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Systematic Review of Couple-Based HIV Intervention and Prevention Studies: Advantages, Gaps, and Future Directions

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Abstract

We conducted a systematic review of couple-based HIV biobehavioral (skills-building, VCT, and adherence) and biomedical (ART, circumcision) prevention and intervention studies designed to reduce sexual-and drug-risk behaviors and HIV transmission and acquisition. Of the 11,162 papers identified in the search, 93 peer-reviewed papers met the inclusion criteria and yielded a total of 33 studies conducted globally. Biobehavioral couple-based prevention and intervention studies have been efficacious in reducing sexual- and drug-risk behaviors, increasing access to HIV testing and care, and improving adherence. Biomedical couple-based studies were found to reduce HIV incidence among HIV-negative sex partners and viral load among HIV-positive partners. Despite much progress, couple-based HIV prevention and intervention studies remain limited; a number of methodological gaps exist and studies focusing on MSM, people who inject drugs, and sex workers are scarce.

Keywords

Systematic review; Couple-based; HIV; Prevention; Intervention

Introduction

The past three decades have seen significant global progress in the reduction of HIV prevalence and incidence [1]. This progress suggests that the HIV epidemic has passed its peak incidence [1, 2] and may be attributed to two major advancements: substantial increases in access to anti-retroviral therapy (ART), with ART coverage globally increasing by 63 %, and improved availability and access to combination HIV prevention services [1, 3]. Despite this progress, recent reports also describe a different scenario among subsets of the population, showing that declines in HIV incidence rates are uneven. HIV incidence rates have risen among people who inject drugs, men who have sex with men (MSM), and sex workers [1, 4]. The micro-social contexts of relationships (i.e. relationship commitment, love, trust, closeness, and interdependence in intimate relationships) in which sexual- and

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Conflict of interest

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drug-risks occur remain drivers of HIV among couples [5–7]. Research has demonstrated that condom use and safe injection practices remain low among people in intimate relationships [8, 9]; however, these issues have not been fully addressed and integrated into biobehavioral and biomedical HIV prevention strategies [10]. HIV prevention interventions generally focus on individuals, rather than on couples as a unit of change and analysis, ignoring the important role that sex partners play in sexual- and drug-risk behaviors and HIV treatment engagement and adherence [11].

There is consensus on the need for a new generation of HIV prevention and intervention strategies such as couple-based modalities for key populations in intimate relationships [9, 12]. HIV prevention efforts where the micro-social context serves as the foundation for sexual- and drug-risk reduction strategies may be more effective in reducing risk behaviors, strengthening healthy behaviors [5–7], and increasing HIV testing and treatment adherence [13]. There are several advantages to using a couple-based approach: it allows for both members to recognize their mutual responsibility in protecting each other from HIV transmission and encourages them to work together to stay healthy; it highlights the relationship's context (i.e. commitment, love, trust) and its connection to HIV acquisition, subsequently drawing attention to the value and power of the relationship in behavioral change; it aids in the creation of a safe environment to discuss sensitive topics such as sexual concurrency, power imbalances, and sexual coercion; it allows for couples to learn about and practice important skills such as communication and problem-solving with the support and guidance of others, such as the facilitator; and finally, it promotes accountability and increases commitment to change [9, 13]. Couple-based prevention has also been shown to increase adherence to ART and has the potential to not only improve the health of persons living with HIV, but also lowering the risk of transmission within the pair by reducing the viral load of the infected partner [9, 13]. Despite these many advantages, couple-based HIV prevention and intervention efforts remain limited, with most focusing on individual approaches.

To date, there has been only one systematic review of HIV couple-based interventions, which was conducted in 2010 and only included attention to behavioral studies [14]. Our paper addresses a gap in the literature by focusing on couple-based HIV prevention and intervention research since the beginning of the HIV epidemic, examining the current state of couple-based HIV research and focusing on both biobehavioral and biomedical HIV intervention and prevention studies. This paper includes couple-based studies that deliver interventions to couples one-on-one or to a group of couples. We include studies that define couples in various ways, including dyads, sexual partners, married or cohabiting partners, studies that allowed participants to self-define their couple status, as well as couples in long and short-term relationships. The paper describes the types of studies, intervention/prevention modalities, and core components, and examines the populations of focus, theories, inclusion and exclusion criteria, and how couples are being defined. The paper also examines advantages and gaps in the current state of couple-based HIV prevention and intervention efforts and offers recommendations for future directions.

Methods

This systematic review followed core PRISMA [15] guidelines, including pre-defining the rationale and objectives for the review, inclusion/exclusion criteria, search strategy and study selection, and data collection/extraction procedures.

Inclusion and Exclusion Criteria

In this review, we included studies explicitly targeting couples for HIV treatment, prevention, and/or intervention. Studies designed to reduce sexual- and drug-risk behaviors, HIV transmission and acquisition, as well as those focused on promotion of HIV testing, ART treatment, treatment adherence, and circumcision among couples were included. We included studies focused on serodiscordant, concordant, at-risk, and HIV status unknown couples. For any study where initial recruitment or services were directed toward an individual partner, we included the study if at least one or more intervention/prevention modality focused on the couple. We included RCTs, quasi-experimental, prospective, and observational cohort studies. As previously noted, we included studies defining couples in a myriad of ways including dyads, sexual partners, married or cohabiting partners, studies that allowed participants to define their couple-status, and studies that recruited couples who were together for any length of time. We excluded articles that had a clear lack of relevance, were modeling studies, were epidemiological/surveillance in nature, were primarily prevention of mother-to-child transmission (PMTCT)-focused studies (even if couple-based), lacked published outcomes or that were non-intervention/prevention-based.

Literature Search and Data Extraction

Electronic searches through PubMed, Biomed Central, PsycInfo, CINAHL, and Sociological Abstracts were conducted in late June 2013. We did not limit the search by year of publication. We limited our search to published papers available in English and excluded dissertations. To cast the widest net, search terms included “HIV” in conjunction with “VCT,” “CVCT,” “prevention,” “intervention,” “treatment,” or “adherence” as well as “couples,” “MSM,” “partners,” “dyad,” or “married.”

All articles were first crossed-referenced for duplication and then one author screened all remaining abstracts for relevance. A liberal approach was utilized to review abstracts; abstracts needed to indicate delivering an intervention or prevention to more than one person. In instances where abstracts were seemingly relevant or unclear (e.g. it was unclear if the intervention was delivered to an individual, couple, group, or family, or the study was intervention/prevention-focused rather than epidemiological), full-text articles were reviewed independently by both authors who then met to discuss them in accordance with the inclusion criteria. All relevant articles were reviewed by the two co-authors independently and only those that met the inclusion criteria were included in the review. When multiple papers reported data from the same dataset/project, the authors examined the articles together and reported them here accordingly. In cases where it was unclear if articles referenced the same or a different study, attempts were made to reach out to investigators for clarification. References of relevant articles were also examined for additional studies, but

this strategy did not yield any additional studies. Specific information on the search terms and strategy may be obtained by request.

For studies that met the inclusion criteria, data extraction included study location, study design, type of study, sample size, aims, core components and guiding theories, definition of couple, inclusion/exclusion criteria, targeted serostatus and sexual orientation of couple, study outcomes and power, adverse events, and study quality.

Results

5,460 records were yielded from PubMed, 302 from BioMed Central, 2950 from PsycINFO, 1485 from CINAHL, and 965 from Sociological Abstracts. Once we removed duplicates, we screened the remaining 7,735 records for relevance using their titles and abstracts. We excluded papers lacking clear relevance, leaving 412 full-text articles for review. Of the 412 full-text articles retrieved, 93 were deemed relevant according to the inclusion criteria. Upon closer review of these articles, we identified a total of 33 studies published through late June 2013 (see Fig. 1 for more detail on the flow of the review process).

