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Vaginal Prostate Specific Antigen (PSA) Is a Useful Biomarker of Semen Exposure Among HIV-Infected Ugandan Women

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Abstract

The practical feasibility of using prostate specific antigen (PSA) as a biomarker of semen exposure was examined among HIV-infected Ugandan women. Vaginal fluids were obtained with self-collected swabs and a qualitative rapid test (ABAcard®p30) was used to detect PSA. Trained laboratory technicians processed samples on-site and positive PSA tests were compared to self-reported unprotected vaginal sex (UVS) in the last 48 h. A total of 77 women submitted 126 samples for PSA testing at up to three study visits. Of these samples, 31 % (n = 39/126) were PSA positive, and 64 % (n = 25/39) of the positive PSA samples were accompanied by self-report of no UVS at the study visit the PSA was collected. There were no reported difficulties with specimen collection, storage, or processing. These findings provide preliminary data on high levels of misreported UVS among HIV-infected Ugandan women using practically feasible methods for PSA collection and processing.

Keywords

Self-report; Condom use; Biomarker; Prostate specific antigen; HIV

Introduction

HIV prevention research often relies on self-report to determine the efficacy of behavioral and biomedical treatments on study outcomes such condom use and adherence to antiretroviral therapy (ART). Of the hundreds of published studies on behavioral interventions targeting condom use, there is a near universal reliance on self-report [1], which has significant repercussions for the field. In sub-Saharan Africa (SSA)—where high

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Compliance with Ethical Standards: **Conflict of Interest** The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

HIV incidence and prevalence has led to a proliferation of HIV prevention research—self-report of sensitive HIV-related behaviors (e.g., condom use, substance use) has been shown to be inaccurate when compared to objective biomarkers [2, 3]. As such, an exclusive reliance on self-report can lead to misclassification, masked intervention effects, and ambiguity in the interpretation of study findings [2]. Indeed, the VOICE trial—a randomized controlled trial (RCT) of ART as preexposure prophylaxis for HIV among women living in SSA [4]—is one example of how a disparity in self-reported and biologically-confirmed adherence can significantly interfere with the determination of treatment efficacy. As "prevention with positives" continues to become the dominant HIV-prevention paradigm, trials assessing intervention impact on condom use among HIV-infected adults must have reliable and valid measurements to estimate efficacy and effectiveness. This is particularly important when assessing the sexual risk behavior of HIV-positives given the risk of onward transmission, which may elicit concerns about social desirability and/or the possible negative consequences of disclosing unprotected sex (e.g., stigma from partners and medical providers)—precisely the conditions under which sensitive questions are most prone to misreport [5].

Though HIV medication adherence research routinely employs well-validated methods for objectively supplementing self-report (e.g., drug concentration in bodily fluids [6]), research on sexual risk behavior has been slower to routinely use objective measures of unprotected sex, despite their availability and recent validation [7–9]. Biomarkers of semen exposure allow for the comparison of self-reported condom use to a biological reference standard. Candidate biomarkers for semen exposure fall into two broad categories and include constituents of seminal plasma (e.g., prostate specific antigen) and of spermatozoa present in semen (e.g., Y-chromosome DNA) [9]. Prostate specific antigen (PSA)—a protein secreted by the prostate into the urethra during ejaculation—is the best-validated semen biomarker, is found in high concentrations in vaginal fluids immediately after semen exposure, and is detectable up to 48 h after unprotected sex [2, 7–9]. Vaginal fluid for PSA testing can be obtained from self-collected swabs and tested using a simple qualitative rapid test—the ABAcard®p30 [2, 8]. This immunochromatographic strip assay uses specimens that can be processed in laboratories with limited equipment and personnel, making it an ideal semen biomarker test for estimating misreport among women in low-income settings [2]. Studies that have used PSA to examine the accuracy of self-reported condom use among HIV-uninfected women have revealed significant levels of misreport among women in SSA [7, 10–12]. For example, an experimental study of HIV-uninfected women from Zimbabwe designed to compare audio computer assisted self-interview to face-to-face interviews, found that regardless of interview mode, misreport of unprotected sex was high with only 52 % of women with positive PSA tests self-reporting unprotected sex in the previous 48 h [12]. These data highlight the importance of using objective measures to supplement self-reported condom use, and underscore the need for similar work with HIV-infected women given the increased potential for socially desirable responding discussed previously.

