support group based on cognitive theory of stress and coping, and cognitive-behavioural treatment strategies for sexual trauma Duration: 15 weekly, 90-minute sessions	16 months	Sexual risk behaviour: Decreased counts of unprotected vaginal and anal intercourse

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Williams et al, 2008; [64] Los Angeles, CA	RCT, attention control	African-American and Latino men with histories of childhood sexual abuse (n=137)	Cognitive-behavioural intervention adapted from the evidence-based Women's Enhanced Sexual Health Intervention [62], aimed to reduce risk through cultural- and gender-specific concepts. Duration: 6 weekly, 2-hour sessions	6 months	Sexual risk behaviour: Decreased unprotected anal intercourse
Wolitski et al., 2005; [55] New York, NY; San Francisco, CA	RCT, active control	Gay and bisexual men (n=621)	Peer-led behavioural intervention addressing issues such as sexual and romantic relationships, HIV and STI transmission, drug use, and mental health Duration: 6 weekly, 3-hour sessions	6 months	Incidence of HIV/STI: No difference Sexual risk behaviour: No difference
Wingood et al., 2004; [54] Birmingham, AL; Anniston, AL; Atlanta, GA	RCT, attention control	Women (n=366)	Risk reduction intervention based on social cognitive theory and theory of gender and power, emphasizing on increasing knowledge, attitudes, self-efficacy, and skills regarding safer sex Duration: 4 sessions, 4 hours each	12 months	Incidence of HIV/STI: Decreased incidence of gonorrhea and chlamydia * Sexual risk behaviour: Decreased frequency of unprotected anal sex
Margolin et al., 2003; [48] New Haven, CT	RCT, active control	People who inject drugs (n=63)	Comprehensive manual-guided risk reduction and health promotion intervention aimed at promoting hard reduction skills and HIV risk reduction Duration: 6 sessions, 2 hours each	9 months	Sexual risk behaviour: Decreased likelihood of reporting engagement in unprotected sex
Grinstead et al., 2001; [68] California, USA	non-randomized controlled trial, attention control	Prisoners (n=81)	Pre-release peer-led intervention aimed at decreasing HIV risk behaviour and increasing utilization of community services Duration: 8 days over 2 weeks, 2-2.5 hours each	Average of 8 months	Sexual risk behaviour: Increased likelihood of condom use
Kalichman et al., 2001; [46] Atlanta, GA	RCT, active control	People living with HIV (n=256)	Theory-based behavioural intervention led by community-based facilitators Duration: 5 sessions, 2 hours each	6.5 months	Sexual risk behaviour: Decreased unprotected vaginal or anal intercourse *
Lewis et al., 2000; [70] Atlanta, GA	non-randomized controlled trial, attention control	Homeless persons (n=59)	Comprehensive HIV education, housing support, and 12-step recovery program in a day treatment program Duration: 3 months	3 months	Knowledge, attitudes, and behaviours: Higher score on HIV knowledge test * Sexual risk behaviour: Increased condom use *

Experimental studies of counseling, testing and referral services among people living with HIV/AIDS

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Sikkema et al., 2011; [52] New York, NY	RCT, attention control	MSM (n=50)	Brief risk reduction intervention with sexual health information and disclosure decision making components Duration: 3 sessions	6 months	Sexual risk behaviour: Decreased unprotected anal intercourse
Metsch et al., 2008; [49] Atlanta, GA; Baltimore, MD; Los Angeles, CA; Miami, FL	RCT, attention control	People recently diagnosed with HIV (n=254)	Brief case management intervention aimed at linking HIV-infected persons to HIV primary care Duration: 5 sessions, 3 months	12 months	Sexual risk behaviour: Decreased unprotected vaginal or anal sex