Description of Included Studies

We catalogued 33 HIV couple-based studies conducted globally (see Tables 1, 2). The earliest studies were conducted in the late 1980s, with many more beginning in 2000. We categorized the studies into two types: (1) bio-behavioral, which includes: (a) psycho-educational and skills-building focused studies designed to reduce sexual-and drug-risks and acquisition and transmission of HIV, (b) HIV voluntary testing and counseling studies, and (c) ART adherence studies that promote medication uptake and address barriers to HIV testing and engagement in care and treatment; and (2) biomedical studies designed to evaluate the efficacy of HIV treatment options, including PrEP, combination therapies, ART, and circumcision. Twenty-seven studies were categorized as biobehavioral and six were identified as biomedical. Among the 27 bio-behavioral studies, 13 were psycho-educational skills-building studies, 13 focused on VCT, and one focused on adherence. The majority of the biomedical studies focused on PrEP, combination therapies, and ART, while only one focused on male circumcision. (See Tables 1, 2 for more information on biobehavioral and biomedical studies.)

Study Regions

Ten of the 13 biobehavioral skills-building studies were conducted in the U.S., with the remaining conducted in Asia and Africa (see Table 1). Seven of the VCT studies were conducted in Africa, two in Asia, one in the Caribbean, one in the U.S., and two were multi-country studies (see Table 1). The only adherence study was implemented in the U.S. (see Table 1). All but one of the biomedical studies were conducted in Africa; the remaining study was conducted in three regions: Asia, Africa, and the U.S. (see Table 2).

Design and Sample Size

Of the 27 biobehavioral studies, roughly half were randomized control trials, with the remainder using quasi-experimental, prospective or observational study designs (see Table

1). Four of the six biomedical studies were randomized control trials; one was a prospective cohort study, and the other an observational cohort study (see Table 2). Sample sizes varied from fewer than 20 couples to more than 4,500 couples. The smallest biobehavioral study included only 12 couples [16] and the largest invited 1,995 couples to enroll [17]. The majority of the psychosocial and skills-building studies reported lack of power to detect biological endpoints where recorded. The smallest sample size among the biomedical studies was 250 couples [18] and the largest 4,758 couples [19].

Sample Size and Power Analysis

Among most of the biobehavioral studies, power analyses were not typically reported in the articles. However, among skills-building, VCT, and adherence papers that did report power analyses, studies aimed to achieve 80–90 % power [8, 20–31]. Among the biomedical studies, power analyses were consistently reported and aimed to achieve at least 80–90 % power to detect differences for major study endpoints [18, 19, 32–37].

Types of Couples

Among the 13 biobehavioral skills-building studies, 12 studies included heterosexual couples, and one included MSM couples. Four studies included people who use or inject drugs and none specifically recruited sex workers (see Table 1). The adherence study included both heterosexual and MSM couples [31]. Of the 13 VCT studies, none included MSM couples and only one specified recruiting any other high-risk group (see Table 1).

Five of the six biomedical studies recruited serodiscordant couples, and one required at least one HIV seropositive partner (see Table 2). With one exception, only heterosexual couples were recruited; Cohen et al. [34] appeared to include heterosexual and MSM couples (see Table 2). None of the six studies provided information on the inclusion of injection drug users and/or sex workers.

Inclusion and Exclusion Criteria

Among the biobehavioral skills-building studies, the most common inclusion criteria noted were: (1) age of participants (18 or older)—only two studies included couples under age 18 (these studies focused on parenting adolescents aged 14–23/25) [38, 39]; (2) engagement in sexual-risk behaviors (number of unprotected sex acts and sexual partners); (3) drug-risk (injecting and use of illicit substances, including methamphetamine); and (4) length of the relationship (being together 3–6 months and planning to stay together for a year) (see Table 1 for more information regarding inclusion criteria). Exclusion criteria for the majority of biobehavioral skills-building studies included reports of severe violence, severe mental health impairments, and pregnancy. The adherence study required participants to be a minimum of 18 years old and the HIV-positive partner to have been on ART for a minimum of 1 month [31, 40]. Among the VCT studies, several did not specify their inclusion/exclusion criteria. Where noted, major inclusion criteria included a minimum age of 18 and willingness to enroll with and disclose test results to partners (see Table 1). Five studies specifically recruited pregnant women for enrollment into their study (see Table 1).

All six biomedical studies, with one exception, reported minimum or maximum CD4 counts and confirmed serostatus of partners (see Table 2). A minimum age requirement (of 18 or older) was used in five of the six studies (see Table 2). Biomedical studies also often required no concurrent participation in any other biomedical intervention and/or adequate biological functioning to be eligible for enrollment.

Definition of a Couple

The majority of biobehavioral studies (not including VCT and adherence) defined "couple" by length of the relationship. Both members of the dyad had to independently report being together for a minimum of 3 or 6 months (sexual relationship) and intention to stay together for a minimum of 1 year. Four of the biobehavioral studies defined a couple differently: one study required the couple to be married [16], another allowed the couple to self-identify as a couple [41], and the remaining two were defined by their co-parenting status (i.e. the couple had to be parenting a child together) [38, 39].

Biomedical, VCT, and adherence studies, the majority of which were conducted in Africa and Asia, primarily defined a couple by their marital or co-habiting status or perceived definition as a couple (see Tables 1, 2). Those that did not require the couple to be married, co-habiting, or self-identified as a couple, required participants to have engaged in a minimum number of sexual acts during the prior 3–6 months (see Tables 1, 2).

Core Components of the Interventions

There is homogeneity of intervention core components among the skills-building couple-based studies: knowledge building about HIV and sexually transmitted infections, skills-building in condom use, couple communication, negotiation skills, problem-solving, and goal setting; addressing power imbalances associated with decision-making; and offering strategies to promote and maintain healthy relationships [8, 16, 22–26, 28, 38, 39, 41–49]. Studies that included people who use or inject drugs also covered content related to the micro-social context of drug use in intimate relationships, such as the meaning of sharing or refusing to share needles or drugs in intimate relationships, the relationship between refusal to share needles/syringes and partner violence, and strategies to manage negative reactions when refusing needle/syringe sharing [8, 23, 24, 42].

The adherence study's core components included information sharing about the importance of medication and adherence, consequences of non-adherence, role of the supportive partner, discussions regarding barriers to adherence, and strategies to improve adherence, including problem-solving, communication, self-monitoring, and motivation [31, 40]. The core components of VCT studies included individual and couples HIV (rapid) testing and counseling, education and role-play (skills-building and self-efficacy), condom distribution, and information and referral for treatment, where necessary [12, 17, 20, 21, 27, 29, 30, 50–57].

Core components of the biomedical studies included distribution of medication (single or combination) and tracking adherence outcomes, including seroconversions and/or observation of outcomes to medication uptake [18, 19, 32–36]. The one circumcision study [37] focused on circumcision of male partners after enrollment of couples.

Guiding Theories of Studies

Almost all of the biobehavioral skills-building studies described the theoretical frameworks underpinning the design of their interventions. The most frequently cited theories included theory of gender and power [58], social cognitive theory [59], theory of reasoned action [60, 61], HIV risk-reduction (based on social cognitive theory), and ecological systems [23, 38, 39, 42–44, 48, 49, 62]. Other, but less frequently noted theories included the healing the wounded spirit framework and the integrated behavioral change model [38, 39, 45].

In general, the VCT study papers did not typically note the theories guiding their research. Only Jones et al. [25, 26] described their use of the theory of reasoned action and planned behavior. The adherence study employed the theory of social action [31, 40]. Among the biomedical studies, no guiding theories were noted in the articles reviewed.

Study Outcomes

A variety of behavioral endpoints were used across bio-behavioral studies (see Table 1). Study endpoints included reduced unprotected sex acts [23, 24, 38, 39, 47, 49]; increased protected sex acts [8, 22–24, 26, 41, 42, 47]; fewer sexual partners [49]; increased consistent condom use with main and other sex partners [22]; decreased unsafe injection [42] and illicit drug use [49].

A number of biobehavioral studies also focused on improving the intervention mediators and found greater intention to use condoms and increased HIV/AIDS knowledge [26, 38, 39]; positive attitudes towards condoms [26]; improved mental health outcomes [16]; improved comfort levels regarding discussions with their partners about sex and condoms and ability to use learned intervention skills with their partner [46]; and increased acceptability of barrier products [25].

