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A Systematic Review of the Quality of Trials Evaluating Biomedical HIV Prevention Interventions Shows that Many Lack Power

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Abstract

Purpose—Several randomized, controlled trials (RCTs) have tested strategies to prevent sexual acquisition of HIV infection, but their quality has been variable. We aimed to identify, describe, and evaluate the quality of RCTs studying biomedical interventions to prevent HIV acquisition by sexual transmission.

Method—We conducted a systematic review to identify all RCTs evaluating the efficacy of biomedical HIV prevention interventions. We assessed seven generic and content-specific quality components important in HIV prevention trials, factors influencing study power, co-interventions provided, and trial ethics.

Results—We identified 26 eligible RCTs. The median number of quality components judged to be inadequate or unclear was 3 (range, 1-4) in 1992-1998, 3 (range, 1-4) in 1999-2003, and 0 (range 0-2) in 2004-2008 ($p < 0.001$). Common problems that may have biased results included low retention (median 84%), poor adherence to interventions requiring ongoing use (median $\leq 78\%$), and lower HIV incidence than expected *a priori* (in 8 of 11 trials where evaluable).

Conclusion—Reporting of trials of biomedical HIV prevention interventions has improved over time. However, quality improvement is needed in several key areas that influence study power,

including participant retention, adherence to interventions, and estimation of expected HIV incidence.

Keywords

HIV; primary prevention; clinical trial; systematic review; research methodology; statistical bias

Introduction

In 2007, 2.7 million adults became infected with the human immunodeficiency virus (HIV) worldwide, predominantly through sexual transmission [1]. Because behavioral risk reduction programs have had limited effectiveness at reducing sexual transmission [2-5], more effective methods to decrease this risk are urgently needed. One biomedical intervention, male circumcision [6-8], has demonstrated efficacy in randomized controlled trials (RCTs). Other interventions, such as sexually transmitted disease (STD) control, diaphragm use, microbicides, pre-exposure prophylaxis with antiretroviral agents, and candidate vaccines, have yielded inconclusive, equivocal, or negative results to date [9, 10]. These RCTs have yielded important lessons about the design of effective interventions, and have also taught us the importance of HIV prevention trial quality [10].

Opportunities for rigorous evaluation of HIV prevention interventions are limited, since such studies tend to be both logistically challenging and very costly. Accordingly, trials must be of high quality to ensure efficient use of research funds. Systematic reviews of specific preventive interventions for HIV have been published or are planned [9, 11-13]; however, a systematic review of the quality of biomedical intervention trials has not been conducted. Our objective was to identify, describe, and evaluate the quality of all RCTs that have investigated the efficacy of biomedical interventions to prevent sexual acquisition of HIV. We aimed to determine whether trial quality had improved over time and to highlight common challenges to be addressed in future trials.

Methods

Types of studies

We included RCTs of preventive interventions aimed at reducing the incidence of sexually transmitted HIV infections in adolescents and adults. The unit of randomization could be either individuals or clusters of individuals (e.g., communities). We excluded studies that used historical controls.

Types of participants

We included studies of adolescent or adult populations. Studies of pregnant women were only included when a primary objective of the study was the prevention of HIV acquisition in the mother (e.g., from a sexual partner) and not to prevent mother-to-child transmission. Studies that enrolled injection drug users were included if the intervention tested was also hypothesized to prevent sexual transmission.

Types of interventions

We included biomedical interventions for prevention of HIV transmission. We excluded interventions aimed at behavior change, which included interventions to promote Abstinence, Being faithful to a single partner, or using Condoms (the so-called “ABC’s” of HIV prevention) or targeting other risk behaviors such as decreasing needle sharing among injection drug users. Interventions aimed at secondary prevention of HIV transmission (e.g., risk reduction or biomedical interventions targeting HIV-seropositive persons) were

excluded. We included studies where the comparators were placebo, routine HIV prevention services, or deferral of the intervention.

Types of outcome measures

We included only trials where HIV incidence was a prespecified primary or secondary outcome measure.

Search methods

With the help of an expert librarian, electronic databases of Medline (1950 – March 2009), Embase (1980 – March 2009), and the Cochrane Central Register of Controlled Trials (through March 2009) were searched for eligible articles. We also reviewed abstracts presented from March 2007 through March 2009 at four major HIV conferences: the International Acquired Immune Deficiency Syndrome (AIDS) conference, International AIDS Society conference, the AIDS Vaccine conference, and the Conference on Retroviruses and Opportunistic Infections. We reviewed the reference lists of identified trials and recent review articles, as well as preliminary data from registered trials. An example of the search terms used (for Medline) is presented in Supplemental Information 1.

Data collection and analysis

One author (SMG) scanned the titles of all identified studies for obvious exclusions. Potential abstracts were reviewed for eligibility and selection of articles for further review, using strict inclusion and exclusion criteria as described above. We reviewed the full texts of all remaining published articles and extracted data from eligible studies using a standardized form. When trials referenced previous publications containing details of trial design or baseline characteristics, we reviewed the full text of the earlier article. Data were independently extracted by two reviewers (SMG, ZCVA). Discrepancies regarding non-quality items were resolved through consensus while disagreements regarding quality criteria were resolved by an independent third review (PS) and subsequent consensus.