Experimental studies of comprehensive risk counseling and services among people living with HIV/AIDS					
Reference, date; location	**Study design, comparison group**	**Sample characteristics (sample size at follow-up)**	**Description of intervention**	**Follow-up**	**Outcome measure**
Kurth et al., 2014; [47] Seattle, WA	RCT, attention control	People living with HIV (n=238)	Computerized counselling with audio-narrated assessment, tailored feedback, skill-building videos, health plan and printouts Duration: 4 sessions at 3-month intervals over 9 months	9 months	Sexual risk behaviour: Reduced odds of sexual transmission risk (unprotected sex or condom use errors) *
Schwarcz et al., 2013; [72] San Francisco, CA	non-randomized controlled trial, active control	MSM (n=374)	Adapted version of personalized cognitive counselling (PCC) for HIV-infected MSM Duration: 2 sessions with 6 months interval	12 months	Incidence of HIV/STI: Decreased incidence of gonorrhea, decreased incidence of chlamydia Sexual risk behaviour: Decreased episodes of unprotected anal intercourse with non-primary partner
Golin et al, 2012; [65] Three clinics in North Carolina	RCT, attention control	People living with HIV (n=490)	Multicomponent motivational-interviewing-based safer sex program Duration: 4 monthly sessions, 40-60 minutes each	12 months	Sexual risk behaviour: Decreased unprotected vaginal or anal sex with people of HIV-negative or unknown serostatus
Lovejoy et al., 2011; [34] New York, NY; Atlanta, GA; Philadelphia, PA; Cincinnati, OH; Columbus, OH	RCT, attention control	Older adults (n=62)	Telephone-delivered motivational interviewing intervention aimed at reducing risky sexual behaviour Duration: 4 sessions, 45-50 minutes	6 months	Sexual risk behaviour: Decreased unprotected sex *
El-Bassel et al., 2010; [43] Atlanta, GA; Los Angeles, CA; New York, NY; Philadelphia, PA	RCT, attention control	African-American serodiscordant couples (n=535)	Behavioural intervention incorporating components of social cognitive theory, cultural beliefs and traditional African concepts Duration: 8 weekly, 2-hour sessions	12 months	Incidence of HIV/STI: STD incidence did not differ Sexual risk reduction: Decreased unprotected sex
Myers et al., 2010; [50] Chapel Hill, NC; Boston, MA; Baltimore, MD; New York, NY; Seattle, WA; Sacramento, CA; San Diego, CA; Birmingham, AL; Philadelphia, PA; Decatur, GA; Miami, FL; Chicago, IL; Tucson, AZ	RCT, active control	People living with HIV (n=2,135)	Behavioural intervention based on Transtheoretical Model, motivational interviewing, and/or harm reduction, delivered by a medical care provider, specialist, or both Duration: Between 1-9 sessions, over 12 months	12 months	Sexual risk reduction: Decreased transmission risk behaviour in Medical provider-delivered arm; Decreased sexual risk in Specialist-delivered arm; Decreased sexual risk in multi-provider arm
Petry et al., 2010; [51] Hartford, CT	RCT, attention control	People who use drugs (n=170)	Contingency management intervention addressing both health and substance use behaviours Duration: 24 weeks	12 months	Sexual risk behaviour: Increased condom use *
Rose et al, 2010; [66] Northern California	RCT, attention control	People living with HIV (n=386)	Medical care provider-delivered intervention with prevention messages tailored to the patient's transmission risk behaviour Duration: 2 sessions, 2 hours each, plus booster session at 4 weeks	6 months	Sexual risk behaviour: Increased any unprotected vaginal or anal sex with person of HIV-negative or unknown status

