EDITORIAL REVIEW

Setting the Bar High or Setting Up to Fail? Interpretations and Implications of The EXPLORE Study (HPTN 015)

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Abstract Controlled studies show that HIV risk reduction counseling significantly increases condom use, reduces unprotected sex and prevents sexually transmitted infections. Nevertheless, without evidence of reducing HIV incidence, these interventions are generally discarded. One trial, the EXPLORE study, was designed to test whether ten sessions of risk reduction counseling could impact HIV incidence among men who have sex with men in six US cities. Based on epidemiologic models to define effective HIV vaccines, a 35 % reduction in HIV incidence was set a priori as the benchmark of success in this behavioral intervention trial. Results demonstrated a significant effect of the intervention, with more than a 35 % reduction in HIV incidence observed during the initial 12–18 months following counseling. Over an unprecedented 48-month follow-up, however, the effect of counseling on HIV incidence declined to 18 %. The current review examined how the scientific literature has thus far judged the outcomes of the EXPLORE study as well as the policy implications of these judgments. We identified 127 articles that cited the EXPLORE study since its publication. Among articles that discuss the HIV incidence outcomes, 20 % judged the intervention effective and 80 % judged the intervention ineffective. The overwhelmingly negative interpretation of the EXPLORE study outcomes is reflected in public policies and prevention planning. We conclude that using a vaccine standard to define success led to a broad discrediting of the benefits of behavioral counseling and, ultimately, adversely impacted policies critical to the field of HIV prevention.

Introduction

The ultimate goal of any approach to HIV prevention is a meaningful reduction in new HIV infections. There are, unfortunately, few prevention interventions that have examined HIV infections as their endpoint and very few have achieved the goal of reducing HIV incidence. However, once demonstrated to reduce HIV incidence, interventions have had an impact on public health policy [1–3]. In order to use HIV incidence as their endpoint, clinical trials must be large in size, expansive in scope, and expensive in cost. For these reasons, HIV prevention trials typically rely on proxy outcomes, such as non-HIV incident sexually transmitted infections (STI), and behaviors that mediate (i.e., unprotected sex and injection equipment sharing) or mitigate (i.e., condom use and injection equipment cleaning) HIV transmission [4, 5]. Findings from numerous carefully controlled randomized clinical trials are remarkably positive and consistent; behavioral interventions that are guided by principles of behavior change effectively increase protective practices across nearly every population of importance in HIV prevention [6–8]. Unfortunately, because these intervention outcomes focus on behavior change, the results have been met with skepticism and often dismissed with claims that self-report is invalid and behavior change does not necessarily lead to disease prevention [9–11].

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The next generation of HIV prevention trials answered the limitations of self-reported behavior change by increasing the size and scope of studies to include incident STI as their endpoint. This shift in direction allowed for reasonable approximations of HIV prevention without the expense of conducting trials powered for detecting reductions in incident HIV infections. The inference that an incident STI approximates HIV transmission risk is based on the fact that HIV is itself an STI. In addition, there is high-prevalence of other STI in populations at greatest risk for HIV infection and STI play a pivotal role in HIV susceptibility and infectiousness [12, 13]. Findings from prevention trials that have included incident STI as their endpoint mirror those trials that report only behavioral outcomes [14, 15]. Nevertheless, skeptics of behavioral interventions for HIV prevention remain unsatisfied, claiming that the biological bases and transmission dynamics of incident STI are too different from HIV to permit inferences regarding HIV prevention. Thus, once again the goal posts were pushed back; the only convincing evidence of HIV prevention efficacy would be reducing HIV incidence [16].

In the current paper, we examined the outcomes of the EXPLORE study—the only behavioral intervention trial aimed to detect differences in sexually transmitted HIV incidence. We set out to review how the outcomes of the EXPLORE study have been judged in the years following its completion. We begin with an overview of the design of the trial and rationale for evaluating its effectiveness. We then provide a review of the published research that has cited the EXPLORE study outcome paper [17] to determine how the HIV incidence outcomes have been judged. Finally, we discuss how interpretations of the EXPLORE study have influenced HIV prevention policy.