Only one study, to our knowledge, has used PSA to estimate misreport of unprotected sex among HIV-infected women in Africa [13]. As part of the Partners in Pre-Exposure Prophylaxis (PrEP) Study in Kenya—a RCT of PrEP for the prevention of HIV acquisition among HIV-serodiscordant couples—trained clinicians collected vaginal specimens from

125 female participants (73 % of whom were HIV-infected) in the baseline appointment of the trial [13]. These specimens were tested for PSA using an enzyme-linked immunosorbent assay, and positive PSA tests were compared to self-report of 100 % condom use in the previous month. A total of 13 women (10.5 %) tested positive for PSA, and 77 % (10/13) of the PSA positive women reported 100 % condom use in the previous month [13].

These findings offer preliminary data on the importance of PSA testing in sexual behavior research with HIV-infected women in Africa; however additional research on the use of PSA in this population is needed given that: (1) the percent of PSA positive samples in Mose et al. [13] (10.5 %) was lower that what is typically expected (30 %) perhaps due to fact that women were enrolled in an ongoing HIV prevention trial which could have affected the incidence of unprotected sex in the sample and (2) methods for self-collection (vs. clinician-collection) of PSA samples, and a simple qualitative rapid PSA test (the ABAcard®p30), are available, and are likely to be much more practical in resource limited settings.

This study was therefore designed to: (1) establish the practical feasibility [14] of using self-collected samples and on-site processing of the ABAcard®p30 to test for PSA among sexually active, HIV-infected Ugandan women receiving care at a rural HIV clinic and (2) to provide preliminary data on the level of misreported unprotected sex among these women by comparing positive PSA tests to self-report of unprotected vaginal sex in the last 48 h.

Methods

Overview

All procedures were approved by the Institutional Review Boards at the University of California, San Francisco (UCSF), the Mbarara University of Science and Technology (MUST), and the Uganda National Council for Science and Technology. Data for this study were collected as part of two ongoing cohort studies of HIV-infected Ugandan adults entering care at the immune suppression syndrome (ISS) clinic at MUST. The Biomarker Research Among Those with HIV (BREATH) study was designed to examine patterns of alcohol use over time among HIV-infected Ugandan adults [3]. Eligibility for enrollment included: age of 18+, fluency in either English or Runyankole (the local language in this region of Uganda), ability to provide informed consent, self-report of any alcohol use in the prior year at initial clinic visit or suspected alcohol use by clinic counselors, being new to HIV care, and residency within 60 km of the ISS Clinic. The Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS (URBAN ARCH)—Uganda study was designed to investigate the effect of heavy alcohol consumption on HIV disease progression prior to ART initiation, and had the following additional inclusion criteria: (1) both alcohol consumers and abstainers were included, (2) only patients who were not yet scheduled to start ART were eligible, (3) and participants did not have to be new to HIV care.

Participants in both cohorts were administered a structured face-to-face interview at a baseline study visit and quarterly thereafter for one year in BREATH, and every six months until ART initiation in URBAN ARCH-Uganda. Women who were enrolled in either of these studies between September 2012 and August 2013, who reported at least one episode

of unprotected sex in the last 3 months, and alcohol consumption in the last year, were eligible to participate in the current study (the alcohol use criteria was due to a broader study goal of examining the association between alcohol use and unprotected sex with qualitative interviews, which are not reported here). Women were approached after completion of their regularly scheduled BREATH or URBAN ARCH-Uganda study visit, informed about the study, screened for eligibility, and, if appropriate, consented to participate. The informed consent process explicitly informed participants that they would be submitting samples that would be "tested for evidence of recent unprotected sex." Women who submitted samples for PSA testing were approached on subsequent cohort study visits provided the subsequent study visit occurred during the data collection timeframe (September 2012–August 2013), the BREATH/URBAN ARCH-Uganda study team referred the participant, the research assistant was available, and the participant indicated she had the time and/or interest to participate again.