Couple-based VCT, when compared to individual VCT or general health promotion activities, consistently yielded reductions in risk behavior and improvements in sexual safety, HIV knowledge, willingness to get tested, and testing. More specifically, follow-up data indicated increased condom use [27, 51, 52, 54]; fewer biological markers [51, 52]; fewer unprotected sex acts [21]; fewer incidents of coerced sex [63]; increased disclosure [54]; increased HIV knowledge, willingness to get tested [56], and testing [30]; and use of formula if breast-feeding [54].

VCT acceptability and feasibility studies yielded mixed results. Becker, Mlay, Schwandt, and Lyamuya [20] found that fewer women received HIV test results in the couple-based arm, compared to those in the individual-arm, but among those who were HIV positive in the couple-based arm, more participants reported using HIV prevention measures. In contrast, Mohlala et al. [29] found that a higher number of pregnant women who were offered couple-based VCT, compared to those offered pregnancy information sessions (control), brought in their partners. Further, more of the men in the VCT arm, compared to those in the control arm, received HIV testing.

The medication adherence study found that participants in the intervention arm, compared to participants in the control arm, had higher mean medication adherence, both for doses taken

and doses taken within a particular time frame [31, 40]. However, while participants in the intervention arm were more likely to have higher levels of adherence, compared with control participants, these effects were lower during follow-up periods [31, 40].

Among the six biomedical studies, ART endpoints included reductions in viral load and HIV transmissions between serodiscordant couples [18, 19, 32, 34–36]. Reynolds et al. [18] reported on additional outcomes, including greater condom use, but reported no differences in the number of sexual partners or other risk behaviors among those receiving ART and those in the control condition. However, daily acyclovir therapy did not reduce the risk of HIV-1 among those also infected with HSV-2, though it did reduce the occurrence of genital ulcers [33]. The one circumcision study proved ineffective as a sole method for the prevention of HIV transmission between couples and was terminated early due to futility [37].

Adverse Events

Among the biobehavioral skills-building studies, where noted, no adverse events occurred [8, 22, 42, 46]. Similarly, the adherence study paper reported no adverse events [31, 40]. The majority of VCT studies did not report on adverse events. Among those that did, adverse events included reactions to HIV status notification [21] and union breakups and partner violence [30].

Biomedical studies generally included a section or statement on adverse events. Adverse events included death (not related to intervention) and physical issues, including infections, psychiatric and biological disorders, among others [33–35]. Wawer et al. [37] also noted some adverse events related to circumcision (surgical).

Study Quality

Using an adapted version of the QUADAS 2 Tool [64], each study was assessed for its sample representativeness/generalizability, quality and clarity of the inclusion/exclusion criteria, sampling procedures, random assignment/randomization procedures, data analytical approach, power analysis plan and power, and reporting on attrition and loss to follow-up.

None of the reported biobehavioral or biomedical studies included representative/ generalizable sample populations.

All of the biobehavioral skills-building studies utilized appropriate data analytical approaches and ten provided good/clear information about their inclusion and exclusion criteria [8, 22–25, 28, 38, 39, 42, 46, 48, 49]. Similarly, the majority of the studies also had good/clear sampling procedures [8, 22–26, 28, 38, 39, 41, 42, 46, 49]; but, five studies had small sample sizes - under 50 couples [16, 38, 42, 46, 49]. Where applicable, random assignment/randomization procedures were clear and the majority of studies provided some information about attrition and loss to follow-up. Two studies were unclear or did not report on their attrition and loss to follow-up [26, 38]. Finally, fewer than five studies reported power analysis plans, though all 13 studies generally reported sufficient power for main outcomes of interest.

The single adherence study [31] had clear, high quality inclusion/exclusion criteria, sampling procedures, random assignment/randomization procedures, data analytical approach, power analysis plan and power, and reporting on attrition and loss to follow-up.

Among the VCT studies, several studies were unclear or lacked sufficient information about their inclusion and exclusion criteria [17, 27, 52, 54, 56, 65]. Nearly all studies had clear/good sampling procedures and reported attrition and loss to follow-up, and all used appropriate data analytical approaches. Given the nature of and ethical issues surrounding VCT, few studies randomized participants; among those that did, randomization procedures were generally clear [12, 21, 30]. Only three studies reported their power analysis plan [12, 29, 30], but all the studies seemed appropriately powered for several of their outcomes of interest.

All six biomedical studies were generally clear with respect to the inclusion and exclusion criteria with one exception, where very limited information was provided [18]. The clarity of sampling procedures, quality of data analytical approach, and random assignment/randomization procedures, where applicable, were clear in all the studies. Power analyses plans were consistently offered, though not all the studies reported sufficient power for all outcomes of interest [18].

Discussion

To our knowledge, this is the second published systematic review of couple-based HIV prevention and intervention studies since the start of the HIV epidemic. The first review targeted only behavioral prevention and intervention studies, whereas this review includes both biobehavioral and biomedical prevention and intervention studies. In our review, we found 33 couple-based studies conducted globally. Of these 33 studies, 27 were biobehavioral and six were biomedical. Nearly all of the 33 studies were conducted in the U.S., Africa, and Asia and included anywhere from 12 to nearly 5,000 couples. Most studies targeted heterosexual couples.

This review paper shows that the number of HIV couple-based studies conducted globally remains limited despite their potential to reduce sexual- and drug-risks, HIV and STI incidence rates, and improve HIV testing and adherence to ART. In the following section, we highlight a number of methodological weaknesses that characterize the state of the science of HIV couple-based research reviewed in this paper, and provide a few concrete steps that should be considered to address these drawbacks. We have focused on major methodological limitations that we believe are of high importance for advancing couple-based HIV interventions.

First, the majority of the studies we reviewed used a narrow definition of a “couple.” More specifically, the majority of studies reviewed used stringent inclusion criteria such as relationship length (for example, being together for six or more months), commitment level (for example, intention to stay together for a year), and/or relationship status (for example, being married or living together). Most studies also used a verification assessment screening prior to study participation to confirm whether the couple was “truly a couple.” Moreover,

experience of severe physical or sexual abuse reported by one or both parties in the relationship was used as an exclusion criterion among many of the studies. Such criteria may have excluded couples that would have benefited from the interventions.

In order to reach out to more diverse couples who need HIV interventions and services, we advocate for the use of a flexible, broad definition of a "couple" for research studies and implementation efforts in real world settings, such as permitting participants to self-define their status (i.e. both parties in the dyadic relationship state they are a couple or sexual partners). In real-world settings, it would be unethical not to provide HIV services to couples who have been together for a short period of time, and HIV transmission risks can exist at any stage of a relationship. Thus, though we acknowledge the reasons for using relationship length or status as potentially indicative of a couple's commitment to one another, and couple verification assessment as a method to ensure "true couples" in studies [66], we suggest using shorter verification screening assessments that include consistency across three to four questions. For example, drawing on McMahon et al.'s paper [66], one might ask each partner when the couple first met, length of time together, and living arrangement to determine if the dyad is a couple. Recognizing the immense cost of recruiting and retaining couples, as well as potential challenges in maintaining statistical power, requirements for length of relationship can vary based on the type and length of the intervention. For example, a onetime VCT session study may not need to consider the length of the relationship, whereas a multi-session couple-based intervention study may need to consider the length of relationship.