The EXPLORE Study (HPTN 015)

Designed as the definitive test of behavior change interventions to reduce HIV incidence, the EXPLORE study [17] enrolled 4,295 men who have sex with men between 1999 and 2003 in six US cities—Boston, Chicago, Denver, New York, San Francisco, and Seattle. The counseling in this trial was based on principles of motivational interviewing and social-cognitive behavioral skills building models for health behavior change [18]. Preliminary studies identified key behavioral targets aimed directly at reducing HIV risks. For example, as a result of initial developmental studies, sexual pleasure was considered the basis for engaging in unprotected anal sex and was incorporated into the counseling. Substance use was also a prominent feature of risk and became a major focus in counseling. Men randomized to the EXPLORE study

experimental counseling received ten prevention counseling modules in just as many sessions over 4–6 months. Each session lasted an average of just under 40 min. Nearly 75 % of EXPLORE participants had received all of the counseling sessions, with an additional 12 % receiving between six and nine sessions. EXPLORE also provided maintenance counseling every 3 months, as well as HIV testing every 6 months for the duration of the study. Men in the comparison intervention received HIV testing every 6 months accompanied by ongoing risk reduction counseling that has itself been demonstrated highly-effective for reducing incident STI in long-term follow-up [19].

Rationale for Defining Success

The EXPLORE study defined effectiveness a priori as reducing HIV incidence by 35 %. The decision rules described in the trial executive summary state:

> To be specific, the EXPLORE study was designed so that the intervention strategy would be declared beneficial if the reduction in HIV incidence was statistically significantly above 10 % (that is, that the lower bound of the confidence interval was above 10 %). If not, and the reduction in HIV incidence was statistically significantly below 35 % (that is, the upper bound of the confidence interval was below 35 %), the benefit of the intervention strategy would be ruled out. In case neither was true, the intervention would be considered plausibly efficacious with merit for further evaluation, possibly with select refinements. With the target sample size of 4,350 and an expected HIV incidence of 1.55 per 100 person years in the standard arm, if the true reduction in HIV incidence was 35 %, there would be 3.0 % chance of ruling out benefit, 50.0 % chance of declaring benefit, and 46.9 % chance of stating plausibly efficacious. Furthermore, if the true reduction in HIV incidence was 0 %, there would be an 75.0 % chance of ruling out benefit. [(EXPLORE Executive Summary [20], p. 3)].

Defining HIV prevention success as 35 % reduction in HIV incidence appears rooted in epidemiological models used to estimate vaccine efficacy. The benchmark of 35 % reduction in HIV incidence may therefore be practical for 'permanently' protective interventions, such as vaccines and male circumcision. However, it is unreasonable to expect that the effects of any behavioral intervention would hold for the duration of one's lifetime. Is expecting a 35 % reduction in HIV incidence over 48 months a legitimate standard to apply to behavioral interventions? Furthermore, given that permanently protective interventions are rare (there is no

effective HIV vaccine), limited by risk group (data suggest limited benefits of male circumcision for MSM) and partially protective (male circumcision is 50 % effective), is it reasonable to declare behavioral interventions that are effective over 18 months but not 48 months as unsuccessful? [8, 21].

Over 48 months of follow-up, the HIV incidence for men who received the EXPLORE counseling was 1.9 infections per 100 person years, compared to 2.3 per 100 person years for men who received semi-annual testing and counseling, an 18 % difference in HIV incidence. Thus, over the course of 4 years (average follow-up 3.25 years), the difference between the conditions was not deemed significant. However, the 12-month follow-up outcomes exceeded the 35 % bar set for reducing in HIV incidence, demonstrating a difference between conditions of 39 % [22]. The impact of the EXPLORE counseling has therefore been judged against two standards. As a behavioral intervention, a 39 % reduction in HIV incidence over 12–18 months is an irrefutable success. As discussed by Coates et al. [22]. "Had the study terminated when behavioural studies are usually stopped (i.e., at 12 months' follow-up), the intervention would have been declared effective." (p. 672) In contrast, when held to a standard set for HIV vaccines, an 18 % reduction in HIV incidence over 48 months is considered a failure. The policy implications of these two disparate conclusions have the potential to determine the direction of HIV prevention research, policy, and practice. We therefore examined how the field has thus far judged the outcomes of the EXPLORE study.