PSA Collection and Processing

Samples for PSA testing were typically collected on the same day as the cohort study visit, unless the participant expressed a preference to return on a different day (typically the next day). Previously described procedures were used for collection and processing of vaginal specimens [15]. All specimens for PSA testing were self-collected and processed on-site at the MUST laboratory by technicians trained by the study team. Participants were instructed to self-collect vaginal fluids by inserting a cotton-tipped swab into the vagina. Once collected, the samples were immediately delivered to the MUST laboratory and air-dried for at least 2 h (up to overnight). Samples were subsequently stored at −80°C until PSA testing occurred using the ABAcard®p30. At the time of processing, samples were removed from the freezer and placed into labeled tubes of 1 mL of saline. Subsequently, the swab was vigorously mixed with the buffer and then vortexed, at which point 200 μL of the saline solution was removed with a pipette and placed in the sample well of the ABAcard®p30 PSA test device. After a period of 10 min, the PSA test device was examined, and any test with a visible line in the test area was considered positive.

The ABAcard®p30 is highly sensitive (100 %) and specific (96 %) for the detection of >1.0 ng PSA/mL of vaginal swab eluate; however, PSA > 1.0 ng/mL, while highly specific, lacks sensitivity as a measure of exposure to semen. Due to rapid and variable rates of PSA clearance from vaginal fluids, negative PSA tests cannot be interpreted as lack of semen exposure [2, 8]. Thus, only positive PSA tests can be used as evidence of exposure to semen and compared to self-reported unprotected sex as an indicator of misreport.

Misreported Unprotected Sex

Information about unprotected vaginal sex (UVS) was collected in a standard interview format with an adapted version of the Most Recent Sexual Event [16] questionnaire, which was administered to all BREATH and URBAN ARCH-Uganda study participants. Immediately prior to specimen collection, participants were asked for the date of their last episode of vaginal sexual intercourse (which was coded as yes/no for having occurred in the last 48 h), and whether or not a condom was used during this sexual event (yes/no). Positive PSA tests were compared to self-reported UVS over the last 48 h. "Misreport of UVS" was

defined as: a positive PSA test and self-report of no vaginal sex or condom-protected only vaginal sex in last 48 h (yes/no).

Results

A total of 199 women were approached to participate in PSA testing immediately following their regularly scheduled cohort study visit. Of these women, 51 % (N = 108) were eligible (i.e., reported at least one episode of unprotected sex in the last 3 months and had consumed alcohol in the last year). Of the eligible women, 76 % (N = 83) consented to participate and submitted samples for PSA testing at up to three study visits, if those visits occurred during the data collection window (September 2012–August 2013). A further n = 6 women were excluded during data analysis due to: being HIV-uninfected (n = 1), lost to follow-up (n = 3), and a data entry error (n = 2). A total of 77 women submitted at least one sample for PSA testing. Of these women, 45 % (n = 35) submitted only one sample for PSA testing, and 55 % (n = 42) submitted >1 sample (see Table 2). Of the 35 women who submitted only one sample for PSA testing, 83 % (n = 29) did not have a BREATH or URBAN ARCH-Uganda cohort study follow-up visit within the PSA data collection window. The remaining six women (17 %) were seen for a BREATH or URBAN ARCH-Uganda cohort study follow-up visit within the PSA data collection window, but did not submit samples for PSA testing. Reasons for refusal included menstruation, not having time, and/or having no interest in participating again.

The average age of the participants was 26 (Interquartile range = 22–30), 65 % (n = 50) of the women were married, and 35 % (n = 27) had more than a primary education. Based on responses to the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C), a majority of the women reported using alcohol at either a non-hazardous (40 %; score = 1–2) or a hazardous (39 %; score ≥ 3) level in the last 3 months (see Table 1). No specimen collections were aborted, no issues with transferring or storage of the samples were noted, and the laboratory reported no difficulties processing the samples or using the ABAcard®p30 test device.

Misreport of UVS

Results from PSA testing are described in Table 2. A total of 77 women submitted 126 samples for PSA testing over the course of 1–3 study visits. Of these samples, 31 % were PSA positive (n = 39). Twenty-five of the 39 positive PSA tests (64 %) were from visits in which the participant reported no UVS in the last 48 h. The percentage of positive PSA tests (~30 %) and proportion of misreported UVS (50–65 %) were similar across the study visits (see Table 2).