Review of quality components

To evaluate trial quality, we focused on important quality components as recommended by the CONSORT guidelines [14, 15]. We classified each component of methodologic quality as adequate, inadequate, or unclear, using the criteria of the Cochrane Collaboration's "risk of bias" tool [16], tailored specifically for HIV prevention trials. We rated seven quality components for each trial (Table 1): allocation sequence generation, allocation concealment, blinding of assessors and subjects, handling of attrition, non-selective reporting, sample size estimation, and inclusion of subjects in analysis [16]. We noted when blinding was not possible due to the nature of the intervention or to the lack of an adequate placebo at the time, and did not classify this as inadequate.

Review of factors influencing study power

We also summarized data on additional factors that may have introduced bias by reducing trial power. Data related to study power included number of participants enrolled, target enrolment, percent of target met, number per group as randomized, actual versus planned follow-up duration, loss to follow-up per group, and percent retention. Where actual follow-up was not specifically reported, mean follow-up was calculated as the total number of person-years divided by the total number of participants in the primary analysis. Reported median adherence in the intervention group and the method of adherence assessment (e.g., self report, biologic testing) were noted. Reported condom use in each group after follow-up was abstracted, selecting the latest reporting period available. We classified contamination as definite when it was reported in trial results and as possible if the intervention could have

been obtained outside the trial or from another participant. Incidence and expected incidence in the control group were abstracted as presented in the trial publication. If one was expressed as a proportion (e.g., 4% at 2 years) and the other as a rate (e.g., 2/100 person-years of observation), these data were presented but no direct comparison made.

Review of co-interventions and ethics

Prevention interventions offered to all study participants were viewed as co-interventions, since they also may have the effect of reducing study outcomes. These co-interventions included HIV counseling and testing, condom provision, screening and treatment for STDs, and needle exchange for intravenous drug users. In addition, information was noted regarding care provided to both ineligible candidates and participants, informed consent, and ethical approvals.

Data synthesis and analysis

We summarized trial attributes using medians and ranges for continuous data, and frequencies and percentages for categorical data. Because preliminary graphs showed a gradual improvement in quality with no specific change point, we divided the trials into 3 periods of 5-7 years each: 1992-1998 ($n = 3$), 1999-2003 ($n = 6$), 2004-2008 ($n = 17$). Trends over time in reporting of quality components were analyzed with Cuzick's nonparametric test for trend across ordered groups for binary variables [17] and Kruskal-Wallis tests for continuous variables. Comparison of actual versus expected incidence in control groups was made using the Wilcoxon signed ranks test. Heterogeneity of interventions precluded a summary statistic of effectiveness. All analyses were performed using Stata (version 9.0, Stata Corporation, College Station, Texas, USA).

Results

Search results

We identified 26 full-text articles and 2 abstracts reporting RCTs that met our search criteria (Figure 1). Over 109,000 participants were enrolled in these trials. Microbicides ($n = 11$) and STD control interventions ($n = 8$) were the most frequently tested strategies (Table 2). No quasi-randomized studies (randomized based on days of week, odd/even date of birth, hospital number, etc.) were identified. Twenty-five studies compared a single intervention versus control group; two studies had three arms: one community-randomized trial compared both a behavioral intervention alone and the same intervention with improved STD control to routine services [18], and one microbicide trial compared two different gel products to placebo or no gel [19].

Trial Outcomes

The median sample size in the included studies was 2,350 (range, 138 – 20,516), and the median duration of follow-up was 18 months (range, 6 – 36 months). Overall, 13 of the 28 trials were terminated early (Table 2). All three trials of male circumcision were stopped early due to strongly positive findings of a preventive effect [6-8]. At least two microbicide interventions may have increased HIV risk: a trial testing a cellulose sulfate gel was stopped early for harm [20], while an earlier trial of a nonoxynol-9-containing gel was completed but also reported a higher risk of HIV-1 acquisition in more frequent users [21]. These findings led to the early stopping of an additional RCT [22], and confirmed the lack of efficacy in previous studies [23-25], two of which had been stopped for futility [23, 24]. Several additional RCTs were stopped for futility: two RCTs and one arm of an ongoing trial that tested newer microbicide candidates [26, 27, 28], one STD control trial [29], and two vaccine trials [30, 31]. The only published study of pre-exposure prophylaxis was stopped

after two trial sites were closed, one due to concerns from the host country about the standard of post-trial care for seroconverters, and the other due to repeated noncompliance with the protocol by research staff at the site [32].

Quality of Trials

We excluded two abstracts from detailed quality review because we were unable to obtain information regarding trial details [19, 31]. We found that most of the twenty-six included studies adhered to CONSORT guidelines for the reporting of results (Table 3) [14, 15]. In all studies, follow-up and outcome ascertainment procedures were the same in each randomized arm. In addition, all trials achieved baseline balance in important participant characteristics in the study arms. A modified intention-to-treat analysis, including only participants with at least one follow-up evaluation and excluding participants found to be ineligible after randomization, was presented for every RCT assessed; therefore, inclusion in analysis was adequate in all RCTs and is not presented in the table. We did not judge blinding to be inadequate or unclear when it was not possible. Of seven quality components, the median number judged inadequate or unclear across trials was 1 (range, 0-4). The median number of components judged inadequate or unclear was 3 (range, 1-4) in 1992-1998, 3 (range, 1-4) in 1999-2003, and 0 (range 0-2) in 2004-2008 ($p < 0.001$). This improvement in trial quality is primarily driven by the difference between the two earlier periods and the most recent period ($p=0.0002$). Each quality component is discussed briefly below.

