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Biological Markers of Sexual Activity: Tools for Improving Measurement in HIV/Sexually Transmitted Infection Prevention Research

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Abstract

Research on interventions to prevent HIV and other sexually transmitted infections (STIs) is heavily influenced by participant reporting of sexual behavior, despite uncertainty about its validity. Exclusive reliance on participant self-report often is based, overtly or by implication, on 4 assumptions: (1) no feasible alternatives exist; (2) misreporting can be minimized to levels that can be disregarded; (3) misreporting tends to underreport sensitive behaviors; and (4) misreporting tends to be nondifferential with respect to the groups being compared. The objective of this review are to evaluate these assumptions, including a review of studies using semen biomarkers to evaluate the validity of self-reported data, and to make recommendations for applying biological markers of semen exposure detectable in women to further strengthen research on HIV/STI prevention. Increasing evidence shows that semen biomarkers provide an important means of assessing and augmenting the validity of studies on HIV/STI prevention. Additional biomarkers are needed to assess male exposure to vaginal sex and both male and female exposure to anal sex. Methods and study designs that incorporate biomarkers into studies collecting self-reported behavioral data should be considered where possible.

Three decades into the HIV epidemic, research on prevention of HIV and other sexually transmitted infections (STIs) still relies heavily on participant reporting. Results of randomized controlled trials (RCTs) of biomedical interventions (e.g., diaphragm, microbicides, and preexposure prophylaxis)—which use biological outcomes as end points—often are difficult to interpret because of uncertainty surrounding participants' adherence to study product use. Moreover, measuring the degree of exposure to HIV/STI risk often depends on self-reports of sexual activity, partner risk, and condom use.

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Although participant reports on the frequency of sexual activity and condom use are vulnerable to social desirability and recall bias and misclassification,^{1,2} their use has long been supported by 4 assumptions: (1) feasible alternatives are lacking; (2) misreporting can be minimized to levels that can be disregarded; (3) misreporting is in the direction of underreporting of sensitive behaviors; and (4) misreporting is nondifferential with respect to study arms being compared. The objectives of this review are to evaluate these assumptions, which are often implicit and are not universally held, and then to offer examples of applying semen biomarkers (SBMs) to strengthen clinical and behavioral research on HIV/STI prevention. Because current biomarkers provide evidence of exposure to semen in vaginal specimens only, we focus specifically on self-reports of the frequency of vaginal sex and condom use among women.

ASSUMPTION 1: NO FEASIBLE ALTERNATIVES EXIST

“The general consensus is that the reliability and validity of self-reporting is questionable; but there is also agreement that it is, by and large, the only feasible way to measure sexual behaviors.”³

Despite this common belief, alternatives are available. Depending on the research question, laboratory-confirmed STIs, including HIV, could be the obvious measure. HIV/STIs might not always be suitable, given that risk depends on the infection status and infectiousness of partners and given the high rate of spontaneous resolution or use of interim antibiotic therapy for bacterial STIs. Furthermore, depending on the prevalence of infection in the population, these outcomes might be low-frequency events, making them prohibitively difficult and expensive to study.

Other possible measures include biological markers of semen exposure among women, most notably prostate-specific antigen (PSA), Y-chromosome DNA (Yc-DNA), and semenogelin. Four decades ago, researchers discovered PSA while trying to identify a substance in seminal fluid to improve forensic investigation of alleged rape cases.⁴ The prostate gland secretes PSA in an alkaline liquid into the urethra during ejaculation where it liquefies semen in the seminal coagulum and allows sperm to swim freely. Because PSA is expressed independently of spermatozoa, the protein is useful in identifying semen even from men with low-count or absent spermatozoa. Despite its name, PSA is not specific to the prostate gland but can be found in men and women in various tissues and body fluids including blood, urine, and breast milk. However, because PSA levels in the semen of male individuals exceed those detectable in other sources by several orders of magnitude, identification of PSA in vaginal fluid above a certain threshold is an indicator of women's recent exposure to semen.⁵

Forensic research suggests that PSA clears from vaginal fluid in an average of 20 to 27 hours and completely clears in approximately 47 hours.⁶ A controlled clinical trial found high sensitivity (99%–100%) for detecting PSA in vaginal swabs collected immediately after women were inseminated with various amounts of their partner's semen.⁷ In a similar controlled trial, researchers measured PSA in vaginal fluid before and after inseminating women with different amounts of their partner's semen.⁸ Concentrations of PSA in participant-collected vaginal swabs were high immediately after exposure, decreased dramatically by 24 hours, and returned to background levels (<1 ng/μL) at 48 hours for almost all samples (Fig. 1). Thus, assays for PSA are highly sensitive immediately after exposure; however, given the rapid clearance of the biomarker from vaginal fluid, the absence of PSA detection should not be interpreted as evidence that semen exposure did not occur in the previous 48 hours.

