

# Results of the NIMH Collaborative HIV/Sexually Transmitted Disease Prevention Trial of a Community Popular Opinion Leader Intervention

*The NIMH Collaborative HIV/STD Prevention Trial Group\**

**Objective:** To determine whether community populations in community popular opinion leader intervention venues showed greater reductions in sexual risk practices and lower HIV/sexually transmitted disease (STD) incidence than those in comparison venues.

**Methods:** A 5-country group-randomized trial, conducted from 2002 to 2007, enrolled cohorts from 20 to 40 venues in each country. Venues, matched within country on sexual risk and other factors, were randomly assigned within matched pairs to the community popular opinion leader intervention or an AIDS education comparison. All participants had access to condoms and were assessed with repeated in-depth sexual behavior interviews, STD/HIV testing and treatment, and HIV/STD risk-reduction counseling. Sexual behavior change and HIV/STD incidence were measured over 2 years.

**Results:** Both intervention and comparison conditions showed declines of approximately 33% in risk behavior prevalence and had comparable diseases incidence within and across countries.

**Conclusions:** The community-level intervention did not produce greater behavioral risk and disease incidence reduction than the comparison condition, perhaps due to the intensive prevention services received by all participants during the assessment. Repeated detailed self-review of risk behavior practices coupled with HIV/STD testing, treatment, HIV risk-reduction counseling, and condom access can themselves substantially change behavior and disease acquisition.

**Key Words:** group-randomized clinical trial, HIV, behavioral intervention, community norms, sexually transmitted disease

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## INTRODUCTION

More than 33 million persons worldwide are living with HIV infection or AIDS.<sup>1</sup> The vast majority live in developing resource-poor countries or in regions undergoing difficult social transitions, and most of the world's HIV infections are contracted through unprotected sex. Interventions that reduce levels of high-risk behavior in vulnerable community populations are essential for primary public health HIV prevention efforts.

Behavioral interventions to reduce transmission of HIV and sexually transmitted diseases (STDs) have often taken the form of individual counseling. However, a program of research based on diffusion of innovation theory<sup>2</sup> has also shown that training and engaging the “popular opinion leaders” of high-risk populations to personally endorse HIV-risk prevention through messages to others can change norms for HIV-related risk behavior in a population. This intervention approach has been found successful with community populations of gay men,<sup>3</sup> African American men who have sex with men,<sup>4</sup> and women<sup>5</sup> in the United States but has not been systematically tested in developing countries with high HIV and STD incidence.

Between 2002 and 2007, the National Institute of Mental Health Collaborative HIV/STD Prevention Trial Group conducted the first large, international, multisite study designed to evaluate rigorously the outcomes of a community-level HIV prevention intervention in 5 countries with different populations vulnerable to the disease. Twenty to 40 venues, social congregating points for high-risk populations, in each country were selected using data from an ethnographic study. This article presents the trial's primary outcomes.

## METHODS

### Trial Methodological Overview

Study sites in China, India, Peru, Russia, and Zimbabwe each implemented a common intervention trial protocol with an at-risk community population for which high behavioral

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The members of the NIMH Collaborative HIV/STD Prevention Trial Group are listed in Appendix 1.

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risk or HIV/STD prevalence had been verified through epidemiological studies. Each country site conducted in-depth risk behavior assessment interviews at baseline and at 12-month and 24-month follow-up points with longitudinal cohorts of 40–188 participants recruited in each of the 20–40 community venues per country. HIV and STD testing, manual-based counseling, and treatment of incident cases took place at each assessment point, and condoms were available to all study participants. After baseline data collection, pairs of venues in each country were matched and randomized to either receive an AIDS education comparison condition or an experimental intervention consisting of the AIDS education activities and the community popular opinion leader (C-POL) intervention. The trial was designed to determine whether the community populations in venues that received the C-POL intervention showed greater reductions in their sexual risk practices and had lower HIV/STD incidence than community populations in comparison condition venues between baseline and final follow-up. The study was approved by the institutional review boards at participating US and host country institutions.

Although the trial's design and methods are briefly described here, a more thorough description was published in a special issue of the journal *AIDS*. That issue provides an extensive overview of the trial's methods,<sup>6</sup> followed by 9 articles describing specific aspects of the study in detail.<sup>7–15</sup>

## Study Venues

The trial was conducted in community venues that were social congregating points for a high-risk population in each country because this intervention requires informal opportunities for conversations during which the trained C-POLs can deliver messages endorsing HIV/STD prevention. A preliminary ethnographic study identified social gathering points at each country site, and an epidemiological study established that initial levels of STDs or high-risk sexual behavior were sufficiently high to be able to detect meaningful change over time and to determine sample size requirements for the main trial.<sup>6,11</sup> Venues were also selected based on presence of population members from the local area, nontransience, geographic separation from other study venues, opportunities for C-POLs to informally talk with others, and community support for the study.

In 3 countries, a venue was a physical structure in which population members lived (trade school dormitories in St. Petersburg, Russia), drank alcohol, and socialized (wine shops in Chennai, India) or worked (vendor markets in Fuzhou, China). In the other 2 countries, a venue was defined as a neighborhood setting such as barrios in Peru and growth point neighborhoods in rural Zimbabwe. Study venues and populations in each of the 5 trial countries are described in a previously published article.<sup>7</sup>

## Study Populations and Recruitment

To be eligible for study participation, individuals recruited in a study venue needed to report that they (1) were regularly present in that venue and (2) planned to remain in the area for at least 2 years. China excluded participants who reported having no sex in the 6 months before baseline unless

an STD was present at baseline. Peru excluded participants who reported having no sex during the 6 months before baseline. Participants were excluded in all countries if they could not give informed consent or if they had a serious cognitive or communication disability that would preclude study participation. The core age of the participants in the 5 countries was 18–30 years. Because populations were selected based on risk behavior and STD prevalence rather than on age, site-to-site age variation was planned. The average number of participants per venue ranged from 92 in Russia to 185 in Zimbabwe.

