Contemporary Clinical Trials 32 (2011) 512–516

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Short communication

What predicts non-retention in microbicide trials?

Paul J. Feldblum [a,*], Vera Halpern [a], Che-Chin Lie [a], Orikomaba Obunge [b], Folasade Ogunsola [c], William Ampofo [d], Kofi Opoku [e]

[a] FHI, P.O. Box 13950, Research Triangle Park, NC 27709, USA
[b] Teaching Hospital, University of Port Harcourt, Port Harcourt, Nigeria
[c] College of Medicine, University of Lagos, Lagos, Nigeria
[d] Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana
[e] Komfo Anokye Teaching Hospital, Kwame Nkrumah University of Science & Technology, Kumasi, Ghana

ARTICLE INFO

Article history:
Received 8 December 2010
Accepted 1 March 2011
Available online 5 March 2011

Keywords:
Randomized controlled trials
Microbicides
HIV prevention
Retention
Loss to follow-up
Proportional hazards modeling

ABSTRACT

Background: Poor retention can reduce study power and thwart randomization, possibly resulting in biased estimates of effect. Some HIV prevention trials conducted in developing countries have been challenged by high loss to follow-up. Identifying factors associated with non-retention could lead to recruitment of women more likely to remain in the trial, potentially yielding greater efficiency and validity.
Methods: We summarized retention rates and, using Cox regression, evaluated factors associated with non-retention in four trials of two candidate vaginal microbicides (1% C31G or SAVVY® and 6% cellulose sulfate or CS) conducted in multiple sub-Saharan African countries. We defined retention as completion of the trial, including those with an HIV outcome. Non-retention comprised participants randomized to a study arm who were either lost to follow-up or discontinued prior to infection with HIV.
Results: 7367 women were enrolled and randomized in the four trials; 7086 are included in this analysis. 1514 (21.4%) participants were either lost to follow-up or had early discontinuation. In the final Cox model, the following baseline factors were associated with non-retention: younger age (hazard ratio [HR] = 0.95); less education (HR = 0.97); condom use at last sex (HR = 1.18); larger number of sex acts in a typical week (HR = 1.01); and baseline candidiasis or bacterial vaginosis (HR = 1.12).
Conclusions: Younger and less educated women were more difficult to retain in these microbicide trials. But these same traits may be associated with higher HIV infection rates. Enhanced retention methods focused on those at highest risk of non-retention and possibly infection will optimize study efficiency and validity.

1. Introduction

Several HIV prevention clinical trials have been hindered by reduced power to detect an effect of the treatment. [1] One important source of reduced study power can be poor retention of trial participants, which leads to diminished person-time of observation and numbers of study endpoints. Low retention can also produce a biased estimate of the true treatment effect, since the effect observed among retained participants may not be comparable to the effect among those lost to follow-up. [2] Thus, high retention is essential for confidence in the study findings, and is a mark of quality research.

HIV prevention trials conducted in developing countries, especially among women at higher risk of infection, have sometimes been challenged by high loss to follow-up rates. Yet women at high risk of HIV and other sexually transmitted infections represent an important target for HIV prevention research, as they are the likely users and beneficiaries of prevention products.

* Corresponding author at: FHI, P.O. Box 13950, Research Triangle Park, NC 27709, USA. Tel.: +1 919 544 7040x11237; fax: +1 919 544 7261.
E-mail address: pfeldblum@fhi.org (P.J. Feldblum).

1551-7144/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.cct.2011.03.008

Identification of factors associated with trial retention could lead to recruitment of women who would yield more information and greater efficiency in future HIV prevention trials. From 2004–2007, FHI and CONRAD sponsored four large randomized trials of candidate microbicides. Here we summarize retention rates and evaluate factors associated with retention in the trials.