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Velasquez et al., 2009; [53] USA	RCT, active control	MSM with alcohol use disorders (n=216)	Transtheoretical model- and motivational interviewing-based intervention aimed at reducing HIV transmission through alcohol use and risk behaviour reduction Duration: 4 individual, 4 group sessions	12 months	Sexual risk behaviour: Reduced number of days of unprotected sex *
Gilbert et al., 2008; [44] San Francisco, CA	RCT. attention control	People who use drugs (n=284)	Risk-reduction counselling delivered through a "video doctor" based on principles of motivational interviewing Duration: 2 sessions, 3 months	6 months	Sexual risk behaviour: Decreased reported unprotected sex *
Healthy Living Project Team, 2007; [45] Los Angeles, CA; Milwaukee, WI; New York, NY; San Francisco, CA	RCT, attention control	People living with HIV (n=936)	Individually delivered cognitive behavioural intervention Duration: 15 sessions, 90 minutes each	25 months	Sexual risk behaviour: Decreased transmission risk acts *
Mausbach et al., 2007; [67] San Diego, CA	RCT, attention control	MSM with methamphetamine use (n=182)	Social cognitive theory-based intervention aimed to increase safe sex behaviours in the context of methamphetamine use Duration: 5 weekly session, plus 3 monthly booster sessions, 90 minutes each	12 months	Sexual risk behaviour: Decreased unprotected sex
Purcell et al., 2007; [59] Baltimore, MD; Miami, FL; New York, NY; San Francisco, CA	RCT, active control	People who inject drugs (n=821)	Peer mentoring intervention Duration: 7 group sessions, 2 individual session, 1 peer volunteer activity, over 5 weeks	12 months	Sexual risk behaviour: Decreased sexual transmission risk behaviours
Naar-King et al., 2006; [58] USA	RCT, attention control	Youth (n=51)	Individual motivational intervention targeting multiple health risk behaviours and health outcomes Duration: 4 sessions, 60 minutes each, over 10 weeks	3 months	Sexual risk behaviour: Decreased number of unprotected intercourse acts
Rotheram-Borus et al., 2004; [60] Los Angeles, CA; San Francisco, CA; New York, NY	RCT, attention control	Drug-using young people (n=175)	Phone intervention: Individualized, aimed at improving physical health, sexual and substance use acts, and mental health In-person intervention: Individualized, aimed at improving physical health, sexual and substance use acts, and mental health Duration: 18 sessions, 2 hours each	15 months	Sexual risk behaviour: Both arms increased number of protected sexual acts *
Wyatt et al, 2004; [62] Los Angeles, CA	RCT, attention control	Ethnically diverse women with childhood sexual abuse histories (n=147)	Cognitive behavioural therapy encouraging risk reduction behaviour by exploring the impact of childhood sexual abuse Duration: 11 weekly, 2.5-hour sessions	3 months	Sexual risk behaviour: Increased safe sex behaviour *
Sorensen et al., 2003; [61] San Francisco, CA	RCT, active control	People who use drugs (n=151)	Case management program including elements of service brokerage and counseling delivered by a former consumer of HIV or substance abuse treatment services Duration: 12 months	18 months	Sexual risk behaviour: Decreased sexual risk behaviour index

Rotheram-Borus et al., 2001 [73] Los Angeles, LA; New York, NY; San Francisco, CA; Miami, FL	non-randomized controlled trial, attention control	Youth (n=110)	Two-module intervention focused on coping with one's serostatus, healthy routines, disclosure, and substance use and unprotected sexual acts reduction Duration: 23 sessions, 2 hours each, over 12 months	3 months	Sexual risk behaviour: Decreased unprotected sex acts

Experimental studies of other interventions among people living with HIV/AIDS

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Wolitski et al., 2010; [56] Baltimore, MD; Chicago, IL; Los Angeles, CA	RCT, attention control	Homeless or unstably housed (n=630)	Housing Opportunities for People with AIDS (HOPWA) rental assistance with case management; amount of assistance varied depending on fair market rent and participants' monthly income Duration: ongoing	18 months	Sexual risk behaviour: No difference in unprotected sex partners
Margolin et al., 2007; [71] USA	non-randomized controlled trial, active control	People who use drugs (n=25)	Manual guided-, spiritually focused, psychotherapy integrating modern cognitive-behavioural psychotherapeutic techniques with Buddhist psychological principals Duration: 12 weekly sessions	3 months	Sexual risk behaviour: Decreased risk behaviour

Experimental studies of combined individual and group interventions among people living with HIV/AIDS