Each participant provided written, signed, voluntary informed consent and completed all baseline assessment study procedures including the behavioral interview; provision of blood specimens, urine specimens, and vaginal swabs for STD/HIV testing; and counseling in HIV risk reduction.

## Intervention

For ethical reasons, participants in both the intervention and comparison conditions received substantial and similar access to prevention services throughout the study.

## Comparison Condition Procedures

In comparison condition venues, HIV/STD prevention brochures and pamphlets; educational materials; and information about HIV/STD counseling, testing, and treatment were visibly placed and maintained. Free or inexpensive condoms were also available in or near each venue. Three times during the study (baseline, 12 months, and 24 months), research participants were tested for HIV and 5 other STDs and, if positive, were treated or referred for treatment. As part of this process, research participants received extensive HIV/STD pre- and posttest counseling according to a detailed interview protocol. They also were interviewed at each of the 3 assessment times for approximately 45 minutes about their sexual risk behavior, alcohol and drug use, symptoms of illness, and health-seeking behaviors.

## Intervention Condition Procedures

Participants in C-POL intervention venues received all of the same services and also the community-level intervention. This intervention is grounded in principles from the theory of the diffusion of innovation, which posits that innovations and changes often originate with a subset of the population who are its opinion leaders and whose views are adopted by others in the community.<sup>2</sup> Through this process, social norms about HIV/STD risk-reduction behaviors could change.

In this study, C-POLs were identified as natural leaders in each intervention venue based on study staff ethnographic observations, nominations by venue gatekeepers and other key informants, nominations by other population members, or self-nomination. Approximately 15%–20% of the total target population in the venue was selected as potential C-POLs and invited to attend a series of 4–5 small group-training sessions led by 2 study staff facilitators. Skill training–based sessions taught C-POLs basic information about HIV and STDs and how to deliver theory-based HIV/STD prevention messages to others. The sessions used facilitator instruction, modeling, and

role play practice to help C-POLs refine their skills for educating friends about risk, recommending risk-reduction behavior changes, and personally endorsing the benefits of taking such risk-reduction steps. C-POLs also wore logos on T-shirts, hats, or other apparel to stimulate conversations with friends and neighbors.

Because the intervention was implemented across multiple varied cultures and differing HIV/AIDS risk circumstances, the specific content of C-POL prevention messages were tailored by country and by population. However, training always taught C-POLs to convey messages to others that provided AIDS-related knowledge and information on risk-reduction steps; suggested skills or strategies that the message recipient could use to reduce risk; instilled positive attitudes and confidence for using condoms or avoiding unprotected sex; and personally endorsed the benefits and importance of making or attempting to make risk-reduction behavior change. Although these message content areas were emphasized in C-POL training across all sites, C-POLs were encouraged to formulate and deliver risk-reduction measures using language and vernacular comfortable to them and in styles congruent with their culture. Core elements of the intervention, C-POL training modules, and procedures used to tailor the intervention across cultures and populations are more fully described elsewhere.<sup>8,9,13</sup>

C-POLs agreed to deliver HIV/STD prevention endorsement messages during everyday conversations with friends and acquaintances after these group-training sessions, which were usually held weekly. Outcomes of conversations were reviewed in subsequent meetings with C-POLs, and any problems encountered were discussed. Reunion sessions were held after the main training phase to encourage C-POLs to continue these conversations to diffuse HIV/STD prevention messages and to instill a sense of being part of a social movement.

## Assessment

Study outcomes were measured with assessments of sexual risk behaviors and the testing of biologic specimens for 6 STDs including HIV infection.

### Sexual Risk Behavior Assessment

Demographic characteristics and sexual risk practices during the past 3 months were assessed at baseline and at 12- and 24-month follow-up points in private, individual, computer-assisted personal interviews administered by a trained interviewer and lasting about 45 minutes. At each interview, participants were asked to report on their total number of vaginal and anal intercourse acts, as well as the number of times when a condom was used during intercourse acts during the 3-month recall period. Additionally, specific information of this type was requested for up to 5 of the participant's most recent sexual partners during the 3-month recall period. Participants also labeled the type of relationship with each partner (ie, spouse, cohabiting, casual, new, and commercial) to distinguish between spousal or live-in partners and partners of other types. Follow-up interviews measured participant exposure to the community-level intervention. All interviews were conducted in the language of the site's target population (Mandarin, Tamil, Spanish, Russian, Shona, or

Ndebele), refined through processes of translation and back translation, and certified as culturally appropriate by local experts.

## Biological Assessment

Participants provided blood and urine specimens at each assessment point, and females additionally were asked for vaginal swab specimens. Testing in a study-certified local laboratory was performed to assess HIV, herpes simplex virus type 2 (HSV-2), syphilis, gonorrhea, chlamydia infection, and trichomoniasis (women only) using standard laboratory procedures. A complete discussion of these procedures is presented elsewhere.<sup>6,12</sup>

All nonviral STDs were treated following guidelines of the US Centers for Disease Control and Prevention or the World Health Organization or were referred for treatment based on national best practice guidelines. People found to be HIV-infected were referred for follow-up care at existing local treatment centers. STD treatment was also offered for primary sexual partners of infected individuals. According to the protocol, participants were to be informed of their HIV and STD test results within 4 weeks. Counseling concerning HIV/STD risk reduction was provided for approximately 15–20 minutes to each participant at the time specimens were collected and when test results were returned. Persons found to have an STD or HIV infection often received further personalized risk-reduction counseling when they received treatment.

## Randomization

Venues were matched within each country based on rates of STD prevalence observed in epidemiological studies that preceded the main trial. In addition, city was used to stratify venues before matching in Peru, and area of country and language were used to stratify venues before matching in Zimbabwe. After administration of the baseline assessment to all participants within each matched pair of venues, the Data Coordinating Center (DCC) randomized one venue of the pair to the intervention condition and the other to the comparison condition.

## Statistical Power

### General Considerations

The data from the epidemiological studies were used to determine sample size and to estimate power for detecting effects within and across countries using the primary biological and behavioral end points. Specific power calculations provided by Murray and Hannan<sup>16</sup> for group-randomized cohort designs were used to compute the sample sizes (eg, number of venues and number of participants per venue) for each country.