2. Methods

2.1. Clinical trials

The effectiveness of potential vaginal microbicide gels—1% C31G (SAVVY®) and 6% cellulose sulfate (CS)—was evaluated separately in four Phase III trials conducted in Nigeria (SAVVY/Nigeria and CS/Nigeria), Ghana (SAVVY/Ghana), and Benin, Uganda, India and South Africa (CS/Multi-country) between 2004 and 2007. [3–6] All four trials were approved by ethical committees of the participating institutions, and of FHI or CONRAD, and all participants signed written informed consent forms before screening and enrollment. The double-blind, randomized, placebo-controlled trials enrolled women who were HIV-seronegative, reported behaviors which presumably put them at higher risk of infection with HIV, were non-pregnant and were not desiring to become pregnant for the duration of the study. While definition of 'at higher risk of HIV' differed slightly between the trials, it generally included multiple coital acts per week and multiple sexual partners, although sex workers were not specifically targeted at all locations. Study procedures for these trials have been described in detail elsewhere. [3–6] Briefly, participants 18–35 years of age (18 or older in CS/Multi-country trial) were screened for eligibility and tested for sexually transmitted infections, and were randomized during a second visit to use active gel or placebo gel along with condoms for all coital acts for 12 months. Participants were to make monthly visits for up to 12 months, but all four trials were stopped early on the recommendation of their respective Data Monitoring Committees (DMC),* so many participants were not followed for the full 12 months. The trials did not have stand-alone retention plans, but each described detailed outreach and retention procedures in their respective Study Manuals.

2.2. Study participants and endpoints

A total of 7367 women were enrolled and randomized in the four African microbicide studies, and 7086 are included in this analysis: 1644 (23.2%) in CS/Nigeria; 2153 (30.4%) in SAVVY/Nigeria; 1147 (16.2%) in CS/Multi-country; and 2142 (30.2%) in SAVVY/Ghana. (We excluded data from 281 participants from the India sites in the CS/Multi-country trial because they were sufficiently different operationally, culturally and demographically to potentially confuse interpretation.) We defined trial retention as completion of the trial, including those who had the primary outcome of HIV infection. Women who remained in active follow-up until DMC termination of the trial were deemed retained, albeit with the final study visit prior to 12 months. Non-retention comprised participants who were randomized to a study arm but were either lost to follow-up or discontinued (i.e. the participant announced a decision to end participation) prior to being infected with HIV (Table 1).

2.3. Statistical analyses

We used Cox proportional hazard models, stratified by site nested within the study, to determine baseline factors associated with non-retention. All models controlled for randomized treatment group, and impacts of all risk factors were assessed using likelihood ratio tests. We first fit models to assess each risk factor separately. Factors individually significant at the 0.10 level were included in a full model, after which we arrived at a final model by omitting factors not significant at the 0.05 level. Likelihood ratio testing revealed no evidence of violation of the proportional hazards assumption ($p = 0.859$).

3. Results

Intent-to-treat study cohorts were similar across the three West Africa trials (Table 1). In comparison, study participants in the CS/Multi-country study were generally older, less likely to be employed, and more likely to use effective contraception. They also reported higher-risk sexual behavior at baseline than their counterparts in the other three trials.

A total of 1514 (21.4%) participants were either lost to follow-up or had early discontinuation prior to study completion/DMC termination: 487 (29.6%) in CS/Nigeria, 550 (25.5%) in SAVVY/Nigeria, 154 (13.4%) in CS/Multi-country, and 323 (15.1%) in SAVVY/Ghana (Table 2).

The adjusted hazard ratio (HR) for age was 0.95 ($p<0.001$), indicating for each one-year increase in age at screening, the hazard of non-retention diminished by an estimated 5% (Table 3). In further exploratory analysis, the estimated hazard ratios for non-retention were 2.11 ($p<0.001$), 1.50 ($p = 0.001$), and 1.22 ($p = 0.116$) for women 20 or younger, 21–25, and 26–30, respectively, when compared to women more than 30 years old.