Allocation and blinding—Allocation sequence generation and allocation concealment were adequate when reported. Blinding of participants was often not possible due to the nature of the intervention (male circumcision [6-8], diaphragm [33], and community STD interventions [18, 34, 35]). Blinding was judged inadequate in one microbicide trial (comparing a sponge to a placebo gel that was switched to a cream) [23]. One study reported problems with false positive ELISA results at its first interim analysis, but there is no indication that this was related to problems with blinding [26]. The proportion of trials reporting adequate allocation sequence generation increased over time (2 of 3, 3 of 6, and 16 of 17 in each time period, $p=0.058$), as did reporting of allocation concealment (1 of 3, 2 of 6, and 14 of 17; $p=0.025$) but not adequacy of blinding when this was possible (1 of 2, 2 of 2, 12 of 12; $p=0.831$).

Handling of attrition—In all included RCTs, participants were deemed lost to follow-up when they could not be reached despite tracing efforts after missed visits. Other participants withdrew, discontinued participation due to various reasons, or were known to have died. Exclusions were made if no HIV test was available during follow-up (i.e., outcome ascertainment not possible) or if the participant had a positive PCR test for HIV at enrolment (i.e., should have been excluded but test not available in real time). Balance across arms in attrition rates (including deaths) and exclusions was adequate in nineteen studies, but unclear in seven studies. In the four community-randomized studies, participants included both HIV-infected and HIV-uninfected persons, although HIV incidence during follow-up was analyzed in the initially uninfected subgroup. In each of these trials, no data is presented on trial balance specifically in the HIV-uninfected subgroup, making it impossible to say whether differential loss-to-follow-up occurred in the intention-to-treat cohort [18, 29, 34, 35].

Two circumcision trials and one microbicide trial reported differential loss to follow-up; in all three cases, it was unclear if this difference was related to the study outcome [6, 7, 23]. Since blinding was not possible in the circumcision trials and was inadequate in the microbicide trial, small differences in loss to follow-up could indicate attrition bias. For example, in the microbicide trial, women assigned to a nonoxynol-9 sponge had lower

follow-up rates [23]. It is conceivable that genital irritation caused by the sponge was more severe in women with more frequent use and that more frequent use was related to both HIV risk and drop-out, thereby biasing results. Adequacy of reported handling of attrition did not improve significantly over time (1 of 3, 4 of 6, and 14 of 17 in each time period, $p = 0.083$).

Freedom from selective reporting—Fifteen of the 26 studies were judged free of selective reporting based on trial registration with posted information on objectives and planned analyses; six of these studies made the trial protocol available as supplemental information with the trial publication. Five additional trials had published details of the study design prior to trial completion.[18, 29, 34, 36, 37] Trials that had no publication on study design and were not registered could not be adequately reviewed and were judged unclear. One vaccine trial reported a subgroup analysis demonstrating efficacy among ethnic minority participants despite a negative overall result [37]. These analyses have been criticized for limited subgroup sample size, but were in fact planned *a priori* [38]. The number of RCTs with protocol information available prior to publication increased significantly over time (1 of 3, 2 of 6, and 17 of 17 in each time period, $p = 0.001$).

Analytical bias—Two studies were determined inadequate with respect to sample size reporting because they did not include a rationale for the numbers enrolled [24, 39]. There was no significant difference in reporting of sample size over time (3 of 3, 4 of 6, and 17 of 17 in each time period, $p = 0.262$).

Factors Influencing Trial Power

We collected information on other factors that may have biased results by decreasing power to detect an important effect, as summarized in Table 4. Common problems that may have biased results included low retention, poor adherence to interventions, and lower HIV incidence than expected. These and other factors are discussed below.

Enrolment and retention—All but three studies reported data on individuals who were screened but did not enroll [23, 24, 25]. Six of twenty-four trials for which target sample size information was available did not enroll the intended number of participants. Reasons were early stopping [20, 22, 32] and slow enrolment, necessitating an extension of recruitment or the follow-up duration [35, 40, 41]. Two studies with slow enrolment had more endpoints than expected and so were judged to have sufficient power [40, 41]. One study was stopped due to slow enrolment and low retention of participants [23]. Median retention in these RCTs was 84% (IQR, 72%-89%). Retention of at least 80% of participants has been a customary goal for clinical trials [42]; 11 of the 26 RCTs included had a retention rate <80%.

Adherence—The definition of adherence and method of assessment varied by intervention (e.g., direct observation of circumcision status, self-reported microbicide use). Median adherence in the intervention group was 94% for circumcision, 90% for STD control (when this could be individually assessed), 84% for vaccination, 78% for microbicides, 74% for pre-exposure prophylaxis, and 73% for the diaphragm (Table 4). In trials in which a more stringent biologic method was used to supplement self-report or pill count for interventions requiring daily administration, adherence was lower by the more stringent method (i.e., 96% by self-report vs. 41% by applicator testing; 90% by pill count vs. 33%-67% by urine testing) [41, 43].