The majority of biobehavioral studies included assessment of intimate partner violence in their screening procedures and, in many cases, excluded couples that reported severe abuse. However, given research linking the relationship between violence and HIV [67, 68], we propose that couple-based studies broaden inclusion criteria to include couples that report history of severe partner abuse or whom are currently experiencing severe violence. Understanding the potential dangers and ethical concerns of including couples experiencing violence, it is critical to integrate robust screening and safeguard procedures. We advocate that intimate partner violence screenings become routinely integrated into study recruitment and enrollment procedures of HIV couple-based studies. For those couples where either active or recent abuse is present and/or risk of violence is high, for ethical and safety reasons, we suggest that the affected member of the dyad is asked separately if he/she feels safe in participating in a study where sensitive issues about sex, relationships, drugs, adherence to ART, or linkage to care are discussed. Further, we recommend that safety planning is concurrently integrated into this assessment, and that regular, ongoing check-ins and safety planning occur with the participant as to their ongoing comfort and safety in participating in the study. Suspicion or witnessing that one or both partners is verbally, physically, or sexually abusive during or outside the sessions should be taken seriously; the facilitator who delivers the intervention sessions should be appropriately trained and follow a safety plan to ensure that the abused individual has access to resources and services to deal with the situation. The sessions may be terminated if the abusive relationship continues to escalate, as it is dangerous to have the couple attend the sessions together. Some of the core components may also be delivered separately to participants—for example, to single gender groups, where female and male participants first meet separately to discuss sensitive issues

in a couple-context. As an alternate recommendation to including couples with active violence, another useful approach may be to screen for active violence in the past 3 or 6 months and to subsequently follow the safety guidelines presented above as a precautionary measure. Finally, we suggest that among biobehavioral and biomedical studies, where violence remains unaddressed in the core components, integration of intimate partner violence assessment and safety planning is critical.

Second, couple-based biobehavioral and biomedical HIV intervention studies have rarely targeted MSM or drug-involved couples, and none have targeted couples in casual, short-term relationships, sex workers who have regular sexual partners, or transgender couples. For example, despite research indicating that among MSM, 33–68 % of new HIV infections are transmitted by a main partner [69, 70], HIV couple-based prevention for MSM remains low. Of the 33 studies, only one was adapted for MSM couples and an additional two specifically recruited MSM and heterosexual couples. Future research would benefit from attention to these key populations, and careful attention should be given to developing and testing couple-based HIV prevention interventions for different types of couples. Recent research focused on risk behaviors and relationship dynamics among sex workers in relationships [6, 7] and MSM couples [71–79] provide useful insight and important considerations for future studies that seek to target these groups for prevention, such as the role of avoidance in discussing sexual practices [6, 7] and sexual concurrency, as well as attachment and intimacy [73].

Third, most couple-based HIV prevention approaches are guided by individual-based theories, such as social learning and cognitive behavioral theories [80–85]. These theories assume that couples are motivated to take protective actions, and often overlook many relationship, dyadic, and structural factors. There is also a significant gap in the theoretical and conceptual models in understanding the dynamics that may influence decisions regarding sex and HIV risks, especially in short-term relationships and non-traditional relationships. It is essential to apply theoretical frameworks that allow the inclusion of multiple influences (e.g. individual, interpersonal, social, and structural) such as the ecological theory [86] that has been used to understand the dynamic among various personal, interpersonal and environmental factors. Measurement in couple-based intervention research needs to incorporate these multi-level factors.

Fourth, data analytical approaches have mainly targeted the individual, not the couple, as the unit of attention. That is, although data from existing prevention and treatment studies were collected from couples, most of the studies reviewed employed individual-data analytical approaches. We propose that more attention be given to couple-data analytical techniques. Further, a number of the psycho-educational and skills-building couple-based studies included small sample sizes and/or lacked biologically confirmed HIV and STI endpoints. Further, none have been sufficiently powered to examine new STI and HIV infections as outcomes. Future studies would benefit from including larger sample sizes and using biological endpoints.

Fifth, few studies to date have examined whether couple-level interventions are effective in reducing sexual concurrency. Sexual concurrency should be of central interest in light of

evidence indicating increased HIV and STI risk among different populations in the U.S. and other countries [87]. As it stands, it is unclear whether existing couple-based HIV prevention approaches reduce HIV risk with extra-dyadic partners. A recent meta-analysis [88] suggests that behavioral couple-based approaches may be effective in reducing concurrency, however, condom use (uptake and consistency) with extra-dyadic partners remains unclear. From a measurement point of view, the literature has underscored the complexity of measuring these behaviors because they rely not only on accurate recall, but also on the start and end of the relationship [87]. However, collecting data on concurrency may be challenging given the stigma surrounding concurrency and if the members of the couple feel unsafe disclosing this behavior. To reduce these challenges, we suggest that, during the initial assessment phase when a couple comes together for research purposes, confidentiality must be secured by making sure that each individual partner is in a separate room, and that context-specific and appropriate methods are used (e.g. face-to-face interviews or technology such ACASI) to collect data on sensitive issues, such as questions about the sexual relationship and concurrency and type of couples (casual, long-term, etc.) [22, 89]. An additional strategy for addressing issues of concurrency might be to deliver select content in single-gender groups -where female and male participants first meet separately in single gender groups to discuss and assess how to best share sensitive issues in a couple-context.

Sixth, studies of couple-based HIV prevention interventions have been unable, so far, to determine the optimal intervention modality. It is unclear whether interventions are more effective when sessions are delivered individually to each couple, when sessions are delivered using a mixed format of individual and group sessions, or when content is delivered to a small, single-gender group of individuals who are in coupled relationships. A recent meta-analysis of behavioral interventions [88] suggests that delivery of material to individual couples is more effective than when delivered to a group, but it is not clear whether a mix-method approach would be more effective. The next generation of research on couple-based HIV interventions should tackle these questions using different designs that allow these scientific questions to be answered.

Finally, applying evidence-based HIV prevention and treatment approaches to real-world settings, and training clinicians to use such approaches, is an important step in making a strong public health impact on the epidemic. None of the studies reviewed in this paper focused on effectiveness or implementation research in real-world settings. We suggest that there is an urgent need for attention and resources to disseminate evidence-based couple-focused prevention and treatment research into real-world settings, as it has the potential to reduce HIV acquisition and transmission among vulnerable populations. Expanding the scope of dissemination and scaling up couple-based HIV interventions will require commitment by governments and donors to fund research on dissemination and implementation as well as training for providers in couple-based approaches. With the increased emphasis and use of a “seek, treat, and retain” HIV prevention and treatment paradigm [13, 89], a couple-based modality can be used at each stage on the continuum of this process. Engaging the couple together at each stage may lead to better outcomes where the responsibility is placed on the dyad and not simply on recruiting a partner to treatment, while also engaging them in forging linkages with support in their community, and

improving retention in treatment and care. This approach requires a shift in HIV prevention where the emphasis moves from the individual to dyadic contexts. The shift also requires training service providers and increased funding to focus on the couple as unit of change rather than the individual clients.

Implementation of couple-based prevention strategies must also address a number of organizational barriers such as the service providers' high caseloads, time constraints on engaging the couple, scarce funding for agencies to expand work with couples, health insurance and billing regulations that may not consider both individuals as a single "client," HIPAA regulations that prevent information being shared with others, and a lack of training and technical assistance in using couple modalities (an individual-oriented approach is the norm). The next generation of couple-based research must also tackle these issues in order to make the prevention applicable to real-word settings.

In sum, the use of a couple-based modality is important for both HIV biobehavioral and biomedical prevention interventions, for all types of relationships (long-term, short-term, casual, etc.) and key populations (MSM, people who use drugs, sex workers). HIV couple-based research is in its infancy and needs to pay more attention to the methodological barriers discussed in this paper. Finally, more attention should be given to disseminating and translating couple-based modalities to real-world settings. For successful implementation of couple-based approaches in real-world settings, an ideological shift from focusing on the individual to the dyad must occur, with an emphasis on navigating existing organizational and funding barriers.