Similarly, the hazard ratio of non-retention for women with more education was 0.97 ($p<0.001$), although an interaction with time was also apparent: with longer time in the study, the apparent protective effect of higher education became stronger.

Women who reported condom use at last intercourse had a higher hazard of non-retention ($HR = 1.18$; $p = 0.003$), as did women with candidiasis or bacterial vaginosis at baseline ($HR = 1.12$; $p = 0.038$). Finally, the hazard of non-retention increased with the number of reported coital acts per week at baseline ($HR = 1.01$; $p<0.001$).

4. Discussion

The overall non-retention rate in these four microbicide trials was 21.4%. In our secondary analysis of trial participants, we found that younger age, less education, and higher self-reported rates of vaginal intercourse were significantly associated with non-retention.

In a systematic review of biomedical HIV prevention interventions, the median retention rate was 84%; 15 of the 26 reviewed trials achieved a retention figure of 80% or better. [7]

* The SAVVY trials were stopped due to the low likelihood of detecting an effect. The CS trials were stopped due to concerns that the product might increase the HIV risk.

Table 1
Selected baseline characteristics by study and overall.

Characteristic	SAVVY/Ghana n = 2142	SAVVY/Nigeria n = 2153	CS/Nigeria n = 1644	CS/Multi [a] n = 1147	All n = 7086
Continuous variables (mean ± SD)					
Age in years	22.7 ± 3.6	23.6 ± 3.7	23.4 ± 3.6	29.9 ± 9.4	24.3 ± 5.6
Years of school completed	7.8 ± 3.4	11.0 ± 3.5	10.4 ± 3.7	8.1 ± 4.0	9.4 ± 3.9
Sex partners in last month	5.8 ± 10.1	12.7 ± 29.4	9.7 ± 24.5	34.7 ± 60.4	14.5 ± 36.3
Vaginal sex acts in average week	9.3 ± 7.4	11.0 ± 11.5	7.0 ± 7.3	13.0 ± 16.4	9.9 ± 10.8
Categorical variables (%)					
Living with a man	10.3	8.1	3.3	18.3	9.3
Occupation:					
Student	3.4	35.8	25.1	2.4	18.1
Trade/commerce	63.5	36.0	39.4	10.5	41.0
None	20.8	15.5	23.8	50.0	24.6
Other	12.2	12.6	11.4	36.9	16.1
Contraceptive method:					
IUD, implants, injectables	2.8	2.3	1.7	32.5	7.2
Oral	11.7	14.3	16.2	7.5	12.8
Condoms	47.1	74.9	56.0	47.1	57.6
None/other	38.2	8.4	26.1	12.7	22.2
Condom use during last sex	39.8	66.5	60.4	57.4	55.5
Baseline positive for any STI	9.4	12.6	10.3	18.5	12.1
Baseline positive for any RTI	56.0	42.6	66.6	53.8	54.0

SD = standard deviation; STI = sexually transmitted infections: gonorrhea, chlamydial infection, syphilis or trichomoniasis; RTI = reproductive tract infections: candidiasis or bacterial vaginosis.
[a] Excludes women from the India sites.

A review restricted to HIV vaccine preparedness studies in (mainly) developing countries showed 12-month retention rates from 77 to 85%. [8] These solid if unspectacular rates prevailed in diverse cohorts including men who have sex with men, intravenous drug users, female sex workers, conscripts, police officers and military men, and discordant couples. Neither article reported analyses of predictors of retention.

Younger age was associated with loss to follow-up in a multivariate analysis of HIV vaccine trials. [9] But the reviewed trials were all conducted in the U.S., where a constellation of other factors also increases the likelihood of loss, including drug use, sex work, unstable housing, and a lack of health insurance.