HIV incidence—The median target reduction in HIV incidence was 50% (IQR, 50% – 50%; range, 33% – 75%). Actual incidence was lower than expected in 8/11 trials (73%) for which this was evaluable, although this difference did not reach significance ($p = 0.083$).

Sample size was increased due to low HIV incidence in three studies [33, 36, 43], and follow-up was prolonged in two of these [36, 43]. Two microbicide studies were halted because they would have needed to enroll too many additional women, given incidence in the ongoing trial [26, 27].

Co-Interventions and Ethics

All but one trial reported provision of HIV counseling and testing to trial participants [34]. Condom provision was reported in all but three trials [30, 34, 37] and STD care was provided in all but four trials [30, 32, 37, 44]. Vaccine trials were less likely to report routine provision of condoms and STD treatment to participants [30, 37, 44]. Of note, the only trial that recruited injection drugs users could not provide clean needle exchange at study sites, as this was illegal in the host country [44]. HIV care referral was not specified by any trial published prior to 2005; after this year, all but two trials specified that referral of screenees and participants testing HIV-seropositive for care was available [35, 40]. Two trials included partner STD treatment as a benefit to study participants [7, 8]. All studies specified that informed consent was sought from participants, and all but one RCT [34] provided information on relevant ethical approvals.

Discussion

No comprehensive review of the quality of HIV-1 prevention trials has been conducted previously. Where meta-analyses of specific interventions have been conducted, detailed quality assessment was not a key feature [9, 11, 13]. For example, a meta-analysis of nonoxynol-9-containing microbicides for HIV prevention considered the quality of the 5 included trials to be fair to high, but only ratings on allocation concealment were presented [13]. Narrative reviews representing expert opinion on HIV prevention trials have recently been published [10, 45], but have included little data abstracted from trials. This is the first study to evaluate the quality of these trials as a group, despite their similar objective (HIV prevention), target population (adults at high risk for sexual acquisition), and design (long-term follow-up with periodic HIV testing after randomization).

Our systematic review of trials that evaluated biomedical interventions to reduce HIV acquisition risk found evidence that the overall quality of HIV prevention trial reporting has improved over time, with significant improvement in several key areas, including allocation concealment and availability of protocol information by publication or registration before study completion. Although the CONSORT statement has been available since 1996, its adoption has increased more recently [14, 15, 46]. Improvement in trial reports is likely attributable at least in part to clear guidance on the requirements for quality trial reporting. The requirement that RCTs be registered before enrolling subjects has encouraged clear documentation of study objectives, endpoints, and an overview of planned analyses. Registration and on-line posting of protocols should further reduce the likelihood of selective reporting in this as in other fields [47-49]. Because full trial protocols were available for review for only a minority of RCTs, we are unable to say whether improved quality ratings are also due to better trial design.

One potential criticism of these prevention studies is the lack of blinding. Blinding was impossible in eight studies and inadequate in one study. We have not judged as inadequate studies where blinding was not possible. In some situations, blinding may not be considered desirable (for instance, when changes in behavior may be induced in both groups under study); one recent microbicide study included a blinded placebo gel arm and an open-label “no gel” arm to address this concern [19]. However, unblinded studies may be biased if the knowledge of treatment allocation affects participant outcomes through differential co-interventions, cross-over, drop-outs, or outcome ascertainment [16]. Outcome assessment

and data analysis were rigorously blinded in these RCTs, but participant and research staff unblinding may have led to differences in risk reduction counseling or individual behavior; this possibility was discussed in several RCT reports.[6, 7, 33, 50] In such cases, it is critical to evaluate imbalances in attrition, adherence, or reported risk behaviors and conduct a sensitivity analysis to determine the degree to which bias may have influenced results.

Our review indicated that a significant issue for HIV prevention studies was adequate sample size. The anticipated reduction in HIV incidence was 50% in the vast majority of trials, with only 3 RCTs designed to detect a smaller difference [29, 33, 35] and one small RCT, perhaps unrealistically, expecting a 75% reduction [23]. Therefore, most trials were not powered to detect a moderate effect (e.g., 30%-40%) that could be clinically important and may have been more realistic for the intervention tested. Factors exacerbating this problem include under-enrollment, high attrition, poor adherence to interventions, and contamination or cross-over between groups. Strong adherence promotion and monitoring are crucial to future trials of microbicides or oral prophylaxis regimens [32, 40, 43, 51], although such measures may limit the applicability of trial results. High retention is a key goal regardless of intervention. To compound these challenges, many trials had a lower HIV incidence than anticipated, a decline which may have a temporal component in several trials [21, 23, 33, 37, 41]. Observed low HIV incidence may be due to effective co-interventions, the Hawthorne effect (in which behavior improves under observation), attrition bias (in which high-risk subjects are lost to follow-up), or a combination of factors [33, 40, 52]. These effects must be taken into account in planning trial size, and should be based on feasibility studies of the target population where possible [53].