Reference, date; location	Study design, comparison group	Sample characteristics (sample size at follow-up)	Description of intervention	Follow-up	Outcome measure
Lapinski et al., 2009; [69] Michigan, USA	non-randomized controlled trial, active control	MSM (n=66)	Individual-level counselling (ILC): Based on the AIDS risk reduction model and the stages of change model. A certified HIV-prevention counselor assisted the participant in assessing HIV risk and in the development of individualized HIV risk reduction plans. Duration: 3 individual sessions, 45 minutes each; over 12 weeks Group-level sessions and individual-level counselling (GLS-ILC): group sessions were facilitated by an HIV+ male. They were designed based on theory of reasoned action and social cognitive theory, and the content dealt specifically with living with HIV Duration: 6 group sessions, 90 minutes each, plus 3 individual sessions, 45 minutes each; over 12 weeks	4.5 months	Knowledge, attitudes, and beliefs: increased knowledge among GLS-ILC participants Sexual risk behaviour: Decreased risk behaviour among GLS-ILC participants
Fogarty et al., 2001; [57] Baltimore, MD	RCT, active control	Women living with HIV (n=322)	Access to both comprehensive reproductive health services and to peer advocate services. Trained peer advocates worked with women individually and in groups on condom use skills and contraceptive use Duration: 6 months	18 months	Sexual risk behaviour: No difference in condom use

***Statistically significant effects (p<0.05)**

Table 2: Meta-analysis and Quality of Evidence of HIV Prevention Interventions for People Living with HIV in High-income Settings

Intervention Type	Comparison Group	Outcome Measure	Number of data sets (k)	Summary Effect Size (Odds Ratio (OR) or Standardized Mean Difference (SMD) with 95% Confidence Intervals, p value	I2 (%)	Quality of Evidence
Individual level health education	Attention control	Risk behaviour [34,34,36,36,37,37,39,39]	5	SMD: -0.08 (-0.17 to 0.004), p=0.063	0	⊕⊕⊕◯
	Active control	Risk behaviour [33,41]	2	SMD: -0.36 (-0.61 to -0.11), p=0.005*	0	⊕⊕◯◯
Group level health education	Attention control	HIV/STI incidence [32,54]	2	OR: 0.26 (0.12 to 0.56), p=0.001*	0	⊕⊕⊕◯
		Risk behaviour [28,32,35,42,54,63,64,68,70]	10	SMD: -0.55 (-0.90 to -0.20), p=0.002*	85	⊕◯◯◯
		Knowledge, attitudes and beliefs [70]	1	SMD: 0.58 (0.06 to 1.10), p=0.030*	-	⊕◯◯◯
	Active control	HIV/STI incidence [55]	1	OR: 0.84 (0.40 to 1.78), p=0.654	-	⊕◯◯◯
		Risk behaviour [29,30,38,40,46,48,55]	8	SMD: -0.09 (-0.20 to 0.02), p=0.114	0	⊕⊕⊕◯
		Knowledge, attitudes and beliefs [29,31,48]	3	SMD: 0.27 (0.11 to 0.44), p=0.001*	0	⊕⊕◯◯
Combined individual and group level health education	Active control	Risk behaviour [57,69]	2	SMD: -0.22 (-0.81 to 0.37), p=0.456	29	⊕◯◯◯
		Knowledge, attitudes and beliefs [69]	1	SMD: 0.15 (-0.36 to 0.65), p=0.566	-	⊕◯◯◯
Counseling, testing and referral services	Attention control	Risk behaviour [49,52]	2	SMD: -0.06 (-0.28 to 0.16), p=0.595	0	⊕⊕◯◯
Comprehensive risk counseling and services	Attention control	HIV/STI incidence [43]	1	OR: 0.70 (0.12 to 4.24), p=0.701	-	⊕◯◯◯
		Risk behaviour [34,43-45,47,51,58,60,62,65-67,73]	14	SMD: -0.35 (-0.49 to -0.20), p=0.000*	72	⊕⊕⊕◯
	Active control	HIV/STI incidence [72]	2	OR: 0.64 (0.31 to 1.29), p=0.207	0	⊕◯◯◯
		Risk behaviour [50,53,59,61,72]	7	SMD: -0.15 (-0.25 to -0.05), p=0.003*	0	⊕⊕⊕⊕
Other (Housing assistance)	Attention control	Risk behaviour [56]	1	SMD: -0.17 (-0.42 to 0.09), p=0.208	-	⊕⊕⊕◯
Other (Spiritual therapy)	Active control	Risk behaviour [71]	1	SMD: 0 (-0.79 to 0.79), p=1.00	-	⊕◯◯◯

