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A META-ANALYSIS OF CONDOM EFFECTIVENESS IN REDUCING SEXUALLY TRANSMITTED HIV

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Abstract—Before condoms can be considered as a prophylaxis for sexually transmitted human immunodeficiency virus (HIV), their efficacy must be considered. This paper reviews evidence on condom effectiveness in reducing the risk of heterosexually transmitted human HIV. A meta-analysis conducted on data from *in vivo* studies of HIV discordant sexual partners is used to estimate the protective effect of condoms. Although contraceptive research indicates that condoms are 87% effective in preventing pregnancy, results of HIV transmission studies indicate that condoms may reduce risk of HIV infection by approximately 69%. Thus, efficacy may be much lower than commonly assumed, although results should be viewed tentatively due to design limitations in the original studies.

Key words—HIV prevention, sexual behavior, condoms, meta-analysis

INTRODUCTION

In the absence of an effective treatment or vaccine, control of the spread of human immunodeficiency virus (HIV) infection must be accomplished by minimizing exposure to the virus. While exposure due to transfusion has been greatly reduced, IV drug abuse and sexual contact continue to play major roles in the spread of AIDS in the general population [1]. In fact, the majority of AIDS cases both nationally and internationally are due to sexual transmission [2, 3]. While most of the cases in the United States are due to male–male sexual contact, the number of cases due to heterosexual transmission is increasing and directly affects increases in perinatal exposures [1]. For women, heterosexual sexual contact represents the second largest risk factor [4]. A variety of public health recommendations have been made to retard the spread of HIV [5]; among them are guidelines specifically to reduce sexual transmission [6,7]. The 'safe sex' guidelines suggest that sexual transmission of HIV can be avoided if penetrative sexual activities are avoided or if condoms are used during those activities [8].

While it is acknowledged that sex with condoms may not be truly safe [9–12], it is unclear how much protection condoms do provide. Before condoms can be recommended as a prophylaxis for sexually transmitted HIV, their efficacy must be considered. In this review, the available evidence on condom effectiveness in reducing sexually transmitted HIV is examined and the amount of risk reduction due to condom use is estimated. The physical properties of condoms also suggest that they should provide an effective barrier to HIV. In addition, research on other sexually transmitted diseases [13] and contraception [14] suggests that condoms should provide an effective barrier against HIV. Unfortunately, laboratory tests of condom effectiveness have had too few observations to accurately estimate failure rates and human studies in general have not controlled for sources of bias and confounding. Furthermore, many of these reports are outside of the scientific peer-review process and appear only as 'correspondence' or 'letters to the editor' in scientific journals.

The principal argument presented for the impermeability of condoms (and surgical gloves) to HIV has been the size of the virus compared to surface porosity [15–22]. Some have suggested that spermicide may have virucidal effects [21–23] and if used in conjunction with a condom, may make condoms more effective. Laboratory studies have used a variety of models (culture growth, pressure/inflation stress, and mechanical models simulating intercourse), but none has used proper scientific controls (such as blinding) nor an adequate sample size to estimate HIV permeability. Scientific studies of condom permeability have been limited to tests of less than a dozen condoms per test. Such small sample sizes, even when no 'failures' are observed cannot rule-out the possibility that condoms may leak active HIV. Confidence intervals constructed around reported failure rates indicate that 'true' permeability rates could be as high as 30–97% (Table 1) [24]. New data indicate that some condoms do leak HIV and that leakage is not necessarily related to whether or not they are made of latex [25].

Estimates of condom failure rates must also take into account other known condom problems like 'user failure' in addition to product failure. Some have argued that condom failure rates with respect to contraception, demonstrate that sex with a condom is not truly 'safe' [9]. While this argument has face validity, contraceptive failure rates are often misunderstood and sometimes misrepresented [26]. The contraceptive literature suggests that condom failure rates are approximately 9–14% [14]. This means that of 100 couples using condoms exclusively for contraception for one year, approximately 12 will become pregnant. This is equivalent to saying that 12 out of 10,000 acts will result in pregnancy (*if* each couple has sexual intercourse twice a week for 52 weeks) [27]. The 'failure rate,' however, should be compared to that for 'no method' in order to evaluate the reduction in the number of pregnancies *due* to condom use. Since approximately 89 pregnancies per 100 couples will occur without contraception [14], the ratio 0.12/0.89 represents a 0.13 reduction or 87% effectiveness in preventing pregnancy that is due to condom use.