### Within-Site Sample Sizes

The study was designed so that each country would have at least 80% power to detect the relevant effect for either the primary biological or the primary behavioral end point (based on site-specific risk data from the epidemiological studies) and operating with a type I error rate (2 sided) of 5%. Sample sizes were computed to detect a 33% lower STD incidence in the intervention (I) versus the comparison (C) venues for the

biological end point and a 10% absolute difference in the change in high-risk sexual behavior between I and C venues for the behavioral end point. The calculations assumed that 20% of the study participants in the cohort were C-POLs and would be excluded from the primary analysis. A detailed description of the number of venues in each site (country) and the power calculations for within site and across sites were published previously.<sup>6</sup>

### Primary End points

Two primary outcomes were used to determine efficacy in the trial, 1 behavioral and 1 biological. The primary behavioral outcome was defined as the change between the 24-month follow-up assessment and baseline in the proportion of participants reporting unprotected acts with nonspousal/non-live-in partners in the past 3 months. The 24-month period was chosen to measure long-term change, whereas the 3-month recall interval at each assessment was brief enough to minimize recall bias.

The primary biological outcome was the incidence of any new STD, including chlamydia infection, gonorrhea, HIV, HSV-2, syphilis, and—for women—trichomoniasis observed across the 12-month and 24-month follow-up points. The pathogenesis, treatment, and transmission dynamics of each of these STDs varies, as well as the sensitivity and specificity of each of the assays. For each participant, a composite binary variable was constructed to indicate whether or not a new case of at least 1 of the 6 STDs was detected at either follow-up visit. Individuals with chlamydia infection, gonorrhea, syphilis, and trichomoniasis were to be treated following positive test results at their baseline, 12-month, and 24-month follow-up assessments as specified in the protocol. HIV and HSV-2 cannot be eliminated. Thus, an individual was classified as having a new case of any of the 6 infections during follow-up if there was a positive test for chlamydia infection, gonorrhea, syphilis, or trichomoniasis (and evidence of treatment for prior positive cases); HSV-2 (if negative at baseline); or HIV (if negative at baseline). Otherwise, an individual was classified as negative for the composite if at least two-thirds of the tests used in the individual's assessment were available (ie, negative, but not missing). If there was no new positive test and more than a third of the individual's tests were missing (not done or indeterminate), the composite variable was set to missing. The primary biologic outcome was unable to be determined for approximately 12% of participants, most of who were not tested at either follow-up assessment. Less than 1% participants were missing the outcome because they had some, but fewer than two-thirds, of the required test results.

### Quality Control/Quality Assurance Procedures

The trial established and implemented well-defined quality control (QC) procedures to ensure consistency over time, and it employed careful cross-site quality assurance (QA) monitoring procedures to ensure fidelity to the protocol in the areas of ethnography, assessment, intervention delivery, laboratory test procedures, and STD treatment. QC procedures entailed development of protocols and procedural manuals for all cross-site activities, central training of key site personnel,

certification of field and laboratory personnel on completion of training, and detailed procedures to maintain fidelity of intervention delivery. QA assurance procedures included external QA monitors from the DCC that documented implementation of the ethnographic assessment, intervention, laboratory maintenance, and data maintenance activities at all study sites.<sup>6</sup>

### Statistical Analysis

Analysis of the primary end points was conducted within each of the 5 countries separately and across all countries. Data from participants in the intervention venues who had been C-POLs were excluded from the primary analysis but included in a secondary data analysis. Because an intent-to-treat analysis was used, any venue assigned to the intervention was considered treated. Data collected between 10 and 18 months after the baseline interview were used as the 12-month assessment, and data collected between 19 and 31 months after baseline were used as the 24-month assessment. The test statistic within a country was taken as the average difference, I minus C, across venue pairs with equal weight to each pair. For the biologic outcome, differences between I and C venues were computed as the percent of participants with a new STD detected at either the 12- or 24-month follow-up visit. For the behavioral outcome, differences between I and C venues were calculated as the change in the percent of participants who reported unprotected sex with a nonspousal/non-live-in partner between the 24-month follow-up and baseline. The across-country statistic was the average of these country-specific average differences with equal weight to each country. Hypotheses regarding the study end points within each country and across countries were evaluated using permutation tests. Thus, tests were based simply on the randomization of venues within venue pairs to the I or C condition. Statistical significance was computed by considering all possible values each test statistic could have taken by permuting the random assignment of venues within venue pairs. Under the null hypothesis of no difference between I and C conditions, the statistical significance of the observed result was taken as the rank of the observed statistic among the possible permutations. *P* values reported are 2 sided. Permutation test-based 95% confidence intervals within each country are also given for the test statistics using a method described by Gail et al.<sup>17</sup> Additional detail is available on request.

In secondary analyses, the C-POLs were included in the data, and hypothesis testing was repeated for both end points based on test statistics as defined above. For both the primary biologic and behavioral end points, comparisons between I and C venues were made with adjustment for baseline differences. Variables used for adjustment were chosen by examining associations between baseline characteristics and each outcome at the level of the individual using logistic regression models for each country separately. Indicator variables for the venue pairs and the baseline value of the dependent variable were included in all models, and a backward elimination procedure was used to select baseline variables associated with the outcome with a significance level of *P* = 0.05 for remaining in the model. A table describing the variables evaluated and selected is available on request. The final country-specific

models were used to compute a predicted probability of the behavioral outcome and the biologic outcome for each individual in the country without regard to study condition. The residuals were then used as adjusted outcomes for permutation test-based analysis of study condition differences.<sup>17</sup>

Additional secondary behavioral and biologic outcomes were defined, and differences between I and C venues were evaluated using test statistics and hypothesis testing based on permutation tests as for the primary outcomes. First, the distribution of the number of episodes of unprotected sex with a nonspousal partner reported at baseline was examined in each country, and an upper percentile of the distribution was chosen in each country (the median number of episodes was 0 in most countries). The hypothesis of no difference between I and C venues in each country on the change between baseline and 24 months in the percentile value was tested. Another secondary biologic outcome was defined as any new STD during the second follow-up period only (between 12 and 24 months). Further, hypothesis testing was conducted for individual biologic outcomes in countries where incidence rates during the follow-up period were large enough for each disease. Finally, model-based analyses were also conducted using longitudinal models that utilize a generalized estimating equation approach for variance estimates.