Because PSA detected in the blood is a marker of the presence and progression of prostatic cancer, quantitative assays capable of detecting very low concentrations of PSA have been developed (e.g., Architect Free or Total PSA; Abbott Diagnostics, Abbott Park, IL), and many clinical laboratories throughout the world have the necessary expertise and specialized equipment to conduct this testing. In vitro testing of swabs spiked with known amounts of semen suggests that testing for free and total PSA could be expected to yield similar concentrations of PSA.⁹ Given that the assay for total PSA has a higher limit of detection and has been used in previous studies, its use might be preferred over the assay for free PSA. Detailed procedures for conducting this testing have been published elsewhere.⁹

Prostate-specific antigen also can be detected using a rapid, semiquantitative immunochromatographic strip assay, such as ABACard (Abacus Diagnostics, West Hills, CA), which does not require special instruments, is relatively easy to perform, is less expensive than quantitative assays (approximately US \$5 vs. \$20 per test, respectively), and has been validated against a quantitative assay.¹⁰ A training module for ABACard (<http://cdc.train.org>; course ID: 1030498) is available from the Centers for Disease Control and Prevention, and recent laboratory evidence suggests that using swabs with a large capacity and immediately storing them at -80°C after collection are optimal for the identification of PSA.⁹ In vitro research suggests that certain lubricants and other gels could interfere with PSA detection with ABACard.¹¹ If these findings are confirmed in vivo, then other assays should be used for testing for PSA.

Although PSA is the most widely used SBM in HIV/STI research, other markers exist. Y-chromosome DNA contained in sperm cells has a half-life of approximately 4 days and can remain detectable in vaginal fluid using polymerase chain reaction for up to 14 days.¹² Compared with PSA detection, the assay for Yc-DNA detection is more expensive and requires more specialized equipment and laboratory training. Rapid immunochromatographic strip tests for semenogelin are available,¹⁰ but the lack of controlled clinical data on semenogelin's clearance from vaginal secretions limits its routine use as a marker of women's exposure to semen.

ASSUMPTION 2: MISREPORTING CAN BE MINIMIZED AND SOMETIMES DISREGARDED

“...when appropriate assessment conditions are established, well-designed questions concerning sexual-risk behaviors result in reasonably reliable and valid self-reports.”¹³

The belief that self-reported data are reasonably reliable and valid is based on evidence from studies examining the consistency of paired responses from different data collection points (e.g., repeated interviews with the same participant or interviews with couples on their mutual behaviors).² For example, in a qualitative study of female former participants in a microbicide trial in Cameroon, few women acknowledged having misreported in the original trial.¹⁴ However, responses in the follow-up study could have been susceptible to the same self-presentation bias that may have caused women to misreport in the original trial; even in-depth questioning still could fail to elicit accurate reports. Similarly, couples might independently fail to report proscribed behaviors such as engaging in unprotected sex.

In contrast, Table 1 includes published studies that have assessed the validity of self-reports by asking women whether they had recently engaged in unprotected sex and then comparing their responses to biological evidence of semen in their vaginal fluid.^{15–21} Study populations included sex workers and lower-risk women in Africa as well as women attending STI and other clinics in the United States. Rates of biomarker detection (PSA, Yc-DNA, or

semenogelin) ranged from 6% of women who reported no sex to 56% of women who reported condom use for all sex acts within the biomarker's window of detection. The high proportions of biomarker detection among women who reported consistent condom use are probably an indication of (intentional or unintentional) overreporting of condom use, but it may also capture instances of incorrect use or condom failure. It is important to note that because PSA begins to clear immediately after exposure and returns to background levels within 48 hours,⁸ the rates from studies using PSA represent the lower bounds of underreporting of exposure. Together, these studies call into question the claim that the degree of participant misreporting is negligible enough to be disregarded.