Contraceptive failure rates are conservative estimates of exposure, since each exposure does not result in pregnancy. The Federal Food Drug Administration quality control standards allow for a maximum failure rate (due to water leakage) of 4/1000 [28, 29]. Thus, approximately 40 out of 100 couples purchasing a condom in the U.S. would experience a condom failure due to leakage or rupture (40/10,000 acts.) *In vivo* tests, though, report much higher rates due to rupture and slippage (approximately 0.0083 [30] and 0.049 [12] for vaginal intercourse and 0.0045 [30], 0.0367 [31], 0.080 [32], 0.100 [33] and 0.445 [33] for anal intercourse).

It is clear that *in vitro* test results cannot substitute for *in vivo* estimates of performance. Estimates based on contraceptive failure rates may be too conservative and current estimates of breakage rates vary considerably. Data pertaining to condom effectiveness in reducing HIV among homosexual men [34] or reduction rates of other sexually transmitted disease [13] (i.e. gonorrhea) are equally unclear. Studies in which partners' infectivity is not confirmed, confound condom effectiveness with actual exposure. For example, if condom use is associated with having a greater number of sexual partners and thus a higher likelihood of exposure than non-users, condom effectiveness will be underestimated. On the other hand, if individuals choosing to use condoms practice other 'low risk' behaviors (i.e. fewer partners and low risk partners), then condom effectiveness will be overestimated.

The best 'test' of condom effectiveness is provided by transmission rates within HIV discordant couples. It is in this 'natural', although unfortunate, 'experiment' that better estimates of effectiveness can be obtained. Thus, this review focuses on results from studies in which the sexual partner is known to be positive for HIV antibodies. Because these studies, to date, are among heterosexuals, all data on condom effectiveness in heterosexuals are reviewed.

METHODS

This report attempts to provide a comprehensive review of published research on condom effectiveness in reducing heterosexually transmitted HIV. All reports published prior to July 1990 as peer-review articles or letters to journal editors are considered. Computerized data bases (MEDLINE and AIDSLINE) and reference lists were searched. Studies had to meet three criteria for inclusion: (1) the study had to be about heterosexual individuals who have a sexual relationship with an HIV infected person(s), (2) HIV status was determined by a blood test, and (3) an inquiry was made about condom usage. Studies selected for review are those in which researchers tested for HIV antibody (as opposed to self-reported HIV status) and inquired about condom use, because respondents have the potential of being blind to their HIV status when they respond to the sexual history questionnaire. Most of the studies done to-date on condoms and sexual transmission have been cross-sectional, with a questionnaire on sexual behaviors and a simultaneous HIV antibody test. Most have compared current examined HIV status with reported condom use in a cohort of exposed individuals; few have attempted prospective longitudinal designs with multiple tests of partners.

Articles reviewed here include studies on female prostitutes, female partners of HIV positive male hemophiliacs, partners of individuals infected by a single transfusion, and mixed studies including both male and female partners of index cases with various sources of infection (hemophiliacs, IV drug users, and bisexual men). These articles comprise the main body of evidence for condom effectiveness in reducing heterosexual transmission of HIV. A meta-analysis is conducted on the data from the studies to provide an overall estimate of the amount of risk reduction afforded by condom use. Risk reduction is estimated with a maximum likelihood estimate of the risk ratio between condom users and non-users.

Table 1. 95% binomial confidence intervals [24] for observed failure rates

Observed failures per sample size	95% confidence interval for true failure rate	Laboratory studies
0/1	0%, 97.5%	Kish *et al.* [8]
0/2	0%, 84.2%	Van de Perre *et al.* [17] Dalgleish *et al.* [20]
0/3	0%, 70.8%	Minuk *et al.* [16]
0/4	0%, 60.2%	Arnold *et al.* [19]
0/10	0%, 30.9%	Rietmeijer *et al.* [21]

Table 2. Transmission rates from prostitute studies

	HIV+ with always condom	HIV+ with some condom[a]	HIV+ with no condom	n	γ^b	P^c
Mann *et al.* [35]	0/6	26/79	74/288	373	−0.09	0.69
Darrow [38] (CDC [37])	0/22	49/438	13/108	568	−0.16	0.28
Ngugi *et al.* [39, 40]	0/1	23/49	20/28	78	+0.49	0.02

[a]All intermittent categories of users.
[b]Ordinal correlation coefficient, gamma [36], measuring dose–response association.
[c]Probability from χ^2 trend test, with three condom usage categories.