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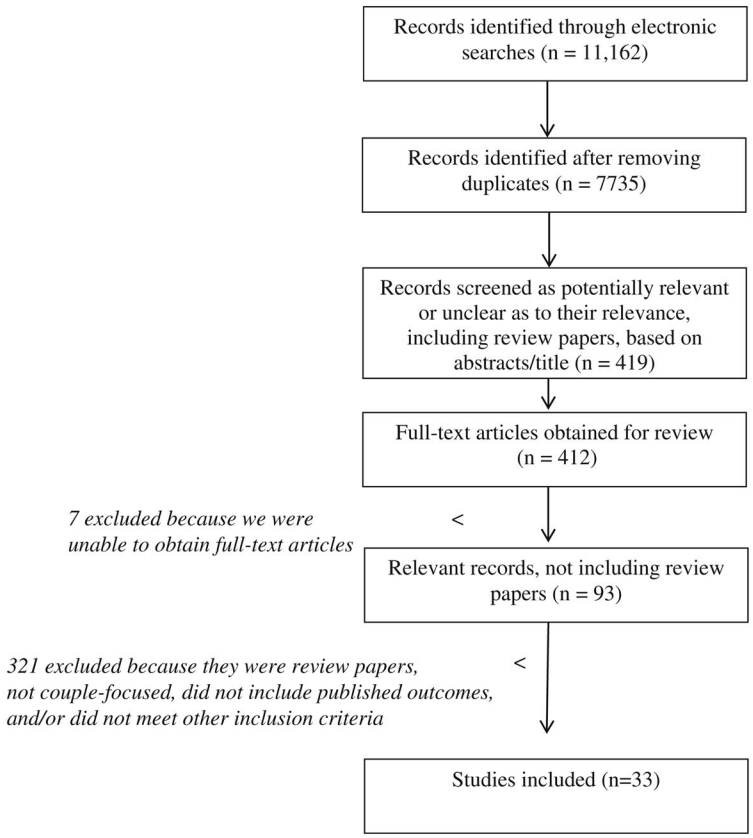

Fig. 1.
Flow diagram of systematic review search process

Table 1

Biobehavioral studies

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings
El-Bassel et al. [23, 24], Witte et al. [47] Project Connect	U.S.	Behavioral; RCT Test the efficacy of a relationship-based behavioral HIV/STD prevention program for heterosexual couples— delivered to the couple (experimental arm) and women only (experimental arm); one-session education (control)	217 couples 18–55 years; had at least 1 episode of unprotected vaginal or anal sexual intercourse with main partner during past 30 days; did not report experiencing any life-threatening abuse within the past 6 months; was a patient at one of the hospital's outpatient clinics; Had a regular male sexual partner identified as a boyfriend, spouse, or lover; in a long-term relationship with them defined either involvement with them for past 6 months and intention to stay with them for at least 1 year Woman had to also report either knowing or suspecting her partner of engaging in one of the following: sexual relations with other men or women in the past 90 days; being diagnosed with or exhibiting symptoms of a STD in the past 90 days; injecting drugs in the past 90 days; or having a HIV-positive status	Heterosexual	Male partner had to be at-risk for or test positive for HIV	**1** 12 month post-intervention data indicated declines in reported unprotected sex acts and increases in protected sexual acts among those in both experimental arms, compared with those in control arm; **2** No significant differences were observed between those in the two experimental arms
Gilbert et al. [42]	Kazakhstan	Behavioral; RCT Test the feasibility of an adapted couples-based risk reduction intervention on HIV risk behavior among couples who are injection drug users	40 couples 18 years or older; at least one partner reported unprotected vaginal or anal sex with the other partner at least once during past 30 days; at least one partner reported injecting drugs during	Heterosexual	At-risk	**1** 3 month follow-up data indicated increased condom use among participants in the couple-based treatment arm. Those in the couples-based treatment compared to those in the control arm (wellness promotion arm);

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings	
			past 30 days; neither partner reported plans to relocate; past 30 days; neither partner reported plans to relocate; past 30 days; neither partner reported plans to relocate; Mutual identification each that the other is their main partner, considering them as a boyfriend/girlfriend, spouse, lover, and/or parent of his or her child; minimum of 6 months together, with intention to stay together for at least 12 months			**2**	3 month follow-up data indicated decreases in unsafe injection acts among those in the couple-based treatment arm compared to those in the control arm (wellness promotion arm)
Kraft et al. [28], Harvey et al. [45] PARTNERS Project	U.S.	Behavioral; RCT Test efficacy of a psycho-educational intervention on unintended pregnancy, HIV, and other STDs among 18–25 year old females and their male partners	301 couples randomized At the Los Angeles site, women had to identify as Latina; in Oklahoma City, any ethnicity; 18–25 years old (women); 18 or older (partner) years; one reported act of unprotected sex in past 3 months; at least one other risky behavior	Heterosexual	At-risk	**1**	6 month follow-up data indicated no significant effects on contraceptive use between study arms—contraceptive use increased in both arms
						2	6 month follow-up data also indicated similar changes on the importance of avoiding pregnancy and including women in decision-making around contraceptive use between study arms;
						3	6 month follow-up data indicated more improvement on measures of positive expectations of partner support for contraceptive use among participants in the intervention arm
El-Bassel et al. [8] Project Connect II	U.S.	Behavioral; RCT with three arms Test the efficacy of a HIV risk reduction intervention among drug-using heterosexual HIV-negative couples in low-income communities	346 couples (baseline); 282 randomized 18 or older with at least one partner between 18–40; tested HIV negative; at least 1 partner reporting using illicit drugs during past 90 days and seeking or in treatment; at least one partner reporting having had unprotected sex	Heterosexual	HIV-negative	**1**	12 month follow-up data indicated a declines in unprotected sex acts with main partners among those in the intervention arm compared to those in the control arm;
						2	12 month follow-up data indicated greater declines in unprotected sex acts among those in the couple-

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings
			during past 90 days; at least 1 partner reporting some HIV risk: sex with another person during past 90 days; injection drug use during past 90 days; self-repor Mutual identification of each other as main partner; mutual reporting of having been together for at least 6 months; Intention to stay together for at least a year			based intervention arm; compared to those in the individual-based intervention arm
El-Bassel et al. [22], NIMH [43] Project EBAN	U.S.	Behavioral; Cluster RCT Assess the efficacy of a HIV/STD risk reduction intervention among serodiscordant African American couples	535 couples At least 18 years old; at least 1 partner reported unprotected sex with their partner during past 90 days; no plans to relocate far away; At least 1 partner self-identified as African American or Black; at least 1 partner reported no intention for pregnancy within 18 months; both partners were aware of the other's HIV status; only 1 partner was HIV seropositive and had known for a minimum of 3 months; A minimum of 6 months together; intention to stay together for at least 12 months	Heterosexual	Serodiscordant	**1** 12 month follow-up data indicated a greater proportion of condom-protected sex among couples in the intervention arm compared to those in the control arm; **2** 12 month follow-up data indicated greater consistency of condom use among couples in the intervention arm **3** 12 month follow-up data indicated no significant differences in the cumulative STD incidence between study arms **4** 12 month follow-up data indicated overall HIV seroconversion rate of 935 per 100 000 population across arms
Koniak-Griffin et al. [38]	U.S.	Behavioral; Quasi-experimental, longitudinal study Test the efficacy of a six-session culturally appropriate HIV prevention intervention targeted towards adolescent	49 couples 14–23 years old; English or Spanish speaking; expecting a child or co-raising a biological child; In a relationship for three or more months	Heterosexual	Not explicitly specified, but appears to be at-risk	**1** 6 month follow-up data indicated a significant decline in the likelihood of unprotected sex among those in the intervention arm compared to those in the control arm; **2** 6 month follow-up data indicated significantly

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings	
		mothers and their partners mothers and their partners					higher intention to use condoms among those in intervention arm compared to those in the control arm
						3	Data indicated reported increases in AIDS knowledge among participants across study arms
						4	Data indicated significantly greater intention to use condom and lower probability of having unsafe sex among women in both both arms compared to men in both arms
Jones et al. [26] Partner Project	Zambia	Behavioral; RCT Test the efficacy of an adapted 4-session cognitive behavioral group intervention in reducing sexual risk behaviors among HIV + women	180 women; 152 men 18 years of age or older; sexually active women; HIV-positive women; partners living in the area Couples definition not explicitly stated other than partner living in the area	Heterosexual	HIV + women; men could have seropositive, negative, or unknown status	**1**	Post-intervention data indicated increased condom use, more positive attitudes towards condoms, increased intention for safe sex, and less alcohol use among female participants whose partners were assigned to the high-intensity treatment arm
Wu et al. [48, 49]	U.S.	Behavioral pilot; Pre/post-test Examine the feasibility of a couple-based behavioral risk reduction intervention among methamphetamine-using, black MSM couples	34 couples 18 or older; African American and/or Black (participant or partner); unprotected anal sex with non-main partner during past 60 days (participant or partner); use of methamphetamine use during past 60 days (participant or partner); not in or seeking drug treatment; not newly diagnosed with HIV during past 6 months; identification of each other as main partner; Male partner with an ongoing sexual relationship during past 6	MSM	At-risk or HIV positive, but not newly positive in past 6 months	**1**	2 month follow-up data indicated significantly fewer sexual partners among participants
						2	2 month follow-up data indicated significantly fewer unprotected anal sex acts among participants
						3	2 month follow-up data indicated significantly less methamphetamine use, any illicit drug use, and number of illicit drugs used among participants

