

Executive Summary

TRIAL DESIGN

HIVNET 015, EXPLORE, was designed as a multi-site two arm, randomized controlled Phase IIb trial to test a behavioral intervention in preventing acquisition of HIV infection among men who have sex with men. Men who were HIV antibody negative were recruited in six cities in the United States: Boston, Chicago, Denver, New York City, San Francisco, and Seattle. Men were eligible if they were 16 years of age or older and reported anal sex with one or more men in the past year. Men were excluded if they reported that they had been in a mutually monogamous relationship for two or more years with a known HIV antibody negative male partner.

The initial enrollment period was planned for one year starting in January 1999. However, in order to meet the recruitment goal of 4,350 men, the protocol was amended to extend the recruitment period through February 2001. Recruitment strategies varied by city but included advertising; outreach on the street and at dance clubs, bars, bathhouses and sex clubs; referrals from other cohort studies, other study participants, and STD clinics; and mailings.

At an initial screening visit, data were collected on demographics, reasons for participating in the study, STD history, use of post-exposure prophylaxis, and histories of counseling and psychotherapy. Computer-assisted self-interviewing technology with an audio component (ACASI) was used to collect data on attitudes about safer sex, social activities within the gay community, depression, recent alcohol and drug use, and recent sexual behaviors. Blood specimens were collected for HIV antibody testing and stored for future HSV-2 antibody testing. Urine was collected and a rectal swab was done for screening for urethral and rectal gonorrhea, respectively. All testing was accompanied by pre- and post-test counseling.

Men who were confirmed as being HIV antibody negative were asked to enroll in the trial and were randomized to the intervention or control conditions in a 1:1 ratio. Every six months, participants returned for an ACASI behavioral assessment and HIV testing until study completion (July 31, 2003).

Intervention and control conditions

The intervention consisted of ten core counseling modules delivered at one-on-one counseling sessions, typically with one module of counseling material being delivered per session and with the goal of completing within four to six months of randomization. After the initial ten sessions, maintenance sessions were delivered every three months through the end of the study. An intervention manual detailed the materials to be covered at each of the ten core behavioral intervention sessions. The first three sessions established rapport between the counselor and participant and provided detailed personalized risk assessments to guide future focus of the intervention sessions. The remaining sessions covered sexual communication, knowledge of HIV serostatus (one's own and others') in making sexual decisions, and alcohol and drug use in conjunction with risk behavior. Modules also were offered on how unsafe sex could be triggered by meeting different types of partners, by places or events related to partner-selection, and by cognitive or emotional cues associated with risk-taking. Motivational interviewing techniques were employed to help participants make and sustain changes in knowledge, attitudes, beliefs,

and behaviors. The standard (control) condition was standard semi-annual risk reduction counseling based on the CDC Project Respect model, and used the same counselors as those that provided the behavioral intervention.

Several approaches were used to assess and ensure adherence to the intervention and standard arm protocols. First, sessions were audiotaped and a planned 10% random sample of tapes was selected for review by raters at the intervention-coordinating center (11.5% of tapes were selected). The sessions were scored on numerous items specific to the session. The quality assurance (QA) scores were percentages of the total possible score and sessions with scores above 80% were considered to follow the protocol and therefore, acceptable. Another approach was to assess duration of sessions since the interventions sessions were designed to be longer than the standard arm sessions. The final approach was to assess the number of interim visits completed. Interim visits were made available for participants if they needed HIV testing due to a potential exposure or other services. However, the interim visits were not be utilized to deliver additional material to the standard arm participants.

Definition of HIV outcomes

HIV antibodies were detected by enzyme-linked immunosorbent assay (ELISA). Sera shown to be reactive after a first test were retested in duplicate. Repeatedly reactive samples were confirmed by Western blot assay or immunofluorescence assay. Participants with a positive test result at any follow-up visit were referred for medical and social services. In the case that the tests deviated from the standard procedure, the HIV serostatus was determined by the study endpoint verification committee on a case-by-case basis.

