What Do We Really Mean By "Adherence" in Vaginal Microbicide Trials?

A COMPARATIVE STUDY

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Background

As we know…

- To interpret results of coitally dependent microbicide trials, we need to collect data on sexual behavior and microbicide use.
- While biomarkers and advances in smart devices will greatly assist our ability to understand adherence within future trials, they will not solve all of our problems.
- There is much we still do not understand about the dynamics of adherence within microbicide trials.

A Comparative Study of Adherence Measures in Past Vaginal Microbicide Trials

Research Questions:

- How are trials actually measuring adherence?
- How are trials actually calculating adherence?
- How are trials reporting adherence in primary manuscripts?

Methods

- Trial teams were contacted about the comparative study and asked if they would be willing to participate.

- Participating trials provided requested study materials, which were then analysed to determine how adherence was measured, estimated, and reported:
  - Trial protocols
  - Trial case report forms
  - Trial statistical analysis plans (SAP)
  - Primary manuscripts published in journals

Methods

Trial teams were then contacted via a “trial team survey” so that:

- I could share my understanding of their methods so far
- They could clarify the methods they used
- They could share lessons learned

Included Trials in Comparative Study

	Trial Name/Sponsor	Candidate Product	Hazard Ratio [95% CI]	Locations	Participants
1	CAPRISA 004	Tenofovir gel	0.63 [0.42-0.94]	South Africa	889
2	MDP 301	PRO2000	1.05 [0.82-1.34]	South Africa, Tanzania, Uganda, Zambia	9385
3	HPTN 035	BufferGel PRO2000	1.10 [0.75-1.62] 0.70 [0.46-1.08]	Malawi, South Africa, Zambia, Zimbabwe, USA	3101
4	Carraguard Population Council	Carraguard	0.87 [0.69-1.09]	South Africa	6202
5	CS CONRAD	Cellulose Sulfate	1.61 [0.86-3.01]	Benin, India, South Africa, Uganda	1398
6	CS FHI	Cellulose Sulfate	0.8 [0.3-1.8]	Nigeria	1644

Primary Manuscripts

THE LANCET

PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial

varied between centres (figure 2). The mean percentage reported gel use at last sex act was 89% (95% CI 86–91) after enrolment. This percentage changed little during the

AIDS

OFFICIAL JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women

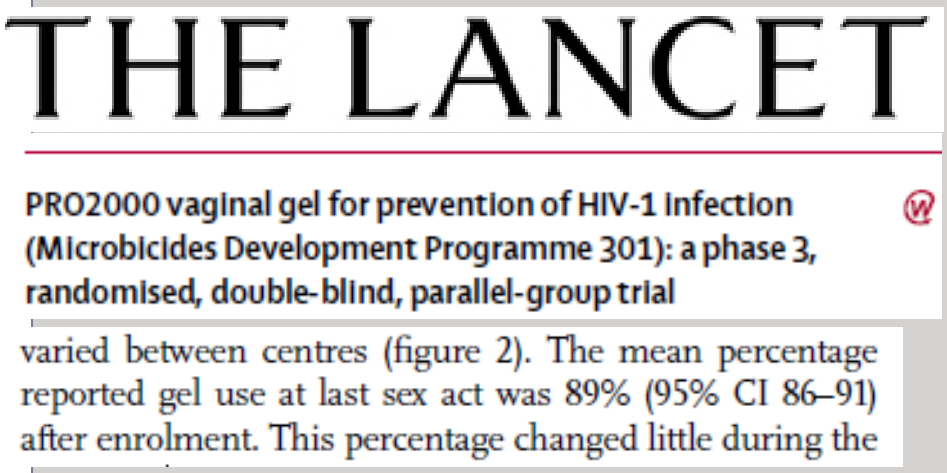
accordance with the study protocol. Women reported using gel in 81.1% of last sex acts. Gel adherence was similar in the three gel arms. Self-reported condom

Results in Primary Manuscripts

Trial	Summary Adherence Estimate in Primary Manuscript		
	Summary Estimate 1	**Summary Estimate 2**	**Summary Estimate 3**
CAPRISA 004 **Science 2010**	72% (average), 60.2% (median) sex acts covered by two doses of gel	61.3% (median) gel adherence for women who did not acquire HIV: 59.2% (median) for women who did acquire HIV	40% of women had median adherence below 50%
MDP 301 **Lancet 2010**	89% gel use at last sex act		
HPTN 035 **AIDS 2011**	81% last sex acts covered by gel	69.1% condom free last sex acts covered by gel	61.3% last sex acts with gel and condom
Carraguard **Lancet 2008**	42.1% sex acts covered by gel	96.1% sex acts covered by gel	
Cellulose Sulfate CONRAD **NEJM 2008**	87% of all sex acts covered by gel	78% of sex acts with primary partners covered by gel	45.8% condom free sex acts covered by gel
Cellulose Sulfate FHI **PLoS ONE 2008**	81% sex acts covered by gel	50% condom free sex acts covered by gel	

Where did these numbers come from?

How…


THE LANCET

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Trial
Case Report Forms

5 Did you use the gel the last time you had sex?

Yes ☐

No ☐

Summary Estimates

Source Variables

Looking at the Manuscript + SAP for Each Trial:
in How Many Trials Could I Be Sure How the Reported Numbers Were Calculated?

0 trials/6 trials

Where Was There Lack of Clarity?