Method of Review

We conducted a systematic search using Thomson Reuters Web of Knowledge (version 1.0) and Google Scholar to identify all published articles that have cited the EXPLORE study outcome paper by Koblin et al. [17]. Our initial search was conducted in October 2012 and we performed a final search in March 2013. We retrieved the full text for all published papers and searched the articles for the EXPLORE study citation. We extracted the verbatim text where the EXPLORE study was cited in the original content. We then coded the extracted text blind to author, title, and journal.

Articles were first sorted into two groups. The first group was defined as non-judging, that is the EXPLORE study was cited but not judged as to its effectiveness for preventing HIV infections. These articles cited EXPLORE for use in secondary analyses, use of measurement instruments, with reference to the type of counseling, or with respect to the non-HIV outcomes without drawing conclusions on the impact of the intervention on HIV incidence. For example, one article that cited the EXPLORE study stated "Reviews showed that intervention programs for MSM are effective in reducing risk behaviors among HIV risk groups" [23], without drawing conclusions on the HIV incidence endpoint. In addition, articles that discussed the rates of behavior and disease in the trial without reference to the intervention effects were considered non-judging; for example, "In the EXPLORE cohort study, a significant increase in the risk of HIV infection was associated with recently acquired and prevalent HSV-2 infection-by 3.6-fold and 1.5-fold, respectively" [24]. Finally, articles that made broad statements about intervention outcomes without specifically discussing EXPLORE were coded as non-judging; for example, "Behavioral interventions, contingency management programs and referral to outpatient treatment programs have shown promise in decreasing methamphetamine use and reducing risk behaviors associated with the spread of HIV infection." [25].

The balance of articles judged the impact of EXPLORE counseling on HIV incidence. These articles were subjected to a second stage of coding to determine how the outcomes were judged: (a) favorable HIV outcomes (i.e., demonstrated significant reduction in HIV incidence), (b) unfavorable outcomes (i.e., failing to significantly reduce HIV incidence). Two independent coders (the first two authors) examined the extracted text and reached 92 % agreement. Discrepancies were settled by discussion.

Interpretation of the EXPLORE Study in Peer-Reviewed Literature

Results showed that the EXPLORE study outcome paper was referenced soon after publication, with 53 articles citing the outcomes in the first four years after publication, 19 in the fifth year, and 23 articles citing the outcomes in the sixth year. In total we identified 127 articles citing the EXPLORE outcome paper. For the sake of comparison, we conducted a similar citation search for the primary outcome study from Project RESPECT, which demonstrated reductions from counseling in non-HIV STI that was widely heralded as successful and formed the basis for the control condition in the EXPLORE study. Results showed that in the first 8 years after Project RESPECT was published it had been cited 299 times, more than twice as often as the EXPLORE study, a statistically significant difference, $t(14) = 4.04$, $p < 0.001$ (see Fig. 1).