Study monitoring

Data forms, informed consent forms, and data on endpoints were reviewed and monitored on a regular basis by Abt Associates, Inc. and PPD, (a research CRO). The Center for AIDS Prevention Studies (CAPS) at University of California, San Francisco monitored delivery of the counseling materials and counseling notes and performed quality assurance assessments. The HPTN Study Monitoring Committee and NIH Data Safety and Monitoring Board reviewed the study approximately every 8 months.

Statistical methods

This "Screening" or Phase IIb trial was designed to have a high probability to establish benefit for a highly efficacious intervention or to rule out benefit for a totally ineffective intervention. Furthermore, for interventions with less striking yet important levels of efficacy, (e.g., 35% efficacy), this Phase IIb trial would have high probability to either establish benefit or to indicate plausible efficacy deserving of further study and, in that instance, to inform the development of those future efficacy trials.

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.

Per intent-to-treat, comparisons were made between the participants randomized to the intervention arm and those to the standard arm, regardless of the amount of counseling received. The primary analysis was to assess the intervention effect on HIV incidence. A proportional hazards model was adopted on the discrete time scale of semi-annual visits, with the intervention-arm indicator as the only covariate. The odds ratio of HIV infection was estimated and the intervention effect was defined as one minus the odds ratio, i.e., the percent of reduction in HIV infection. It was assumed in the analysis that HIV serostatus was negative at a missing semi-annual visit if there was not a positive result at an earlier visit and an assessment was made at a subsequent semi-annual visit.

As secondary endpoints, serodiscordant (i.e., with HIV positive or unknown partner) unprotected anal intercourse (SDUA), and unprotected anal intercourse (UA) were assessed at semi-annual visits. For each endpoint, a logistic regression model was adopted with visit-independent intervention effect and visit-specific intercepts. The GEE approach was used to account for within-participant correlation of repeated outcome measures, with an independent working correlation.

For both the primary endpoint and secondary endpoints, additional analyses were performed to adjust for baseline characteristics. Specifically, for HIV incidence, in the proportional hazards model, we added the following baseline variables as additional covariates: age, injection drug use, sex with HIV positive male partner, sex with HIV positive female partner, unprotected receptive anal sex, and unprotected insertive anal sex, as well as site and race/ethnicity as stratification variables. This was an attempt to account for imbalances in randomization and lost-to-follow-up with respect to baseline characteristics. For SDUA, its baseline measure was added to the logistic regression model as a visit-independent effect. The same approach was used in the adjusted analysis of UA by adding its own baseline measure to the regression model.

Prior to the final data analyses, we identified three potential effect modifiers, alcohol use, non-injection drug use and depression. Alcohol use was categorized as none, light, moderate and heavy use, and non-injection drug use and depression were categorized as yes or no. Subgroup analyses were performed for HIV infection, SDUA, and UA for each potential effect modifier.

RESULTS

Accrual and baseline characteristics

Of the 4,862 men screened for the EXPLORE study from January 1999 to February 2001, 4,296 (98.8% of target enrollment goal) men enrolled and were randomized (Figure 1). The final analysis was based on 4,295 participants: one participant was not included in the analysis since he was randomized in the absence of informed consent.

The mean age of the participants was 34.0 years, 19.0% were 25 years of age or younger. The majority (72.75%) of men were white, 15.2% were Latino and 6.5% were African-American; 35.8% had less than a college degree; and 40.3% had an annual household income of less than \$30,000. While the enrolled men reported a median of 7 male sex partners in the six months prior to screening (25% quartile: 3; 75% quartile: 18), 42.2% reported having 10 or more male partners and 28.4% reported having an HIV-infected partner. With regard to specific sexual risk behaviors, 69.1% reported any unprotected anal (UA) intercourse, 48.0% reported unprotected receptive anal intercourse and 54.9% reported unprotected insertive anal intercourse. About half (47.9%) of men reported unprotected anal intercourse with a serodiscordant or unknown status (SDUA) partner. Heavy alcohol and non-injection drug use was reported by 11.0% and 64.7% of men, respectively. At baseline, 47.3% of men had symptoms of depression as determined by a validated short form of the CES-D.