ASSUMPTION 3: MISREPORTING TENDS TO BE IN THE DIRECTION OF UNDERREPORTING SENSITIVE BEHAVIORS

“For most sexual behaviour variables, it is assumed that higher levels of reporting [of risky behaviors] indicate more valid reporting...”²²

Conventional wisdom also suggests that misreporting will tend to be in the direction of underreporting risky behaviors (e.g., underreporting sexual activity and overreporting condom use) because of social desirability bias. However, certain social norms could encourage individuals to exaggerate sexual behaviors (e.g., adolescent boys overreporting their number of partners or coital frequency). Also, low-frequency events are more salient, which could cause telescoping (i.e., recalling salient events as occurring more recently than they did). Furthermore, participants might be motivated to overreport if they believe that their study enrollment or continued participation requires them to report risky behaviors. This last explanation might have been the case in a study in which 132 former participants in a microbicide trial completed audio computer-assisted self-interview (ACASI) surveys on the veracity of their reporting during the initial microbicide trial.²³ In the follow-up study, 79% of women acknowledged having provided false or misleading information at least once during the initial trial. Notably, women described more underreporting in the initial trial than overreporting of condom use. Thus, evidence indicates that misreporting can occur in more than 1 direction.

ASSUMPTION 4: MISREPORTING TENDS TO BE NONDIFFERENTIAL

“Inaccuracy in self-reports may not pose a problem for scientific questions in which a degree of inaccuracy can be tolerated. For example, if the interest is to compare mean shifts in condom use for persons randomly assigned to an experimental or control group, and if all self-reports tend to underestimate actual behavior by 10% to 15%, this bias will be present in both groups, and it will not affect the estimate of the mean difference in true condom use between groups.”¹³

Contrary to the assumption that misreporting occurs randomly and can be ignored, evidence from a study that tested for spermatozoa in vaginal swabs suggests that misreporting could differ by participant or study factors.²⁴ Having discordant biological and self-reported measures of semen exposure was associated with study site, young age, race/ethnicity, HIV, human papillomavirus, bacterial vaginosis, and lack of self-reported injection drug use. Notably, if the validity of reporting is related to HIV risk, research on HIV prevention that relies on participant reports of unprotected sex may have confounding that cannot be addressed. In contrast, the ability to detect the SBM and its clearance window is unlikely to systematically differ by these factors.

Furthermore, the validity of reporting could change over time during the course of a longitudinal study. For example, changing social norms about the need for condom use and repeated condom messaging could lead to more overreporting of use. Consequently, putative

trends of increased condom use in specific populations might represent changes in the reporting of condom use rather than actual changes in use. Finally, the validity of reporting could be affected by study participation or the intervention itself. Studies have evaluated the effectiveness of abstinence-only interventions or interventions to promote condom use based only on self-reported outcomes.²⁵ Participants who have been counseled on abstinence or condom promotion, though, might have more motivation to report the specific behavior than those who did not receive this counseling.

APPLICATION OF BIOMARKERS TO STRENGTHEN BEHAVIORAL RESEARCH

In addition to using SBMs to assess the validity of self-reported data (Table 1), we present 4 potential applications of biomarkers for strengthening HIV/STI research. Semen biomarkers can be used to evaluate methods designed to improve the accuracy of participant reports. For example, some research has concluded that using ACASI yields more valid data than face-to-face interviews by assuming that more frequent reporting of sensitive behavior with ACASI represents more accurate data.²² In contrast, 2 RCTs of sexually active, HIV-negative women in sub-Saharan Africa used SBMs to compare the validity of data collected from ACASI versus face-to-face interviews.^{18,19} One study found no difference between the 2 interview modes in the rates of underreporting of recent semen exposure.¹⁸ The second study measured discordance using a qualitative test for semenogelin at enrollment and at 3 follow-up visits.¹⁹ Whereas the ACASI arm had less discordance than the face-to-face interview arm at enrollment, no difference was detected between arms at the remaining study visits. Thus, ACASI might improve reporting only at certain study visits or in certain populations, settings, or studies. Furthermore, even if using ACASI leads to less misreporting, the overall magnitude of misreporting still could be high.^{15–21}

Currently, regulatory approval of new condom types in the United States requires data from 2 study types: condom “functionality” studies, which measure frequency of self-reported condom malfunctions (e.g., slippage and breakage), and “contraceptive efficacy” studies, which measure pregnancy rate among women assigned to use the condom. Both study designs may be vulnerable to bias and confounding.