The MIRA trial in southern Africa achieved an outstanding retention of 93% despite its lengthy follow-up of 12–24 months per participant. [10] Their analysis of predictors of retention found that not caring for children and use of hormonal contraceptives were associated with loss to follow-up. However, the MIRA trial found no evidence that younger age was associated with loss. The investigators emphasized the utility of preparedness research for estimating likely retention in trials, and the importance of tailored retention plans at each study site. The recent CAPRISA 004 trial of tenofovir gel for HIV prevention retained nearly 95% of study participants. [11] The trial employed cohort managers and other outreach workers; developed visit scheduler software; collected and updated detailed locater information for each participant; distributed visit diaries with target visit dates noted; contacted participants just before scheduled visits and immediately after any missed visits; made home visits if needed; held Saturday clinics for working participants; and engaged the study communities before and throughout the trial. Those plans and procedures are invariably expensive, but are surely less costly than "flat" and uninformative randomized trials. [1].

Table 2
Participant status by study.

End of study status	SAVVY Ghana	SAVVY Nigeria	CS Nigeria	CS Multi [a]	All Trials
Completed final visit [b]: N (%)	1819 (84.9)	1603 (74.5)	1157 (70.4)	993 (86.6)	5572 (78.6)
Days in study among women completing [b]: mean (median)	290 (334)	339 (361)	324 (361)	285 (338)	310 (346)
Lost to follow-up: N (%)	311 (14.5)	501 (23.3)	485 (29.5)	133 (11.6)	1430 (20.2)
Discontinued early: N (%)	12 (0.6)	49 (2.3)	2 (0.1)	21 (1.8)	84 (1.2)
Total enrolled	2142	2153	1644	1147	7086

CS = cellulose sulfate.
[a] Excludes women from the two India sites.
[b] Includes women who completed 12 months of follow-up, women still in active follow-up at the time of DMC study termination, and women who became infected with HIV.

One limitation of our analysis is that all four trials were terminated early. Since women still in follow-up at the time of study termination did not have a subsequent opportunity to discontinue or be lost, the retention rates were likely exaggerated somewhat. At the same time, due to early trial termination, some of the women classified as retained in our analysis might have been lost with further follow-up. The retained and non-retained groups may overlap more than we observe, and our results may therefore be biased toward the null.

A further limitation is that with 19 factors in the initial model, we were likely by chance alone to find at least one that was significant at the 0.05 level. Also, the effect sizes of the significant factors were fairly small: e.g. the upper bound of the 95% CI for age is 0.98, meaning that each year increase in age at baseline is associated with as little as a 2% reduction in the hazard of non-retention.

Finally, the findings from this analysis of microbicide trial data may not be generalizable to cohorts in other HIV prevention trials comprising men, intravenous drug users, women

Table 3
Hazard ratio of non-retention (early discontinuation or loss to follow-up) for various risk factors, adjusted for randomized treatment group.