Baseline characteristics were well-balanced between the intervention arm compared to the standard arm with the exception of unprotected insertive anal intercourse (Table 1).

Adherence to counseling

The number of session-modules completed was defined as the maximum number of modules or sessions completed within six months of randomization. Of the 2,144 men assigned to the intervention, 74.5% completed all initial 10 session-modules and 7.2% completed 7-9 sessions-modules. Only 13.4% completed three or fewer session-modules (Table 2). Over 70% of the men in the intervention arm received maintenance sessions except at the 33-, 39- and 45-month visits (Figure 1).

For the initial 10 sessions, 83.3% met the quality assurance criterion of a score of 80% or higher as did 77% of the maintenance visits for the intervention arm. There were no significant differences in the percent of semi-annual visits meeting the quality assurance criterion by arm of the study (Table 2). An examination of the duration of the sessions at the semi-annual visits indicated that the intervention sessions were on average 16.1 minutes longer than the standard arm sessions (Table 2). Intervention arm participants had a greater number of interim visits compared to standard arm participants. The number of participants who had at least one interim visit was higher in the intervention arm than the standard arm (Table 2).

Retention

Visit retention rates were above 83% in the intervention arm and above 87% in the standard arm over the course of the follow-up period (Figure 1). Retention was consistently higher in the standard arm than in the intervention arm. Lower retention, as determined by final visit retention status, was significantly associated with minority group status (89.5% whites retained vs. 83.9% others), younger age (89.8% >25 years old vs. 80.0% ≤25 years old), reporting female sex partners at baseline (88.5% no female partners vs. 74.2% 1+ female partner) and reporting unprotected receptive anal intercourse (URA) at baseline (89.0% no URA vs. 86.7% yes URA). In the intervention arm, retention also was significantly associated with completion of the initial ten session-modules (92.2% 9+ session-modules retained vs. 63.6% <9 session-modules).

Primary analysis

The overall HIV incidence in the study cohort was 2.1 per 100 person-years (95% CI: 1.9, 2.4). In the intervention and standard arms, there were 6,037 and 6,203 person-years of follow-up, respectively. There were 115 intervention participants and 144 standard participants who became infected with HIV over the course of the study. Based on an intent-to-treat analysis approach, the odds ratio was 0.818 (95% CI: 0.640, 1.047) for the intervention arm relative to the standard arm (Figure 2). This translates to an 18.2% (95% CI: -4.7%, 36.0%) reduction in HIV acquisition in the intervention arm. The data suggest that the reduction in HIV incidence was more favorable in the first 12 to 18 months of the study (Figure 2).

After adjustment for study site and baseline characteristics associated with retention and distributed differently in the two arms, the estimated odds ratio for the intervention was 0.843 (95% CI: 0.656, 1.084), translating to a 15.7% (95% CI: -8.4%, 34.4%) reduction in HIV acquisition in the intervention arm. Subgroup analyses of HIV incidence by baseline alcohol use, non-injection drug use and depression score were consistent with overall results (data not shown).

Secondary behavioral analysis

The estimated odds ratios of reporting SDUA and UA in the intervention arm relative to the standard arm is 0.852 (95% CI: 0.775, 0.937) and 0.861 (95% CI: 0.785, 0.944), respectively. This translates to a reduction in the intervention arm of 14.8% (95% CI: 6.3%, 22.5%) in SDUA and a reduction of 13.9% (95% CI: 5.6%, 21.5%) in UA, relative to the standard arm.

See Figure 3 for reported sexual behavior change by semi-annual visit and study arm, EXPLORE (serodiscordant unprotected anal sex, SDUA, and unprotected anal sex, UA; intervention = I, standard = S).

Effect modifiers

The results for subgroup analysis of HIV incidence by baseline alcohol use, non-injection drug use, and depression, were reasonably consistent with global results. Results of the subgroup analyses of behavioral outcomes showed similar results as global results.