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings
			months; emotional bond/relationship strongest with this person months; emotional bond/relationship strongest with this person months; emotional bond/relationship strongest with this person			
McGrath et al. [46]	India, Thailand, and Uganda	Behavioral Assess the acceptability of a group-based brief intervention in increasing condom use; determine participation in intervention	43 couples Willingness to enroll regular sexual partner into study where they had disclosed or would be willing to disclose their HIV status to; willingness to attend intervention and be interviewed; report inconsistent condom use; no report of partner violence with current partner; Minimum 6 months relationship; intention to stay together	Heterosexual	Serodiscordant	**1** Data indicated general acceptance of the intervention and interest in meeting similar couples; **2** Follow-up data indicated improved comfort levels re: discussions about sex and condoms with partners among participants **3** 3 month follow-up data indicated a high number of participants reporting ability to use learned intervention skills with their partner
Padian et al. [41]	U.S.	Behavioral (counseling and social support); Prospective study Assess whether counseling sessions along with social support reduces sexual risk behaviors and HIV seroconversion among discordant couples	175 couples Discordant couple; current partner; participation in an intake session (HIV seronegative partner must only be at risk for HIV through HIV seropositive partner) Couples status appears participant defined	Heterosexual	Serodiscordant	**1** 144 couples were retained for follow-up and for which data were reported. Follow-up data (which ranged from 3 months to 5.5 years) indicated increases in condom use over time; **2** Follow-up data (which ranged from 3 months to 5.5 years) indicated increases in sexual abstinence increased over time; **3** Follow-up data indicated greatest behavioral changes after the first visit with declines over subsequent visits **4** Data indicated no HIV seroconversions after 193 of couple years
Koniak-Griffin [39]	U.S.	Behavioral; RCT Determine efficacy and sustainability of a 12 hour couple-	168 couples 14–25 years; co-parenting a child at least	Not specified in article, but appears to be heterosexual	No targeted serostatus	**1** 6 month follow-up data indicated a decline in the proportion of unprotected

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings
		focused HIV prevention intervention, geared towards young Latino parents in: 1) reducing unprotected sex; 2) increasing intent to use condoms; and 3) improving HIV/AIDS knowledge	3 months old; English and/or Spanish speaking; Couples defined by their co-parenting a child together			sex acts, and those in the intervention arm. **2** 6 month follow-up data indicated an increase in the intent to use condoms among those in the intervention arm, but that these effects were not present at the 12 month follow-up **3** Follow-up dated indicated improved AIDS knowledge among both groups and that improvements in knowledge were maintained among the intervention arm through 12 months, but not beyond **4** Follow-up data indicated that female participants, compared to male participants, in both arms reported significantly more knowledge and intent to use condoms
Pomeroy et al. [16]	U.S.	Behavioral; quasi-experimental. Pre/ post-test design Determine the effectiveness of a psycho-educational group on depression, anxiety, and marital satisfaction among serodiscordant couples	12 couples Serodiscordant; emotionally and physically able to participate Married	Heterosexual	Serodiscordant	**1** Post-test data indicated significantly better outcomes on depression, anxiety, and marital satisfaction among those in the intervention arm, compared to those in the control arm
Jones et al. [25] NOW2 Study	U.S.	Behavioral; RCT Evaluate the impact of a HIV risk reduction strategy on the acceptability of sexual barrier use among HIV seroconcordant and discordant couples, when delivered in a group format	216 couples 18 or older; HIV positive seroconcordant or discordant; sexually active during prior month; willingness to get tested for those in a discordant relationship; willingness and able to provide informed consent; ability to	Heterosexual	Seroconcordant and discordant	**1** 6 and 12 month follow-up data indicated that the acceptability of sexual barrier products increased more among female group participants than female participants in the individual arm **2** Follow-up data indicated that acceptability of male

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		compared to an individual format	understand and communicate in English; Minimum of 6 months together and both members willing to enroll and attend study				condoms increased more among serodiscordant couples in the group arm compared to those in the individual arm
						3	6 month follow-up data indicated acceptability HIV/STD and pregnancy prevention products increased more among group format seroconcordant couples, which were maintained at 12 months
Remien et al. [31, 40] SMART Couples	U.S.	Adherence; RCT Test the efficacy of a couple-based intervention to improve adherence to medication	215 couples ≥18 years; English-speaking; Self-reported serodiscordant couple; 6 months minimum relationship; HIV + partner in primary care and on ART for a minimum of 1 month	Heterosexual and MSM	Serodiscordant	**1**	Post-intervention follow-up data indicated that mean medication adherence was higher among participants in the intervention arm, compared to participants in the control arm
						2	Follow-up data indicated level of adherence was more likely to be higher among participants in the intervention arm, compared participants in the control arm, but these effects declined at the 3- and 6 month follow-ups

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Allen et al. [51] ZUHRP	Zambia	VCT; Comparison groups Determine the effects of VCT on sexual behavior among serodiscordant couples	963 couples 48 or younger for women; 65 or younger for men; attendance at least one follow-up appointment after enrollment; residence in Lusaka; Minimum of 6 cohabiting in a sexual relationship	Heterosexual	Serodiscordant	**1** **2** **3**	12 month follow-up data indicated large increases in reported condom use among discordant couples Follow-up data indicated declines in biological markers among those who reported 100 % condom use Follow-up data indicated that among those couples who always reported using condoms, reporting was not always accurate
Farquhar et al. [54], Katz [55]	Kenya	VCT; prospective cohort study among women in an antenatal clinic Examine the effect of partner involvement and counseling on HIV prevention behaviors	116 couples received counseling together; 192 received counseling individually During their first antenatal visit, women were consented and asked to return (no further inclusion/ exclusion criteria were noted) Definition of “couple” was not explicitly stated; appears to be participant defined	Heterosexual	Women who were HIV + or HIV− were asked to return with partners for optional VCT as a couple or individually	**1** **2**	At follow-up, partner participation was associated with increased disclosure and condom use At follow-up, among HIV seropositive women, participants counseled as a couple were more likely to use formula (in place of breast-feeding) and receive nevirapine
Becker et al. [20]	Tanzania	VCT; RCT Examine the acceptance and effectiveness of couple-based VCT (CVCT) compared to standard individual VCT	761 randomized to individual VCT; 760 randomized to CVCT arm Pregnant women, not more than 6 months pregnant, attending their first antenatal care appointment were eligible. Women were required to be married (legal or traditional marriage or living with partner for 2 years)	Heterosexual	Sero-concordance or discordance was not required. Women attended to get tested	**1** **2**	Significantly fewer women received test results in the CVCT arm than individual VCT arm Follow-up data of HIV + women in the CVCT arm (subgroup analysis) indicated they were more likely to use preventive measures against HIV transmission and received nevirapine for themselves and their infants more often than the women in the individual VCT arm