Prostitutes

Three studies are often cited among the evidence of condom effectiveness and, thus, are reviewed here (See Table 2). In a report (letter) from Zaire [35], HIV status of 373 prostitutes was correlated with their estimate of the proportion of their clients that used condoms. In the report condom use was broken-down into five categories: none, 1–25%, 26–49%, 50–74% and ⩾75%. The authors report "a significant difference in seropositivity among the 8 women reporting condom use by half or more of their partners (none of 8), as compared with women reporting less frequent use (26 of 77, 34 percent) ($P = 0.046$ by Fisher's exact test)." However, a χ^2 test of the data with the original five categories of use is not significant ($P = 0.28$), nor is a dose–response effect present (ordinal correlation $\gamma = -0.0943$[36]; χ^2 trend test, $P = 0.476$). The relationship between HIV and condom use also is not significant when condom use is dichotomized as 'half or more' (⩾50%) and 'less frequent' (<50%) (one tail Fisher's $P = 0.08$). The relationship only becomes statistically significant when all non-users of condoms (288/373 or 77% of the total sample) are omitted and a one-tail Fisher's probability is reported. The authors, however, offer no justification for ignoring 77% of the data. Furthermore, if condom use is defined as 'none' vs 'any', the data show a *higher* rate of HIV positivity *with* condom usage ($P = 0.22$).

In the United States, the Centers of Disease Control obtained sexual history data on 568 of 835 female prostitutes tested for HIV (with ELISA and Western Blot) [37, 38]. Half of the women reported a history of IV drug abuse. A higher rate of HIV positivity was found among women reporting 'unprotected vaginal exposure' (60/546, 11%) than among those reporting condom use with each vaginal exposure (0/22, 0%). The difference, however, was not statistically significant after controlling for IV drug abuse ($P = 0.10$) nor was a significant dose–response effect present $\gamma = -0.159$; χ^2 trend test $P = 0.284$) when the data were expressed as ordinal categories ('never,' 'sometimes,' 'always').

From a study done in Kenya on the effects of an educational intervention, data were reported on the association between condom use and HIV serostatus [39, 40]. The data indicate a significant association and a dose–response effect ($\gamma = 0.492$, χ^2 trend test $P = 0.0046$). However, it is not entirely clear if the data represent the amount of condom use in groups that have knowledge of their serostatus or if only those individuals who were HIV negative at the beginning of the study were later reevaluated for condom use and seroconversion.

Studies of prostitutes and individuals with partners of unknown serostatus do not provide the best test of condom effectiveness, because results are confounded with actual exposure. In the extreme case, studies that have found a co-occurrence of a relatively high rate of condom usage and no HIV infection among prostitutes [41–43] cannot legitimately conclude that the absence of HIV infection is due to condom use. A comparison group of HIV positive prostitutes is necessary to demonstrate such an association. Without an HIV-positive comparison group, it is quite possible that the women were not exposed. Furthermore, in areas where the prevalence of HIV is approximately 1% [43] or condom usage is 3% [44] it would take an extremely large sample to provide an adequate test of the hypothesis. Sample size calculations indicate that as prevalence of HIV drops from 20 to 10%, sample size requirements increase from 300 to almost 600. When prevalence is as low as one percent, a total sample size of approximately 5000 would be necessary to detect a 0.20 difference in proportions (0.05 alpha, 0.20 beta).

Hemophiliacs

There are several published reports examining HIV transmission and condom usage among female sexual partners of HIV infected male hemophiliacs. Seven of the studies deal exclusively with sexual partners of hemophiliacs [45–51]; one study included other high risk individuals [52]. Each examined a cohort of exposed women and correlated present HIV status with reported condom use. Index cases had varying degrees of HIV related disease: asymptomatic, ARC and AIDS. Some assessed index cases for T-helper cells [45, 46], Walter Reed staging [47, 48], and the presence of HIV antigen [46–48]. Female partners were tested for HIV with enzyme-linked immunosorbent assay [45, 46, 50–52] (ELISA) and/or Western Blot techniques [45–52] (one report/letter did not say [49]). Minimum duration of sexual contact with the index case ranged from 6 months to 3 years.

Most of the studies categorized condom use into two categories. Usage was variously defined as 'any vaginal intercourse without a condom during the past year' vs always used condoms [45]; no condom use vs 'consistent' use [50]; 'no condom' use vs 'routine' use

[50]; those that 'did not adhere to the use of condoms' vs those that 'always used condoms' during intercourse [49]; and nonuse vs 'regular' use [46, 52]. Some attempted to estimate the amount of 'unprotected' exposure [47, 51, 53]. In addition, some of the studies asked about the reported on: anal intercourse [45–47, 50, 52], oral sex [46, 47, 50], and sex during menses [45, 48].