Our assessment of study ethics focused on a description of services available to study participants alongside the interventions being studied. While there is no universally accepted “standard of care” for such services, most studies have included, at a minimum, individualized counseling about risk behaviors and the free distribution of condoms. Many also provided STD treatment, which is a valuable benefit to participants.[54] Studies may also offer circumcision referrals to eligible male volunteers. One recent vaccine trial reported that uptake of circumcision during follow-up was associated with higher baseline behavioral risk [55]. Co-interventions such as circumcision, condom use, and behavior change have the potential to significantly reduce HIV incidence in the study population. Finally, it is also noteworthy that recent trials all reported referral for HIV care. While such referral is not strictly a co-intervention, it indicates the increasing availability of antiretroviral therapy in the trial communities; this greater availability may also reduce population HIV incidence [56, 57].

One limitation of our review is that we assessed quality based on available information from published reports and did not contact primary authors for clarification. Some studies may have failed to report on certain criteria that were actually adequately addressed in study planning and execution [58]. However, the methodological quality and reporting quality of studies are thought to be highly related [59]. Another limitation is that we did not focus on issues specific to particular interventions. For example, it has been pointed out that in studies of vaginal microbicides, HIV acquisition via unprotected anal sex would render the intervention ineffective and bias results towards no apparent effect on vaginal transmission [27]. For studies of interventions contraindicated in pregnancy, family planning is an important means of retaining participants [44, 60]. Testing of microbicides for safety and acceptability among pregnant women would help address this issue.

Conclusion

In conclusion, most trials of biomedical HIV prevention interventions were rated as acceptable on the key quality components we reviewed, and reporting has improved significantly over time. However, several common challenges in HIV prevention trial design and execution tend to bias results towards the null. Our review of the quality of HIV prevention studies compiles useful information on the experiences of previously reported RCTs, and highlights a need for quality improvement in several key areas that influence study power, including participant retention, adherence to interventions, and estimation of expected HIV incidence. Investigators should assume that incidence may be lower than predicted or decrease during follow-up, and account for this in the planning of trials. The HIV epidemic continues to claim lives, and effective prevention strategies are urgently needed. Attention to lessons learned from previous studies can optimize trial design for promising new interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selection of Trials for Inclusion

Table 1

Quality Components and Criteria for Rating*

Component	Adequate	Inadequate	Unclear
<i>Allocation sequence generation</i>	Use of: <ul style="list-style-type: none"> • Random number tables • Random number generator • Random permutation by computer • Coin-tossing • Dice • Drawing lots • Shuffling 	Use of any alternative method	Method not clearly stated
<i>Allocation concealment</i>	Allocation by: <ul style="list-style-type: none"> • Numbered or coded bottles or containers held by a central pharmacy • Serially numbered opaque, sealed envelopes, or other descriptions convincing of concealment • Any other method with rigorous safeguards to maintain strict concealment 	Allocation by: <ul style="list-style-type: none"> • Alternation • Reference to case numbers or to date of birth • A method without adequate safeguards (e.g., non-opaque envelope) 	Method not clearly stated
<i>Blinding of assessors and subjects</i>	Neither assessors nor subjects were able to identify the allocated treatment	Assessors or subjects could identify the allocated treatment (A note was made if blinding was not possible for the intervention used.)	Possibility that allocated treatment was revealed unclear or not presented
<i>Handling of attrition</i>	Missing outcome data due to loss to follow-up and any reasons for exclusions balanced across groups	Imbalance in loss to follow-up or exclusions, likely related to outcome	Insufficient information provided to evaluate balance across study arms
<i>Non-selective reporting</i>	Information on study protocol available through registration or publication; all pre-specified outcomes reported as planned	Not all pre-specified analyses presented or one or more primary outcomes not pre-specified	Insufficient data available about pre-specified outcomes and planned analyses
<i>Sample size estimation</i>	Clearly stated sample size calculation that could be repeated	Failure to report any sample size estimation	Some information on sample size estimation included, but not enough to repeat calculation
<i>Inclusion of subjects in analysis</i>	Analysis by: <ul style="list-style-type: none"> • Intention-to-treat with all enrolled subjects included • Modified intention-to-treat, including only participants with at least one follow-up evaluation and excluding participants found to be ineligible after randomization (e.g., HIV-seropositive at baseline) 	Exclusion of one or more subjects for reasons related to protocol adherence or other administrative reasons that might introduce bias	Lack of sufficient detail to assess

* Modified from the Cochrane Collaboration's "risk of bias" tool [16].