Descriptive statistics at baseline and follow-up by condition were computed to give equal weighting to each venue within country and to each country for summarization across countries. The associated standard errors take into account random effects for the individual participant and the venue.

## RESULTS

A total of 18,147 participants from 138 venues across China, India, Peru, Russia, and Zimbabwe were enrolled, with pairs of venues within a country matched and randomized to I or C conditions (Fig. 1). The majority of participants were

enrolled between 2002 and 2004. After initial randomization, 10 venues in China and 4 venues in India were replaced due to closing of food markets in China and the 2004 tsunami that destroyed 4 venues in India. These new venues were also matched and randomized to I or C conditions. Included among enrolled participants were 1127 of the trained C-POLs in the intervention venues who completed study assessments.

Participant cohorts ranging in size from 2212 to 5543 participants at baseline were recruited from 20 to 40 venues in each of the 5 countries. The percentage of eligible individuals selected for assessment who participated were 89.4% in China, 97.6% in India, 94.9% in Peru, 93.7% in Russia, and 71.6% in Zimbabwe. The overall response rate for the interview at the 12-month follow-up was 84.4% (range 79%–95% across countries) with 15,309 participants interviewed, and at 24-months, the response rate was 82.0% (range 80%–92% across countries) with 14,888 participants interviewed. Among the 18,147 participants enrolled, 74% had HIV/STD testing at all 3 assessment points. This figure is lower than the overall participation rate because some individuals agreed to be interviewed but declined repeated biospecimen collection.

### Participant Characteristics at Baseline

Characteristics of participants in the I and C venues (excluding C-POLs who participated in assessments) were similar at baseline with respect to demographic characteristics, the percent of people reporting unprotected sex with nonspousal/non-live-in partners in the last 3 months, and the prevalence of any positive test for the 6 STDs being studied (Table 1). The baseline prevalence of any positive test among the 6 STDs ranged from approximately 8% in Russia to 38% in Zimbabwe. The percent of participants reporting unprotected sex with a nonspousal/non-live-in partner in the 3 months before baseline ranged from 7% in China to 56% in Peru. Baseline prevalences of each of the 6 STDs separately for each country are available on request.

### Changes in Primary End Points

Table 2 displays results for the behavioral outcome, the change between baseline and 24 months in the percent of participants reporting unprotected sex with nonspousal/non-live-in partners, by country and overall. A negative value on the average difference (I – C) indicates a more favorable change in the intervention group than in the comparison group. The proportion of participants reporting unprotected sex with nonspousal/non-live-in partners was reduced more between baseline and 24 months on average in the intervention venues than in the comparison venues in China, Russia, and Zimbabwe, whereas in India and Peru, the reduction was greater in the comparison venues. No statistically significant differences were found between I and C venues on the behavioral outcome in China, Peru, Russia, or Zimbabwe. In India, the difference between I and C venues was marginally significant (mean = +2.85; *P* = 0.053); however, this positive difference represents a less favorable change in the intervention venues. Across countries, the difference between I and C venues was not significant (mean = –0.36; *P* = 0.71).

Table 3 presents results based on the biological outcome, incidence of any of the 6 STDs during the study, by country

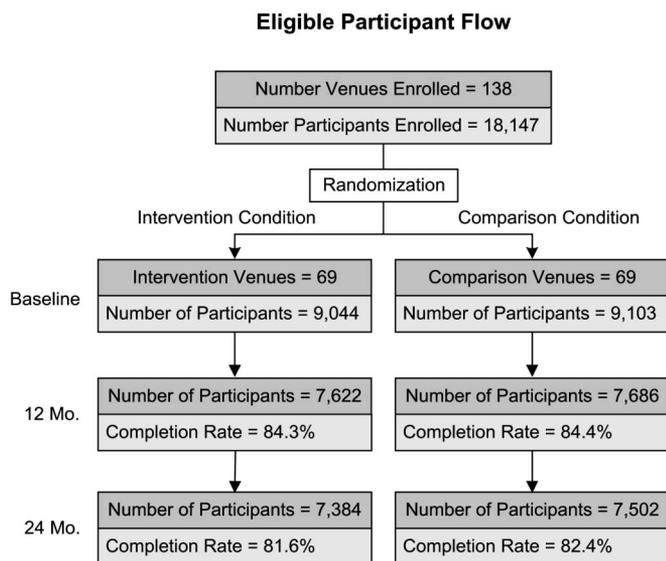


FIGURE 1. Eligible participant flow.