Each study examined one to two dozen female sexual partners (see Table 3). The average transmission rate of HIV to female sexual partners of hemophiliacs across the studies was approximately 14%; ranging from 4% [52] to 19% [50]. These rates are comparable to other reports [54, 55]. Some of the studies could not rule-out needlesticks as a possible source of transmission [47], although some did rule-out other risk factors [46, 47, 50]. Although most of the studies found a higher rate of HIV positivity among those who did not use condoms regularly, none showed a statistically significant relation between condom use and HIV status.

Transfusions

A study of sexual transmission among sexual partners of individuals infected by a single transfusion reported on 80 of 197 recruited for participation [56]. Of the index cases, 66 had AIDS and 14 were asymptomatic; 25 were women and 55 men; and the median age was approximately 55 years. HIV status was established with ELISA and Western Blot techniques. With a single source of infection and a known date of occurrence, sexual partners' total exposure could be estimated. Partners were interviewed separately and seropositive male partners were interviewed twice to assess the presence of other risk factors. Sexual partners with other high risk factors (male–male sexual contact or IV drug use) were excluded. Condom use was defined as none vs 'any' condom use. The overall HIV transmission rate was 15% with non-significant differences between seropositive and seronegative individuals in terms of condom use and total exposure.

Mixed partner studies

Studies of HIV transmission have been conducted with sexual partners of individuals from a variety of risk groups. Mixed studies, especially studies including sexual partners of IV drug abusers, may have special methodological problems. Transmission rates are higher among these couples [3] and it is not clear if the higher rates are due to higher infectivity or if the sexual partner may have unreported IV drug use. Also, partners of bisexual men may be more likely to engage in anal intercourse.

In one study examining heterosexual transmission of HIV, 97 females who had sexual contact with an HIV infected male were interviewed and tested for HIV [57, 58]. Risk category of male partners was recorded (bisexual, hemophiliac, IV drug user) as well as number of sexual partners, sexually transmitted diseases, type of exposure (vaginal, oral, anal), and condom use. Women who used IV drugs or who received a recent transfusion were eliminated from analysis. Anal intercourse and having more than 100 contacts (vaginal, oral, and/or anal) were associated with increased risk of HIV infection. The authors found that, "condom use was not significantly associated with protection from infection."

Another study whose objective was to assess asymmetries in transmission between males and females, included a question on condom use [59]. Index cases were defined as HIV seropositive men or women with

Table 3. Transmission in HIV discordant couples

	HIV+ with condom	HIV+ W/O condom	n	P[a]	RR[b]	95% CI
Hemophiliacs						
Ragni *et al.* [50, 53]	0/9	3/13	22	0.19	0.20	0.02, 2.40
Smiley *et al.* [47]	1/9	2/9	18	0.50	0.50	0.06, 4.56
Kim *et al.* [46]	0/7	1/7	14[c]	0.50	0.33	0.02, 6.32
Goedert *et al.* [45]	0/6	4/18	24	0.29	0.30	0.02, 3.76
Laurian *et al.* [49]	0/14	3/17	31	0.15	0.17	0.01, 2.06
Van der Ende *et al.* [48]	0/2	0/11	13[d]	—	—	
Transfusions						
Peterman *et al.* [56]	0/6	12/74	80	0.36	0.43	0.03, 5.39
Mixed						
Padian *et al.* [57, 58]	5/31	11/42	73[e]	0.23	0.62	0.24, 1.56
Johnson *et al.* [59]	0/4	15/74	78[c]	0.42	0.48	0.04, 5.78
Roumelioutou-	0/37	12/16	53	< 0.0001	0.02	0.01, 0.07
Karayannis [52]	0/21	1/4	25[f]	0.16	0.08	0.01, 0.84
Fischl *et al.* [60]	3/12	21/33	45	0.0001	0.27	0.14, 0.52
	1/10	12/14	24[g]	0.0004	0.12	0.04, 0.38
European study [61]	0/11	42/44	155	0.03	0.14	0.02, 1.10

[a]Probability values are one-tail Fisher's exact probabilities.
[b]In tables with zero cells, 0.5 was added to cells prior to calculating the risk ratio and confidence interval.
[c]Actual frequencies provided by senior author of original article.
[d]Because both numerators are zero, this study is omitted in analysis.
[e]Female contacts of male index cases.
[f]Subset of subjects that were partners of hemophiliacs.
[g]Subset of subjects who were HIV− at entry and remained sexually active.

a known risk factor (e.g. bisexuality or IV drug use). Contact cases were partners (casual and regular) who were involved with an index case in a heterosexual relationship (either currently or within the last year). Partners with a history of IV drug use were excluded. The number of acts of 'unprotected' vaginal intercourse were estimated and the authors report no differences between seropositive and seronegative partners. Amount of condom use was explicitly mentioned only for female contacts: 0/4 female partners who reported using condoms 'all of the time' were seropositive and, thus, 15/74 of non or intermittent users were seropositive.