Table 2

Characteristics of Identified Studies, by Intervention Type

Author	Year	Specific Intervention vs. Comparator	Unit Randomized	Target Population (all HIV-negative)	Region (n sites)	Total Enrolled	Early Termination?
<i>Circumcision</i>							
Auvert[6]	2005	Male circumcision vs. deferral	Individual	Uncircumcised men	Africa (1)	3,274	Yes, for effectiveness
Bailey[7]	2007	Male circumcision vs. deferral	Individual	Uncircumcised men	Africa (1)	2,784	Yes, for effectiveness
Gray[8]	2007	Male circumcision vs. deferral	Individual	Uncircumcised men	Africa (1)	4,996	Yes, for effectiveness
<i>Diaphragm</i>							
Padian[33]	2007	Diaphragm and lubricant plus condoms vs. condoms alone	Individual	High-risk women	Africa (3)	5,045	No
<i>Microbicide</i>							
Kreiss[23]	1992	Nonoxonyl-9 sponge vs. placebo glycerine suppository, later switched to water-based cream	Individual	Female sex workers	Africa (1)	138	Yes, for fertility
Roddy 1[25]	1998	Nonoxonyl-9 film vs. placebo film	Individual	Female sex workers	Africa (2)	1,317	No
Richardson[24]	2001	Nonoxonyl-9 gel vs. placebo gel	Individual	Female sex workers	Africa (1)	278	Yes, for fertility
Roddy 2[50]	2002	Nonoxonyl-9 gel plus condoms vs. condoms alone	Individual	High-risk women	Africa (1)	1,251	No
Van Damme 1[21]	2002	Nonoxonyl-9 gel vs. placebo gel	Individual	Female sex workers	Multiple (6)	1,005	No
Peterson 1[26]	2007	SAVVY® gel vs. placebo gel	Individual	High-risk women	Africa (2)	2,142	Yes, for fertility
Feldblum[27]	2008	SAVVY® gel vs. placebo gel	Individual	High-risk women	Africa (2)	2,153	Yes, for fertility
Halpern[22]	2008	Cellulose sulfate gel vs. placebo gel	Individual	High-risk women	Africa (2)	1,644	Yes, for fertility
Skoler-Karpoft[41]	2008	Carraguard gel vs. placebo gel	Individual	High-risk women	Africa (3)	6,202	No
Van Damme 2[20]	2008	Cellulose sulfate gel vs. placebo gel	Individual	High-risk women	Multiple (5)	1,425	Yes, for fertility and possible harm
Karim[19]*	2009	BufferGel and PRO2000/5 gel vs. placebo gel vs. no gel (open label)	Individual	High-risk women	Multiple (8)	3,099	No
<i>Pre-Exposure Prophylaxis</i>							
Peterson 2[32]	2007	Daily tenofovir vs. placebo tablet	Individual	High-risk women	Africa (3)	936	Yes, for administrative problems
<i>STD Control</i>							
Grosskurth[34, 61]	1995	Improved STD treatment vs. standard care	Cluster	Adults in rural communities	Africa (1)	12,537	No
Wawer[29, 62]	1999	Presumptive STD treatment vs. standard	Cluster	Adults in rural communities	Africa (1)	12,726	Yes, for fertility

Author	Year	Specific Intervention vs. Comparator	Unit Randomized	Target Population (all HIV-negative)	Region (n sites)	Total Enrolled	Early Termination?
Ghys[39]	2001	Improved STD treatment vs. standard care	Individual	Female sex workers	Africa (1)	542	No
Kamali[18, 63]	2003	Improved STD treatment plus behavioral interventions vs. behavioral interventions alone vs. standard care	Cluster	Adults in rural communities	Africa (1)	20,516	No
Kaul[36, 64]	2004	Presumptive azythromycin vs. placebo tablet	Individual	Female sex workers	Africa (1)	466	No
Gregson[35]	2007	Improved STD treatment plus behavioral interventions vs. standard care	Cluster	Adults in rural communities	Africa (1)	9,454	No
Celum[40]	2008	Twice daily acyclovir vs. placebo tablets	Individual	HSV-2 infected high-risk adults	Multiple (8)	3,277	No
Watson-Jones[43]	2008	Twice daily acyclovir vs. placebo tablets	Individual	HSV-2 infected high-risk women	Africa (1)	821	No
<i>Vaccine</i>							
Flynn[37, 65]	2005	Recombinant gp120 vaccine vs. placebo injections	Individual	High-risk adults	Multiple (61)	5,417	No
Pitisuttithum[44]	2006	Recombinant gp120 vaccine vs. placebo injections	Individual	Injection drug users	Asia (17)	2,546	No
Buchbinder[30]	2008	Adenovirus vector vaccine vs. placebo injections	Individual	High-risk adults	Multiple (34)	3,000	Yes, for futility
Gray[31]*	2008	Adenovirus vector vaccine vs. placebo injections	Individual	High-risk adults	Africa (5)	801	Yes, for futility

* Abstract only; full text not available.

HIV = human immunodeficiency virus, HSV-2 = herpes simplex virus, type 2, STD = sexually transmitted diseases

Table 3

Quality of Published Articles, by Intervention Type

Author	Allocation sequence generation	Allocation concealment	Blinding of subjects and researchers	Handling of attrition	Free of selective reporting?	Sample size Calculation
<i>Circumcision</i>						
Auvert[6]	Adequate	Adequate	Not possible	Unclear	Adequate	Adequate
Bailey[7]	Adequate	Adequate	Not possible	Unclear	Adequate	Adequate
Gray[8]	Adequate	Adequate	Not possible	Adequate	Adequate	Adequate
<i>Diaphragm</i>						
Padian[33]	Adequate	Adequate	Not possible	Adequate	Adequate	Adequate
<i>Microbicide</i>						
Kreiss[23]	Adequate	Unclear	Inadequate	Unclear	Unclear	Adequate
Roddy 1[25]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate
Richardson[24]	Adequate	Unclear	Adequate	Adequate	Unclear	Inadequate
Roddy 2[50]	Adequate	Adequate	Not possible	Adequate	Unclear	Adequate
Van Damme 1[21]	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate
Peterson 1[26]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Feldblum[27]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Halpern[22]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Skoler-Karpo[41]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Van Damme 2[20]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
<i>Pre-Exposure Prophylaxis</i>						
Peterson 2[32]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
<i>STD Control</i>						
Grosskurth[34, 61]	Unclear	Unclear	Not possible	Unclear	Adequate[60]	Adequate[60]
Wawer[29, 62]	Unclear	Unclear	Not possible	Unclear	Adequate[61]	Adequate[61]
Ghys[39]	Unclear	Unclear	Not possible	Adequate	Unclear	Inadequate
Kamali[18, 63]	Unclear	Unclear	Not possible	Unclear	Adequate[62]	Adequate
Kaul[36, 64]	Adequate	Adequate	Adequate	Adequate	Adequate[63]	Adequate
Gregson[35]	Adequate	Adequate	Not possible	Unclear	Adequate	Adequate
Celum[40]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Watson-Jones[43]	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate

Author	Allocation sequence generation	Allocation concealment	Blinding of subjects and researchers	Handling of attrition	Free of selective reporting?	Sample size Calculation
<i>Vaccine</i>						
Flynn[37, 65]	Adequate	Unclear	Adequate	Adequate	Adequate[64]	Adequate[64]
Piisuttithum[44]	Adequate	Unclear	Adequate	Adequate	Adequate	Adequate
Buchbinder[30]	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate

Note: Inclusion in analysis was adequate in all studies, and so is not presented.

Factors Related to Study Power, by Intervention Type

Table 4

Author	Enrolled/ Target	% Enrolled	Groups as Randomized	Actual/Planned Follow-up	Lost to Follow- up	% Retained	Adherence	Method	Condom Use	Contami- nation	Control incidence	Expected incidence	Lower than expected? *
<i>Circumcision</i>													
Auvert[6]	3274/ 3035	108	1582 vs. 1546	18.1 months (mean)/ 21 months	151 vs. 100	92%	94% circumcised vs. 90% delayed circumcision	Directly observed	N/A (partners 7.5 vs. 6.4 Months 13- 21)	Definite	2.1/100 pyo	2.2/100 pyo	Marginally
Bailey[7]	2784/ 2776	100	1391 vs. 1393	24 months (median)/ 24 months	126 vs. 114	86%	96% circumcised vs. 99% delayed circumcision	Directly observed	36% vs. 41%	Definite	4.2% over 2 years	2.5/100 pyo	Unclear
Gray[8]	4996/ 5000	100	2474 vs. 2522	16.8 months (mean)/ 24 months	114 vs. 115	90%	94% circumcised vs. 99% delayed circumcision	Directly observed	19% vs. 19%	Definite	1.3/100 pyo	Missing	Unclear
<i>Diaphragm</i>													
Padian[33]	5045/ 5000	101	2523 vs. 2522	18.7 months (mean)/ 12-24 months	142 vs. 127	93%	73% diaphragm use (no placebo)	Self-report	54% vs. 85%	Definite	3.9/100 pyo	3.5%-5% per year	Unclear
<i>Microbicide</i>													
Kreiss[23]	138/ 138	100	74 vs. 64	15.4 months (mean)/ Unclear	14 vs. 8	84%	81% active gel vs. 90% placebo	Self-report	58% vs. 63%	Possible	41% over 24 months	20% per year	No
Roddy 1[25]	1292/ 1000	129	644 vs. 648	14 months (mean)/ 12 months minimum	129 vs. 112	73%	84-89% active film vs. 81-87% placebo film	Self-report	95% vs. 96% with clients, 76% vs. 80% with non- clients	Possible	6.6/100 pyo	10/100 pyo	Yes
Richardson[24]	278/ N/A	N/A	139 vs. 139	11.9 months (mean)/ Unclear	31% vs. 39%	65%	75% active gel vs. 80% placebo gel	Self-report	50% vs. 54%	Possible	12.9/100 pyo	Missing	Unclear
Roddy 2[50]	1251/ 1200	104	625 vs. 626	5.2 months (mean)/ 6 months	7 vs. 13	93%	76% active gel use (no placebo)	Self-report	81% vs. 87%	Possible	4 infections, pyo not reported	20/100 pyo	Unclear
Van Damme 1[21]	892/ 892	100	449 vs. 443	13.1 months (mean)/ 12 months	35% vs. 30%	68%	79% active gel vs. 81% placebo gel	Self-report	95% vs. 96%	Possible	10.3/100 pyo	5.0% per year	Unclear
Peterson 1[26]	2142/ 2142	100	1073 vs. 1069	9.2 months (mean)/ 12 months	143 vs. 167	86%	75% active gel vs. 77% placebo gel	Self-report	89% vs. 90%	Possible	1.1% over 12 months	5.0/100 pyo	Unclear
Feldblum[27]	2153/ 2142	100	1076 vs. 1077	10.2 months (mean)/ 12 months	251 vs. 251	77%	78% active gel vs. 79% placebo gel	Self-report	87% vs. 87%	Possible	1.5% over 12 months	5.0/100 pyo	Unclear