**TABLE 1.** Baseline Characteristics for Individuals in Intervention Versus Comparison Venues by Country\*

Characteristic, value (SE)†	Country					
	China (N <sub>I</sub> = 7917; N <sub>C</sub> = 9103)	India (N <sub>I</sub> = 1447; N <sub>C</sub> = 1933)	Peru (N <sub>I</sub> = 1651; N <sub>C</sub> = 1766)	Russia (N <sub>I</sub> = 1176; N <sub>C</sub> = 1561)	Zimbabwe (N <sub>I</sub> = 1036; N <sub>C</sub> = 1071)	Total (N <sub>I</sub> = 2607; N <sub>C</sub> = 2772)
Percent male						
Intervention	44.8 (2.1)	83.6 (0.4)	88.3 (2.8)	52.3 (6.1)	51.6 (1.3)	64.2 (1.4)
Comparison	45.0 (1.4)	82.8 (0.5)	91.5 (2.3)	49.8 (3.9)	53.8 (1.7)	64.5 (1.0)
Mean age						
Intervention	36 (0.46)	29 (0.31)	24 (0.48)	20 (0.20)	22 (0.15)	26 (0.15)
Comparison	35 (0.40)	31 (0.53)	24 (0.44)	20 (0.34)	22 (0.18)	26 (0.18)
Percent with 7–12 yr of education						
Intervention	52.0 (1.8)	50.3 (2.1)	84.4 (2.8)	41.8 (3.2)	90.7 (0.6)	63.9 (1.0)
Comparison	49.7 (1.4)	46.8 (3.0)	87.5 (1.9)	45.6 (6.1)	91.6 (0.5)	64.2 (1.4)
Percent married or living with partner						
Intervention	91.7 (1.4)	54.6 (2.0)	28.7 (3.5)	5.6 (1.1)	23.6 (1.8)	40.8 (1.0)
Comparison	92.1 (0.9)	63.4 (3.1)	26.3 (3.4)	7.3 (1.5)	27.4 (2.1)	43.3 (1.1)
Percent reporting unprotected sex past 3 mo with nonspousal partner						
Intervention	7.3 (0.8)	44.8 (3.9)	55.2 (3.0)	36.0 (2.2)	22.2 (2.2)	33.1 (1.2)
Comparison	6.6 (0.6)	43.5 (3.8)	56.9 (3.8)	36.2 (1.7)	21.9 (1.7)	33.0 (1.2)
Percent with any positive STD						
Intervention	20.0 (1.3)	19.8 (1.4)	32.8 (2.9)	7.9 (1.1)	36.6 (1.4)	23.4 (0.8)
Comparison	20.5 (1.5)	23.9 (1.4)	32.0 (2.6)	8.6 (1.2)	39.0 (2.4)	24.8 (0.9)

\*Overall, 17,020 non-C-POL participants were included. C-POLs were excluded.

†Percent/mean (standard error) shown. Percents and mean age were estimated as the average of the percents/mean across venues in each study condition within country. Information was missing for marital status: 1 participant, education: 4, unprotected sex with a nonspousal partner: 23, and prevalence of any STD: 47.

N<sub>I</sub>, number of participants in the intervention condition; N<sub>C</sub>, number of participants in the comparison condition.

and overall, unadjusted for baseline differences. A negative value on the average difference (I – C) across venues indicates a result in favor of the intervention (lower incidence of the combined STD biological end point). In general, the differences favored the intervention condition (not significant) for China, India, Russia, and Zimbabwe. In Peru, the incidence rate was lower overall in the comparison venues. No statistically significant differences were found between the I and C venues on the percent of participants with any new

STD over the 24 months in any country or across countries (mean = -0.71; P = 0.29).

Generally, in every country, the percent of participants reporting unprotected sex with nonspousal/non-live-in partners at each study visit decreased over time, and the incidence of any of the 6 STDs decreased between the first follow-up period (0–12 months) and the second follow-up period (12–24 months) in both I and C conditions (Fig. 2; note the vertical scales vary by country). The “absolute” decrease in percent of

**TABLE 2.** Summary of the Behavioral Outcome Data—Change from Baseline to 24 Months in Proportion of People Reporting Unprotected Sex

Country	No. Venue Pairs	Intervention (I)			Comparison (C)			Difference in Change I – C‡			
		No. Participants*	People Reporting Unprotected Sex (%)†		No. Participants*	People Reporting Unprotected Sex (%)†		Point Estimate (95% Confidence Interval)	P		
			Baseline	24 Mo		Change	Baseline			24 Mo	Change
China	20	1130	6.59	4.59	-1.99	1587	5.01	4.32	-0.68	-1.31 (-2.96 to 0.34)	0.11
India	12	1340	43.46	19.15	-24.32	1474	43.16	16.00	-27.16	2.85 (-0.03 to 5.85)	0.05
Peru	10	922	54.37	43.95	-10.42	1279	56.79	45.53	-11.26	0.85 (-5.40 to 6.69)	0.74
Russia§	10	690	35.61	28.02	-7.60	730	36.06	32.11	-3.95	-3.65 (-10.40 to 2.93)	0.23
Zimbabwe	15	2056	21.29	11.86	-9.43	2218	21.30	12.38	-8.92	-0.51 (-5.09 to 3.48)	0.86
Overall	67	6138	32.27	21.51	-10.75	7288	32.46	22.07	-10.39	-0.36	0.71

\*Analysis is based on 13,426 participants, excluding CPOLs, with non-missing baseline and 24-month information.

†Within country and condition, the statistics reported for baseline, 24 months, and change are averages over venues with equal weighting for each venue. Across country within condition, the statistics reported are averages over the 5 country averages with equal weighting for each country.

‡Within country, the point estimate is the average of the difference in venue pair change with equal weighting for each pair. Across country, the point estimate is the average over the 5 country averages with equal weighting for each country. The 95% confidence intervals and the P values are based on permutation tests.

§Two venue pairs are excluded in Russia due to limited sample sizes at 24 months.

**TABLE 3.** Summary of the Composite Biologic Outcome Data—Proportion of People Diagnosed With Any of 5 (for Men) or 6 (for Women) STDs Including HIV Between Baseline and 24 Months

Country	No. Venue Pairs	Intervention (I)		Comparison (C)		Difference in Incidence I – C‡	
		No. Participants*	Incidence†	No. Participants*	Incidence†	Point Estimate (95% Confidence Interval)	P
China	20	1241	10.62	1669	10.99	–0.37 (–2.96 to 2.22)	0.77
India	12	1445	7.07	1577	8.38	–1.31 (–4.48 to 1.38)	0.42
Peru	10	1038	14.07	1443	12.26	+1.80 (–1.47 to 4.95)	0.24
Russia§	11	805	9.07	867	11.15	–2.08 (–5.90 to 1.25)	0.26
Zimbabwe	15	2261	19.63	2415	21.22	–1.59 (–4.86 to 1.66)	0.31
<b>Overall</b>	<b>68</b>	<b>6790</b>	<b>12.09</b>	<b>7971</b>	<b>12.80</b>	<b>–0.71</b>	<b>0.29</b>

\*Analysis is based on 14,761 participants, excluding CPOLs, with non-missing baseline and follow-up information. No adjustment is made for baseline variables.