Randomized crossover trials using SBMs have evaluated the effectiveness of male and female condoms.^{26,27} Participants collected a vaginal swab immediately before and after each protected coital act to be tested for PSA. By comparing the proportion of postcoital swabs with PSA detected (as a measure of condom failure), these studies obtained an objective measure of the relative degree of protection provided by each condom type. This alternative study design has been proposed as a methodological advancement for evaluating new condom types for Food and Drug Administration regulatory approval.

Semen biomarkers could be used to evaluate the effectiveness of behavioral interventions to prevent HIV/STIs. Among the first examples of this type of research, the Assessing Counseling Message Effectiveness study was conducted among women treated syndromically for cervicitis or vaginal discharge at a Jamaican sexually transmitted disease (STD) clinic.²⁸ The RCT evaluated the effectiveness of counseling interventions to prevent infection of partners while participants were on the short-course (~1 week) treatment. No difference in effectiveness was found between a standard counseling message (to refrain from sex while on treatment) and a hierarchical message (to refrain from sex backed up with condom promotion in case sex was to occur) in terms of preventing unprotected sex as measured with PSA detection in vaginal swabs collected at the 1-week follow-up visit.

Semen biomarkers could be used to examine changes in levels of condom use in HIV/STI intervention studies. For example, the Methods for Improving Reproductive Health in Africa trial found an intervention promoting use of the diaphragm and condoms not to be superior to an intervention promoting only condom use in preventing HIV acquisition.²⁹ However, secondary analyses found that women randomized to the condom-only arm were more likely to report condom use. Under this scenario, differential condom use could have masked a protective effect of the diaphragm. Also, because condoms are highly effective in preventing sexual transmission of HIV/STIs, their use can reduce study power to detect a beneficial intervention effect. Use of SBMs in this context would have allowed monitoring to detect possible differences in exposure to unprotected sex between study arms.

Researchers could use SBMs to more objectively assess whether (and the extent to which) unprotected intercourse (and, by proxy, condom use) differs between study arms or changed during the course of a study. This information could be used during study implementation to refine procedures for reducing the effect of differential condom use or afterward in secondary analyses to assess the effectiveness of the intervention among condom nonusers. Semen biomarkers also could be used during a study run-in phase to identify and enroll a study population of condom nonusers, which could increase study power by targeting participants at higher risk for exposure. Once successful interventions for HIV/STI prevention (e.g., microbicides and circumcision) are identified and scaled up, SBMs could be used to monitor whether their introduction seems to cause less condom use from risk disinhibition (i.e., increased risky behavior from perceived or real decreases in risk).

LIMITATIONS AND FUTURE RESEARCH

Semen biomarkers will need to be paired with detailed qualitative and quantitative interviewing to collect other data necessary for improving our understanding of sexual behaviors. Furthermore, current biomarkers only provide evidence of exposure to semen in vaginal specimens; additional SBMs are needed to assess male exposure to unprotected vaginal sex and male and female exposure to anal sex.

The narrow window of detection for SBMs is a major limitation. Because of its rapid clearance, PSA cannot be used to identify all participants exposed to semen. However, biomarkers offer the advantage of detecting relative differences in the presence of SBM between study groups in intervention trials. Furthermore, under certain research questions and study designs, a short residence time could be advantageous. In the randomized crossover trials using repeated (precoital and postcoital) sampling to evaluate condom functionality,^{26,27} PSA's rapid clearance was useful for pinpointing specific exposures. Other biomarkers such as Yc-DNA could help with describing exposure to unprotected intercourse in research in which a longer interval is desirable. Future research should systematically evaluate potential biomarkers and their clearance time.

The cost of quantitative assays for detecting PSA (~20 US dollars per test) could be a barrier to their wider adoption in research; more recently, studies have started using inexpensive, rapid tests for SBMs (~4.50 USD per test).^{10,19,28} Furthermore, the total costs of collecting questionnaire data likely are often underestimated, and even quantitative assays, in comparison, might be economical in terms of overall costs. In addition, the biological significance of PSA concentrations in relation to risk of HIV/STIs and pregnancy is unknown. Although the magnitude of risk has yet to be defined for semen (measured with either self-reports or biological data), this issue is less important for studies using SBMs to make randomized comparisons.