A study conducted in Greece [52] estimated the transmission rates to females from four groups of HIV positive males: bisexuals (5/18 female partners were positive) IV drug users (2/6), heterosexuals (4/4), and hemophiliacs (1/25). (The subset of 25 hemophiliacs was described in the hemophiliac section.) Sexual relationships had a minimum duration of 6 months. The transmission rate for all groups combined was 0% (0/37) with 'regular' condom use and 75% (12/16) with non use. These data indicate a protective effect with regular use of condoms ($P < 0.0001$).

Another statistically significant finding, appears in a study by Fischl *et al.* [60]. Fischl *et al.*studied the sexual partners of 45 individuals recently diagnosed with AIDS. All participants were tested for HIV upon entry to the study (by ELISA) and then again at approximately 6, 12 and 18 months. However, a substantial number of individuals (27/45) were *not* tested at 18 months, suggesting that the 18 month observations, where present, should not have been included in the analyses. Fischl *et al.*'s results show a significant association between condom use and HIV transmission. Of the 32 sexual partners who were initially seronegative, 8 choose to abstain from sexual relations. Of the 24 sexually active individuals, 10% (1/10) of those reporting routine condom use and 86% (12/14) of non-routine users were positive for HIV antibody ($P = 0.0004$). Although a strength of the study is the longitudinal design, allowing initially HIV positive individuals to be screened out, multiple HIV testing makes it unlikely that subjects were blinded to their own HIV status. Knowledge of HIV status may affect both reported and actual condom use.

In a collaborative European study [61], 155 female partners of HIV positive men were studied to determine risk factors for sexual transmission of HIV from men to women. Couples were interviewed regarding a variety of risk factors, including contraceptive behavior. Women with any non-sexual risk factors for transmission were excluded. HIV status was determined by ELISA. Of couples using condoms as their usual contraceptive method, 0/11 were positive for HIV compared to 42/144 who were positive who did not use condoms ($P < 0.03$). This apparent relation between condom use and HIV transmission, however, is overshadowed when other factors are also considered. In a logistic regression analysis only the clinical state of the index case (full-blown AIDS), history of STD in the last 5 years, and anal intercourse were significant predictors of HIV transmission. Duration of relationship, frequency of sexual contacts, sexual practices (other than anal intercourse) and contraceptive behavior (condom use) were no longer significantly associated with transmission of HIV.

RESULTS

Sixteen studies were initially selected for review. However, the studies on prostitutes contain unclear and possibly contradictory information. These studies are summarized in Table 2. The major limitation of the prostitute studies is that exposure is not confirmed for each individual. For this reason, only the studies with partners of HIV positive individuals were considered further. The remaining thirteen studies met the inclusion criteria, including *known* exposure to an HIV infected person. In addition, two hemophiliac studies were omitted. In one study [51], exposure was defined as the amount of time prior to the initiation of condom usage. The assumption that exposure did not occur after initiation of condom usage does not permit estimation of efficacy. Therefore, the study was eliminated. Another study, by Van der Ende *et al.* [48], is included in the summary in Table 3, but is not included in the meta-analysis because there are no seroconversions (0/2 and 0/11). The use of the continuity correction (adding 0.5 to all cells), in this case, would provide an inaccurate and probably unfair estimate of the risk ratio showing a harmful effect of condom usage. Therefore, the Van der Ende *et al.* study is omitted from the meta-analyses. Thus, eleven studies are included in the final analyses.

The primary purpose of these studies has been to document and estimate rates of heterosexual transmission. As such, this set of articles is minimally affected by 'publication' bias, where only statistically significant findings tend to be published. In fact, most of the tests of condom effectiveness have been statistically *non*significant. With the exception of three studies [52, 60, 61] most lack the statistical power to detect even a moderate effect. The sample sizes necessary to detect a difference can be quite large depending upon the HIV transmission rate and the proportion of condom users [62]. Statistical power can be increased by combing results across studies, if studies are comparable. A combined test of statistical significance indicates that the level of protection provided by condoms is greater than chance (Fisher's combined test, $\chi^2[22] = 83.189$, $P < 0.001$) [62–64].