†Within country and condition, the statistic reported is average incidence of any of the 6 STDs over venues with equal weighting for each venue. Across country within condition, the statistic reported is the average over the 5 country averages with equal weighting for each country.

‡Within country, the point estimate is the average of the differences in incidences across venue pairs with equal weighting for each pair. Across country, the point estimate is the average over the 5 country averages with equal weighting for each country. The 95% confidence intervals and the P values are based on permutation tests.

§One venue pair is excluded in Russia due to limited biologic follow-up.

people reporting unprotected acts between baseline and 24 months was similar in each treatment condition (I vs. C participants with all 3 measures: China, 2% vs. 0.6%; India, 24.7% vs. 27.7%; Peru, 10.7% vs. 11.3%; Russia, 9.1% vs. 4%; Zimbabwe, 10.7% vs. 9.5%; overall, 11.5% vs. 10.6%). These decreases were fairly substantial relative to the baseline percents (33% over countries; 11%–64% depending on country and treatment condition), but they occurred in both study conditions. In general, incidence rates showed modest declines between the first and second follow-up periods in both groups or remained flat (absolute change I and C: China, –1.0%, –1.1%; India, –2.1%, –3.9%; Peru, –2.3%, +0.2%; Russia, +0.1%, –0.5%; Zimbabwe, –0.2%, –0.7%; overall, –1.1%, –1.2%).

## Secondary Analyses

The analyses in Tables 2 and 3 were repeated with adjustment made for baseline characteristics. After adjusting for baseline variables, results for both end points were similar to unadjusted results within and across countries (behavioral outcome adjusted mean across countries = –0.57;  $P = 0.53$ ; composite biological outcome adjusted mean across countries = –0.64;  $P = 0.33$ ; variables used for adjustments available on request). Next, the primary unadjusted analyses were repeated with data from the C-POLs included. No statistically significant differences were found on either outcome when C-POLs were included.

Changes in additional end points were examined using permutation tests as for the primary outcomes. The change in the number of episodes of unprotected sex with a nonspousal partner reported at baseline and the 24-month assessment was not significantly different between I and C venues in any country. Differences were estimated between I and C venues based on incidence in the 12- to 24-month period to determine whether the intervention had a larger effect after the first year. Again, significant differences were not found between I and C venues by country or overall.

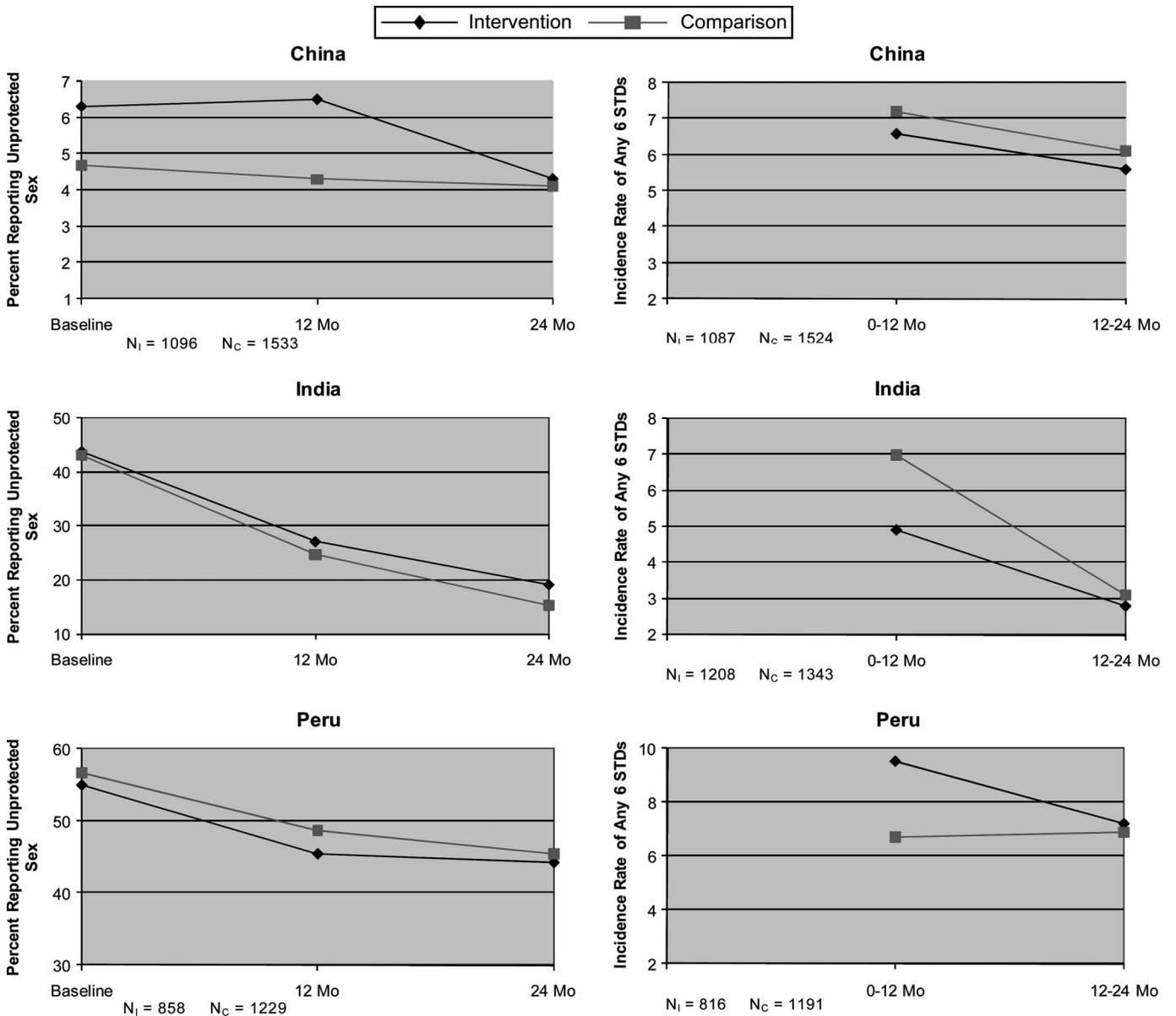
Where incidence rates allowed, individual STDs were examined separately. Specifically, we examined differences between I and C groups on incidence of HSV-2 (in all