Risk factor	N	Number not retained	Percentage not retained	Hazard ratio (95% CI) from initial models	Hazard ratio (95% CI) from final model [a]
Age [b]				0.95 (0.94, 0.96) [c]	0.95 (0.94, 0.96) [c]
>23	3139	537	17.1		
≤23	3947	977	24.8		
Years of school completed [b]				0.97 (0.95, 0.98) [c]	0.97 (0.95, 0.98) [c]
>10	3189	657	20.6		
≤10	3897	857	22.0		
Condom use during last time of vaginal sex					
Yes	3938	949	24.1	1.26 (1.13, 1.40)	1.18 (1.06, 1.31)
No	3147	564	17.9	1	1
Number of vaginal sex acts in an average week [b]				1.01 (1.01, 1.02) [c]	1.01 (1.01, 1.01) [c]
>6	3114	699	22.4		
≤6	3972	815	20.5		
Baseline positive candidiasis or bacterial vaginosis					
Yes	3833	860	22.4	1.15 (1.04, 1.28)	1.12 (1.01, 1.25)
No	3246	651	20.1	1	1
Primary contraceptive method					
Injectables	368	45	12.2	0.96 (0.68, 1.34)	–
IUD, implants, sterilization	142	16	11.3	0.77 (0.46, 1.29)	–
Oral hormonal	913	168	18.4	0.90 (0.74, 1.09)	–
Condoms	4086	997	24.4	1.15 (1.00, 1.33)	–
None/other/emergency	1577	288	18.3	1	–
Living with man					
Yes	663	104	15.7	0.83 (0.68, 1.01)	–
No	6422	1409	21.9	1	–
Ever been pregnant					
Yes	5524	1149	20.8	0.85 (0.76, 0.96)	–
No	1562	365	23.4	1	–
Total number of pregnancies [b]				0.94 (0.91, 0.97) [c]	–
>1	3420	680	19.9		
≤1	3664	834	22.8		
Total number of vaginal deliveries [b]				0.91 (0.87, 0.96) [c]	–
>0	3008	574	19.1		
0	4069	938	23.1		
Number of different men had vaginal sex with in last 3 months [b]				1.00 (1.00, 1.00) [c]	–
>0.4	2885	741	25.7		
≤0.4	4200	772	18.4		
Number of new men had vaginal sex w/in last 3 months [b]				1.00 (1.00, 1.00) [c]	–
>1	3155	769	24.4		
≤1	3865	732	18.9		
Number of acts unprotected by condoms in last 7 days prior to enrollment [b]				1.02 (1.00, 1.04) [c]	–
>0	1418	285	20.1		
0	5668	1229	21.7		
Ever used spermicide					
Yes	287	62	21.6	1.10 (0.85, 1.43)	–
No	6799	1452	21.4	1	–
Douche					
Yes	4205	930	22.1	0.93 (0.83, 1.04)	–
No	2880	584	20.3	1	–
Number of vaginal sex acts in last week [b]				1.01 (1.01, 1.02) [c]	–
>4	3345	749	22.4		
≤4	3741	765	20.4		
Sex in 30 days prior to enrollment					
Anal	174	39	22.4	1.08 (0.78, 1.49)	–
Oral	817	172	21.1	1.00 (0.85, 1.17)	–
Both	88	17	19.3	1.05 (0.65, 1.70)	–
None	6005	1286	21.4	1	–
Baseline positive gonorrhea, chlamydia, syphilis, or trichomoniasis					
Yes	858	194	22.6	1.12 (0.97, 1.31)	–
No	6215	1316	21.2	1	–
Number of condoms [b] given				1.00 (1.00, 1.01) [c]	–
>42	3071	765	24.9		
≤42	4012	748	18.6		

[a] As a last test, the final model was compared to a model that included all listed covariates using the likelihood ratio test (p-value = 0.4818).
[b] Responses for continuous risk factors were split at the median for purposes of presenting percentages with events by sub-populations.
[c] Hazard ratio estimates represent unit changes in continuous risk factors.

with fewer sexual partners, or trials conducted in more affluent settings.

Investigators planning HIV prevention trials must account for countervailing participant characteristics. The same younger, less educated cohort members who are least likely to remain in the study may have the highest risk of infection, as was found in a recent analysis of the pooled data set analyzed here. [12] (They were also at higher risk of pregnancy during these trials. [13]) Yet retention is at least partially amenable to improvement with retention plans, supportive counseling and resources for outreach. HIV prevention trialists must continue to target higher-risk participants for recruitment. Data from this analysis and others suggest that retention efforts should be focused on younger and less educated participants to optimize the validity and effective study size of microbicide trials.