Content coding of the articles that cited EXPLORE showed that 92 (72 %) of the 127 articles citing the study did not judge the HIV incidence outcomes. A total of 34 articles drew conclusions regarding the effects of EXPLORE counseling on HIV incidence. Table 1 shows
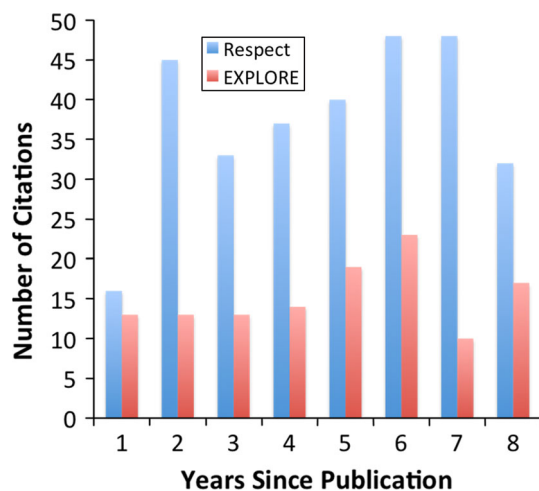
Fig. 1 Number of articles citing project respect (1999–2006) and the EXPLORE study (2005–2012)

the positive and Table 2 shows the negative coded judgments of the EXPLORE study HIV incidence outcomes. Results showed that 27 of the articles (80 %) judged EXPLORE as ineffective at reducing HIV incidence and 7 (20 %) judged EXPLORE as effectively reducing HIV incidence. Examining the content of Table 2 shows that even the most positive interpretations of the EXPLORE study outcomes take into account the 48-month follow-up and do not suggest overwhelming success. Thus, across all citations of the EXPLORE outcome paper, only 5 % judged the trial effective in reducing HIV incidence compared to 21 % that judged the outcomes ineffective.

Interpretations of the EXPLORE Study in Public Policy

Whether or not EXPLORE counseling should be held to the same standard as an HIV vaccine may be worthy of academic debate. Nevertheless concluding that EXPLORE was not effective in reducing HIV incidence has had a significant real world impact on public health policy. At worst, the 48-month outcomes from the EXPLORE study have provided long-time skeptics of behavioral interventions with a definitive confirmation for their beliefs that risk reduction counseling is ineffective. For example, in their 2006 HIV Testing Guidelines, the CDC refers to EXPLORE as offering limited evidence of efficacy for risk reduction counseling. Specifically, as part of their basis for removing the requirement to conduct risk reduction counseling in conjunction with HIV testing, the CDC stated the following about EXPLORE;

> The benefit of providing prevention counseling in conjunction with HIV testing is less clear. HIV counseling with testing has been demonstrated to be an

effective intervention for HIV-infected participants, who increased their safer behaviors and decreased their risk behaviors; HIV counseling and testing as implemented in the studies had little effect on HIV-negative participants. However, randomized controlled trials have demonstrated that the nature and duration of prevention counseling might influence its effectiveness. (referenced the EXPLORE study) Carefully controlled, theory-based prevention counseling in STD clinics has helped HIV-negative participants reduce their risk behaviors compared with participants who received only a didactic prevention message from health-care providers. A more intensive intervention among HIV-negative MSM at high risk, consisting of ten theory-based individual counseling sessions followed by maintenance sessions every 3 months, resulted in reductions in unprotected sex with partners who were HIV-infected or of unknown status, compared with MSM who received structured prevention counseling only twice yearly. (references the EXPLORE study). [[26] p. 15].

The implication is that risk reduction counseling may change behavior and may even reduce the risks for STI, but not HIV.

The CDC has also identified EXPLORE counseling as an 'effective intervention' for distribution in its Diffusion of Effective Behavioral Interventions (DEBI) program. (see http://www.cdc.gov/hiv/topics/research/prs/resources/factsheets/EXPLORE.htm) In describing the "Key Intervention Effects", the CDC notes that EXPLORE decreased risk behavior. They specifically state, "Men in the intervention group were significantly less likely to report any unprotected anal sex, serodiscordant unprotected anal sex, and serodiscordant receptive unprotected anal sex at the 12 and 18-month follow-ups as compared to men receiving the standard comparison intervention (p's < 0.001)." However, under a separate heading, "Considerations", The CDC states, "A modest 18 % reduction in HIV incidence, the primary outcome, was observed in the intervention relative to control arm; however, this did not achieve statistical significance."