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Coates et al. [21] The Voluntary HIV-1 Counseling and Testing Efficacy Study Group	Kenya, Tanzania, and Trinidad	VCT; RCT Examine the efficacy of VCT in reducing unprotected sex among individuals and couples.	3,120 individuals and 586 couples ≥18 years (or legally married); Intention to stay in the area for 1 year; not known to be infected with HIV-1; Participants self-presented as individuals or couples. (I.e. some individuals were married.) No criteria were specified to meet the definition of a couple	Heterosexual	HIV-negative concordant	**1** Follow-up data (mean of 7 months after baseline) indicated unprotected sex declined more among participants in the intervention arm than those in the control arm, and changes were sustained at the second follow-up **2** Follow-up data indicated HIV-1 positive men were more likely to report reductions in unprotected sex with both primary and non-primary partners than HIV-men **3** Follow-up data indicated that HIV-1 positive women were more likely to report reductions in unprotected sex with primary partners than HIV-negative women **4** Follow-up data indicated that couples in the intervention arm reported fewer unprotected sex acts with their study partners than those in the control arm, but these effects were not significant in relation to non-study partners **5** Follow-up data indicated that serodiscordant couples and seropositive-concordant couples were more likely to report reductions in unprotected sex with their study partners than seronegative-concordant couples among both study arms
Allen et al. [52], Roth [63] Project San Francisco (Part of RZHRZ)	Rwanda	VCT; Longitudinal, prospective study Determine effects of VCT and male-focused counseling on male partners in	1,258 women reported being married or cohabiting. VCT services were offered to male partners over a several year period	Heterosexual	1992 paper-serodiscordant couples; 2001 paper-focused on male partners who had not previously been tested. Women were +/−	1992 paper: **1** 1 year follow-up data indicated increased condom use among

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		reducing sexually risky behaviors and seroconversion among those in a discordant relationship	No inclusion criteria were stated in either paper. Couples who were married and co-habiting were evaluated in these papers			serodiscordant couples in the study **2** Seroconversion rate among HIV negative men was 4 per 100 person years and for women, 9 per 100 person years. Reported condom use was lower among those who seroconverted 2001 paper: **1** 1 year follow-up data indicated increases in reported condom use among men who received counseling services in year 3 and that even higher rates of use were reported among those who also had VCT services **2** Follow-up data indicated increases in reported condom use among serodiscordant couples who had previously participated in VCT services and where the male participated in counseling; **3** Follow-up data indicated fewer incidents of coercive sex among women whose partners attended counseling
Kempf [17] Zambia-Emory HIV Research Project—(part of RZHRZ) *Note, other papers have been published in relation to RZHRZ's work in Zambia. These include: Allen et al. [50], Wall et al. [90] and discuss various	Zambia	VCT; Observational study Following the success of trials in Rwanda, the RZHRZ team administered couples-VCT in Zambia. Couples VCT was offered between 1994 and 1998. Couples testing together and among whom had at least one positive	1995 couples were invited to enroll/ participate in study No explicit inclusion criteria were stated in the paper. However, it was noted that couples had to report co-habiting for a minimum of 12 months to be eligible. Further, only HIV serodiscordant couples were invited to continue participation in	Heterosexual	Serodiscordant	**1** Data indicated that couples where the male partner was positive were more likely than couples where the female partner was HIV positive to be eligible and enroll into the study and less likely to be lost to follow-up **2** Data indicated predictors of attrition among both types of couples included

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strategies to engage couples in testing including the use of Influential Network Agents		person were invited back for further testing and counseling. Paper sought to examine predictors of enrollment and retention among serodiscordant couples	the study following initial HIV testing				being at a distance from the clinic, being young, female partner's age being 17 or younger at first intercourse. Additional predictors of attrition were noted among couples where the female was HIV seropositive and included: 2 or fewer lifetime sex partners, no history of STIs among the woman, and recent extramarital contact by their male partner
Mehendale et al. [57]	India	VCT and couples counseling for risk reduction; Prospective study Examine the HIV transmission rate among married couples in India	457 couples No inclusion criteria were noted. However, authors note that both partners were aware of their partner's HIV status prior to entry into the study Married	Heterosexual	Serodiscordant	**1**	Follow-up data indicated HIV incidence rate of 1.22 per 100 person years
						2	Data indicated HIV incidence was higher among exposed male than female partners
						3	Follow-up data indicated HIV incidence rate was almost 3.5 higher among those with multiple partners than those with single partners, though this was not statistically significant
Kamenga et al. [27]	Zaire	VCT and couples counseling; Prospective study Examine the effect of HIV counseling on seroconversion and reported condom use among married serodiscordant couples	149 couples No inclusion criteria were noted. However, serodiscordancy among couples was required and confirmed twice (biologically) at the outset Married	Heterosexual	Serodiscordant	**1**	1 month (post-notification and counseling) follow-up data indicated high reports of consistent condom use among couples
						2	18 month follow-up data indicated that approximately three-quarters of the participants reported continued use of condoms during all acts of sexual intercourse
						3	Data indicated that upon notification of HIV-1 serostatus some couples reported experiencing acute psychological

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						4	Data indicated low rates of HIV-1 seroconversion among those who were notified of their HIV-1 serostatus and received intensive counseling. i.e. 3.1 per 100 person-years
Deschamps et al. [53]	Haiti	Behavioral Counseling; Prospective Study Assess the incidence of HIV among couples and whether counseling reduces risk behaviors	475 couples Ability to provide informed consent; Ambulatory status; residence within 30 km of the client; Those receiving an HIV test with a seropositive outcome were asked to return with their regular sex partners for testing, upon which testing was provided in addition to counseling for the couple	Heterosexual	Serodiscordant	**1**	Data indicated an HIV incidence rate of 5.4 per 100 person years
						2	Data indicated 38 couples ceased sexual activity during the course of the study
						3	Data indicated that among couples who were sexually active and reported 100 % condom use (42 couples), 1 seroconverted
						4	Data indicated that HIV incidence among those who were sexually active, but used condoms on an infrequent basis or not at all was 6.8 per 100 person years
Khoshnood et al. [56]	China	VCT; pre/post-test Determine the efficacy of VCT among an educated cohort of pregnant women attending antenatal clinics-willingness and knowledge; and assess effect of couples VCT compared to individual VCT	300 couples Women in their first trimester. No other criteria were specified by authors Women brought in their male partners (socio-demographic data indicated all participants were married)	Heterosexual	No pre-determined targeted serostatus given nature of study	**1**	Follow-up data indicated that HIV knowledge increased significantly among women
						2	Data indicated that HIV knowledge was significantly associated with willingness to get tested
						3	Data indicated that women in both the intervention arm and control arm were

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							more willing to receive HIV testing at follow up more willing to receive HIV testing at follow up more willing to receive HIV testing at follow up
Mohala et al. [29]	South Africa	VCT; RCT Assess the acceptability and feasibility of asking pregnant women to bring in their male sexual partners to the antenatal clinic and attend VCT to reduce of HIV-1 transmission rates. Control group was invited to attend the clinic for a pregnancy information session (PIS)	1,000 couples Gestational age of less than 30 weeks; willingness to give informed consent Couples were defined by pregnancy partner—for women: the male partner who impregnated her in the current pregnancy. For men: the woman he impregnated in the current pregnancy	Heterosexual	No pre-determined targeted serostatus given nature of study	**1** **2** **3** **4**	Data indicated that all women accepted the invitation letters and agreed to invite their partners to attend VCT or PIS (pregnancy information sessions) Data indicated that more pregnant women given VCT invitations brought their partners in than women who were given PIS invitations Data indicated that men in the VCT arm were significantly more likely to receive HIV testing than men in the PIS arm Data indicated that fewer women and men in the VCT arm reported unprotected sex during pregnancy than participants in the PIS arm
McMahon et al. [12] Harlem River Couples Project	U.S.	VCT; RCT Assess the effectiveness of a couple-based counseling and testing intervention against a women-only counseling and testing intervention and standard counseling and testing intervention in reducing HIV risk (i.e. two experimental arms and one control)	330 couples Women: 18 years or older; HIV seronegative (self-reported); English or Spanish speaking; use of crack/cocaine or heroin during past 30 days; primary male partner willing to enroll into study; not threatened/fearful of participation in the study because of partner; no participation in another HIV/AIDS	Heterosexual	HIV-negative women and their partners	**1** **2**	Data (collected over a 9 month period) indicated that those in the couples-based testing and counseling arm reported significant reductions in HIV risk than those in the control arm (standard counseling/testing arm) and the womens-only counseling/testing arm Data indicated no significant differences in HIV risk reduction among those in the womens-only arm and control arm