A more important question, though, concerns the *amount* of protection. Effectiveness is defined as one minus the failure rate. The failure rate is estimated by the ratio of two conditional probabilities. This risk ratio is the probability of HIV positivity given con-

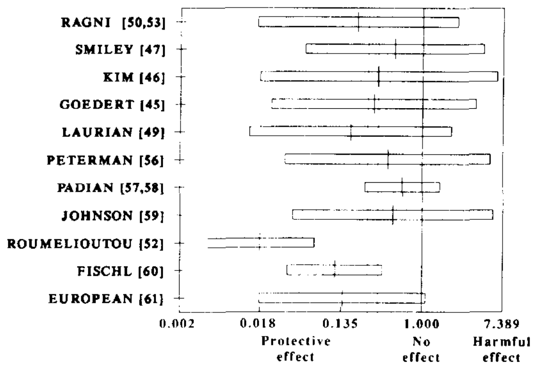

Fig. 1. The risk interval captured by 10 studies extends from the lower-limit of the Padian Study to the upper-limit of the Fischl Study.

dom use divided by the probability of HIV positivity without condom use. It is not adequate simply to use the proportion of HIV positive condom users as an estimate of the failure rate *due* to condoms, because that estimate is confounded with the probability of infection. For example, if 0.10 (1/10) of exposed individuals using condoms acquired HIV, but 0.10 of individuals not using condoms also required HIV, then the probability of a failure *due to condom use* would be 1.0 or 100%.

The failure rate is estimated here with a maximum likelihood estimate of the risk ratio, calculated from the original studies [65]. Because the studies are not case-control studies, the conditional probabilities and, thus, the risk ratio can be estimated directly from the data. Risk ratios and confidence intervals for the eleven individual studies are presented in Table 3 and Fig. 1 (a continuity correction was used in tables containing a zero cell). 'Pooled' estimates are presented for sub-groups of studies and for all studies together. Heterogeneity is tested with the likelihood ratio (G^2) test.

The first group consists of the six hemophiliac/transfusion studies. Although the studies vary in their definitions of sexual partner and condom use, four of the studies, Ragni *et al.* [50, 53], Smiley *et al.* [47], Kim *et al.* [46] and Peterman *et al.* [56], are similar ('monogamous' sexual partners for at least one year and condom use is defined as none-use vs sometimes/always). The relative risk of HIV infection given condom use is similar across the four studies allowing for a pooled estimate of the risk ratio of 0.35 (95% CI:0.10, 1.22). Two additional studies, Goedert *et al.* [45] and Laurian *et al.* [49], examined sexual partners of hemophiliacs with relationships longer than one year, and appear to have classified intermittent condom use with non-use. The odds ratio is homogeneous across these two studies allowing for a combined estimate of 0.22 (95% CI:0.04, 1.33). Together, all six studies, regardless of varying definitions of condom usage and length of recall period, are homogeneous ($G^2[5] = 2.79$, $P = 0.73$). The pooled risk ratio for all 6 studies together is 0.30 (95%CI:0.11, 0.83).

The second group of studies contains the five mixed partner studies. The pooled risk ratio for all five studies (using the subjects from Fischl *et al.* [60] who were initially negative) is 0.20 (95% CI:0.12, 0.35). The heterogeneity among the mixed partner studies is statistically significant ($G^2[4] = 19.918$, $P = 0.0005$) and noteworthy. The Fischl *et al.* study shows a stronger protective effect than most of the cross-sectional studies, possibly due to screening-out of individuals who were HIV positive prior to initiation of condom use. HIV positivity in individuals prior to initiation of condom use, would result in an underestimation of the magnitude of a protective effect *if* condom use is not correlated with other variables. However, the cross-sectional study of Roumelioutou-Karayannis *et al.* [52] shows the strongest effect of all studies. The Roumelioutou-Karayannis *et al.* study is probably an outlier. While most hemophiliac studies show a 14% transmission rate for their hemophiliac patients, they showed a 4% transmission rate among their hemophiliac patients, possibly due to such a short exposure period (6 month minimum sexual relationship).