The US National HIV Prevention Strategy, arguably the single most important policy statement guiding US HIV prevention efforts, only cites the EXPLORE study once. Consistent with the bulk of the research literature and the conclusions of the CDC, the National Strategy cites EXPLORE by stating the following, "Even though these [risk reduction] interventions have not been proven to reduce HIV infections, they promote responsible sexual behaviors that may lower a person's risk for becoming infected with HIV and some have been associated with reducing STIs" [[27], p. 17] Given the importance of the

Table 1 Negative interpretations of the EXPLORE study HIV incidence outcomes in published articles

First author/reference	Years	Unfavorable interpretation
Auerbach et al. [33]	2006	A large multisite behavioural intervention trial in the United States among men who have sex with men, and which included HIV incidence as an outcome measure, found an 18.2 % lower rate of HIV infection (15.7 % after adjustment for baseline covariates) in the intervention group compared with the control group and a 20.5 % lower incidence of unprotected receptive anal intercourse with partners who were HIV-positive or of unknown serostatus in the intervention group compared with the control group. Although the behavioural outcome was statistically significant, the HIV incidence outcome was not
Bedoya et al. [34]	2012	It was previously reported that the EXPLORE intervention did not significantly reduce the risk of HIV infection: a modest 18 % (95 % CI −5, 36 %) reduction in risk of HIV infection was observed
Berg et al. [35]	2011	We emphasize that although not statistically different, the rate of HIV acquisition in the EXPLORE Study was almost 16 % lower in the first 18 months of follow-up among MSM receiving MI compared with MSM receiving twice yearly counseling on risk reduction. This is a clinically important result
Brown et al. [36]	2006	Although there was no significant reduction in HIV incidence (intervention effect 5.7, 95 % confidence interval (CI) –8.4, 34.4), a statistically significant reduction of 20.5 % (95 % CI 10.9, 29.0) in unprotected receptive anal intercourse with an HIV-positive or unknown serostatus partner was detected in the behavioral intervention arm. The intensive, 10-session risk reduction behavioral intervention tested in the EXPLORE study did not reduce HIV incidence to a statistically significant degree
Golden et al. [37]	2005	Unfortunately, these data are discouraging, with a large, intense ten-session intervention trial demonstrating no significant impact on HIV incidence
Grant et al. [3]	2010	Intensive counseling in behavioral risk reduction for such subjects has not been shown to be better than standard counseling
Grant et al. [38]	2005	Even as available and proven prevention interventions are used, the HIV pandemic will not be stopped solely by talking to those at-risk
Gross et al. [39]	2006	The most labor-intensive counseling strategy evaluated to date has demonstrated no sustained impact on rates of HIV acquisition.
Herbst et al. [40]	2007	In one study, incident HIV at the 6-month post-baseline follow-up was in the desired direction but non-significant (p 0.07); results reported at subsequent follow-ups ranging from 12 to 48 months post-baseline were inconsistent and non-significant
		The EXPLORE study, a trial conducted in six US cities, reported a significant reduction in self-reported UAI (OR 0.81, 95 % CI 0.71– 0.93) and a borderline significant decrease in incident HIV (OR 0.62, 95 % CI 0.36 –1.06) after 12 months of follow-up
Lyles et al. [41]	2007	Four interventions were identified as having produced a significant reduction in new STDs over a minimum of 12 months after exposure to the intervention. The intervention that measured HIV incidence did not significantly reduce the number of new infections
Mansergh et al. [42]	2010	Randomized trials of HIV risk behavioral interventions—particularly for MSM—have generally used two-group designs: an attention-control group (e.g., content materials unrelated to intervention content) or a standard group (e.g., HIV counseling and testing), but rarely both. These interventions generally found no difference between the two groups in HIV risk outcomes
Mimiaga, et al. [43]	2009	Among participants reporting CSA (child sexual abuse), the EXPLORE intervention had no effect in reducing HIV infection rates. Participants reporting CSA were significantly more likely to have symptoms of depression and use nonprescription drugs
Miranda et al. [44]	2007	HIV counseling can be an important HIV prevention strategy, although its efficacy in reducing risk behaviors is still being evaluated (CDC 2001). Koblin et al. [17] show that no long-term change is possible
Morgenstern et al. [45]	2009	For example, the most recent large-scale HIV prevention behavioral intervention among MSM failed to find a significant effect in reducing HIV risk behaviors.
Morin et al. [46]	2008	Prior behavioral intervention trials have observed decay of intervention effects over time
Padian et al. [16]	2010	All seven behavioral interventions yielded flat results