countries), HIV (in Zimbabwe), chlamydia infection (in China, Peru, Russia, and Zimbabwe), and trichomoniasis (in women in China, India, and Zimbabwe). Comparisons could not be made for gonorrhea or syphilis due to small incidence rates in all countries. No statistically significant differences were found between I and C venues on incidence of HIV in Zimbabwe, on incidence of chlamydia infection in any of the 4 countries examined or overall in those countries, or on incidence of trichomoniasis in women in any of the 3 countries studied or across the 3 countries. Statistically significant differences were found between I and C groups on incidence of HSV-2 in China (average difference on incidence across venues: –1.26;  $P = 0.012$ ) and Russia (average difference: –1.50;  $P = 0.016$ ) but not in India, Peru, or Zimbabwe. Except in Zimbabwe, there were fewer than 100 incident cases of HSV-2 per country. Therefore, this result should be interpreted with caution due to potential volatility caused by the low incidence rates. Model-based analysis using longitudinal models provided results similar to those found for the permutation test analyses.

The proportion of cohort participants who reported having conversations in the 3 months before the baseline and 24-month follow-ups was examined by experimental condition separately for AIDS/STDs and condoms. Over countries at 24 months, the proportion in the intervention group reporting conversations about AIDS/STDs was 63.1%, with 56.7% reporting conversations about condoms. These proportions were higher than in the control group at 24 months (51.0% and 45.8%, respectively) and the intervention group at baseline (50.1% and 46.1%, respectively).

## DISCUSSION

Contrary to expectations, the C-POL intervention and its comparison condition produced similar, significant, and clinically relevant reductions in both STD incidence and self-reported unprotected extramarital sexual acts. These significant reductions represent approximately a 30% reduction in self-reported unprotected acts and a 20% reduction in incidence of STDs. It is important to recall that the comparison condition was a community-wide AIDS educational



**FIGURE 2.** Behavioral and biologic outcomes over time among the subset of participants with all measurements: percent of people reporting unprotected sex with nonspousal/non-live-in partners during the 3 months before baseline, 12-month and 24-month visits and incidence of any of the 6 STDs between baseline and 12 months and between 12 and 24 months.  $N_i$  = number of intervention participants;  $N_c$  = number of comparison participants. ♦ = intervention group; ■ = comparison group. Ranges of standard errors over time and study condition for the percent of people reporting unprotected sex were China, 0.47–0.86; India, 1.3–3.9; Peru, 2.6–3.6; Russia, 1.8–4.3; Zimbabwe, 1.4–1.9; overall, 1.0–1.3. Ranges of standard errors for incidence of any STD were China, 0.7–1.0; India, 0.6–1.5; Peru, 0.8–1.3; Russia, 1.1–1.5; Zimbabwe, 0.9–1.4; overall, 0.4–0.5. At baseline, incidence of any of the 6 STDs was not available; baseline prevalences were available but are not shown.

intervention with 3 repeated individual assessments of about 2 hours each that included repeated HIV and STD counseling and testing, extensive manual-based risk-reduction counseling, and an interview during which participants reflected on their HIV-/STD-related risky behaviors. Access to condoms and efficacious treatment were guaranteed in both conditions. For example, in China, where almost all STD treatments are typically provided by pharmacists giving

Chinese herbs, educational workshops regarding antibiotics were conducted for pharmacists in both conditions. The randomized controlled trial (RCT) was designed to examine the added community-level benefit of the shift in community norms addressed by the C-POL intervention. Under these conditions, the overall impact on outcomes in the intervention and comparison conditions was not significantly different. Several factors may account for the strong overall risk