*p<0.05

⊕⊕⊕⊕ - High quality of evidence

⊕⊕⊕◯ - Moderate quality of evidence

⊕⊕◯◯ - Low quality of evidence

⊕◯◯◯ - Very low quality of evidence

SMD: Standardized mean difference

OR: Odds ratio

3.7 Low and Very Low Quality of Evidence

A statistically significant effect with low quality of evidence was found for individual level health education interventions in reducing sexual risk behavior when compared to active controls (k=2, SMD: -0.36, 95%CI=-0.61, -0.11; p=0.005; I^2=0). Similar results were found for group level health education interventions in reducing sexual risk behavior when compared to attention controls (k=10; SMD: -0.55, 95%CI=-0.90, -0.20; p=0.002; I^2=85), however quality of evidence was very low. Group level health interventions, when compared to both attention controls (k=1; SMD: 0.58, 95%CI=0.06, 1.10; p=0.030) and active controls (k=3; SMD: 0.27, 95%CI=0.11, 0.44; p=0.001; I^2=0), also improved HIV knowledge, attitudes, and beliefs, however quality of evidence was very low and low respectively.

The quality of evidence for all other combinations of interventions, comparison groups and outcomes was either low or very low, with non-significant effects (Supplementary material - file 5).

3.8 Risk of bias within studies

Risk of bias summaries present the assessment in five domains for each study separately (Supplementary material - file 6). Study assessments of risk of bias were used in determining quality of evidence.

Selection bias: 11% (n=5) of studies were judged high risk for random sequence generation (not describing a randomized approach to sequence generation), 37% (n=17) were judged low risk (describing a randomized approach to sequence generation), and 52% (n=24) were judged as unclear risk.

For allocation concealment, 7% (n=3) of studies were judged high risk (not using a method to conceal allocation assignment), 28% (n=13) were judged low risk (using a method to conceal allocation with sufficient detail), and 65% (n=30) were judged as unclear risk.

Performance bias: No studies were judged high risk and had no blinding or incomplete blinding of participants and personnel, while 33% (n=15) were judged low risk, taking adequate measures to blind study participants and personnel, and 67% (n=31) were judged unclear risk.

Detection bias: No studies were judged high risk for no or incomplete blinding of outcome assessment. Sixty-three percent (n=29) of studies were judged low risk and took adequate measures to blind outcome assessment, and the remaining 37% (n=17) of studies were judged as unclear risk.

Attrition bias: 9% (n=4) of studies were judged high risk and did not report missing outcome data due to attrition or exclusion from the analysis, 78% (n=36) of studies were judged low risk for incomplete outcome data, and 13% (n=6) of studies were judged as unclear risk.

Reporting bias: No studies were judged high risk (not reporting the study's pre-specified primary outcomes). Four percent (n=2) were judged low risk and reported complete data, while 96% (n=44) were judged as unclear risk because study protocol was not available or it was not possible to judge whether the published study reported all pre-specified expected outcomes.

3.9 Risk of bias across studies

A varying degree of heterogeneity was observed within each intervention, comparison group and outcome combinations. This inconsistency was explored by I-squared statistics (Table 2). On two occasions (group level interventions compared to attention control and comprehensive risk counseling and services compared to attention control) overall quality of evidence has been downgraded because of substantial or considerable heterogeneity (Supplementary material - file 5). Publication bias was examined using funnel plots and was also taken into consideration when rating the quality of evidence (per GRADE methods) [9,74,75]. On two occasions (with individual level interventions compared to attention control and group level interventions compared to attention control) overall quality of evidence has been downgraded because of strongly suspected publication bias (Supplementary material - file 5).