Table 1 continued

First author/reference	Years	Unfavorable interpretation
Pilcher et al. [47]	2010	Meanwhile, although numerous studies have found that individual and small group counseling interventions can reduce self-reported, high-risk sexual behavior, the only randomized trial, to our knowledge, to evaluate a behavioral intervention with use of HIV acquisition as an end point found that repeated counseling sessions were not effective
Ross et al. [48]	2010	In any event, none of the trials showed a statistically significant impact on HIV, either in terms of a reduction or an increase; in fact, none approached statistical significance with the possible exception of the EXPLORE trial [adjusted odds ratio = 0.82, 95 % CI 0.64–1.05]
Rotheram-Borus et al. [49]	2006	There is evidence both supporting Kamb et al. [19] and disputing Koblin et al. [17] the benefit of more extensive counseling for HIV-negative persons. Despite the equivocal evidence on the effectiveness of the type of pretest counseling typically offered HIV seronegative persons, it may be more sensible to target efforts elsewhere, particularly in low-incidence settings and countries
Rotheram-Borus et al. [50]	2011	Randomised controlled trials that test biomedical interventions to reduce STIs have had very mixed results, as have behavioural trials
Safren et al. [31]		In addition, the rate of HIV acquisition in the experimental arm was 18.2 % lower than that in the control arm, although the difference was not statistically significant (95 % CI −4.7 to 36.0 %)
Sanchez et al. [51]	2009	The EXPLORE trial, a phase IIb efficacy trial of a 10-session behavioral intervention showed no significant reduction of HIV incidence when compared with regular counseling
Schneider et al. [52]	2009	Cognitive interventions have not been successful in some other at-risk male populations
Scott-Sheldon et al. [14]	2011	Outcomes from this approach demonstrate that enhanced behavioral HIV prevention using multiple group sessions significantly reduces rates of serodiscordant unprotected anal intercourse over standard HIV prevention in the shorter term, with no differences between groups observed to long -term evaluations
Smith et al. [53]	2012	Project EXPLORE enrolled 4,295 HIV-uninfected MSM from 6 US cities during 1999–2001 into a randomized, controlled behavioral intervention trial in which the active arm did not significantly reduce HIV incidence compared with the control intervention arm
Sullivan et al. [54]	2012	The HIVNET 015 study (colloquially called EXPLORE) one of the few studies of behavioural interventions in MSM for which reduction of the incidence of HIV infection was an endpoint clearly shows the potential and limitations of behavioural approaches
Zenilman et al. [55]	2005	Nevertheless, although not mentioned specifically in the EXPLORE study, the results were clearly disappointing in that the intensive intervention resulted in only a modest effect

US National HIV Prevention Strategy, its conclusion that behavioral interventions have not been proven to reduce HIV infections surely impacts policy decisions, resource allocation, and statewide prevention planning.

Implications

The question as to whether EXPLORE counseling reduced HIV incidence clearly depends on how success is defined. Held to a vaccine standard, EXPLORE′s outcomes over 48 months do indeed fall short. For instance, the most successful HIV vaccine trial has demonstrated 31 % efficacy over 3 years [28]. However, when held to a standard that is fitting for behavioral interventions, 18 months of

follow-up far exceeds what would typically be expected for durability of change in behavior. Thus, reducing HIV incidence over 35 % in this time frame is an unquestionable success. The EXPLORE study outcomes also parallel those of behavioral interventions delivered in far fewer sessions, suggesting the potential for even greater public health impacts of risk reduction counseling [15].