Social impact

Interviewers administered a questionnaire at the semi-annual and follow-up visit to assess the social impact of study participation. The percentage of participants (in the two arms combined) reporting a beneficial effect increased over time, from 81% to 93%. The percentage of participants of both study arms reporting an adverse effect decreased over time, from 19% to 5%. The major disturbances accounted for less than 1% of those completing the questionnaire at any visit.

CONCLUSIONS

EXPLORE is the first study to test a behavioral intervention specifically for MSM over an extended period of time using HIV infection as the primary endpoint. A challenge for behavioral interventions has been completion of the intervention and retention of study participants over

time. Most participants in the EXPLORE intervention arm received all 10 initial session-modules and maintenance sessions, and these were delivered with a documented high fidelity to the protocol. The retention in this study reached a high standard for a behavioral intervention study, with visit retention above 87% in the standard arm and above 83% in the intervention arm over the four-year study.

The primary analysis found that the intervention reduced acquisition of HIV infection by 18.2%; an analysis adjusted for baseline covariates attenuated the intervention effect to 15.7%. Analysis of the behavioral outcomes found that the intervention significantly reduced the occurrence of unprotected anal intercourse with HIV positive and unknown status partners by 14.8% and unprotected anal intercourse by 13.9%.

Although the results from the primary analyses allow one to rule out that the experimental intervention provides a 35% reduction in the rate of HIV acquisition relative to the standard arm, the overall estimate of an 18.2% reduction, together with more favorable estimates of effect in the first 12 to 18 months and comparable reductions in risk behaviors, suggests that prevention of HIV infection among MSM by a behavioral intervention is feasible. Further analyses should be done to generate hypotheses for ways to develop more highly efficacious behavioral interventions.

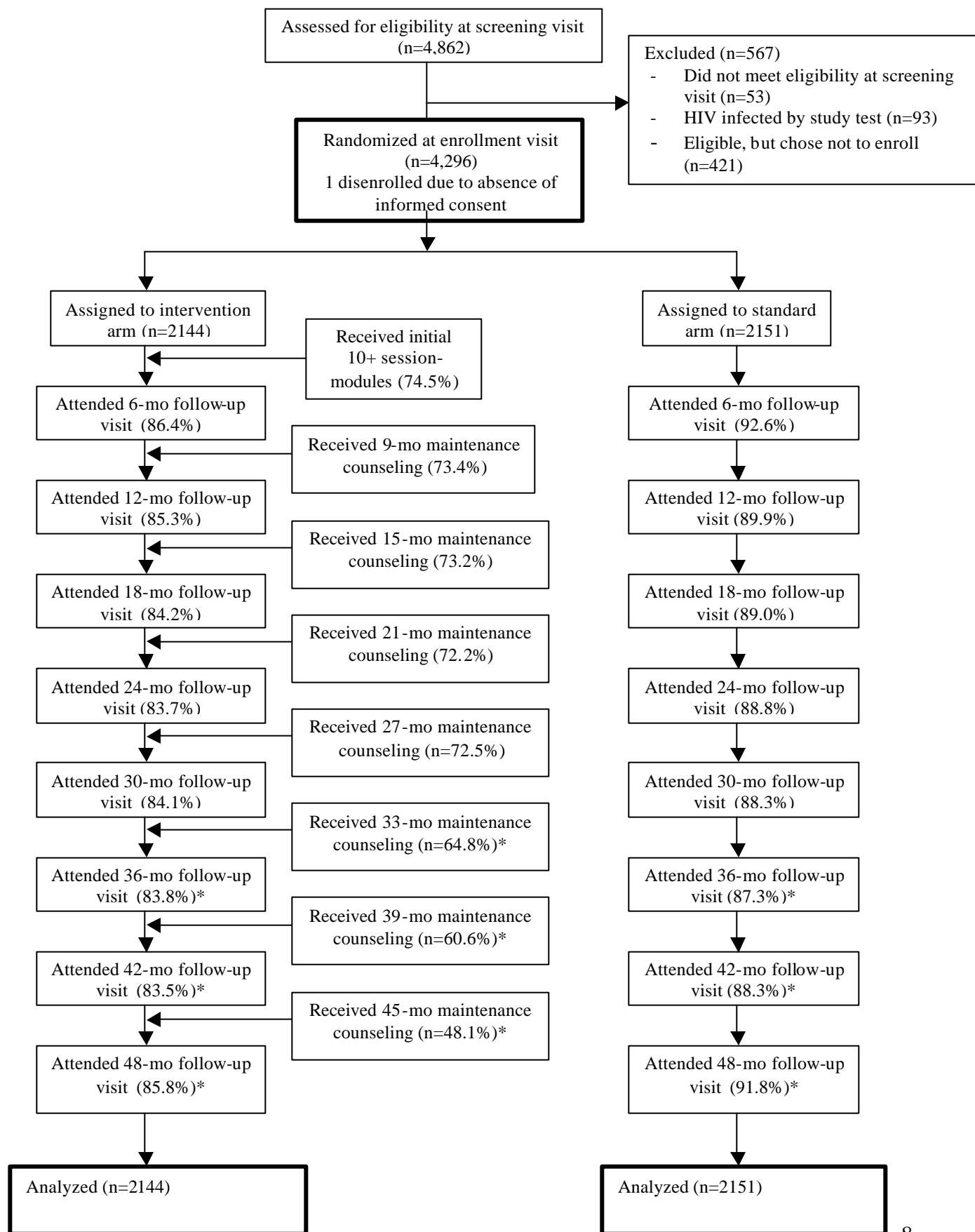
The EXPLORE trial has several limitations. First, the study sample recruited is not necessarily representative of MSM in those cities. In fact, eligibility criteria were established to enroll a high-risk HIV antibody negative population for a trial with an HIV infection endpoint. Second, the standard condition was based on the best available model, the Project RESPECT two-session model, and declines in HIV incidence and sexual risk behaviors were observed in both study arms in the EXPLORE study. Also in addition to the counseling, participants in the both arms received considerable attention over the course of the study, including scheduling and reminder letters or calls for all visits, newsletters, and other activities to maintain involvement and retention. Thus, participation in the control arm would not be equivalent to a 'usual care' in which persons would voluntarily seek often anonymous counseling and testing. The amount of counseling in the standard arm was likely more than that given in most public health settings and, thus, the full effect of the intervention may have been harder to demonstrate than if compared to typical HIV counseling as delivered in the community.