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			study or in HIV testing and counseling during the past 6 months; and identification of a male partner as main/primary partner for a minimum of past 6 m Partner defined as husband (including common-law) or considered boyfriend for at minimum of 6 months Men: 18 years or older			
Orne-Gliemann et al. [30] Prenahtest ANRS 12,127 Study	Cameroon, Dominican Republic, Georgia, and India	HIV pre/post test counseling; RCT Test the efficacy of couples-oriented post-test HIV counseling (COC) against standard post-test counseling on partner HIV testing in low to medium HIV prevalence countries	1,943 women Pregnant; 15 years or older; open to follow-up visits through 6 months post-partum; not previously tested for HIV during current pregnancy; Identification of a primary partner, defined by the woman as a regular partner	Heterosexual	Status unknown	**1** Data indicated significantly higher HIV testing rates among women in the COC group than those in the standard post-test counseling arm in Cameroon and Georgia **2** Data indicated higher HIV testing rates among women from COC group than those in the standard post-test counseling arm in DR and India, but these effects were not significant in DR and marginally significant in India **3** Data indicated that women in the COC arm did not report more sexual violence or breakups than those in the control arm

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings	
						4	Data indicated main factors associated with partner HIV testing were history of HIV testing among men in Cameroon, DR, and Georgia and couples communication re: HIV testing in Georgia and India

Table 2

Biomedical studies

First author and study name, if applicable	Location	Type of study; design; main intervention aims	Sample size and inclusion criteria, including definition of couple status	Targeted sexual orientation	Targeted serostatus	Main findings	
Cohen et al. [34, 35] HPTN 052	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, and U.S.	ART; RCT Test the effect of combination antiretroviral therapy on the prevention of HIV transmission among serodiscordant couples as well as on clinical events among infected participants	1,763 couples > 18 years; willing to disclose HIV test results to partner; No intention to relocate during the study or expectation of a long absence; Intention to maintain a sexual relationship with study partner; 3 months minimum relationship; minimum of -3 sex acts during past 3 months; HIV+/Index Partner: Positive serology within 60 days prior to enrollment; Willingness to be randomized, if pregnant/breastfeeding; CD4 + cell count between 350 and 550; hemoglobin > 7.5 g/dL; Platelet count > 50,000/μL; AST (SGOT), ALT (SGPT), and alkaline phosphatase < 5 × ULN; total bilirubin < 2.5 × ULN; calculated creatinine clearance> 60 mL/min; absolute neutrophil count > 750 mm^3 or 0.750 × 109/L HIV-partner: Negative HIV serology within 14 days prior to enrollment	Not explicitly stated. 97 % of couples recruited were heterosexual	Serodiscordant	**1**	Data indicated that ART reduced HIV-1 sexual transmission by 96 % among sero-discordant couples
Reynolds et al. [18]	Uganda	ART; Observational cohort study Assess impact of ART on HIV-1 transmission among HIV-1 serodiscordant couples	250 couples Married; no other criteria were specified	Heterosexual	Serodiscordant	**1** **2** **3**	Data indicated that HIV-1 incidence was 9.2/100 person-years Data indicated that among those who were HIV-1 positive and had initiated ART, there were no HIV-1 transmissions during the 53.6 person-years Data indicated that among those on ART, couples reported more consistency in their condom use, but there were no significant

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							differences in the number of sexual partners or othe
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							differences in the number of sexual partners or othe
						4	Data indicated that among those on ART, viral load was notably reduced
Celum et al. [33] Partners in Prevention HSV-2/HIV-1 Transmission Study	Botswana, South Africa, Zambia, Kenya, Rwanda, Tanzania, and Uganda	Acyclovir-HSV-2 suppressive therapy; RCT Assess how well the suppression of HSV-2 through acyclovir reduces the risk HIV-1 transmission among HIV-1 serodiscordant couples	3,408 couples enrolled HIV-1 positive partner: ≥18 years; HIV-1 and HSV-2 seropositive; CD4 count of ≥250; no conditions associated with AIDS; no current ART therapy HIV-1 negative partner: ≥8 years; HIV-1 seronegative; HSV-2 seropositive or negative 3 or more acts of vaginal sex during prior 3 months and intention to stay together for 24 months	Heterosexual	Serodiscordant	**1**	Data indicated that following randomization, HIV incidence was 2.7 per 100 person-years
						2	Data indicated a hazard ratio with acyclovir of 0.92 (95 % CI 0.60, 1.41, $p = 0.69$);
						3	Data indicated suppression with acyclovir reduced plasma HIV-1 RNA by 0.25 log10 copies per milliliter and 73 % in the occurrence of genital ulcers due to HSV-2
						4	Data indicated 96 % adherence to the study drug
Bunnell et al. [32]	Uganda	ART; Prospective Cohort Study Examine sexual behavior 6 months before and after initiation of home-based ART and VCT and estimate risk of HIV transmission 6 months after ART	926 individuals Clients with a CD4 cell count ≤250 cells/μL or symptomatic AIDS; living within 100 km^2 Study targeted individuals, but provided home-based ART and VCT to household members, including sexual partners co-habiting with the index client. VCT with HIV− or unknown status partners focused on risk reduction and condom provision	Unspecified, but appears to include heterosexual couples	Recruited participant: HIV + ; partner could be +/−/ status unknown	**1**	Data indicated risky sexual behavior declined significantly after 6 months of ART
						2	Data indicated baseline median viral load among participants engaged in risky sex was 122 500 copies/ml; at follow-up, viral load was < 50 copies/mL
						3	Data indicated estimated risk of HIV transmission declined from 45.7 to 0.9 per 1,000 person years
Baeten et al. [19], Mujugira [36] Partners PrEP Study	Kenya and Uganda	ART; RCT Assess efficacy of oral ART for use as preexposure prophylaxis among HIV-1	4,758 couples HIV-1 infected partner: ≥18 years; sexually active; CDF cell count ≥250 cells/μL; no history of	Heterosexual	Serodiscordant	**1**	Data indicated HIV incidence of 0.65 per 100 person-years in the TDF arm, 0.50 per 100 person-years in the TDF-FTC arm,

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		serodiscordant heterosexual couples and evaluate its safety. serodiscordant heterosexual couples and evaluate its safety. serodiscordant heterosexual couples and evaluate its safety. serodiscordant heterosexual couples and evaluate its safety. HIV-1 seronegative partners were randomly assigned into either (1) once daily tenofovir (TDF); (2) combination tenofovir-emtricitabine (TDF-FTC); or (3) matching placebo. Follow ups were monthly for up to 36 months	couples and evaluate its safety. willing to provide locator information as well as written consent to evaluate its safety. HIV-1 negative partner: ≥18 years and ≤65; sexually active Adequate renal, hepatic, and hematologic function; no chronic active Hep. B. infection, and able and willing to provide locator information as well as written consent Sexually active–at least 6 vaginal intercourse episodes in past 3 months and intention to stay together for the course of the study			and 1.99 per 100 person-years in the placebo arm **2** Data indicated relative reduction of HIV-1 incidence was 67 % with TDF. And 75 % with TDF-FTC, both of which were significant **3** Data indicated the effects of TDF-FTC and TDF were not significantly different and both medications resulted in a significant decline in HIV-1 incidence among participants
Wawer [37]	Uganda	Circumcision; RCT Determine whether circumcision of HIV-infected men reduces transmission of HIV to female sexual partners	922 men and their partners Men: 15–49 years; HIV infected; asymptomatic; CD4 ≥350 cells/μL; uncircumcised Wives or permanent consensual female partners	Heterosexual	Serodiscordant	**1** Data indicated futility—trial was terminated early **2** Modified ITT analysis of 92 couples in the intervention group and 67 couples in the control group were included indicated a) 18 % of women in the intervention group 12 % in the control group acquired HIV during follow-up; b) at 24 months, cumulative probability of HIV infection was 21.7 % in the intervention group and 13.4 % in the control group

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