Acknowledgments

The clinical trials that collected these data, and the secondary analyses reported here, were supported by the United States Agency for International Development (USAID) under cooperative agreements USAID/GPO-A-00-05-00022-00 and USAID/HRN-A-00-98-00020-00, and a grant from the Bill and Melinda Gates Foundation. CONRAD oversaw the manufacturing of the supplies and provided the CS and SAVVY gels for these trials. Leigh Peterson, Vera Halpern, Lut Van Damme and Paul Feldblum were principal investigators of the SAVVY/Ghana, CS/Nigeria, CS/Multi-country and SAVVY/Nigeria trials respectively. William Ampofo and Kofi Opuku; Folasade Ogunsula and Orikomaba Obunge; Michel Alary, Florence Mirembe, Suniti Solomon, Marissa Becker and Roshini Govinden; and Adesina Adeiga and Rashidi Bakare were site investigators of the SAVVY/Ghana, CS/Nigeria, CS/Multi-country, and SAVVY/Nigeria trials, respectively. Doug Taylor, Wes Rountree, Chin-Hua Wang and Mark Weaver, lead biostatisticians, helped to design the trials and participated in the original data analyses.

Paul Feldblum, Vera Halpern, and Che-Chin Lie conceptualized the analyses, interpreted the findings and wrote the manuscript. Orikomaba Obunge, Folasade Ogunsola, William Ampofo, and Kofi Opoku were responsible for the implementation of the studies at the sites, and reviewed the manuscript and contributed to the interpretations herein.

The authors have no conflict of interest relevant to this manuscript.

References

[1] Padian NS, McCoy SI, Balkus JE, Wasserheit JN. Weighing the gold in the gold standard: challenges in HIV prevention research. AIDS 2010;24:621–35.
[2] Van Damme L, Ramjee G, Alary M, Vuylsteke B, Chandeying V, Rees H, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet 2002;360:971–7.
[3] Feldblum PJ, Adeiga A, Bakare R, Wevill S, Lendvay A, Obadaki F, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. PLoS ONE 2008;3:e1474.
[4] Halpern V, Ogunsola F, Obunge O, Wang CH, Onyejepu N, Oduyebo O, et al. Effectiveness of cellulose sulfate vaginal gel for the prevention of HIV infection: results of a Phase III trial in Nigeria. PLoS ONE 2008;3:e3784.
[5] Peterson L, Nanda K, Opoku BK, Ampofo WK, Owusu-Amoako M, Boakye AY, et al. SAVVY (C31G) gel for prevention of HIV infection in women: a Phase 3, double-blind, randomized, placebo-controlled trial in Ghana. PLoS ONE 2007;2:e1312.
[6] Van Damme L, Govinden R, Mirembe FM, Guedou F, Solomon S, Becker ML, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med 2008;359:463–72.
[7] Graham SM, Shah PS, Aesch ZC, Beyene J, Bayoumi AM. A systematic review of the quality of trials evaluating biomedical HIV prevention interventions shows that many lack power. HIV Clin Trials 2009;10:413–31.
[8] Dhalla S, Nelson KE, Singer J, Poole G. HIV vaccine preparedness studies in the non-Organization for Economic Cooperation and Development (non-OECD) countries. AIDS Care 2009;21:335–48.
[9] De Bruyn G, Hudgens MG, Sullivan PS, Duerr AC. Participant retention in clinical trials of candidate HIV vaccines. J Acquir Immune Defic Syndr 2005;39:499–501.
[10] Gappoo S, Montgomery ET, Gerdts C, Naidoo S, Chidanyika A, Nkala B, et al. Novel strategies implemented to ensure high participant retention rates in a community based HIV prevention effectiveness trial in South Africa and Zimbabwe. Contemp Clin Trials 2009;30:411–8.
[11] Karim QA, Karim SSA, Frolich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010;329:1168–74.
[12] Feldblum PJ, Lie C-C, Weaver MA, Van Damme L, Halpern V, Adeiga A, et al. Baseline factors associated with incident HIV and STI in four microbicide trials. Sex Transm Dis 2010;37:594–601.
[13] Halpern V, Lie C-C, Feldblum P, Van Damme L. Microbicide Research Group. Predictors of pregnancy in microbicide trials. Contraception 2011;83:436–40.