Third, a differential in retention existed between arms of the study, with 90% and 86% retained in the standard and experimental groups for final visits, respectively, and with those not retained tending to be from higher risk subgroups. This excess in non-retention in the experimental group can be explained by the low retention rate in those who had lower adherence to the initial ten session-modules. To be specific, while those in the experimental group who completed at least 9 of the initial ten session-modules had a 92% final-visit-retention rate, the remainder of the experimental group had only 64% retention. These EXPLORE data suggest that approaches are needed to improve the capture of longer term outcome results particularly among those participants who have lower levels of adherence to behavioral interventions.

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The challenge for behavioral interventions has been maintenance of behavior change over extended periods of time. The EXPLORE study was conducted during a time period of significant changes in the prevalence of risk behaviors and HIV incidence in MSM communities, likely related to widespread use of highly active antiretroviral treatments and shifts in social norms. This trial provides encouragement for behavioral interventions achieving reductions in risk in the short run. It may, however, not be effective in the long run to engage persons at high risk in intensive interventions over a short period of time and then deliver periodic 'boosters'. A different paradigm should be considered for long-term behavior change, possibly combining enhanced, individualized interventions with community and structural changes to encourage and support behavior change, particularly with regards to unprotected anal sex and disclosure of HIV serostatus.

Figure 1: Flow diagram of trial, EXPLORE



* Due to common close-out date, % is calculated based on those participants due to that visit

Table 1. Baseline characteristics by study arm, EXPLORE

Characteristic	Intervention		Standard		p-value
	N	%	N	%	
Demographics					
Age (years)					
16-19	43	2.01	50	2.32	.9664
20-25	359	16.74	362	16.83	
26-30	450	20.99	463	21.52	
31-35	458	21.36	452	21.01	
36-40	376	17.54	379	17.62	
>40	458	21.36	445	20.69	
Race/ethnicity					
White	1559	72.75	1553	72.20	.5604
Latino	322	15.03	330	15.34	
Black	131	6.11	150	6.97	
Other	131	6.11	118	5.49	
Educational level					
High school or less	198	9.24	209	9.73	.6880
Some college	557	25.98	572	26.62	
College	761	35.49	773	35.97	
Post college	628	29.29	595	27.69	
Household annual income, \$					
<12,000	280	13.07	282	13.14	.8887
12,000-29,999	579	27.03	587	27.35	
30,000-59,999	839	39.17	817	38.07	
≥60,000	444	20.73	460	21.44	
Currently a student	338	15.77	362	16.84	.3450
Employment status					
Full time	1623	75.70	1624	75.50	.8594
Part time	208	9.70	218	10.13	
Unemployed	219	10.21	208	9.67	
Other	94	4.38	101	4.70	
Sexual Risk Behaviors					
No. of male partners					
0	25	1.17	17	0.79	.2563
1	142	6.63	164	7.63	
2-5	678	31.65	704	32.74	
6-9	393	18.35	357	16.60	
≥10	904	42.20	908	42.23	
No. of female sex partners					
0	2056	95.99	2058	95.72	.6643
1+	86	4.01	92	4.28	
HIV+ male partner	595	27.82	620	28.90	.4297
Unprotected anal sex	1442	67.67	1501	70.44	.0506

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Unprotected anal sex with serodiscordant or unknown status partner	999	46.86	1049	49.02	.1574
Receptive anal sex	1587	74.19	1597	74.73	.6870
Unprotected receptive anal sex	1011	47.42	1031	48.52	.4736
Insertive anal sex	1731	80.93	1760	82.05	.3429
Unprotected insertive anal sex	1135	53.34	1206	56.46	.0404
Alcohol and drug use					
Heavy alcohol use	234	10.97	219	10.22	.4279
Non-injection drug use	1392	65.02	1382	64.40	.6723
Popper use	807	37.71	760	35.45	.1242
Injection drug use	222	10.36	217	10.12	.7932
Psychosocial					
Depression *	1024	47.83	1006	46.81	.5053