Results from all eleven partner studies can be considered together in a variety of ways. The first and the simplest is an examination of the risk ratio interval that is captured by all studies (Fig. 1). If there is no interval captured by all studies, we may omit one outlier (in this case, the Roumelioutou-Karayannis *et al.* study [52]) and consider the interval spanned by the remaining studies [66]. Ten of the eleven studies include the interval from the lower limit of the Padian study to the upper limit of the Fischl *et al* study: 0.24–0.38 (76–62% efficacy). Another method is to quantitatively estimate the risk ratio across studies [67–70]. However, in order for such a pooled estimate to be meaningful, risk must be homogeneous across studies. There is significant heterogeneity among the studies ($G^2[10] = 22.81$, $P = 0.01$). Without the Roumelioutou-Karayannis *et al.* study, remaining ten studies are homogeneous ($G^2[9] = 12.24$, $P = 0.20$). The pooled risk ratio is 0.31 (95%CI:0.18, 0.54). For the same ten studies, the pooled log odds ratio is 0.27 (95% CI:0.13, 0.58) and the Mantel-Haenzel summary odds ratio is 0.24 (95% CI:0.12, 0.47). All methods are in general agreement with similar midpoints (67, 69, 73 and 76% effectiveness) although the graphical method provides a slightly tighter interval than the risk ratio (46–82% efficacy) or odds ratio methods. These results indicate that exposed condom users will be about a third as likely to become infected as exposed individuals practicing 'unprotected' sex. Thus, condom effectiveness or the risk reduction due to condom use can be estimated at 69% (one minus the risk ratio).

DISCUSSION

Current evidence suggests that condom use may reduce the rate of sexually transmitted HIV.

Although it is biologically plausible that condoms should provide protection from sexually transmitted HIV, a dose–response relationship and a consistent association across studies remain to be demonstrated. Estimates of condom failure rates from laboratory and human studies are limited by small sample sizes. Because of small sample sizes, *in vitro* estimates of permeability do not rule-out the possibility of HIV leakage. An aggregated estimate of condom effectiveness from *in vivo* studies suggests a 69% reduction in risk, but true effectiveness may be as low as 46% or as high as 82%. This effectiveness is less than that suggested by contraceptive studies and is conceivable, because condoms may leak HIV [25] and HIV may be transmitted through orogenital [50, 60, 71, 72] and anal routes [57, 59]. Such a meta-analysis, however, needs to be viewed tentatively. Most *in vivo* studies suffer from design problems, such as not controlling for degree of exposure, source of exposure, and time of seroconversion. Furthermore, this analysis provides only an estimate of the 'crude' risk ratio, without stratifying or controlling for confounding variables.

The importance of examining several risk factors simultaneously in a multivariate analysis is underscored by the large European Collaborative study [61]. When the clinical state of the index patient, the practice of anal intercourse, and a history of sexually transmitted diseases (STDs) are considered, condom use no longer significantly reduced HIV transmission. Another study of 368 female partners of male index cases [73], published since this analysis was done, indicates that 'often or always' use of condoms (ignoring 'sometimes' users) may have an efficacy of 70% (95% CI: 0.90%). Their crude estimate of efficacy (80%) was reduced (70%) and condoms no longer had a significant protective effect, when other risk factors were considered in a multivariate model. Again, a history of STDs, degree of immunocompetence impairment in the index case, and the practice of anal sex, as well as the frequency of sex, and use of an intrauterine device overshadowed the potentially protective effect of condom usage.

An obvious limitation in many of these studies is in the definition of condom use. What is 'regular use,' 'consistent use' vs 'any unprotected vaginal intercourse?' Are condoms being used correctly? Is recall of sexual behavior over 6 months, 1 year, or 2 year period accurate? Could infection by HIV have occurred prior to initiation of condom use? In addition, there may be other sources of HIV exposure confounding the results, e.g. parenteral (needlestick) exposure or other non-vaginal (oral, anal) sexual contact. Results also may be confounded by degree of exposure, e.g. degree of intermittent condom use, degree of infectivity in the HIV positive partner, duration of sexual relationship, frequency of sexual contact, or presence of a genital ulcerative condition [74]. Confounding can occur when condom use is associated with any of these factors for example, if couples with relationships of longer duration tend to use condoms less.

Another important aspect of study design is the need for 'double-blinding.' Studies have consistently failed to report blinding procedures. Respondents and interviewers (or study coordinators) should be 'blinded' as to the respondents' HIV status. Failure to use this procedure, jeopardizes the validity of results by introducing sources of bias [75]. Prior knowledge of HIV status may affect how questions are asked and answered. Interviewers or study coordinators may, unknowingly, give clues or ask questions that affect participants' responses.