Using biomarkers could introduce issues not present with interview data. For example, participants who know in advance that their specimens will be tested for an SBM could

change their behavior or their reporting of behavior. However, an RCT did not find evidence that knowledge of testing for PSA caused women to report more unprotected sex than women who did not receive this advance knowledge.³⁰ Furthermore, intervention studies can be designed to circumvent possible effects from participants' awareness of biomarker testing. Investigators in the Assessing Counseling Message Effectiveness trial collected an extra swab at study visits for STI testing and then sought participant consent at the end of the final visits (after self-reported data had been collected) to conduct PSA testing retroactively.²⁸ Studies with field-based data collection could face additional logistical challenges including difficulty in securing privacy for specimen collection and unknown acceptability of collecting specimens outside clinics. The acceptability of self-collection of vaginal specimens for STI testing, though, has been demonstrated in various populations.³¹

Research on HIV/STI could be strengthened by the development of new types of biomarkers such as markers of recent exposure to latex (to provide direct evidence of latex condom use or nonuse), markers found in male individuals indicative of recent exposure to unprotected vaginal sex, and taggants added to vaginal products (candidate microbicides or condoms) that are then detectable in a woman's breath.³² Laboratory research also is needed to better characterize and improve the use of existing SBMs. For example, the Centers for Disease Control and Prevention is conducting preliminary testing on the detection of PSA in rectal swabs from men as a marker of semen exposure during unprotected receptive anal intercourse. Also, Yc-DNA potentially could be used to enumerate male partners by determining the individual-specific DNA sequences in a single specimen. Although potential privacy issues would need to be properly addressed, this testing would be useful for research related to partner concurrency, sexual networking, and interventions for reducing the number of sexual partners.

CONCLUSIONS

In summary, studies on HIV/STI prevention based entirely on self-reported sexual activity may be biased and difficult to interpret. This issue is not limited to HIV/STI research; biomarkers have led to similar questions about the validity of self-reported data in research areas as diverse as nutrition and nicotine use.^{33,34} The development of better biological markers of sexual activity could remove pressure on women (and men) to accurately report sensitive measures of sexual behavior. Increasingly, evidence shows that SBMs provide an important means of assessing and augmenting the validity of studies on HIV/STI prevention. Consequently, exclusive reliance on self-report for many studies of recent sexual activity may no longer be justifiable; methods and study designs that allow incorporation of biomarkers should be strongly considered.

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Figure 1.
Vaginal clearance of PSA.

TABLE 1

Studies of Underreporting of Recent Exposure to Semen

Study	Study Design	Population	Interview Method	Outcome
Aho et al. ¹⁵	Ancillary study to a larger longitudinal study on the acceptability and consequences of voluntary counseling and testing of HIV	FSWs in Guinea	Face to face	PSA detected in 36% reporting no unprotected sex in the past 2 d
Gallo et al. ¹⁶	Ancillary study to a larger RCT on the effect of supplementing community-based (male and female) condom promotion with clinic-based counseling	FSWs in Madagascar	Face to face	PSA detected in <ul style="list-style-type: none"> • 39% reporting protected sex only • 21% reporting no sex in the past 2 d
Gallo et al. ¹⁷	Ancillary study to a larger study on the effect of peer education on condom use	FSWs in Kenya	Face to face	PSA detected in <ul style="list-style-type: none"> • 13% reporting protected sex only • 6% reporting no sex in the past 2 d
Minnis et al. ¹⁸	RCT comparing validity of self-reported unprotected sex measured with ACASI or face-to-face interviewing conducted among former participants in a diaphragm RCT	Sexually active, HIV-negative women in Zimbabwe	ACASI and face to face	Among those with PSA detected, 48% reported no unprotected sex in the past 2 d.
Mensch et al. ¹⁹	RCT comparing validity of self-reported unprotected sex measured with ACASI or face-to-face interviewing conducted among participants in a microbicide RCT	Sexually active, HIV-negative women in South Africa	ACASI and face to face	Semenogelin detected in 12%–18% reporting no sex in the past 2 d
Jadack et al. ²⁰	Secondary analysis of a prospective cohort study comparing self-reported data and STD test results	STD clinic attendees in Maryland	Face to face	Yc-DNA detected in 56% reporting condom use for all acts in the past 14 d
Rose et al. ²¹	Secondary analysis using baseline data from an RCT evaluating a HIV prevention program	Young, black clinic attendees in Georgia	ACASI	Yc-DNA detected in 34% reporting condom use for all acts in the past 14 d

FSW indicates female sex workers.