4 Discussion

This review of randomized and non-randomized controlled trials assessed the effectiveness of HIV/STI prevention interventions for people living with HIV in high income settings. Sixty-three datasets from 46 primary studies were grouped by intervention, comparison group, and outcomes resulting in 17 unique combinations which were meta-analyzed and assessed for quality of evidence. Two intervention types reported statistically significant summary effects with high or moderate quality of evidence. These included comprehensive risk counseling and services and group level health education interventions.

High and moderate quality of evidence with a statistically significant summary effect was found for comprehensive risk counseling and services on sexual risk behaviour when compared to both active and attention controls. It can therefore be said with a high or moderate level of confidence that the true effect is likely to be close to the summary effect and that more research on the effects of this intervention on sexual risk behavior would likely not change the findings of the meta-analysis [9]. Although both summary effects were minimal (SMD <0.20), when compared to active controls (SMD = -0.15), the magnitude of effect for attention controls was larger (SMD = -0.35). This trend demonstrates the reduced effects of an intervention when compared to an active control versus an attention control. Similar results were found for group level health education interventions when compared to attention controls. Group level interventions, demonstrated statistically significant summary effects in reducing HIV/STI incidence with moderate quality of evidence

Moderate quality of evidence and statistically non-significant summary effects were found for individual level health education and housing assistance interventions in reducing sexual risk behavior when compared to attention controls. It can be said with moderate level of confidence

that more research on these interventions will likely not change the results of this meta-analysis, and therefore these interventions are unlikely to reduce sexual risk behavior of people living with HIV.

Some group-level health education interventions were found to be effective or promising in reducing HIV incidence as well as HIV knowledge, attitudes, and beliefs, however variation in pooled effects and quality of evidence precludes a clear conclusion on the effectiveness of this intervention. Furthermore, while group-level health education interventions compared to attention controls were shown to be effective in reducing HIV/STI incidence they did not show statistically significant effects in reducing sexual risk behaviors. These findings demonstrate a need for further investigation.

The remaining combinations of interventions, comparison groups and outcomes resulted in low or very low quality of evidence and therefore no conclusive interpretation of the summary effects, whether statistically significant or non-significant, could be made. Low or very low quality of evidence stemmed from a variety of issues including: inadequate randomization, inadequate blinding of participants and personnel, limited number of studies, small sample sizes, heterogeneity of pooled effects, and indirect outcome measures [9].

Common characteristics among effective interventions include sessions that are: theory-based, tailored one-on-one interventions, typically grounded in counseling or case management, targeting multiple health concerns (beyond skills building in relation to safe sex), and delivered over a longer period of time (average of five months). These characteristics are similar to effective prevention interventions among people living with HIV identified by two previous reviews [4,7]. While one other review found individual level health education interventions as promising for HIV prevention among people living with HIV [7], the present review suggests that longer, more comprehensive individualized interventions are more likely to be effective in reducing sexual risk behaviors among people living with HIV. Individual level health education interventions are often focused on sexual risk reduction only and are typically shorter in duration (on average one month). In contrast, comprehensive risk counseling and services are tailored to address an individual's sexual risk behavior in addition to unique life circumstances and health concerns, including mental health, substance use, and physical health. Nonetheless, it is important to acknowledge common barrier to implementation of comprehensive risk counseling and services, including: competing priorities, staff time, and limited financial resources.

Several factors may have contributed to the statistically significant, high or moderate quality interventions. Studies in this meta-analysis were grouped according to the CDC's classification of behavioral interventions; however, the process of categorization of interventions may involve subjectivity.

Very few studies measured change in incidence of HIV/STIs, the most direct outcome measure indicating effectiveness of HIV/STI prevention interventions. Rather, a majority reported measures related to changes in sexual risk behavior. Such self-reported and indirect measures are subject to social desirability bias [76] and do not necessarily result in changes in HIV/STI incidence [9].

Less than half of the studies included in this review reported using appropriate measures for random sequence generation, reducing selection bias, and producing comparable groups in both intervention and control arms. A majority of studies did not report or were unclear about their reporting of blinding study participants; however, it is important to note it is not possible to ensure blinding of participants and personnel, given the nature of behavioral interventions. Across studies, the majority of other domains were rated 'unclear' as study authors failed to explicitly report on risk of bias items, particularly in the domain of reporting bias (96% of all studies). The overall lack of uniform risk of bias reporting practices may have also contributed to a lower quality of evidence. Future trials should aim to improve reporting in several key areas related to risk of bias judgments.