In vivo tests of condom effectiveness present especially difficult design problems. While a cross-sectional design may provide an estimate of the sexual transmission rate, it is not necessarily the best design to evaluate condom effectiveness as a barrier to HIV transmission principally because HIV may have been transmitted prior to the initiation of regular condom usage. Longitudinal designs, on the other hand, are vulnerable to biases resulting from multiple testing procedures. If HIV tests and sexual behavior interviews are repeated it is unlikely that participants will be blind to their HIV status when responding to condom use questions [76].

While researchers may acknowledge the need for 'blinding' in experimental studies on humans, some are not aware that proper scientific controls are equally as important in observational and laboratory studies. In laboratory studies, multiple observers and multiple 'specimens' are necessary to account for sampling variability. The need for proper control procedures was dramatically emphasized in the homeopathic dilution study published in *Nature* [77], where it was claimed that anti-immunoglobulin E antibodies retained their biological effectiveness in concentrations from 10^2 to 10^{120}. A replication of that study found that the observed effect was due to a failure to estimate inter-observer variability between specimens and a failure to blind observers as to which specimens they were about to measure [78].

As large or coordinated, multi-site studies are completed, it is extremely important that researchers present their results in such a way as to facilitate pooling across studies and that journals continue to publish the negative results. Exact procedures and controls should be described. As much care should be taken in asking about and reporting on condom use as with assessing HIV status. Actual wording and response categories used in data collection should be reported. If wording were identical to that in national surveys [79], researchers could take advantage of the enormous amount of work on reliability and validity [80, 81] and comparisons could be made to national data. Reliability of sexual behavior questions can be increased by combining the responses of both partners [82, 83]. Any re-categorization or collapsing of categories that may occur during analysis also should be reported. The coding of intermittent users should be clear as should handling of inconsistencies across time or between partners. At a minimum, condom use should have three categories: none (0% of the time, intermittent 1–99%), and always (100%). Presentation of results should include the frequencies or percentages observed in the data and not just the results of a statistical test. Ideally, small studies should be allowed to publish their data.

Until more is known about condom effectiveness, condom use promotion may have both positive and negative effects. Encouragement of condom use among the general population may result in the indirect benefit of increased public awareness of safer sex practices. Among male homosexuals, HIV awareness has resulted in increased condom usage and decreased number of sexual partners [84]. A negative effect has been the misinterpretation and misinformation regarding condom effectiveness. The public at-large may not understand the difference between 'condoms may reduce risk of' and 'condoms will prevent' HIV infection. It is a disservice to encourage the belief that condoms *will prevent* sexual transmission of HIV.

Condoms will not eliminate risk of sexual transmission and, in fact, may only lower risk somewhat. The results of mathematical modeling [85, 86] indicate that the largest risk reduction comes from selecting a partner from a low risk group or someone that is known to be negative for HIV antibody [85]. As the probability of selecting an HIV infected sexual partner decreases from 0.20 (high risk partner) to 0.002 (low risk partner) to 0.00002 (someone with an HIV negative blood test), the probability of infection after 100 exposures from that partner (without a condom and 0.001 probability of infectivity per exposure) drops from 0.02 to 0.0002 to 0.000002. Thus, risk can be reduced from two to four orders of magnitude by selecting a low risk partner. Condoms, on the other hand, if used 100% of the time can *at most* reduce risk by one order of magnitude. For example, if condoms are 90% effective (as many have assumed) and are used 100% of the time, the probability of HIV infection can be reduced from 0.0002 to 0.00002 (prevalence = 0.002, 100 exposures from one partner, infectivity per exposure = 0.001). Empirical data (reviewed in this report) indicate that a 90% reduction in risk due to condom use may be overly optimistic. The protective effect as estimated from human studies, regardless of use definitions, indicates a possible 69% reduction in risk.

Linking safer-sex practices with voluntary HIV testing may be the only way to meaningfully reduce risk. The largest risk reduction (second only to celibacy or long-term monogamy) comes from choosing a low-risk partner and the lowest risk sexual partner is someone with demonstrated HIV negativity. Goedert [87] recommends a strategy of combining HIV testing with safe-sex practices (monogamy, condom use, no anal sex) and possible re-testing to reduce risk, but also states that "only celibacy and masturbation can be considered truly safe." Thus, high risk behaviors probably should not be avoided, but be eliminated; and condom usage considered a secondary strategy in prevention.

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