* Depression: Equivalent to a score of 16 or higher on CES-D scale

Table 2. Adherence to counseling and retention by study arm, EXPLORE

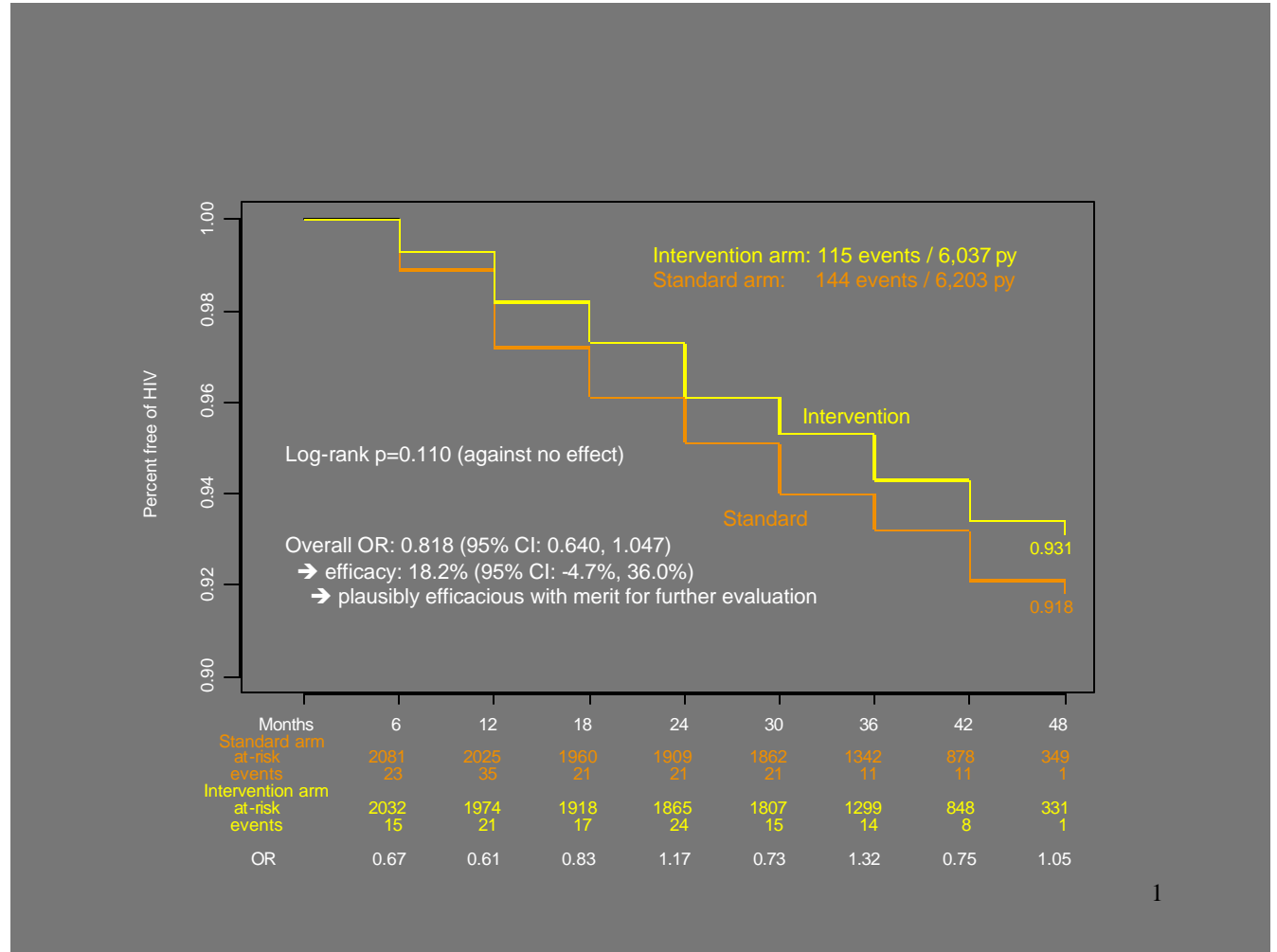
Adherence measure	Intervention		Standard		p-value
	N	%	N	%	
No. of initial 10 session-modules completed					
0	29	1.35	--	--	
1-3	258	12.03			
4-6	105	4.90			
7-9	154	7.18			
10+	1598	74.53			
Quality assurance score $\geq 80\%$					
Initial 10 sessions:	1691	83.3	--	--	
Maintenance visits	652	77.15	--	--	
Semi-annual visits	657	76.9	841	80.7	0.0677
Mean/median session duration (minutes) for semi-annual visits	37.87/35		21.78/20		<0.0001
Interim visits					
Total number overall	1568		1073		
No. of participants with interim visit	726	33.86	463	21.52	

Table 3. Study retention rates by study arm, EXPLORE

	Intervention		Standard		p-value
	N*	%	N	%	
6-month	2144	93.0	2151	95.5	0.0003
12-month	2144	93.0	2151	95.5	0.0003
18-month	2144	91.4	2151	94.1	0.0005
24-month	2144	89.9	2151	93.2	0.0001
30-month	2144	88.7	2151	91.9	0.0003
36-month	1588	87.3	1590	90.4	0.0054
42-month	1061	86.0	1060	89.8	0.0065
48-month	423	85.8	414	91.8	0.0062