Finally, while this review is conducted among people living with HIV, there is wide diversity within this group (e.g. MSM, heterosexual men, women, older adults, youth and individuals from a variety of ethnic backgrounds). Such diversity makes it difficult to estimate the true effect of an intervention for each group separately, given the aggregation of data for various sub-populations to produce a summary effect. Similarly, multiformity of each intervention type (i.e. content, intensity, duration) and variations of length of follow-up across studies may have an impact on the results of the meta-analysis. Such variation also makes it difficult to generalize what intervention strategies contribute to positive impacts, and in what populations they can be successfully implemented.

To our knowledge, this is the most comprehensive systematic review and meta-analysis available on behavioral prevention interventions for people living with HIV in high income settings. Within a landscape of limited public health funding, the findings of the present review can be used as a tool to support public health decision-making by assisting in the prioritization and allocation

of funds for HIV prevention strategies. While other systematic reviews have been conducted on this topic, this review stands out in its use of the CDC classifications of behavioral interventions and GRADE to summarize the quality of available evidence, as well as its assessment of outcome measures such as HIV/STI incidence and knowledge, attitudes and beliefs, in addition to commonly reported sexual risk behavioral [4,7,8].

Few published reviews were identified on the topic. A 2006 meta-analysis [4] of 12 studies by Crepaz et al. demonstrated that prevention interventions significantly reduced unprotected sex and acquisition of STIs. A 2014 meta-analysis of 21 studies by Yin et al. [8] demonstrated a short-term impact of interventions on self-reported unprotected anal intercourse, but no conclusions on long-term effects. A 2014 systematic review of 48 studies on the same topic by Crepaz et al. [7] evaluated each study against established criteria for study design, implementation, analysis, and strength of findings to assess risk of bias and intervention effects. Reviewers identified 14 studies with low risk of bias and significant positive intervention effects, while the remaining 34 studies had high risk of bias and non-significant positive intervention effects. While Crepaz and colleagues evaluated studies on an individual basis, rather than evaluating the body of evidence, its findings are similar to that of present review, pointing to a lack of well-designed and rigorously evaluated primary research.

While there are a number of primary studies evaluating the effects of behavioral interventions among people living with HIV, the dearth of high quality primary literature and reviews on the topic make drawing conclusions regarding effective prevention interventions difficult. Future research should focus on designing and evaluating such interventions within a more rigorous framework.

4.1 Limitations

Several limitations may restrict the validity of the present review. The inclusion of peer-reviewed studies published in English only may have contributed to reporting bias. Another limitation is the lack of subgroup or sensitivity analysis, however this was justified as the number of data sets included in each meta-analysis was small given the numerous intervention, comparison group and outcome combinations meta-analyzed separately. Additionally, non-randomized controlled trials were included in our analysis, which may have introduced selection bias and skewed the results. However, this risk has been minimized by downgrading quality of evidence through assessing risk of bias as part of the GRADE process. Finally, while this review was inclusive of all studies conducted in high income countries, only US studies met eligibility criteria for inclusion. Specific regional, racial, economic, and political and health system-related characteristics unique to the US may limit the generalizability of results and warrant caution in interpretation.

5 Conclusions

People living with HIV are at risk of transmission, in addition to contracting different STIs as well as other strains of HIV. Theory-based behavioral interventions provide an opportunity to reduce risk behavior and HIV/STI transmission among this population. Interventions identified as having statistically significant pooled effects with a high or moderate quality of evidence should be considered by clinics, AIDS service organizations, community-based organizations, and public health agencies. Moreover, given the number of interventions with low or very low quality of evidence, researchers should commit to conducting rigorous evaluations and high quality reporting of studies assessing the effectiveness of HIV prevention interventions. Moving evidence-based prevention research for people living with HIV into practice is one critical step in making a greater impact on the HIV epidemic.

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