In Some Trials…

- SAPs stating that trial teams still determining exactly how they would estimate adherence
- Methods well defined in the SAP, but used a different definition or method in the primary manuscript, or vice versa
- Lack of clarity in SAP or the manuscript as to exactly how the calculations were made, particularly with respect to whether per participant averages were the central unit, or if sex acts were the central unit

Per Participant vs. Total Events Calculations

Participant	# Sex acts	# Sex acts covered by gel	Coverage (adherence)
1	100	1	1%
2	87	2	2%
3	99	5	5%
4	87	0	0%
5	10	10	100%
6	15	14	93%
7	5	5	100%
8	7	6	86%

Per participant calculation=
1+2+5+0+100+93+100+86=387 / 8 participants =

Adherence estimate
48% for trial

Per Participant vs. Total Events Calculations

Participant	# Sex acts	# Sex acts covered by gel
1	100	1
2	87	2
3	99	5
4	87	0
5	10	10
6	15	14
7	5	5
8	7	6

Total events calculation=
100+87+99+87+10+15+5+7= 410 sex acts; 1+2+5+0+10+14+5+6 = 43 gel-covered

43/410 = 10% Adherence estimate for trial

Does It Matter What Recall Period Is Used?
Are Different Recall Periods Measuring the Same Thing?

HPTN 035 Last Sex vs. Last Week

Adherence Estimate Proportion of sex acts covered by gel (per participant calculation) *preliminary data	Last Sex	81%
	Last Week	82%

	Participants	P Value Wilcoxon Sign Rank test
Participants reporting same adherence for both recall periods	1005	
Participants reporting higher adherence for last sex act	614	P = .36
Participants reporting higher adherence for last week	610	
Participants contributing	2229	

MDP 301 Last Sex vs. Last Period (last week or last month)

Adherence Estimate Proportion of sex acts covered by gel (per participant calculation) *preliminary data	Last Sex	85%
	Last Period	82%

	Participants	P Value Wilcoxon Sign Rank test
Participants reporting same adherence for both recall periods	3999	
Participants reporting higher adherence for last sex act	3258	P <.0001
Participants reporting higher adherence for last period	1841	
Participants contributing	9098	

This could be due to the number of sex acts being reported rather than the recall period…

Or Maybe HOW the Question Is Asked?

This is how one trial asked about sex acts "last week"

I know that you are counseled to use condoms for each act of vaginal sex, but I also know that this is not always possible.

2b. In the past week, how many times did you use a male or female condom and not the study gel during vaginal sex? ..... ☐☐ *# of times*

2c. In the past week, how many times did you use study gel and not a male or female condom during vaginal sex? ..... ☐☐ *# of times*

2d. In the past week, how many times did you use study gel with a male or female condom during vaginal sex? ..... ☐☐ *# of times*

2e. In the past week, how many times did you use neither study gel nor a male or female condom during vaginal sex? ..... ☐☐ *# of times*

This is how another trial asked about sex acts “last week”…

. “Now I am going to ask you some more detailed questions about your condom and gel use each time you had sex in the last week

Day/ date	order	sex acts	Partner	Condom	Gel	Gel timing	Vaginal Cleaning	Washing timing	Partner informed
	Order of sex acts	Sex acts in the last week	What **type** of partner was this act with?	Did you use a condom during this sex act?	Did you use gel before this sex act?	If you used the gel how long before sex did you insert it?	Did you clean inside your vagina after sex? **(This includes using a dry cloth)**	If you cleaned, how long after sex was this?	If you used gel, did you your partner about it?
		Codes	1=long-term stable relationship 2=other type of partner 8=don't remember	1=yes 2=no 8=don't remember	1=yes 2=no 8=don't remember	1=less than 1 hour 2= 1 to 3 hours 3= more than 3 hours 8=don't remember 9=didn't use it	1=yes 2=no 8=don't remember	1=less than 1 hour 2= 1 to 2 hours 3= more than 2 hours 8=don't remember 9=didn't clean	1=yes 2=no 8=don't remember 9=didn't us
		1 last sex act	☐	☐	☐	☐	☐	☐	☐
		2 sex act before that	☐	☐	☐	☐	☐	☐	☐
		3 sex act before that	☐	☐	☐	☐	☐	☐	☐
		4 etc.	☐	☐	☐	☐	☐	☐	☐
		5	☐	☐	☐	☐	☐	☐	☐
		6	☐	☐	☐	☐	☐	☐	☐

Are You Sure You Know What "Last week" Means?

"The Use of Respondent and Interviewer Debriefing Studies as a Way to Study Response Error in Survey Data" Campanelli, et al 1991

Interpretations of "Last Week" in survey question:

Interpretation	% of respondents
Sunday-Saturday	17%*
Monday-Friday	54%
Monday-Saturday	9%
Monday-Sunday	6%
Sunday-Sunday	4%
Other	10%

*Sun-Sat was the definition intended by the survey designers,
only 17% of their population understood "week" the way they did

Interesting Points from Trial Team Surveys

- Trial teams were supportive of using triangulation for estimating adherence, especially with biomarkers.
- "Last sex" seems to be a simple and good measure for non-sex worker populations.
- Asking about longer periods of time is beneficial because it can be matched with applicator information for triangulating estimates.
- Better biomarkers and smart devices are great. AND….
- FTFIs were valued for the need to interact with participants and check if they understood the regimen and were correctly using the product. ACASI or just biomarkers would not provide that information. Staff then have an opportunity to clarify proper use and improve trial adherence prospectively.
- Trial teams recommend starting adherence questions by asking about non-use.

Conclusions

- Significant diversity in how trial teams, measured, calculated and reported adherence.
- Assumptions present in methods used.
- Method for how adherence was calculated was often not entirely clear.
- Self-reported adherence questions beginning with asking participants about non-use should be explored.
- Even apparently similar methods or measures may not be identical.
- Greater clarity in methods and standardization would facilitate comparing “adherence” with “adherence”.

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