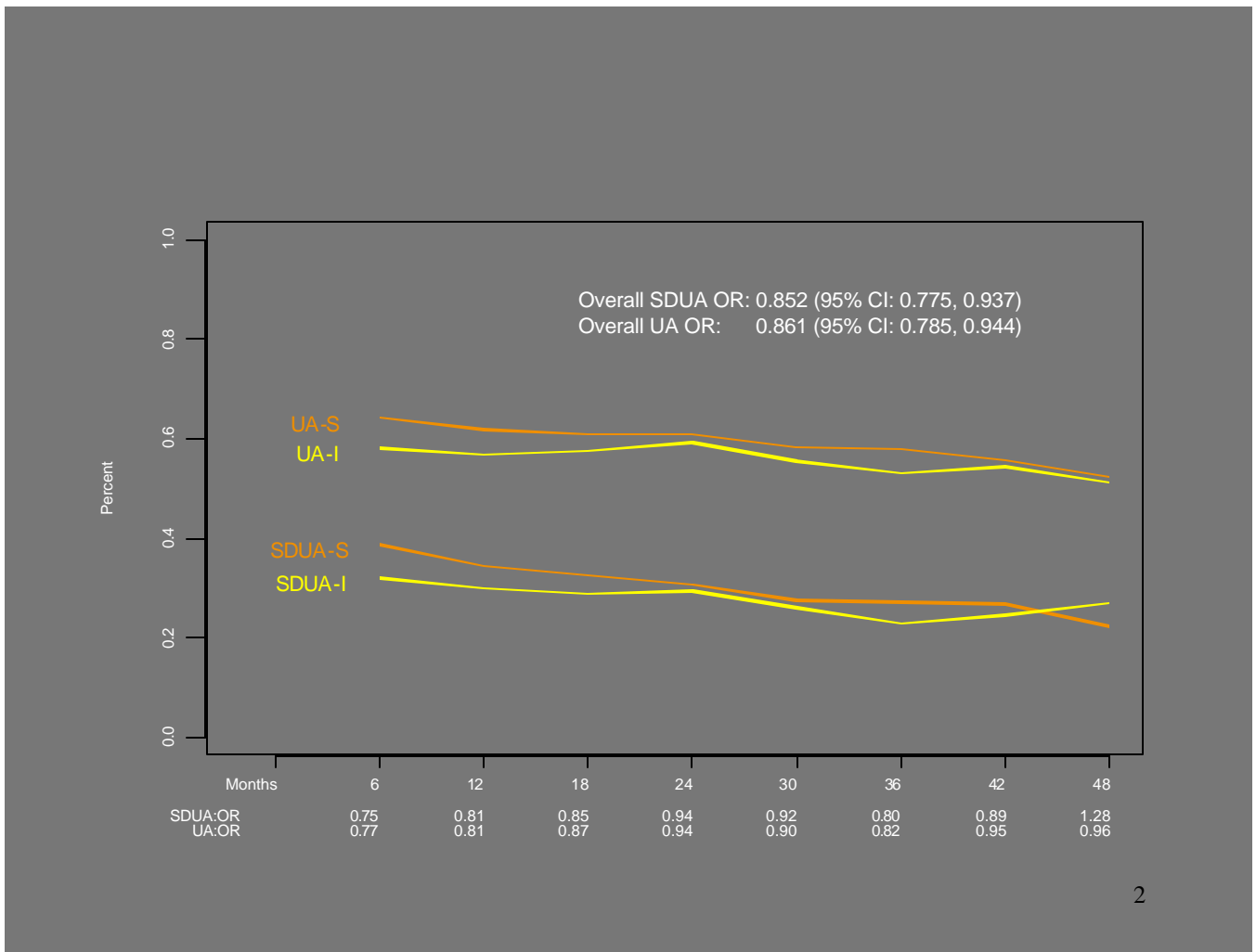
*N is the number of expected semiannual visits, not the number that was completed.

Figure 2: Kaplan-Meier curves of HIV incidence by study arm, EXPLORE



The odds ratio, OR at each time point, is for each discrete interval, not cumulatively from the beginning of the study to each visit.

Figure 3: Reported sexual behavior change by semi-annual visit and study arm, EXPLORE (serodiscordant unprotected anal sex, SDUA, and unprotected anal sex, UA; intervention = I, standard = S)



The odds ratio, OR at each time point, is for each discrete interval, not cumulatively from the beginning of the study to each visit.

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