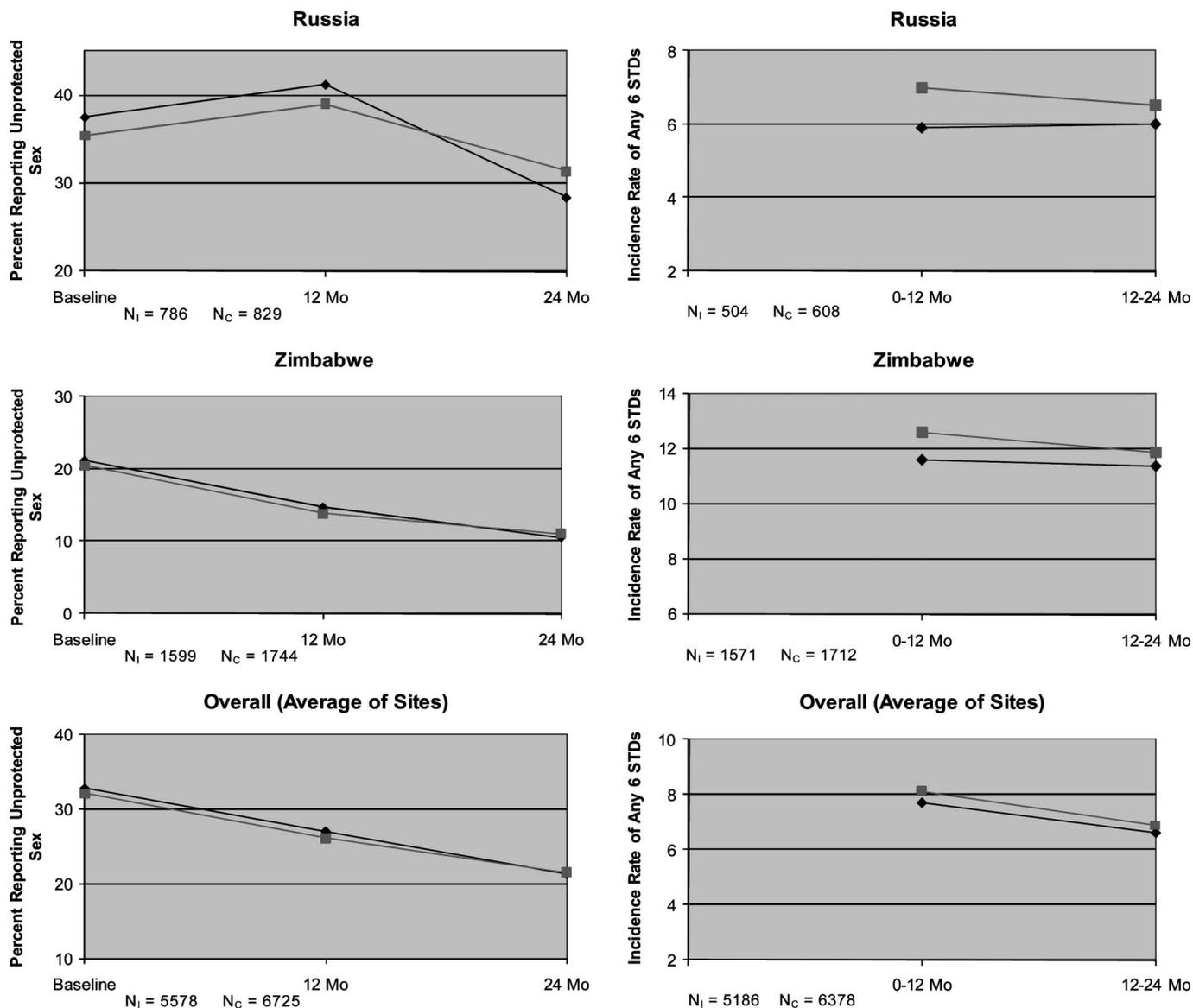


FIGURE 2. (continued).

behavior reductions over time and the absence of differential outcomes between the 2 experimental conditions.

First, historically, HIV prevention research has compared the effect of an experimental intervention against the “standard of care” or an attention control condition. In this study, the effects of the C-POL intervention were compared with a condition that directly focuses a person’s attention on the risks of recent sexual practices, which often reduces subsequent risk behaviors, such as occurs with motivational interviewing.<sup>18,19</sup> In fact, almost every large HIV prevention RCT, whether examining biomedical or behavioral interventions, has demonstrated a significant reduction in sexual risk when coupled with repeated HIV/STD testing, counseling, condom access, and STD treatment.<sup>20–22</sup> Behavioral reactivity

may have been especially strong in this trial because the participants in the comparison group received a substantial and sustained AIDS education intervention.<sup>23</sup>

Although HIV testing and treatment for STDs are available to population members who seek out these services in the sites where this trial took place, intensive prevention and treatment care of the kind provided to study participants in both conditions greatly exceeded usual local standards and is not currently sustainable. In fact, since the trial was completed, the major components of the AIDS education comparison condition have disappeared. At the recent International Society for Sexually Transmitted Diseases Research (ISSTD) meeting, the point was made that it may not be ethical to offer a comparison condition that is not sustainable when the

treatment condition may be.<sup>24</sup> Although there are no cost effectiveness or implementation data on the C-POL intervention in these sites, Pinkerton et al<sup>25</sup> conducted a cost-utility analysis of the intervention with gay men in the United States, which indicated that in addition to being highly efficacious, it is highly cost effective. The overall cost of the intervention (about \$40 per affected individual in the United States) is likely to fall within the budgetary constraints of many community-based AIDS prevention organizations in developing countries. Because the intervention is delivered by community members (not professional counselors) who can be inexpensively trained, it is more likely to be feasible for a resource-poor community to sustain the C-POL intervention than the intensive AIDS education comparison condition.<sup>26</sup>

Second, the long duration of the trial, including its lengthy follow-up period, increased the likelihood that other public health AIDS prevention service programs and research were being carried out in the same communities and concurrently affecting the study's populations. The significant increases in media attention, public health awareness, and diffusion of prevention messages in each country during this trial were likely to have reached populations in all study venues. For example, in India, the Gates-supported Avahan outreach to female sex workers reached virtually all of the women in the Chennai cohort.

Third, there has been emerging recognition that STDs, especially chlamydia infection and trichomoniasis, spontaneously remit over the period of 3–6 months. These data have only emerged in the past 5 years. There are individual differences in the rate of spontaneous remission: for example, older persons and those with a greater number of lifetime partners are more likely to clear infections without treatment.<sup>27</sup> This information was not known at the beginning of this trial. If the intervention was efficacious and individuals in that condition did not contract HIV/STDs, and the individuals in the comparison condition contracted chlamydia infection and trichomoniasis but it spontaneously cleared before the assessment, then, the effect size that we observed would be smaller than it really was.

Fourth, although community-level preventive interventions have been repeatedly called for by public health officials, changes in rates of STD and behavioral risk can only be empirically demonstrated among those with initial risk at the baseline assessment. The constraints of a longitudinal RCT require many more conditions to be met, rather than only the presence of risk. The population must be stable over time (eg, not characteristic of migrants in many countries); the local providers must have capacity to implement an RCT; the site must be close to a certified laboratory; and the officials must be cooperative. Also, successful mobilization of a community is different when the majority of community participants demonstrate risk as indicated in multiple ways here. In China, for example, those with previous STDs, those persons at highest risk of future infections, demonstrated greater reductions over 2 years than those in the comparison condition. Additionally, incident viral HSV infections were significantly lower in the intervention condition in China and Russia compared with that in the comparison conditions. These data suggest benefits of the C-POL intervention for those within the communities who were most likely to transmit STDs.

Different outcomes might have been found if the community-level intervention had been compared with usual and standard community services, which are invariably less than the comparison condition participants received. Our findings illustrate issues that will be confronted in future HIV prevention research that compares the effects of newly developed interventions against comparison interventions already known to be efficacious. This stance sets an ethical bar higher than the one often employed in the past. In some cases, new models may produce stronger effects than the best presently available approaches. In other cases—such as in the present and other trials<sup>28</sup>—they may not. Regardless, the HIV prevention field has advanced to the point of requiring that comparison conditions use interventions of known established efficacy against which new approaches can be compared. The current trial reinforces the challenges of requiring this heightened standard for an ethical but possibly not sustainable comparison condition.

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