Discussion

We successfully conducted rapid PSA testing using the ABAcard®p30 and self-collected specimens with HIV-infected women in a rural HIV clinic in Uganda. Approximately 75 % of the eligible women consented to participate and none of these participants expressed difficulties with specimen collection. Samples were successfully stored and processed on-

site at a laboratory affiliated with the MUST ISS clinic, and laboratory staff reported no difficulties using the ABAcard®p30.

Consistent with prior research [7, 10–12], our results suggest significant under-report of recent UVS among HIV-infected Ugandan women. The level of misreported UVS observed in our study (~65 %) is consistent with previous studies using PSA testing with HIV-uninfected women in Zimbabwe (48 %) [11, 12] and Madagascar (60 %) [7], and was obtained even after explicitly informing the participants that the samples being collected would be used to determine if the participant had recently had unprotected sex (which is also consistent with prior research [17]). The level of misreport we observed is unlikely to be attributable to condom slippage and/or breakage given that the frequency of condom slippage/breakage for male condoms has been reported as quite low [18], and that previous PSA research has found that reports of condom problems did not explain discrepancies between PSA and self-report [12]. Other studies with these and similar cohorts have revealed that under-report of alcohol consumption is common among HIV-infected men and women in Uganda, indicating that sensitive and/or stigmatized behaviors may be particularly vulnerable to socially desirable responding in this population [3, 19].

Our findings raise major concerns over the validity of self-reported condom use with samples of HIV-infected women. Misreport of UVS among women living with HIV/AIDS hampers efforts to decrease sexual transmission of HIV by masking the intervention effects of condom promotion interventions and interfering with the interpretation of study findings related to condom use. Similar to the work conducted by the VOICE study team [20] and work with PSA among women in Jamaica [21], our results would benefit from follow-up qualitative interviews to uncover the reasons for misreported unprotected sex, and to determine correlates of misreport. Continued research on sexual risk behavior should incorporate semen biomarkers such as PSA as an adjunct to self-reported condom use. While both measures suffer from limitations, the combination of the two (i.e., using PSA positive and/or self-report of unprotected sex as an overall indicator of condom use) increases the sensitivity beyond using just one alone [22], and would significantly improve our understanding of condom use interventions designed to interrupt onward transmission of HIV.

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Table 1

Participant demographics (*N* = 77)

	All participants	Participants with a PSA positive visit	Participants with a PSA positive visit and no self-reported unprotected sex in the last 48 h
	N = 77	*N* = 34	*N* = 23
Demographic	***N* (%) or Median (IQR)**	***N* (%) or Median (IQR)**	***N* (%) or Median (IQR)**
Age	26 (22–30)	26 (23–34)	26 (23–34)
Marital status			
Married	27 (35.1 %)	9 (26.5 %)	5 (21.7 %)
Not married	50 (64.9 %)	25 (73.5 %)	18 (78.3 %)
Education			
Primary education or less	50 (64.9 %)	24 (70.6 %)	14 (60.9 %)
More than primary education	27 (35.1 %)	10 (29.4 %)	9 (39.1 %)
Alcohol use in the past 3 months			
None (AUDIT-C = 0)	16 (20.8 %)	5 (14.7 %)	1 (4.4 %)
Non-hazardous (AUDIT-C = 1–2)	31 (40.3 %)	18 (52.9 %)	15 (65.2 %)
Hazardous (AUDIT-C ≥ 3)	30 (39.0 %)	11 (32.4 %)	7 (30.4 %)
Months since HIV diagnosis	5.5 (1.0–27.7)	2.4 (1.0–14.1)	1.7 (0.9–27.6)

Note. Visit = study visit in which a sample for PSA testing was collected, *AUDIT-C* = Alcohol Use Disorders Identification Test-Consumption

Table 2

Comparison of positive PSA tests with self-reported vaginal sexual intercourse in the last 48 h among HIV-infected Ugandan women

Visit	Samples collected	PSA positive	No self-reported unprotected sex in the last 48 h and PSA positive
Visit 1	77 women	24/77 (31 %)	16/24 (67 %)
Visit 2	42 women	13/42 (31 %)	8/13 (62 %)
Visit 3	7 women	2/7 (29 %)	1/2 (50 %)
Total	126 samples	39/126 (31 %)	25/39 (64 %)

Note. Visit = study visit in which a sample for PSA testing was collected, *PSA* = prostate specific antigen