There are other features of the EXPLORE study that question using the 48-month follow-up to define success. Only those participants enrolled in the first year of the study, a fairly small number of men to reliably assess HIV incidence, were represented at 48 months. The HIV incidence in the EXPLORE trial did not decline as a result of epidemiologic trends, therefore yielding adequate statistical power for the analysis. In fact, during the years that the

Table 2 Positive interpretations of the EXPLORE study HIV incidence outcomes in published articles

First author	Years	Favorable interpretation
Chen et al. [56]	2007	Researchers found that in a randomised controlled study an intervention consisting of ten one-on-one counselling sessions followed by maintenance sessions every 3 months, was associated with an 18.2 % overall difference between the controlled and intervention groups
Donnell et al. [57]	2010	An intervention that targets HIV-uninfected individuals is most efficiently studied with an individually randomized design. These have been used in most HIV prevention trials, with intervention efficacies ranging from modest decreases (25–35 %) to substantial reductions (50–60 %)
Ickovics et al. [58]	2008	The EXPLORE Study Team found that among men who have sex with men randomized to ten individual HIV counseling sessions with quarterly maintenance, rate of HIV acquisition was 18 % lower in the intervention compared to standard group, with the effect most favorable 12–18 months after the initial HIV test
Mimiaga et al. [59]	2006	While the intervention did not achieve a targeted level of efficacy (35 %) in preventing new HIV infections compared to semi-annual HIV voluntary counseling and testing, the study results suggest a possible modest benefit of the intervention in reducing new HIV infections
Nielsen et al. [60]	2005	Persons who received intense counseling had an 18.2 % lower HIV acquisition rate than those randomly assigned to the standard intervention, although this difference was sustainable only in the first 12–18 months of follow-up
Rotheram-Borus et al. [61]	2009	These results are encouraging, especially in the face of trials that have shown substantial relapse after initial responsiveness to efforts to prevent the transmission of HIV
Wang et al. [62]	2011	Koblin et al. [17] found in the multi-city Project EXPLORE that a 10-session intervention based in part on ME principles brought about reductions both in self reports of sexual risk behavior and in HIV seroconversion

EXPLORE study was conducted there were no significant reductions in HIV incidence among MSM in major US cities, including cities where the trial was conducted [29]. The epidemiologic context of the EXPLORE study therefore further bolsters confidence in the 18-month reductions in HIV [30].

Concluding that EXPLORE counseling was more effective in reducing HIV incidence than suggested in the original outcome paper requires using the appropriate standard for a behavioral intervention. We are not the first to point out misrepresentations of the EXPLORE outcomes. Others have similarly concluded that the trial outcomes for reducing HIV incidence should be judged against behavioral interventions and that the methodological features of the trial should be taken into account. For example, although Safren et al. [31] draw conclusions that the HIV incidence outcomes were not statistically significant, they described the EXPLORE study as successful on rational grounds after considering the overlapping features of the experimental and comparison conditions as well as the duration of follow-up. In addition, Eaton et al. [32] performed secondary analyses and concluded on statistical grounds that EXPLORE was effective in reducing HIV incidence through direct and indirect effects of the intervention.

As prevention planners and policy makers contemplate the role of risk reduction counseling and other behavioral interventions in a context that sees little hope for an effective HIV vaccine and in a new era of combination approaches to HIV prevention, the interpretation of the EXPLORE study outcomes will become even more critical. We conclude that when held to an appropriate standard for behavioral interventions, the EXPLORE counseling was indeed highly-effective in reducing HIV incidence and offers the potential to significantly alter the course of HIV epidemics. Future references to this uniquely important clinical trial should judge the intervention outcomes more fairly.

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