Author	Enrolled/ Target	% Enrolled	Groups as Randomized	Actual/Planned Follow-up	Lost to Follow- up	% Retained	Adherence	Method	Condom Use	Contami- nation	Control incidence	Expected incidence	Lower than expected?*
Halpern[22]	1644/ 2160	76	820 vs. 824	9.6 months (mean)/ 12 months	242 vs. 247	70%	76% active gel vs. 78% placebo gel	Self-report	84% vs. 89%	Possible	2.1/100 pyo	5/100 pyo	Yes
Skoler-Karpoﬀ[41]	6202/ 6639	93	3103 vs. 3099	16.0 months (mean)/ 24 months	420 vs. 418	87%	96% active gel vs. 96% placebo gel (41% vs. 43% by applicator testing)	Self-report plus biologic testing	64% vs. 64%	Possible	3.8/100 pyo	3.5/100 pyo	No
Van Damme 2[20]	1398/ 2574	54	717 vs. 708	8.2 months (mean)/ 12 months	77 vs. 64	90%	87% active gel vs. 87% placebo gel	Self-report	95% vs. 96%	Possible	3.3/100 pyo	4.0% per year	Unclear
<i>Pre-Exposure Prophylaxis</i>													
Peterson 2[32]	936/ 1200	78	469 vs. 467	6.6 months (mean)/ 12 months	90 vs. 72	83%	74% product use overall (not reported separately)	Directly observed	92% overall (not specified per group)	Possible	2.5/100 pyo	5.0/100 pyo	Yes
<i>STD Control</i>													
Grosskurth[34, 61]	12537/ 12000	104	6142 vs. 6395	24 months (median)/ 24 months	1856 vs. 1836	71%	11,632 cases of STDs treated in intervention units	Directly observed	2% vs. 3% men, 3% vs. 2% women	Definite	1.9% over 2 years	1.0% per year	Marginally
Wawer[29, 62]	12840/ 10000	128	6372 vs. 6468	16.2 months (mean)/ 20 months	4927 vs. 4449	74%	90-94% STD treatment vs. 91- 96% vitamin/anthelmi nth treatment	Directly observed	14% vs. 11%	Definite	1.5/100 pyo	2.0/100 pyo	Yes
Ghys[39]	542/ N/A	N/A	269 vs. 273	13.4 months (mean)/ Unclear	152 vs. 165	42%	43% intensive STD screening vs. 40% symptomatic evaluation	Directly observed	83% vs. 79%	Possible	7.6/100 pyo	Missing	Unclear
Kamali[18, 63]	14554/ 13500	108	4931/4787/ 4836 (round 1)	36.2 months (mean)/ 36 months	N/A by group	69%	STD treatment numbers not reported	N/A	39% vs. 32% ever use; 73% vs. 56% (casual sex)	Possible	0.8/100 pyo	1.5% per year	Unclear
Kaul[36, 64]	466/ 340	137	230 vs. 236	27.9 months (mean)/ 24 months	61 vs. 64	73%	92% DOT on schedule; 3 vs. 2 doses refused	Directly observed	48% vs. 50% with clients	Definite	3.2/100 pyo	15% per year	Unclear
Gregson[35]	9454/ 9600	98	4792 vs. 4662	35.6 months (mean)/ 36 months	2128 vs. 2098	55%	15,516 STI episodes treated in intervention communities; N/A for control	Directly observed	21% vs. 27% men, 6% vs. 21% women (casual partner)	Definite	1.5/100 pyo	2.0% per year	Unclear
Celum[40]	3277/ 3682	89	1637 vs. 1640	14.8 months (mean)/ 12-18 months	388 vs. 353	85%	85% active drug vs. 86% placebo	Directly observed	33% vs. 34% men, 76% vs.	Definite	3.3/100 pyo	3.5% per year	Unclear

Author	Enrolled/ Target	% Enrolled	Groups as Randomized	Actual/Planned Follow-up	Lost to Follow- up	% Retained	Adherence	Method	Condom Use	Contami- nation	Control incidence	Expected incidence	Lower than expected?*
Watson-Jones[43]	821/ 821	100	400 vs. 421	18.8 months (mean)/ 12-30 months	78 vs. 64	83%	90% active drug (33%-67% had active drug in urine) vs. 90% placebo	Directly observed plus biologic testing	72% women (unprotected sex) N/A (25% vs. 28% had >1 partner)	Definite	4.1/100 pyo	10/100 pyo	Yes
Vaccine													
Flynn[37, 65]	5403/ 5300	102	3598 vs. 1805	36 months (median)/ 36 months	326 vs. 172	84%	83% active vaccine vs. 82% placebo vaccine	Directly observed	“Similar over time” (data in Figure)	Unlikely	7.0% over 36 months	1.5% per year	No
Pitisuttithum[44]	2546/ 2500	102	1267 vs. 1260	29.5 months (mean)/ 36 months	46 vs. 42	90%	84% active vaccine vs. 83% placebo vaccine	Directly observed	N/A; (Needle- sharing 16% overall, not specified per group)	Unlikely	8.3% over 36 months	4.0% per year	Yes
Buchbinder[30]	3000/ 3000	100	751/764/743/ 742	13.2 months (mean)/ 52 months	104 vs. 104	93%	94% active vaccine vs. 94% placebo vaccine	Directly observed	“Similar over time” (data not shown)	Unlikely	1.77% per year	50 events per Ad5 strata	Unclear

* This was judged unclear if person-time units differed between control and expected incidence.
N/A = not available, pyo = person-years of observation